Synthesis and inclusion properties of 1,3-*alternate*-bis[(ethoxycarbonyl) methoxy]thiacalix[4]arene-mono(crown-4) ether

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A novel ditopic receptor possessing two complexation sites such as crown ether and (ethoxycarbonyl) methoxy groups bearing 1,3-*alternate* conformation based on thiacalix[4]arene was prepared. The binding behaviours with alkali metals have been examined by ^{1}H NMR titration experiment. The exclusive formation of the heterogeneous dinuclear complexes of 1,3-*alternate*-3 with Li^+ and K^+ was observed.

Keywords: thiacalix[4]arenes, crown ether, conformation, ionophores, allosteric effect

A large variety of host–guest systems have been designed as selective cation, anion or neutral molecule receptors and carriers using three-demensional calix[*n*]arenes as building blocks.[1] More recently, thiacalix[4]arenes,[2] due to their novel features, have been used as potential platforms. Di- or polytopic receptors are those constructed with two or more binding subunits within the same macrocyclic structure.[3] It is well known that these systems are suitable candidates for the allosteric regulation[4] of host–guest interactions with metal cations that play a major role in biological systems.[5]

From the literature it is known that the so-called 1,3-*alternate* conformation of calix[4]arene, which has D_{2h}-symmetry, tube-shape,[6] *etc.*, can be well adapted for the formation of 1 : 1 as well as 1 : 2 complexes owing to its symmetrical ditopic arrangement. On the other hand, calixcrowns (crown ether calixarenes) have an extra intramolecular cavity formed by the crown ether bridge which displays significant levels of selectivity and avidity toward complexation with alkali metal ions. So far, the synthesis of 1,3-thiacalix[4] bis(crown-5) and -(crown-6) ethers have been reported[7,8] as well as the studies of their complexation abilities toward Na^+, K^+, Rb^+ and Cs^+ which show lower extraction efficiencies that those of conventional calix[4]crowns.[9,10]

Lithium complexes of crown ethers are of great interest due to their applications as anionic conductors in manufacturing lithium-based rechargeable batteries and electrolytes and as anion activators in organic synthesis. Despite of the importance of lithium complexes no detailed investigation on the extraction of lithium by calixcrowns-4 has been carried out. Moving from our interest on the synthesis of potentially heteroditopic receptors having two cation binders, we introduced a crown-4 ether function into the *distal*-thiacalix[4]arene. The hydrophilic crown ether cavity has been used as efficient extractant for smaller cation such as Li^+. We report herein the synthesis of the novel receptor bis [(ethoxycarbonyl)methoxy]thiacalix[4]arene-mono(crown-4) ether **3** constraining 1,3-*alternate* conformation, having two different side arms and showing affinity to both alkali metal cations, and the study of their complexation behaviour towards Li^+ and K^+ ions. In fact, some ditopic receptors based on thicalix[4]arene framework have been reported but there is no study concerning the presence of allosteric effect in such systems. Multi-recognition of Li^+ and K^+ by 1,3-*alternate*-**3** is expected, owing to the presence of two ester moieties at one edge of the thiacalix[4]arene cavity[11] and a crown-4 ether moiety at the another edge.

Results and discussion

Based on the importance of the nature of the oligoethylene glycol units for the Li^+ complexation, the triethylene glycol units was linked between the *distal* position in thiacalix[4]arene. Thus *O*-alkylation of tetrathiacalix[4]arene **1** carried out with 2 equiv. of ethyl bromoacetate in the presence of an equiv. of Na_2CO_3 according to the reported procedure produces exclusively the disubstituted product *distal*-**2**.[11] *O*-alkylation of *distal*-**2** carried out with 2 equiv. of triethyleneglycol ditosylate[12] in the presence of 5 equiv. of Cs_2CO_3 according to the reported procedure[13] afforded the desired 1,3-*alternate*-**3** in 80% yield.

The product structure was supported by its spectral and analytical data. The ^{1}H NMR spectrum of 1,3-*alternate*-**3** shows two singlets for the *tert*-butyl protons at δ 1.24 and 1.32 ppm and the singlet signal of the methylene protons of OCH_2COOEt was observed at higher field (δ 4.41 ppm) than that of *distal*-**2** (δ 5.29 ppm)[11] due to the ring current effect arising from the two inverted calix benzene rings.[13] This observation strongly suggests **3** adopts 1,3-*alternate* conformation.

It is expected that the cavity delineated by the crown-4 matches well with Li^+,[14] and the other cavity delineated by ester moieties can work as a switch for complexation and decomplexation in the crown site. The heteroditopic receptor 1,3-*alternate*-**3** displays affinity toward Li^+ as well as larger sized alkali metals such as K^+. The complexation abilities of 1,3-*alternate*-**3** was assessed by ^{1}H NMR spectroscopy.

^{1}H NMR titration experiments with $LiSO_3CF_3$ and KSO_3CF_3 were carried out. The addition of 1 equiv. of $LiSO_3CF_3$, separately, to 1,3-*alternate*-**3** caused immediate complexation as demonstrated by the down field shift of the crown protons (*i.e.* 1,3-*alternate*-**3**⊃Li^+; ArOCH_2CH_2O, Δδ = + 0.07). Similar down field shifts were also observed in the methylene protons of the OCH_2COOEt and calix protons. Only the 1 : 1 complex 1,3-*alternate*-**3**⊃Li^+ was formed even with a large excess of $LiSO_3CF_3$. The results confirm that the crown moiety of 1, 3-*alternate*-**3** composes a stronger ionophoric cavity for Li^+ than the two ester moieties. On the other hand, titration with 1 equiv. of KSO_3CF_3 to 1,3-*alternate*-**3** causes a dramatic down-field shift for the methylene protons of OCH_2COOEt in 1,3-*alternate*-**3** (Δδ = + 0.28 ppm) strongly suggesting that K^+ is bound to the oxygen atoms of the CH_2COOEt and phenolic oxygens (1 : 1 K^+⊂1,3-*alternate*-**3** complex). Spectral changes of the 1 : 1 K^+⊂1,3-*alternate*-**3** complex in the presence of an excess of KSO_3CF_3 were not detectable, which supports the exclusive formation of the 1 : 1 K^+⊂1, 3-*alternate*-**3** complex. The chemical shift changes (Δδ) of OCH_2COOEt protons and methylene protons of crown moieties upon complexation are shown in Fig. 2.

The possible switch on-off of the recognition behaviour of 1,3-*alternate*-**3** upon complexation was studied by a set of ^{1}H NMR titration experiments. First, from 1 up to 5 equiv. of KSO_3CF_3 were added to the solution containing 1,3-*alternate*-**2**⊃Li^+.

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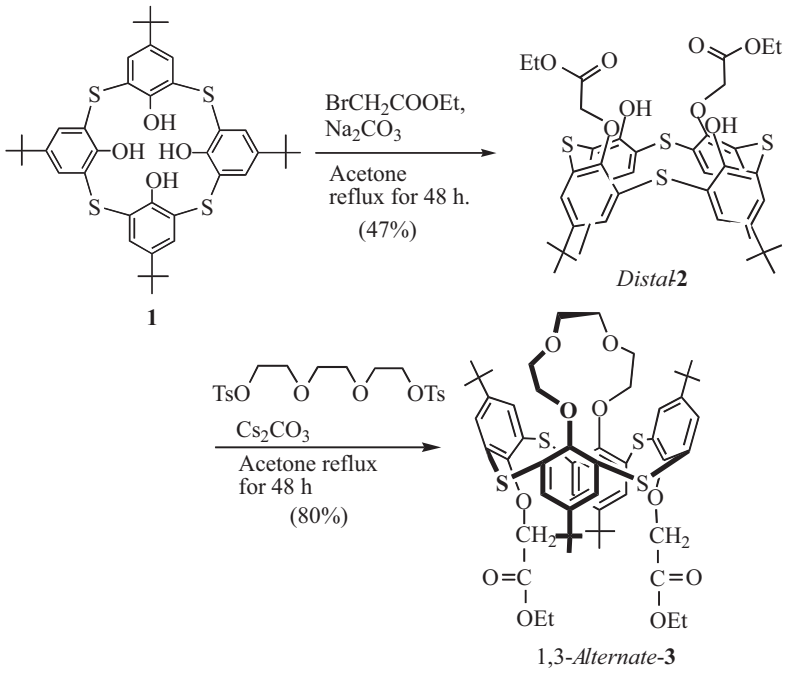

Scheme 1

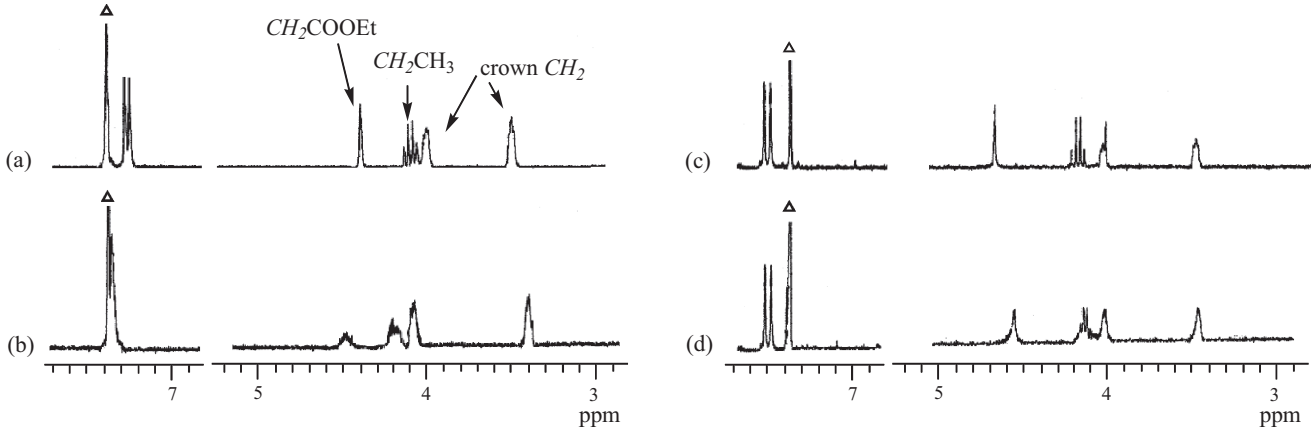

Fig. 1 Partial ^{1}H NMR titration spectra of 1,3-*alternate*-**3** (5×10^{-3} M, in $CDCl_3$: CD_3OD, 1: 1, v/v). (a) free ligand; (b) in the presence of 1 equiv. of $LiSO_3CF_3$; (c) in the presence of 1 equiv. of KSO_3CF_3; (d) addition of 1 equiv. of KSO_3CF_3 into solution of (b); Δ denotes solvent signal.

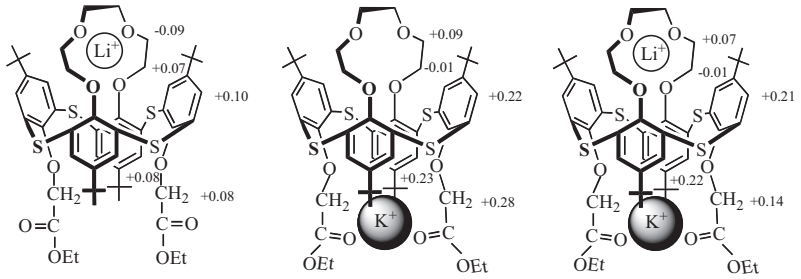

Fig. 2. Binding mode of 1,3-*alternate*-**3**⊃Li^+ complex, K^+⊂1,3-*alternate*-**3** complex and K^+⊂1,3-*alternate*-**3**⊃Li + complex [300 MHz, in $CDCl_3$: CD_3CN 1: 1, 27°C]. $\Delta\delta = \delta$ (metal)– δ (free ligand). (-) denotes a shift to up field. (+) denotes a shift to down field].

The ^{1}H NMR spectra of complex completely changed, but not that of 1,3-*alternate*-**3**⊃Li^+ complex. This finding strongly suggests that heterogeneous dinuclear complexation does occur to form K^+⊂1,3-*alternate*-**3**⊃Li^+. Similarly, when K^+⊂1,3-*alternate*-**3** was titrated with Li^+ same spectra change was observed as K^+⊂1,3-*alternate*-**3**⊃Li^+. These findings suggest not only the dinuclear complexation with Li^+ and K^+ from the crown moiety and ester moieties. However, complete suppression of the recognition of Li^+ derived from the crown moiety upon formation of the K^+⊂1,3-*alternate*-**3** complex was not observed. Thus, the switch-off ascribed by conformational changes upon complexation of K^+ at the ester moieties has not been accomplished.

Conclusions

A novel ditopic receptor 1,3-*alternate*-**3** possessing two complexation sites, crown-4 moiety and (ethoxycarbonyl) methoxy groups in 1,3-*alternate* conformation based on thiacalix[4]arene has been prepared. The exclusive formation of the heterogeneous dinuclear complexes of 1,3-*alternate*-**3** with Li^+ and K^+ was observed. However, the decomplexation of Li^+ from the crown moiety of 1: 1 complex 1,3-*alternate*-**3**⊃Li^+ to form the K^+⊂1,3-*alternate*-**3** complex by addition of KSO_3CF_3 has not been accomplished under the condition used. Complexation of 1,3-*alternate*-**3** with K^+ did not suppress the complexation with Li^+ by the conformational changes induced complexation. Thus, this result shows that ester moiety does not work as an efficient switch-off of the recognition ability of the crown moiety.

Experiment

All melting points are uncorrected. ^{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-HX110A Ultrahigh Performance Mass Spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed by Yanaco MT-5.

Materials

Distal-5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl) methoxy]-26,28-dihydroxy-2,8,14,20-tetrathiacalix[4]arene *distal*-**2**[11] and triethyleneglycol ditosylate[12] were prepared according to the reported procedure.

O-Alkylation of distal-**1** *with triethyleneglycol ditosylate*

To a solution of *distal*-**2** (2.0 g, 2.7 mmol), Cs_2CO_3 (4.40 g, 13.5 mmol) in dry acetone (20 cm^3) was added triethyleneglycol ditosylate (2.5 g, 5.5 mmol). The mixture was reflux for 48 h under Argon, cooled at room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with 1 N HCl. The organic layer was separated, washed with brine (15 cm^3 × 2) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated to dryness to obtain crude product which was subjected to column chromatography (150 g silica gel, 5 : 1 ethyl acetate: hexane) followed by recrystallisation from ethanol to give a pure sample of 5,11,17,23-tetra-*tert*-butyl-25,27-bis [(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arenemono-crown-4(1,3-*alternate*-**3**)(1.86g,80%)ascolourlessprisms,m.p.274°C; δ ($CDCl_3$) 1.24 (18H, s, *t*Bu), 1.32 (18H, s, *t*Bu), 1.78 (6H, t, J = 7.3 Hz, CH_2CH_3), 2.57 (4H, s, CH_2), 3.47–3.50 (4H, m, CH_2), 4.01–4.04 (4H, m, CH_2), 4.08 (4H, q, J = 7.3 Hz, CH_2CH_3), 4.41 (4H, s, CH_2), 7.26 (4H, s, Ar–*H*), 7.29 (4H, s, Ar–*H*); *m/z*: 1006.4 (M^+) (Found: C, 64.20; H, 6.82. $C_{54}H_{70}O_{10}S_4$ (1006.39) requires C, 64.38; H, 7.00%).

^{1}H NMR complexation experiment

To a $CDCl_3$ solution (4 × 10^{-3} M) of 1,3-*alternate*-**3** in the NMR tube was added a CD_3CN solution (4 × 10^{-3} M) of KSO_3CF_3 and $LiSO_3CF_3$, separately. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27°C.

The partial ^{1}H NMR data of the representative complexes are given below.

1,3-*alternate*-**3**⊃Li^+: ^{1}H NMR ($CDCl_3$: CD_3CN, 1 : 1) δ: 3.40 (4H, m, CH_2), 4.09 (4H, m, CH_2), 4.20 (4H, m, CH_2CH_3), 4.49 (4H, broad s, CH_2), 7.26 (4H, s, Ar–*H*), 7.27 (4H, s, Ar–*H*).

K^+⊂1,3-*alternate*-**3**: ^{1}H NMR ($CDCl_3$: CD_3CN, 1 : 1) δ: 3.58 (4H, m, CH_2), 4.01 (4H, m, CH_2), 4.18 (4H, q, J = 7.3 Hz, CH_2CH_3), 4.69 (4H, s, CH_2), 7.48 (4H, s, Ar–*H*), 7.52 (4H, s, Ar–*H*).

K^+⊂1,3-*alternate*-**3**⊃Li^+: ^{1}H NMR ($CDCl_3$: CD_3CN, 1 : 1) δ: 3.56 (4H, m, CH_2), 4.01 (4H, m, CH_2), 4.14 (4H, q, J = 7.3 Hz, CH_2CH_3), 4.55 (4H, s, CH_2), 7.47 (4H, s, Ar–*H*), 7.51 (4H, s, Ar–*H*).

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