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Synthesis and Ion Selectivity of Macrocyclic Metacyclophanes Analogous to Spherand-Type Calixarenes *

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Abstract. Novel macrocyclic compounds, hexahydroxy[1.0.1.0.1.0]- (**2b**) and octahydroxy[1.0.1.0.-1.0.1.0]metacyclophane (**2c**) have been prepared in 50–70% yield by base-catalyzed condensation of 5,5′-di-*tert*-butyl-2,2′-dihydroxybiphenyl (**1**) with formaldehyde in refluxing xylene. An attempted alkylation of the flexible macrocycles **2b** and **2c** with ethyl bromoacetate in the presence of Cs_2CO_3 under acetonitrile reflux gave only one pure stereoisomer **3** and **4**, respectively, while other possible isomers were not observed. The structural characterization of these products is also discussed. The two-phase solvent extraction data indicated that hexaethyl ester **3** and octaethyl ester **4** show strong metal affinity, comparable with that of the corresponding calix[n]arenes, and a high K^+ selectivity was observed for octaethyl ester **4**. ^{1}H-NMR titration of hexaethyl ester **3** and octaethyl ester **4** with KSCN clearly demonstrate that a 1 : 1 complex is formed which is stable on the NMR time scale.

Key words: Spherand-type calixarene, ion selectivity, diastereoselective functionalization.

1. Introduction

Due to their importance in supramolecular chemistry [1] a large variety of macrocyclic compounds such as crown ethers [2], cryptands [3], cyclophanes [4], and spherands [5] have been synthesized and their properties investigated. Our present work is directly related to the studies of Cram and coworkers [5] in designing spherands possessing 1,1′-biarene units which contain enforced, spherical cavities lined with electron pairs of heteroatoms so that no conformational rearrangement is possible upon complexation with metal ions.

Closely related to the spherands are the 'calixarenes', [1$_n$]metacyclophanes, prepared by base-catalyzed condensation of *p*-substituted phenols with formaldehyde [6]. These are attractive building blocks, their phenolic hydroxyl groups being ordered in well-shaped cyclic arrays [6–8] which can be functionalized [7–14] to give novel guest inclusion blocks. The combination of structural elements of both

* This paper is dedicated to the commemorative issue on the 50th anniversary of calixarenes.
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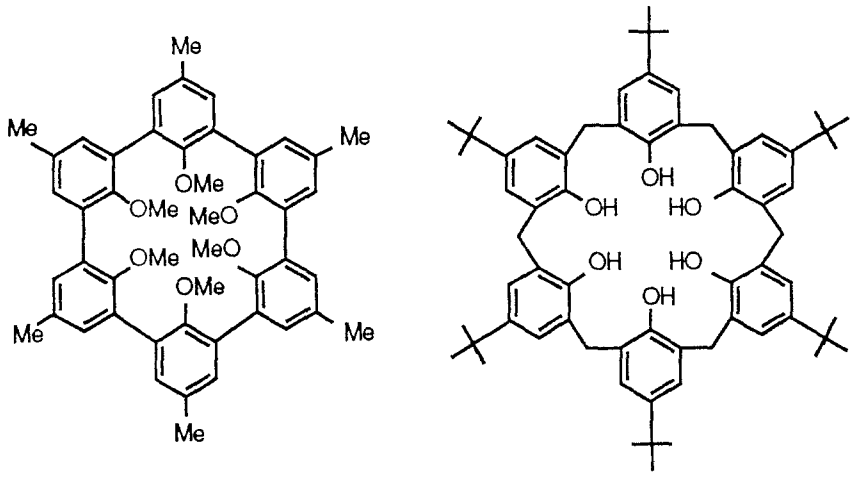


Chart 1.

spherands and calixarenes is expected to lead to novel macrocyclic compounds, which may greatly stimulate future work in the field of host–guest chemistry.

We have recently demonstrated a convenient and selective synthesis of a series of hydroxy[1_n]metabiphenylophanes with three and four biarene units **2** involving base-catalyzed condensation of 5,5′-di-*tert*-butyl-2,2′-dihydroxybiphenyl (**1**) with formaldehyde under refluxing xylene, and we have reported their unique properties [15]. The cyclic trimer **2b** was obtained as a major product with NaOH as base in xylene, while the action of the larger Cs^+ led to the larger macrocyclic tetramer **2c**. These results seem to indicate that the template effect of an alkali metal cation plays an important role in this condensation reaction as previously observed in the preparation of calixarenes [6].

In comparison to the structural characteristics of a calixarene family, spherand-type calixarene analogous metacyclophanes **2** attracted our further interest for the following reasons: (i) macrocycles **2b** with three methylene bridges and three biarene linkages may be regarded as a combination of half structural elements of both spherands and calix[6]arenes; (ii) since the MeO group is bulky enough to inhibit the oxygen-through-the-annulus rotation of macrocycles **2** [15], interconversion between the conformers derived from introduction of the higher alkyl group on the phenolic oxygens of macrocycles **2a** and **2b** should not take place; (iii) the substituent OR group at the 2-position of a biarene unit should be quite removed from the 2′-position in such a configuration, so avoiding steric hindrance at the Ar—Ar σ-bond; (iv) the restricted ring conformation due to the biarene units may increase the selectivity in the binding of metal ions as compared to the same functionalized phenolic units in calix[6]arene and calix[8]arene. We report here the first example of *O*-alkyl derivatives **3** and **4** with three and four biarene units from the reaction of macrocycles **2a** and **2b** with ethyl bromoacetate, their metal

selectivity, and the binding-mode for metals. These compounds are expected to have combined properties of both the spherands and the calixarenes.

2. Experimental

All melting and boiling points are uncorrected. IR (KBr or NaCl): Nippon Denshi JIR-AQ2OM. ^{1}H-NMR: Nippon Denshi JEOL FT-270 in $CDCl_3$, TMS as reference. MS: Nippon Denshi JMS-01SA–2. Elemental analysis: Yanaco MT-5.

2.1. Synthesis

2.1.1. *Preparation of 4,10,17,23,30,36-hexa-tert-butyl-7,13,20,26,33,39-hexahydroxy[1.0.1.0.1.0]metacyclophane* (**2b**). To a mixture of 5,5′-di-*tert*-butyl-2,2′-dihydroxybiphenyl (**1**) (5 g, 16.75 mmol) and paraformaldehyde (1.1 g, 35.75 mmol) in xylene (85 mL) was added aqueous 5 N NaOH (1.5 mL) under nitrogen with vigorous stirring. After the reaction mixture had been refluxed for 16 h, it was cooled to room temperature, acidified with 1 N HCl (50 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was chromatographed over silica gel (Wako, C-300; 500 g) with hexane and benzene as eluent to give 3.20 g of crude **2b** and a trace amount of **2c**, respectively. Recrystallization from hexane gave the *title compound* **2b** (2.72 g, 52%) as colourless prisms; m.p. 253–256°C; ν_{max} (KBr)/cm^{-1} 3297 (OH); δ_H ($CDCl_3$, 20°C) 1.35 (54H, s, C(CH_3)$_3$), 4.02 (6H, ArCH_2Ar), 7.20 (6H, d, J = 2.44, Ar*H*), 7.39 (6H, d, J = 2.44, Ar*H*), 8.48 (6H, broad s, *OH*); δ_H ($CDCl_3$, -50°C), 1.35 (54H, s, C(CH_3)$_3$), 3.79 (3H, broad s, ArCH_2Ar), 4.21 (3H, broad s, ArCH_2Ar), 7.21 (6H, d, J = 2.44, Ar*H*), 7.44 (6H, d, J = 2.44, Ar*H*), 8.48 (6H, broad s, *OH*); *m/z*: 931 (M^+); *Found*: C, 80.90; H, 8.60. *Calcd.* for $C_{63}H_{78}O_6$: C, 81.25; H, 8.44%.

2.1.2. *Preparation of 4,10,17,23,30,36,43,49-octa-tert-butyl-7,13,20,26,33,39,46,52-octahydroxy[1.0.1.0.1.0]metacyclophane* (**2c**). To a mixture of **1** (5 g, 16.75 mmol) and paraformaldehyde (1.1 g, 35.75 mmol) in xylene (85 mL) was added aqueous 5 N CsOH (1.5 mL) under nitrogen with vigorous stirring. After the reaction mixture had been refluxed for 16 h, it was cooled to room temperature, acidified with 1 N HCl (50 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was chromatographed over silica gel (Wako, C-300; 500 g) with hexane and benzene as eluent to give 204 mg (4%) of **2b** and 3.80 g of **2c**, respectively. Recrystallization from benzene gave the *title compound* **2c** (3.44 g, 66%) as colourless prisms; m.p. > 300°C; ν_{max} (KBr)/cm^{-1} 3245 (OH); δ_H ($CDCl_3$, 20°C) 1.30 (72H, s, C(CH_3)$_3$), 4.02 (8H, ArCH_2Ar), 7.08 (8H, d, J = 2.44, Ar*H*), 7.43 (8H, d, J = 2.44, Ar*H*), 8.34 (8H, broad s, *OH*); δ_H ($CDCl_3$, -50°C) 1.29 (36H, s, C(CH_3)$_3$, 1.32 (36H, s, C(CH_3)$_3$), 3.63 (2H, d, J = 14.2,

ArC*H*$_2$Ar), 3.88 (2H, d, J = 14.2, ArC*H*$_2$Ar), 4.15 (2H, d, J = 14.2, ArC*H*$_2$Ar), 4.70 (2H, d, J = 14.2, ArC*H*$_2$Ar), 7.05 (4H, d, J = 2.44, Ar*H*), 7.12 (4H, d, J = 2.44, Ar*H*), 7.43 (4H, d, J = 2.44, Ar*H*), 7.54 (4H, d, J = 2.44, Ar*H*), 8.34 (4H, broad s, *OH*), 8.60 (4H, broad s, *OH*); m/z: 1241 (M^+); *Found*: C, 81.05; H, 8.40. *Calcd.* for $C_{84}H_{104}O_8$: C, 81.25; H, 8.44%.

2.1.3. *Preparation of 4,10,17,23,30,36-hexa-tert-butyl-7,13,20,26,33,39-hexa-[(ethoxycarbonyl)methoxy][1.0.1.0.1.0]metacyclophane* (**3**). A mixture of 4,10,17,23,30,36-hexa-*tert*-butyl-7,13,20,26,33,39-hexahydroxy[1.0.1.0.1.0]metacyclophane (**2b**) (1.5 g, 1.61 mmol) and cesium carbonate (3.46 g, 10.63 mmol) in 100 mL of dry acetonitrile was heated at reflux for 3 h under nitrogen. Then ethyl bromoacetate (3.2 mL, 29 mmol) was added and the mixture heated at reflux for 16 h. After cooling the reaction mixture to room temperature it was filtered. The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess of unreacted ethyl bromoacetate using a Kugelrohr apparatus. The residue was chromatographed over silica gel (Wako, C-300; 300 g) with benzene as eluent to give a solid, which was recrystallized from hexane to afford the *title compound* **3** (2.15 g, 92%) as colourless prisms; m.p. 191–192°C; ν_{max} (KBr)/cm^{-1} 1733, 1762 (C=O); δ_H ($CDCl_3$) 0.82 (6H, t, J = 7.1, OC*H*$_2$C*H*$_3$), 1.01 (6H, t, J = 7.1, OCH$_2$C*H*$_3$), 1.09 (6H, t, J = 7.1, OCH$_2$C*H*$_3$), 1.28 (18H, s, C(C*H*$_3$)$_3$), 1.30 (18H, s, C(C*H*$_3$)$_3$), 1.34 (18H, s, C(C*H*$_3$)$_3$), 3.31 (2H, d, J = 17.1, OC*H*$_2$CO), 3.39 (2H, J = 13.2, ArC*H*$_2$Ar), 3.68 (2H, d, J = 17.1, OC*H*$_2$CO), 3.47–4.02 (18H, overlapped signals due to OC*H*$_2$CO and OC*H*$_2$CH$_3$), 4.14 (2H, s, ArC*H*$_2$Ar), 4.28 (2H, d, J = 17.1, OC*H*$_2$CO), 5.24 (2H, d, J = 13.2, ArC*H*$_2$Ar), 6.89 (2H, d, J = 2.4, ArH), 7.04 (2H, d, J = 2.4, ArH), 7.12 (2H, d, J = 2.1, Ar*H*), 7.31 (2H, d, J = 2.4, Ar*H*), 7.34 (2H, d, J = 2.4, Ar*H*), 7.44 (2H, d, J = 2.4, Ar*H*); *Found*: C, 67.70; H, 7.76. *Calcd.* for $C_{87}H_{114}O_{18}\cdot CHCl_3$: C, 67.44; H, 7.4%.

2.1.4. *Preparation of 4,10,17,23,30,36,43,49-octa-tert-butyl-7,13,20,26,33,39,46,52-octa[(ethoxycarbonyl)methoxy][1.0.1.0.1.0.1.0]metacyclophane* (**4**). A mixture of 4,10,17,23,30,36,43,49-octa-*tert*-butyl-7,13,20,26,33,39,46,52-octahydroxy[1.0.1.0.1.0.1.0]metacyclophane (**2c**) (400 mg, 0.32 mmol) and cesium carbonate (1.89 g, 5.79 mmol) in 30 mL of dry acetonitrile were heated at reflux for 1 h under nitrogen. Then ethyl bromoacetate (1.4 mL, 15.1 mmol) was added and the mixture heated at reflux for 16 h. After cooling the reaction mixture to room temperature it was filtered. The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess unreacted ethyl bromoacetate using a Kugelrohr apparatus. The residue was chromatographed over silica gel (Wako, C-300; 300 g) with chloroform–ethanol (1 : 1 v/v) as eluent to give a solid, which was recrystallized from chloroform–methanol (1 : 1 v/v) to afford the *title compound* **4** (479 mg, 82%) as colourless prisms; m.p. > 300°C; ν_{max} (KBr)/cm^{-1} 1736, 1762 (C=O); δ_H ($CDCl_3$) 1.02 (24H, t, J = 7.3; OC*H*$_2$C*H*$_3$), 1.28 (72H, s, C(C*H*$_3$)$_3$), 3.40 (16H, q, J = 7.3, OC*H*$_2$C*H*$_3$), 3.59 (4H, d, J = 15.1,

ArCH_2Ar), 3.72 (8H, d, J = 17.1, ArOCH_2), 3.99 (8H, d, J = 17.1, ArOCH_2), 5.13 (4H, d, J = 15.1, ArCH_2Ar), 7.02 (8H, d, J = 2.5, Ar*H*), 7.21 (8H, d, J = 2.5, Ar*H*); *Found*: C, 68.74; H, 7.64. *Calcd.* for $C_{116}H_{152}O_{24}\cdot CHCl_3$: C, 68.56; H, 7.52%.

2.1.5. *Preparation of 4,10,17,23,30,36-hexa-tert-butyl-7,13,20,26,33,39-hexa-[(methoxycarbonyl)methoxy][1.0.1.0.1.0]metacyclophane* (**5**). A solution of hexaethyl ester (**3**) (100 mg, 0.069 mmol) and *p*-toluenesulfonic acid (20 mg, 10.63 mmol) in 50 mL of methanol was heated at reflux for a week under nitrogen. After cooling the reaction mixture to room temperature it was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give a solid which was recrystallized from hexane to afford the *title compound* **5** (80 mg, 85%) as colourless prisms; m.p. 235–236°C; ν_{max} (KBr)/cm^{-1} 1735, 1764 (C=O); δ_H ($CDCl_3$) 1.25 (18H, s, C(CH_3)$_3$), 1.28 (18H, s, C(CH_3)$_3$), 1.31 (18H, s, C(CH_3)$_3$), 3.07 (6H, s, OCH_3), 3.20 (6H, s, OCH_3), 3.39 (2H, d, J = 13.2, ArCH_2Ar), 3.40 (2H, d, J = 17.1, OCH_2CO), 3.24 (6H, s, OCH_3), 3.66 (2H, d, J = 17.1, OCH_2CO), 3.67 (2H, d, J = 17.1, OCH_2CO), 3.80 (2H, d, J = 17.1, OCH_2CO), 3.97 (2H, d, J = 17.1, OCH_2CO), 4.04 (2H, s, ArCH_2Ar), 4.16 (2H, d, J = 17.1, OCH_2CO), 5.10 (2H, d, J = 13.2, ArCH_2Ar), 6.94 (2H, d, J = 2.4, ArH), 7.02 (2H, d, J = 2.4, ArH), 7.10 (2H, d, J = 2.4, Ar*H*), 7.31 (2H, d, J = 2.4, Ar*H*), 7.36 (2H, d, J = 2.4, Ar*H*), 7.45 (2H, d, J = 2.4, Ar*H*); *Found*: C, 71.10; H, 7.86. *Calcd.* for $C_{81}H_{102}O_{18}$: C, 71.34; H, 7.54.

2.2. 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 mL); triply distilled water was used for all aqueous solutions. Two phase solvent extraction was carried out between water (5 mL, [alkali picrate] = 2.5×10^{-4} M) and CH_2Cl_2 (5 mL, [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 spectrophotometrically from the decrease in the absorbance of the picrate ion in the aqueous phase as described by Pedersen [31].

3. Results and Discussion

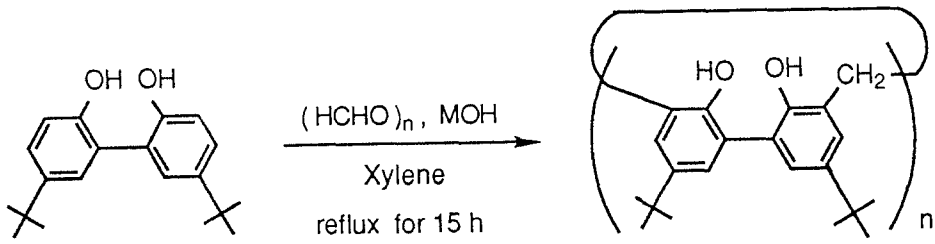
3.1. Base-catalyzed condensation of 5,5′-di-*tert*-butyl-2,2′-dihydroxybiphenyl with paraformaldehyde

The starting compound, 5,5′-di-*tert*-butyl-2,2′-dihydroxybiphenyl (**1**) [16] was prepared in two steps from 2,4-di-*tert*-butylphenol by using the *tert*-butyl group as a positional protective group on the aromatic ring [16–21].

When **1** was treated with paraformaldehyde in refluxing xylene under basic conditions, the expected products 4,10,17,23,30,36-hexa-*tert*-butyl-7,13,20,26,33,39-hexahydroxy[1.0.1.0.1.0]- (**2b**) and 4,10,17,23,30,36,43,49-octa-*tert*-butyl-7,13,20,26,33,39,46,52-octahydroxy[1.0.1.0.1.0.1.0]metacyclophane (**2c**) were obtained [21]. These compounds were easily separated from the crude reaction mixture by column chromatography.

However, under these conditions the formation of the dimer, 4,10,17,23-tetra-*tert*-butyl-7,13,20,26-tetrahydroxy[1.0.1.0]metacyclophane **2a** has not been observed. This finding seems to support the strained nature of **2a** compared to **2b** and **2c**, which have larger rings. The structures of **2b** and **2c** were elucidated from their elemental analyses and spectral data.

The conformations of trimer **2b** and tetramer **2c** have been evaluated from their dynamic ^{1}H-NMR spectra [15]. The conformational ring inversion of macrocycles **2b** and **2c** was observed at room temperature in the same way as Gutsche's hydroxy[1$_n$]metacyclophanes (calix[n]arenes).



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2 a; n = 2
b; n = 3
c; n = 4

3.2. Introduction of (ethoxycarbonyl)methoxy group to phenolic hydroxy group

Introduction of larger alkyl groups on the phenolic oxygens should lead to a situation where the OR groups within a biarene unit cannot pass each other. That means the rotation around the Ar—Ar σ-bond is hindered and each biarene unit is fixed in a certain configuration. For example, in the case of the tetramer **2c** four different diastereomers should be expected, two of which are chiral: (a) a compound in which all biarene units have the same configuration (*RRRR* or *SSSS*, D_4 symmetry);

D_4-symmmetry

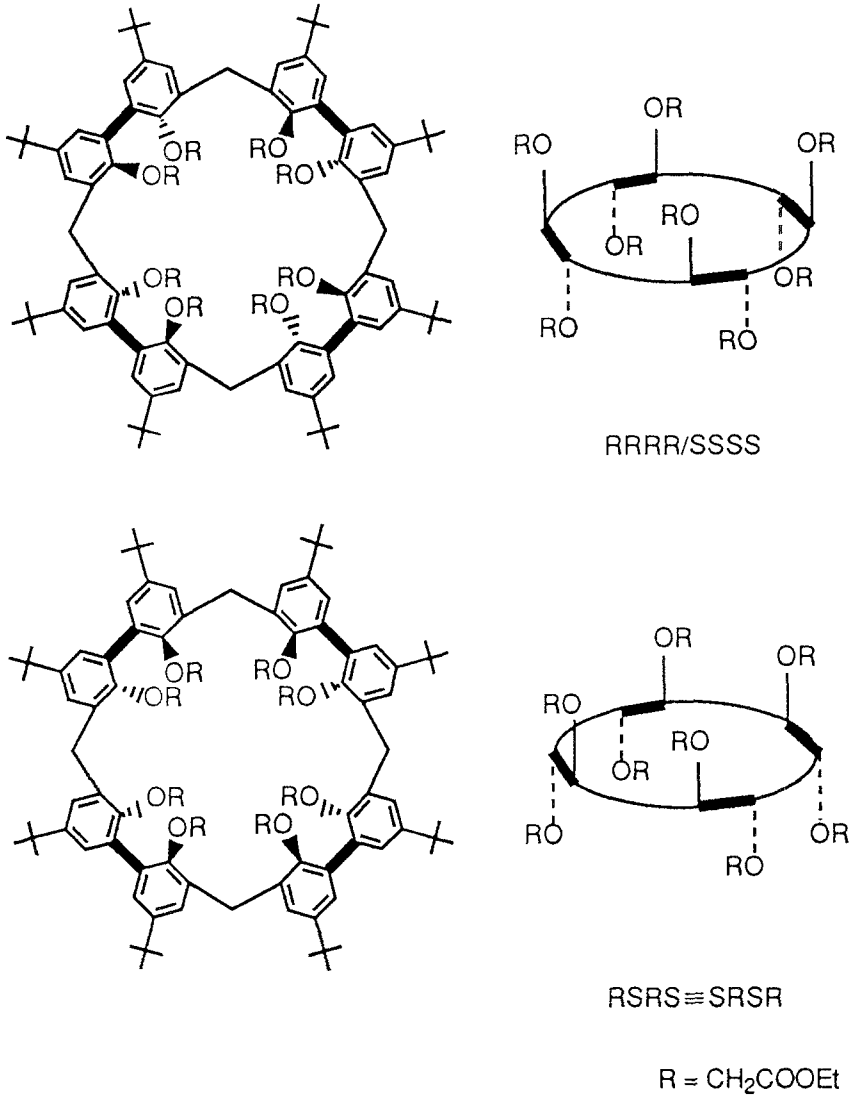
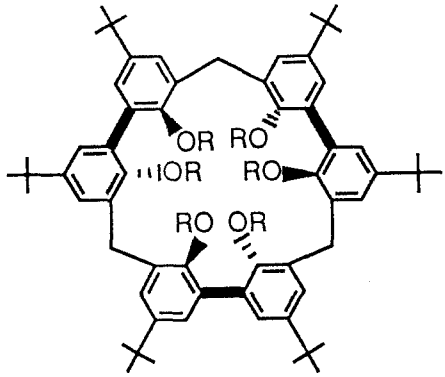
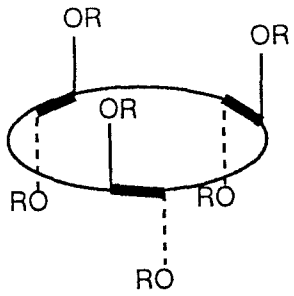


Fig. 1. Stereoisomers of the tetramer **2c**.

(b) a compound in which the configuration of one biphenyl unit differs from that of the other three (*RRRS* or *SSSR*; (c) (*RSRS* ≡ *SRSR*); or (d) *RRSS* ≡ *SSRR* (see Figure 1). Similarly, in the case of trimer **2b** there are two possible stereoisomers (*RRR/SSS* and *RRS/SSR*; D_3 symmetry and C_2 symmetry) (see Figure 2).

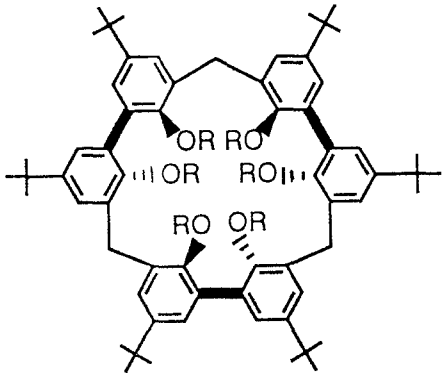
Alkylation of the flexible macrocycles **2b** and **2c** with ethyl bromoacetate in the presence of Cs_2CO_3 under acetonitrile reflux gave only one pure stereoisomer **3** and **4**, respectively. No other possible isomers were observed.

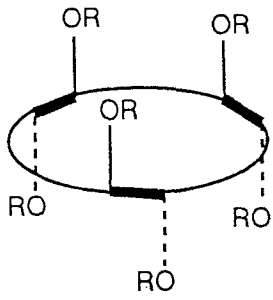




D_3-symmetry

RRR/SSS





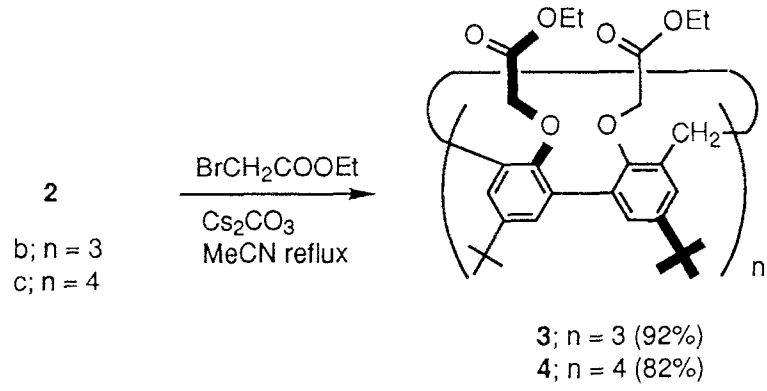
C_2-symmetry

RRS/SSR

R = CH_2COOEt

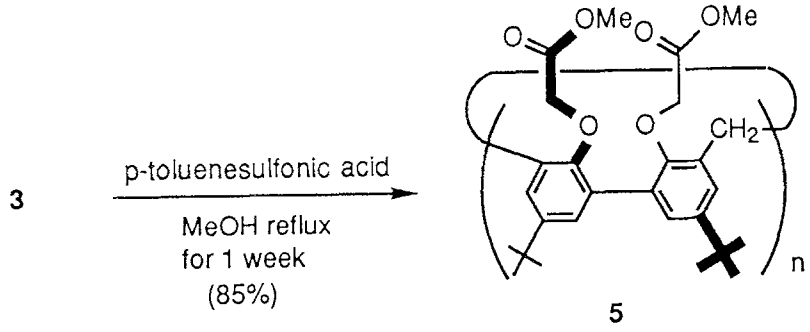
Fig. 2. Stereoisomers of the trimer **2b**.

The ^{1}H-NMR spectrum of **3** shows three signals for the *tert*-butyl protons, three triplets of equal intensity for the methyl protons of the ethyl group, and six doublets of equal intensity for the aromatic protons. Furthermore, the resonance for the ArCH_2Ar methylene protons appeared as a pair of doublets (δ 3.39 and 5.24, J_{AB} = 13.2 Hz) and a singlet (δ 4.14) (relative intensity 1 : 1 : 1). These signals correspond to an asymmetric structure (C_2 symmetry) but not a symmetric one (D_3 symmetry).



3; n = 3 (92%)
4; n = 4 (82%)

The resonances of the OCH_2CO methylene protons have not been assigned because of the overlapped signals due to OCH_2CO and OCH_2CH_3 methylene protons. It was therefore of interest to prepare the hexamethyl ester **5** whose ^{1}H-NMR spectrum might show much more clear patterns due to the $ArCH_2Ar$ and OCH_2CO methylene protons. Transesterification of hexaethyl ester **3**, performed in refluxing methanol in the presence of *p*-toluenesulfonic acid, led to the desired hexamethyl ester **5** in 85% yield.



5

In addition to the three singlets of equal intensity for the OCH_3 methyl protons, three pairs of doublets (relative intensity 1 : 1 : 1) for the diastereotopic OCH_2CO methylene protons and a pair of doublets (δ 3.39 and 5.10, J_{AB} = 13.2 Hz) and a singlet (δ 4.04) (relative intensity 1 : 1 : 1) are observed. These signals are consistent with **3** and **5** having asymmetric structures (C_2 symmetry).

In contrast, the ^{1}H-NMR spectrum of **4** shows resonances for the *tert*-butyl protons at δ 1.28, for the methylene protons at δ 3.59, 5.13 (J_{AB} = 15.1 Hz), and for the aromatic protons at δ 7.02, 7.21, indicating a symmetrical structure. These signals correspond to symmetric structures, *RRRR/SSSS* or *RSRS*, described above. Recently, chiral calixarenes have been reported by many groups [22]. Böhmer and coworkers [23] demonstrated the chirality of dissymmetric calix[4]arenes with

C_2 and C_4 symmetry by interaction with Pirkle's reagent [(*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol]. In fact, in the ^{1}H-NMR spectrum of compound **4** all peaks remained unchanged on addition of this shift reagent. This indicates that macrocycle **4** prepared here might adopt an *RSRS* configuration but not a chiral *RRRR/SSSS* one. Although the structure of **4** has not yet been completely assigned using the available data, one might also assume the more favorable *RSRS* stereoisomer for compound **4** instead of the *RRRR/SSSS* one because the intramolecular hydrogen bonding among OH groups between the diarylmethane units of the starting compound **2c** is stronger than that of biarene units. Unequivocal assignment of the structure of compound **4** must await X-ray analysis.

3.3. TWO-PHASE SOLVENT EXTRACTION OF ALKALI METALS

Ungaro *et al.* [10, 24], McKervey *et al.* [12, 25], Chang *et al.* [11], and Shinkai *et al.* [13, 14, 26–28] discovered that calix[n]arenes can be converted to neutral ligands by the introduction of ester groups into the OH groups. They demonstrated that metal selectivity depends on the calix[n]arene ring size and, in particular, calix[4]arylacetates and acetamides with a cone conformation show remarkably high Na^+ selectivity. Calix[4]arene and spherand-type calixarene analogous metacyclophanes have different ring sizes and ring flexibilities. It is thus interesting to assess what kind of ionophoric cavity the hexaethyl ester **3** and the octaethyl ester **4** provide. To the best of our knowledge, however, no precedent exists for the molecular design of such spherand-type calixarene analogous metacyclophane-based ionophores. We estimated this through two-phase solvent extraction of alkali metal picrates and compared these data with those for calix[n]arene aryl acetates. The results are summarized in Figure 3.

It is already known that the cone-conformer of a calix[4]arene tetraester shows Na^+ selectivity, whereas the partial-cone-conformer of calix[4]arene tetraester shows K^+ selectivity. The two-phase solvent extraction data indicated that hexaethyl ester **3** and octaethyl ester **4** show strong metal affinity, comparable with that of the corresponding calix[n]arenes, and a high K^+ selectivity was observed for octaethyl ester **4**. However, no significant high ion selectivity was observed in hexaethyl ester **3**. In contrast, octaethyl ester **4** shows higher K^+ selectivity than the corresponding calix[8]arene octatester, although the percentage extraction is somewhat lower than that for the partial-cone-conformer of the calix[4]arene tetraester. The effect of the restricted ring conformation due to the biarene units in spite of the larger ring size than that of a calix[8]arene clearly appears in the ion selectivity; i.e., octaethyl ester **4** extracted large ions like K^+ and Rb^+ more efficiently than small ones like Li^+ and Na^+. This behaviour forms a remarkable contrast to that of the partial-cone-conformer of calix[4]arene tetraester which has a rather larger ionophoric cavity than the cone-conformer of calix[4]arene tetraester, which shows notable Na^+ selectivity.

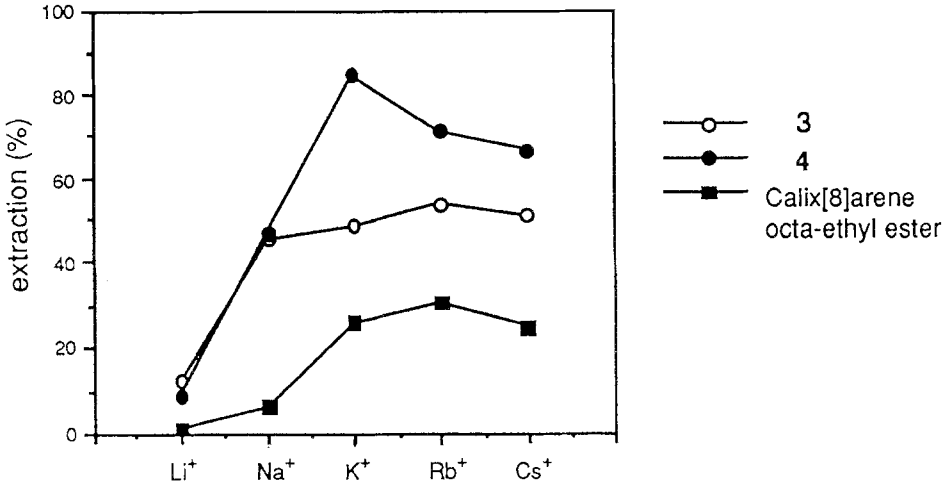


Fig. 3. Extraction (%) of alkali metal picrates by ionophores **3** and **4** in CH_2Cl_2. Extraction conditions: 2.5×10^{-4} M of ionophore in CH_2Cl_2; 2.5×10^{-4} M of picric acid in 0.1 M of alkaline hydroxide at 25°C. Ionophore solution (5.0 mL) was shaken for 2 h with picrate solution (5.0 mL) and % extraction was measured by the absorbance of picrate in CH_2Cl_2. Experimental error was ±2%.

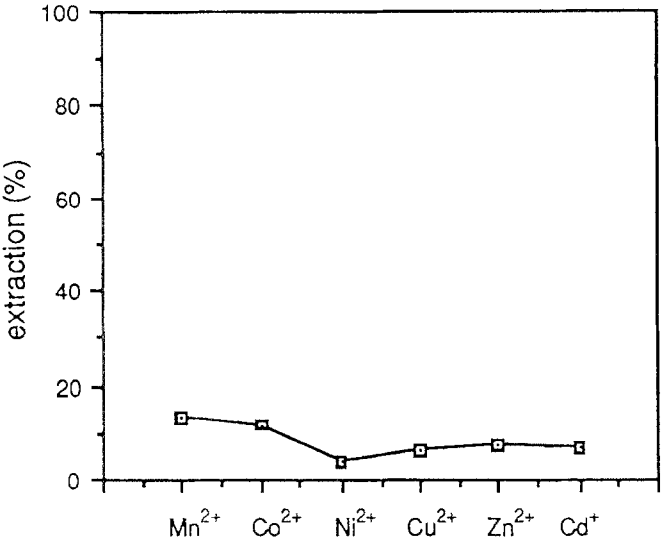


Fig. 4. Extraction (%) of transition metal picrates by ionophore **3** in CH_2Cl_2. Extraction conditions: 2.5×10^{-4} M of ionophore in CH_2Cl_2; 5.0×10^{-4} M of picric acid in 0.1 M of metallic nitrate at 25°C. Ionophore solution (5.0 mL) was shaken for 2 h with picrate solution (5.0 mL) and % extraction was measured by the absorbance of picrate in CH_2Cl_2. Experimental error was ±2%.

Based on these findings, a further investigation was performed on the extraction of transition metals by using ionophore **3**. The results are shown in Figure 4.

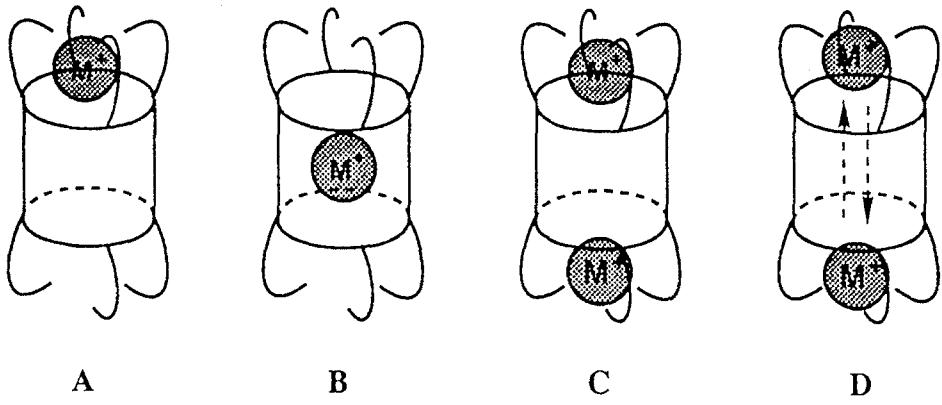


Fig. 5. Possible metal complexations for spherand-type calixarene.

Ionophore **3** exhibits low extractabilities and ion selectivities for transition metals. These results suggest that the effect of the restricted ring conformational flexibility due to the biarene units, despite the larger ring size than that of calix[8]arene, clearly suppress the contribution of the OCH_2CO units to the metal binding due to the conformational changes.

3.4. ^{1}H-NMR SPECTRA OF METAL COMPLEXES

Recently, Shinkai *et al.* reported that the 1,3-alternate conformer of calix[4]arene tetraester can form both a 1 : 1 and a 2 : 1 metal/calixarene complex and the two metal-binding sites display negative allostericity by ^{1}H-NMR titration [26]. In the present systems, due to the existence of two metal-binding sites there are several possibilities for metal complexation modes, as shown in Figure 5. Thus, a 1 : 1 and a 2 : 1 metal complexation of both hexaethyl ester **3** and octaethyl ester **4** might be possible.

In fact, the chemical shifts of the Ar*CH*$_2$Ar methylene protons of hexaethyl ester **3** were altered by titration with KSCN in $CDCl_3$–CD_3OD (1 : 1 v/v): i.e., a 1 : 1 mixture of **3** and KSCN showed a completely different ^{1}H-NMR spectrum, with sharp lines becoming evident for these protons. Their methylene proton peaks were concentrated at δ 3.60 and 4.74 (J_{AB} = 13.1 Hz) as a pair of doublets and δ 4.24 as a singlet in comparison to those in the metal free spectrum, as shown in Figure 6. In addition to this observation, the signals for the aromatic protons slightly downfield shifted (Figure 7) and *tert*-butyl, phenoxy methylene, and ethyl protons also showed different chemical shifts, respectively.

These results strongly suggest that the original C_2 symmetry might remain after the complete metal cation complexation, as shown in Figure 8. Thus the K^+ ion might exist in either the complexation mode **B** or **D**. In the case of the latter mode the rate of an intramolecular hopping between two possible metal-binding sites might be faster than the NMR time scale at room temperature. Despite lowering the

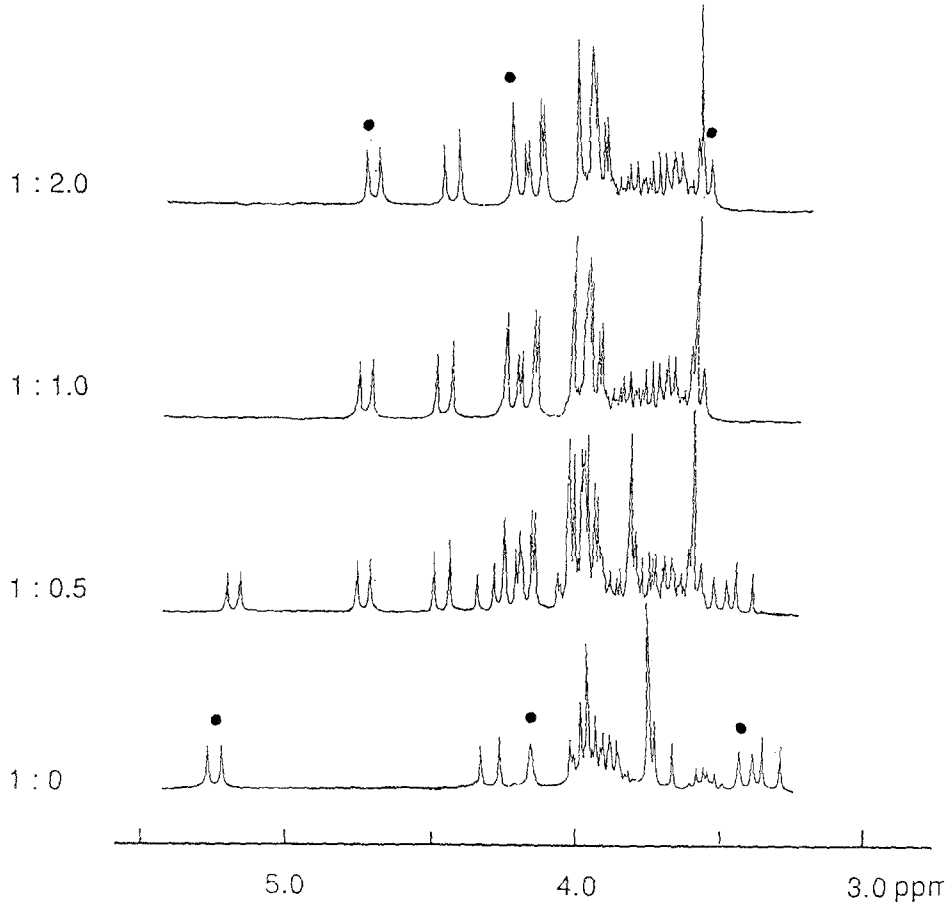


Fig. 6. Partial ^{1}H-NMR titration spectra of hexaethyl ester **3** with KSCN in (5×10^{-4} M), $CDCl_3$: CD_3OD = 1 : 1 v/v, 270 MHz. ArCH_2Ar (*filled circles*). From the top to the bottom, molar ratios of **3** to KSCN of 2.0, 1.0 and 0.5 and in the absence of KSCN.

temperature to -80°C, no clear evidence for the intramolecular hopping behaviour was obtained.

Figure 9 shows the partial ^{1}H-NMR spectrum of octaethyl ester **4** of the free ligand and of its KSCN complex. By adding variable amounts of KSCN in CD_3OD to a $CDCl_3$ solution of the ionophore **4** the ^{1}H-NMR spectrum of the latter also greatly changes in all signals, as is observed with hexaethyl ester **3**. The ^{1}H-NMR titration experiment clearly indicates a 1 : 1 stoichiometry for the KSCN complex with **4**, since all signals remain essentially unchanged after the octaethyl ester **4**/KSCN ratio has reached a value of unity (Figure 9). A pair of doublets for the aromatic protons became split into two pairs of doublets and was shifted downfield. In addition to this observation, the signals for *tert*-butyl, and ethyl protons also showed two different chemical shift, respectively.

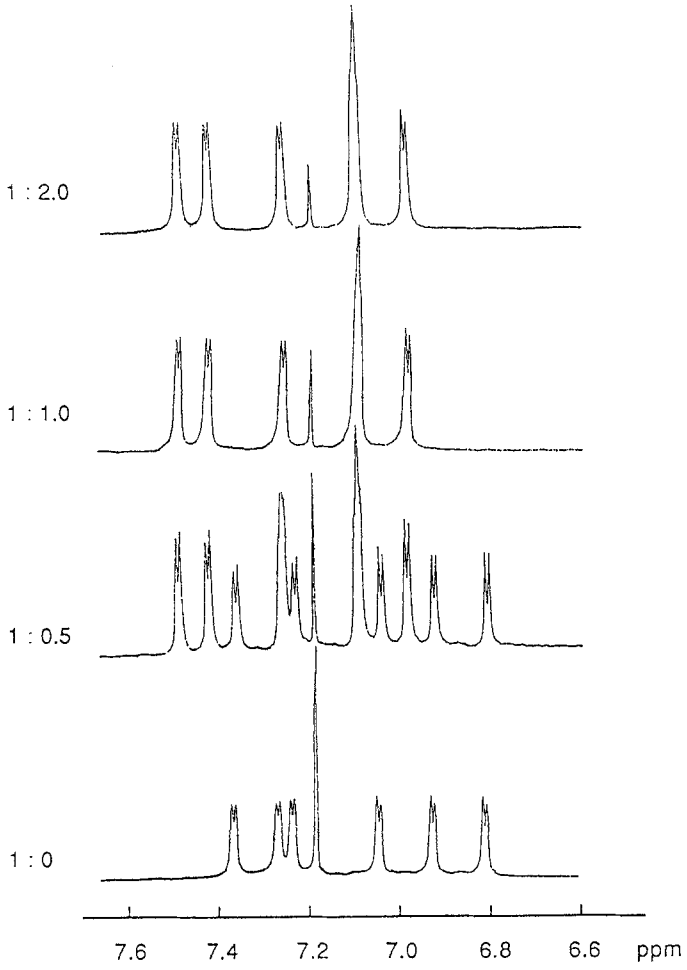


Fig. 7. Partial ^{1}H-NMR titration spectra of hexaethyl ester **3** with KSCN (5×10^{-4} M), $CDCl_3$: CD_3OD = 1 : 1 v/v, 270 MHz. From the top to the bottom molar ratios of **3** to KSCN of 2.0, 1.0 and 0.5 and in the absence of KSCN.

These phenomena may be attributed to the formation of four sets of nonequivalent aromatic protons and two sets of nonequivalent *tert*-butyl and ethyl protons due to the contribution of the asymmetric metal cation complexation on the one side of octaethyl ester **4** (Figure 8). However, no intramolecular hopping between two binding positions could be observed as with biscalix[4]arenes [29, 30]. This result might be attributable to the conformational changes in the other side of the binding site in the process of metal complexation. Further experiments on these metal complexations are currently in progress in our laboratory.

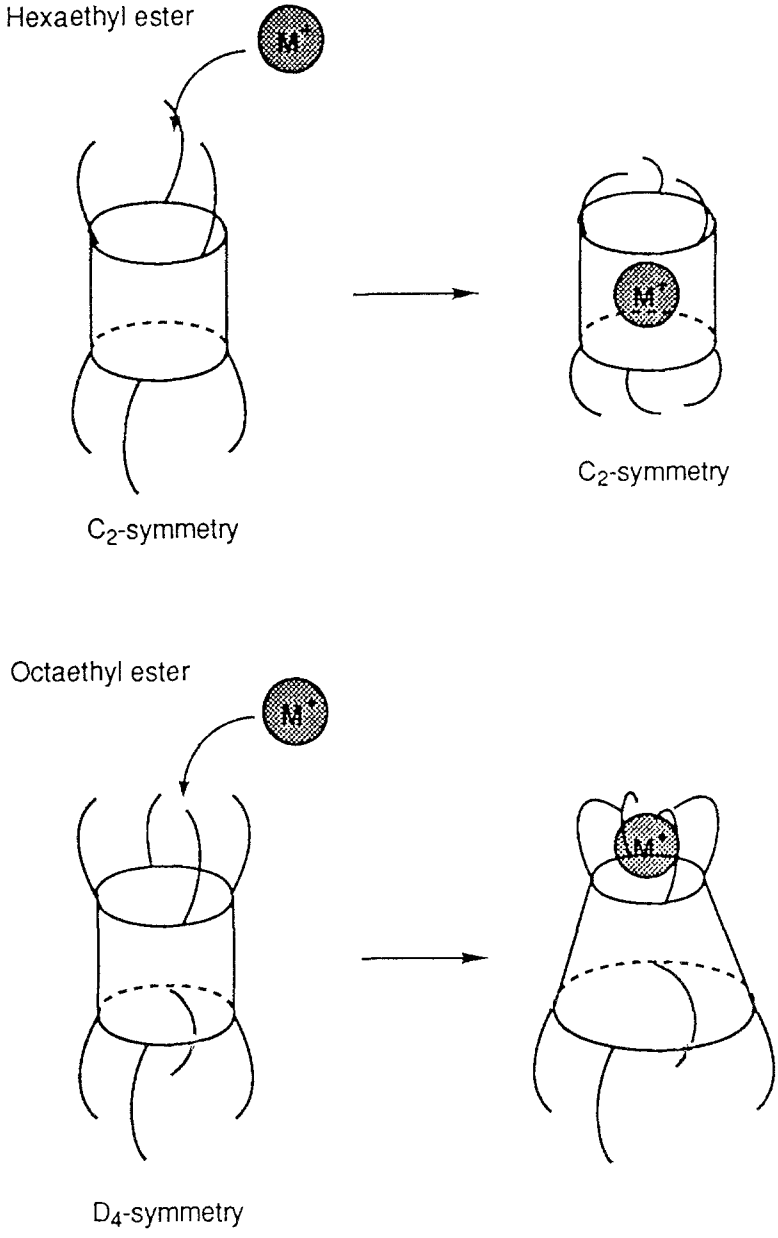


Fig. 8.

4. Conclusion

We have demonstrated for the first time that the derivatives of the spherand-type calixarenes formed by alkylation with ethyl bromoacetate give ionophores with promising complexation properties and interesting stereochemistry. While to date

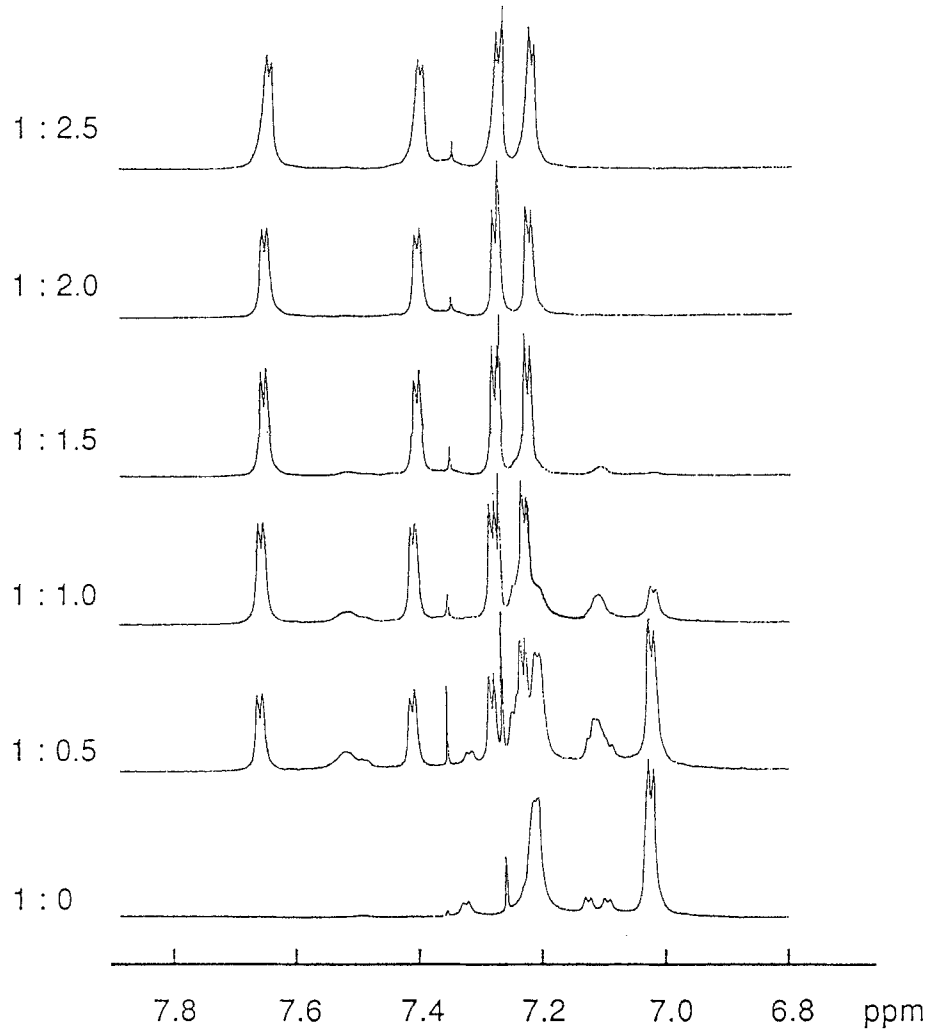


Fig. 9. Partial ^{1}H-NMR titration spectra of octaethyl ester **4** with KSCN in (5×10^{-4} M), $CDCl_3$: CD_3OD = 1 : 1 v/v, 270 MHz. From the top to the bottom, molar ratios of **4** to KSCN of 2.5, 2.0, 1.5, 1.0 and 0.5 and in the absence of KSCN.

only two stereoisomers have been obtained, variation of the alkylation conditions and reagents could lead to the derivatives with D_3 and D_4 symmetry, which will serve as interesting building blocks for larger potential host molecules.

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