Journal of Inclusion Phenomena and Macrocyclic Chemistry **39:** 285–294, 2001.

Synthesis and Ion Selectivity of Tetrakis[(*N*,*N*-dialkylaminocarbonyl) methoxy]homocalix[4]arenes

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(Received: 26 April 2000; in final form: 5 December 2000)

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

Abstract

An attempted *O*-alkylation of the flexible macrocycle **1** with *N*,*N*-dialkylchloroacetamides in the presence of NaH, K_2CO_3 or Cs_2CO_3 gave only one pure stereoisomer 1,4-*alternate*-**2a–c**, while other possible isomers were not observed. In contrast, only an intractable mixture was obtained when Na_2CO_3 was used as base. The structural characterization of these products is discussed. The two-phase solvent extraction data indicated that tetrakis(*N*,*N*-dialkylaminocarbonyl) derivatives **2b–c** show strong alkali metal cation affinity and the extractabilities are much higher than that for the corresponding calix[4]arene tetraethyl ester **4** and homocalix[4]arene tetraethyl ester **3**. High Li^+ and Na^+ extractabilities were observed for tetrakis[(*N*,*N*-diethylaminocarbonyl) derivative **2b**. However, no significant high ion selectivity for alkali metal cations was observed in tetraamide **2b**. ^{1}H-NMR titration of tetraamide **2b** with KSCN clearly demonstrates that a 1:1 complex is formed with retention of the original symmetry to be conformationally frozen on the NMR time scale.

Introduction

Calix[n]arenes have attracted great attention as ionophoric receptors [1–4] and potential enzyme mimics [5] 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 functionalized 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 [6–8]. 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 synthesized by the protection–deprotection method [8–10]. They also found that the cone conformer shows a selectivity for sodium ion [6] and the other conformers show a selectivity for potassium ion [8].

In particular, metal complexation studies of the 1,2-alternate conformer is very limited because of the extreme difficulty in synthesis of the 1,2-alternate conformer [11]. Therefore, it has been very difficult to obtain sufficient amounts of the above compound to investigate its chemical behavior. On the other hand, we have found the convenient preparation of tetrakis[(alkoxycarbonyl)methoxy]-[3.1.3.1]MCPs (MCP = metacyclophane) with 1,4-alternate conformation by the reaction of tetrahydroxy[3.1.3.1]MCP [12] with alkyl bromoacetate in the presence of K_2CO_3 or Cs_2CO_3. Meanwhile several groups have demonstrated that calix[n]aryl ester and amide derivatives serve as neutral ionophores, and amide derivatives usually show an ionophoricity higher than the ester derivatives [13]. Here, it occurred to us that the reaction of tetrahydroxy[3.1.3.1]MCP and *N*,*N*-dialkylchloroacetamide would give the cone 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 [13]. Unfortunately, although the expected cone-tetraamide can not be synthesized in spite of choosing the reaction conditions in *O*-alkylation, we have found that 1,4-*alternate*-tetrakis(dialkyated) amide can be synthesized in almost quantitative yields. In this paper, we describe the convenient preparation and metal complexation properties of propane-bridged homocalix[4]arene tetraamides with 1,4-alternate conformation, which are assumed to have encapsulated cavities.

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

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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 if different conformational isomers of which 1,4-alternate is newly counted, due to the propane bridges in tetrahydroxy[3.1.3.1]MCPs (Figure 1). In contrast to four possible conformations in calix[4]arenes [14], the conformational isomerism in the present system is slightly more complicated. However, there were few reports concerning the introduction of substituents to the hydroxyl groups of dihomocalix[4]arenes [12, 15].

O-Alkylation of the flexible macrocycle **1** with *N*,*N*-diethylchloroacetamide in the presence of NaH under DMF-THF reflux gave only one pure stereoisomer **2b** 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 **2b** was obtained, while the 1,3-disubstituted product was not observed different from the result of *O*-alkylation of **1** with ethyl bromoacetate, in which the ratio of the products dialkylation product to tetraalkylation product is governed by the nature of the alkali metal carbonates used as a catalyst [16]. Thus, in the case of *O*-alkylation of **1** with bromoethyl acetate the smaller alkali metal ions Li^+ and Na^+ give rise to the yield of a dialkylation product, while the action of the much larger K^+ and Cs^+ leads to complete *O*-tetraalkylation. However, in the present *O*-alkylation the alkali metal cation did not play an important role not only for the regioselectivity based on the template effect but also in the number of the *O*-alkylation unlike previously observed in the *O*-alkylation of calix[4]arenes [8, 9, 11, 15].

Similar results were obtained in the *O*-alkylation of **1** with *N*,*N*-dimethylchloroacetamide and 1-chloroacetylpiperidine in the presence of various bases listed in Table 1. Thus, alkylation of **1** with *N*,*N*-dimethylchloroacetamide or 1-chloroacetylpiperidine in the presence of NaH under DMF-THF reflux also gave only one pure stereoisomer **2a** and **2c** in high yield, respectively. However, when Na_2CO_3 is employed for *O*-alkylation with dialkyl chloroacetamide only an intractable mixture was obtained. Similarly, use of K_2CO_3 or Cs_2CO_3 for *O*-alkylation with *N*,*N*-dimethylchloroacetamide or 1-chloroacetylpiperidine gave only tetrasubstituted products **2a** and **2c** in high yield.

Interestingly, *O*-alkylation of **1** with *N*,*N*-diethylchloroacetamide in the presence of K_2CO_3 or Cs_2CO_3 gave a mixture of tetrasubstituted product **2b** and unknown compound A (50 : 50 ratio), whose ^{1}H-NMR pattern was quite similar to that of the 1 : 1 complex of **2b** with KSCN mentioned later. The physical properties of these compounds were very similar to each other, and isolation by column chromatography or preparative TLC was extremely difficult. However, the present mixture was treated with dilute hydrochloric acid to afford a pure **2b** in quantitative yield. In fact, treatment of **2b** with excess alkali metal carbonates in acetone at room temperature for 3 h afforded the same complexes in quantitative yield. These findings strongly suggest that unknown compound A might be a 1 : 1 complex with K_2CO_3 or Cs_2CO_3 used in the *O*-alkylation reaction. The incorporation of metal carbonates as a tight complex was also indicated by the different melting points and infrared spectroscopy. Thus, the IR spectrum of the alkali metal complex of **2b** with K_2CO_3 or Cs_2CO_3 both exhibited the carbonyl stretching band at 1654 cm^{-1}, which can be compared with that of the free ligand **2b** at 1666 cm^{-1} similar to findings for the corresponding *cone*-calix[4]arene tetraethyl ester **4** with NaBr [1b]. Similar phenomena were observed in the case of *O*-alkylation of **1** with *N*,*N*-dimethylchloroacetamide or 1-chloroacetylpiperidine in the presence of K_2CO_3 or Cs_2CO_3 to afford the tetrasubstituted products **2a** and **2c**. This clearly indicates that the high ionophilic abilities of the tetrakis[(*N*,*N*-dialkylaminocarbonyl)methoxy] derivatives **2** for K^+ or Cs^+.

The ^{1}H NMR spectrum of **2b** shows a singlet for the *tert*-butyl protons and a set 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 3.30 and 4.72, J_{AB} = 13.2 Hz), corresponding to a symmetric structure (C_{2v}-symmetry). On consideration of the ^{1}H NMR spectrum there are

Table 1. *O*-Substitution reaction of tetraol **1** with *N*,*N*-dialkylchloroacetamides

Run	R	Base	Solvent	Time (*t*/h)	Product yield (%)[a]
1	Me	NaH	THF, DMF	3	**2a** 85
2	Me	Na_2CO_3	Acetone	24	**2a** 0[b]
3	Me	K_2CO_3	Acetone	23	**2a** 89
4	Me	Cs_2CO_3	Acetone	3	**2a** 90
5	Et	NaH	THF, DMF	3	**2b** 70
6	Et	Na_2CO_3	Acetone	24	**2b** 0[b]
7	Et	K_2CO_3	Acetone	23	**2b** 76
8	Et	Cs_2CO_3	Acetone	3	**2b** 80
9	$(CH_2)_5$	NaH	THF, DMF	3	**2c** 65
10	$(CH_2)_5$	Na_2CO_3	Acetone	24	**2c** 0[b]
11	$(CH_2)_5$	K_2CO_3	Acetone	23	**2c** 61
12	$(CH_2)_5$	Cs_2CO_3	Acetone	3	**2c** 80

[a] Isolated yields are shown.
[b] A mixture of intractable product along with the recovery of the starting compound was obtained.

Table 2. Spectral data of **2b** and complexes with alkali metal carbonates

Compound	m.p. (°C)	IR (cm^{-1}), $\nu_{C=O}$
2b	237-239	1666
2b + K_2CO_3	248-252	1654
2b + Cs_2CO_3	245-248	1654
cone-**4**	154-155	1760
cone-**4** + NaBr	208-210	1750

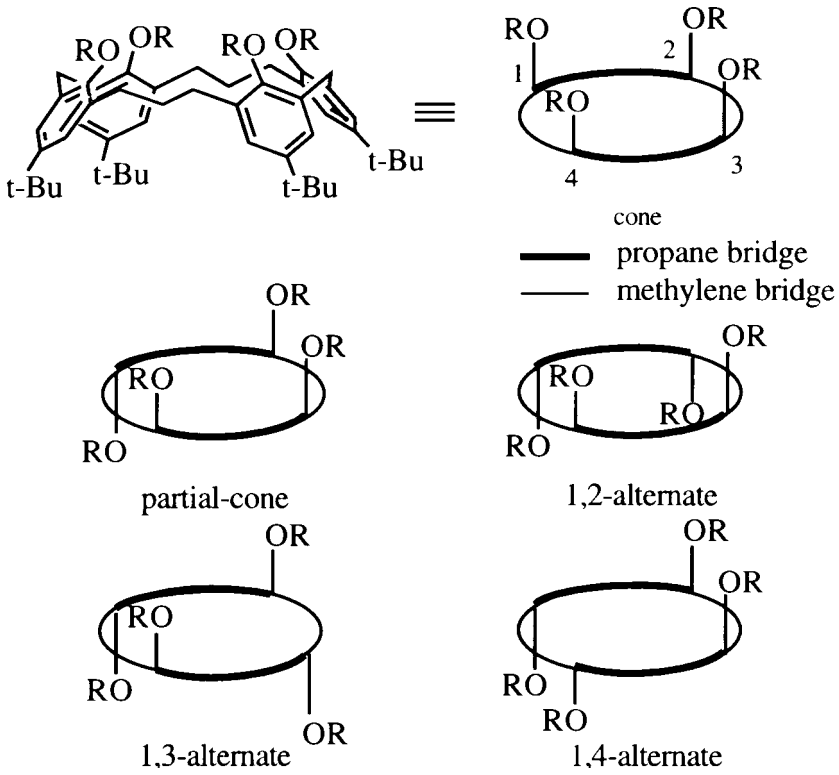


Figure 1. Conformers possible for *O*-tetrasubstitution of tetrahydroxy[3.1.3.1]MCP **1**.

two possible structures for **2b**, the cone or 1,4-alternate structure. It was also found that the middle methylene protons of the propane bridge $ArCH_2CH_2CH_2Ar$ are observed as only one multiplet at δ 1.11–1.24. In contrast, a split multiplet pattern for the middle methylene protons of the propane bridge $ArCH_2CH_2CH_2Ar$ due to the different environment at δ 1.32–1.48 and 1.61–1.88 (relative intensity 1:1) was observed in the ^{1}H NMR spectrum of *cone*-9,16,25,32-tetra(benzyloxy)-6,13,22,29-tetra-*tert*-butyl[3.1.3.1]MCP [12c]. This observation strongly suggests the present pattern corresponds to the 1,4-alternate conformer in the same environment.

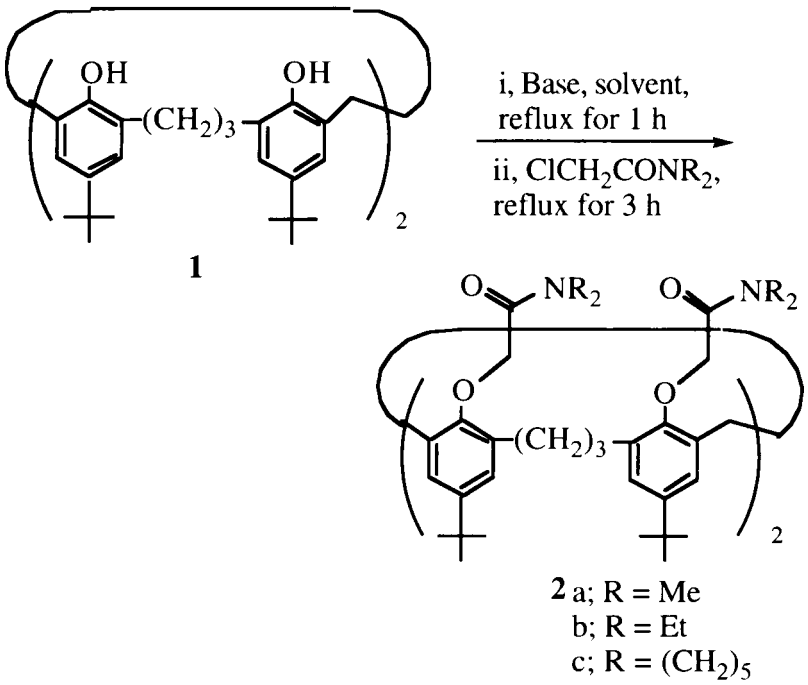
Previously, we have reported the crystal structure of 1,4-*alternate*-tetrakis[(ethoxycarbonyl)methoxy] derivative **3** [16] and the "stepped conformation" of the diphenylmethane moeties like *anti*-[3.3]MCP can be possible [17]. We have assigned the ^{1}H-NMR signals of **2b** by comparison with those of the corresponding 1,4-*alternate*-tetrakis[(ethoxycarbonyl)methoxy] derivative **3**. Thus, the signals for amide **2b** are consistent with those for ester **3** except for the alkyl amide protons.

Since we have already shown that the oxygen-through-the-annulus rotation in the present system is suppressed with substituents larger than the *n*-propyl group [12c], the ring inversion of benzene rings having a (*N*,*N*-diethylaminocarbonyl) methylene group should be impossible during the *O*-alkylation of **2b**. Ring inversion by oxygen-through-the-annulus rotation is inhibited for tetrakis[(*N*,*N*-diethylamino-carbonyl)methoxy] derivative **2b** because of the observation of no change of spectrum pattern for the $ArCH_2Ar$ methylene protons below 150 °C in [D_6]DMSO.

Similarly, the ^{1}H NMR spectrum of dimethyl amide **2a** shows a singlet for the methyl protons at δ 2.99, 3.08, a set of doublets (J = 13.9 Hz) for $ArOCH_2CONMe_2$ at δ 4.46 and 4.99, and two doublets of equal intensity for the aromatic protons at δ 6.84 and 7.06. Furthermore, the resonance for the $ArCH_2Ar$ methylene protons appeared as a pair of doublets (δ 3.33 and 4.66, J_{AB} = 13.2 Hz) (relative intensity 1:1). Since these signals of the ^{1}H NMR spectrum were observed at slightly different chemical shifts from those for the corresponding diethyl amide **2b**, a cone conformation might be expected for dimethyl amide **2a**. However, the middle methylene protons of the propane bridge $ArCH_2CH_2CH_2Ar$ are observed as only one multiplet at δ 1.86–1.98 whose pattern corresponds to the 1,4-alternate conformer because the middle methylene protons of the propane bridge $ArCH_2CH_2CH_2Ar$ are in the same environment. Therefore, dimethyl amide **2a** could also adopt an *anti*-oriented 1,4-alternate-conformation but not a *syn*-oriented cone-conformation. Similar findings were observed in the ^{1}H NMR spectrum of piperidino amide derivative **2c** and therefore a 1,4-alternate-conformation like **2a** and **2b** has been assigned.

It was found by Ungaro et al. [1a], Chang et al. [1b], McKervey et al. [1c,d], and Shinkai et al. [6–8, 18] that calix[n]arenes can be converted to neutral ligands by introduction of ester groups into the OH groups. They demonstrated that metal selectivity is dependent on the calix[n]arene ring size and, in particular, calix[4]arylacetates with a cone conformation show remarkably high Na^+ selectivity as shown in Figure 2.

Ungaro et al. [1a] and Inoue et al. [19] suggested an interesting idea that the bathochromic shift of the absorp-



Scheme 1.

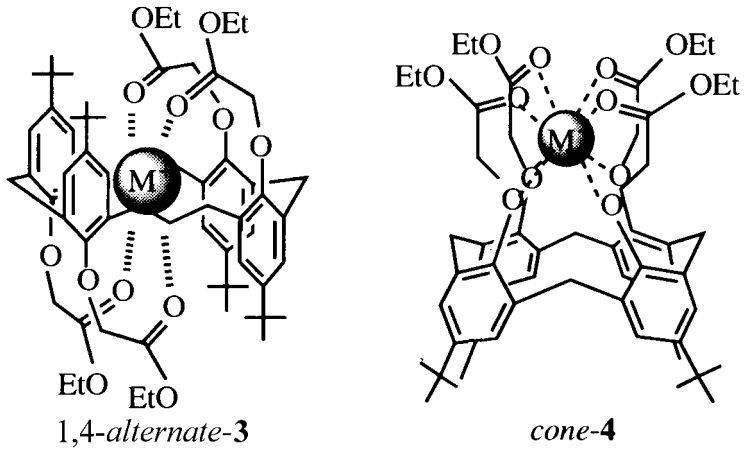


Figure 2. Complexation of 1,4-*alternate*-tetrakis[(ethoxycarbonyl)methoxy][3.1.3.1]metacyclophane 1,4-*alternate*-**3** and *cone*-calix[4]arene tetraethylester *cone*-**4** with metal cation.

tion band of the picrate anion, extracted into the organic phase with a macrocyclic ligand from aqueous metal picrate solutions, serves as a convenient measure for evaluating the ion pair tightness in solution. Also, one can estimate the association constants (K) and stoichiometry from the spectral change. Recently, Shinkai et al. reported that the calix[4]arene tetraethyl ester with cone cnformation forms 1:1 complexes with alkali metal cations and the bathochromic shift for sodium picrate amounts to 31 nm [6]. This shift is equal to that induced by cryptand 222, indicating that the ion pair is considerably solvent-separated [20]. These findings are rationalized in terms of the "encapsulation" effect of ionophores having an ionophoric cavity deeply in the molecule.

To obtain quantitative insights into the metal affinity of 1,4-*alternate*-[3.1.3.1]MCP tetrakis(dialkyl) amide 1,4-*alternate*-**2** and to compare it with that of the confomers of calix[4]arene tetraethyl ester **4**, we have determined the association constants by absorption spectroscopy. It is known that the absorption maxima (λ_{max}) of alkali picrates shift to longer wavelength when they form 1:1 complexes with a calix[n]arene derivative [6]. In THF, for example, the λ_{max} of sodium picrate appears at 352 nm and shifts with an isosbestic point (358 nm) to 380 nm with increasing 1,4-*alternate*-**2b** concentration. By using a simple method to the plots one can estimate the association constants (K) for 1:1 complexes. The results are summerized in Table 3 together with those for calix[4]arene tetraethyl ester **4**, 18-crown-6, and cryptand 222. Examination of Table 3 reveals that 1,4-*alternate*-**2b** showed higher affinity to small metal ions such as Li^+ and Na^+ than to large ion, Rb^+ and Cs^+. Interestingly, tetrakis(diethyl) amide 1,4-*alternate*-**2b** has the ionophoricity for smaller metal ions, being higher than tetraethyl ester 1,4-*alternate*-**3**: i.e., the K for tetrakis(diethyl) amide 1,4-*alternate*-**2b** and Na^+ is greater by about 10-fold than that for tetraethyl ester **3** and Na^+. The highest K

Table 3. Association constants (K)[a]

Ionophore	log K for M^+Pic^-				
	Li^+	Na^+	K^+	Rb^+	Cs^+
1,4-*alternate*-**2b**	5.41	5.43	5.07	4.40	4.31
1,4-*alternate*-**3**	–[b]	4.30	4.84	5.18	4.48
cone-**4**	3.95	3.95	3.08	3.95	1.60
partial-cone-**4**	4.26	4.26	3.52	4.26	2.12
1,2-*alternate*-**4**	–[b]	–	–	–	–
1,3-*alternate*-**4**	4.10	4.10	4.98	4.10	4.41
18-Crown-6	–[b]	4.27	5.33	–	4.91
Cryptand 222	6.69	6.69	8.38	6.69	6.61

[a] $K = [M^+Pic^-, \text{ionophore}]/[M^+Pic^-][\text{ionophore}]$.
[b] The spectral change was too small to determine the association constants (K).

Table 4. Extraction of alkali metal picrates by [3.1.3.1]MCP tetrakis(dialkyl)amides **2a–b** in CH_2Cl_2[a]

Ionophore	Extractability (%)				
	Li^+	Na^+	K^+	Rb^+	Cs^+
1,4-*alternate*-**2a**	69	72	82	81	73
1,4-*alternate*-**2b**	100	100	100	78	35
1,4-*alternate*-**2c**	99	95	97	96	97
1.4-*alternate*-**3**	8.0	9.0	12.0	72.0	20.0
Cone-**4**	15.0	94.6	49.1	23.6	48.9
18-Crown-6	8.7	23.1	77.9	77.3	62.9

[a]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%.

value was obtained for tetrakis(diethyl) amide 1,4-*alternate*-**2b** and Na^+ ($\log K = 5.43$) as comparable with that for 18-crown-6 and K^+ ($\log K = 5.33$).

In comparison of the K for 1,4-*alternate*-**2b** with those for the conformers of calix[4]arene derivatives **4**, tetrakisdiethyl amide 1,4-*alternate*-**2b** shows a higher value by about 10–100-fold than those of *cone*-**4** and *partial-cone*-**4** and the same value as that of 1,3-*alternate*-**4** and larger metal ions, such as K^+, Rb^+, Cs^+. These findings are rationalized in terms of the "encapsulation" effect of 1,4-*alternate*-**2b** having an ionophoric cavity deeply in the molecule.

Interestingly, higher Li^+, Na^+ and K^+ affinities of 1,4-*alternate*-[3.1.3.1]MCP tetrakis(diethyl) amide 1,4-*alternate*-**2b** than that of the 1,2-*alternate*-calix[4]arene tetraethyl ester 1,2-*alternate*-**4** were observed in spite of both adopting the same conformation. This result can be easily explained by the much larger inner ionophilic cavity of [3.1.3.1]MCP tetrakis(diethyl) amide than that of the calix[4]arene tetraethyl ester due to the introduction of two propane bridges into the two methylene bridges of calix[4]arene skeleton as well as the increased electron density charge in the carbonyl carbon attributable to the electron-donating ability of the amino group through conjugation.

The ring size and the ring flexibility are different between calix[4]arene and the uncomplexed homocalixarene analogous metacyclophanes. It is thus interesting to assess what kind of ionophoric cavity the tetrakis(dialkyl) amides **2** provide. To the best of our knowledge, however, no precedent exists for molecular design of such propane-bridged calixarene type 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 Table 4.

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. The two-phase solvent extraction data indicated that tetrakis(dialkyl) amides **2** (extraction %: 100% for **2b** and 99% for **2c**) show stronger Li^+ affinity than that for the corresponding tetraethyl ester **3** and **4** (extraction %: 8.0% for 1,4-*alternate*-**3** and 15.0% for *cone*-**4**) and 18-crown-6 (extraction %: 8.7%) although no significant selectivity for metal was observed under the present experimental conditions. However, the lower ion affinity was observed in tetrakis(dimethyl)amide **2c**. Thus the metal affinity of ionophoric [3.1.3.1]MCP tetraalkyl amides can be changed by the change in the size of the amide alkyl groups the same as that of the corresponding [3.1.3.1]MCP tetraalkyl esters [16]. The increase of the restricted "encapsulation" effect in the 1,4-alternate structure by introduction of the bulkier alkyl groups into the amide groups in spite of the larger ring size than that of a calix[4]arene clearly appears in the ion selectivity; i.e., tetrakis(diethyl) amide **2b** extracted smaller ions like Li^+, Na^+ and K^+ more efficiently than large ones like Rb^+ and Cs^+. This behaviour makes a remarkable contrast to that of the cone-conformer of calix[4]arene tetraethyl ester having the rather smaller ionophoric cavity than the partial-cone-conformer of calix[4]arene tetraethyl ester, which shows notable K^+ selectivity [8].

Based on these findings, a further investigation was performed on the extraction of alkaline earth metals and transition metals by using ionophores **2**. The results are shown in Table 5. Ionophores **2** exhibit higher extractabilities and ion selectivities for both alkaline earth metals and transition metals than those for the corresponding tetraethyl ester **3**. These results suggested that the amide derivatives **2** can interact with metal cations more strongly than the ester derivative like calix[4]arene amide derivatives due to the increased electron density in the carbonyl carbon derived from the electron-donating ability of the amino group through conjugation. It was also found that the larger alkyl group in tetrakis(dialkyl) amides **2** resulted in an increase of the extractabilities for metal cations. This finding might be attributable to the effect of the restricted conformational flexibility of ionophilic OCH_2CONR_2 moieties due to the bulkiness of the alkyl groups.

Recently, 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 complexes and the two metal binding sites display negative allostericity by ^1H NMR titration experiments [8]. In the present systems, due to the

Table 5. Extraction of alkaline earth and transition metal picrates by [3.1.3.1]MCP tetrakis(dialkyl) amides **2a-b** and [3.1.3.1]MCP tetraethyl ester **3** in CH_2Cl_2[a]

Ionophore	Extractability (%)												
	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Mn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Cr^{3+}	Al^{3+}	Ag^{+}
1,4-*alternate*-**2a**	16	57	78	81	42	42	22	27	23	34	24	21	72
1,4-*alternate*-**2b**	32	72	79	75	60	57	42	48	43	50	40	38	100
1,4-*alternate*-**2c**	38	76	87	81	54	53	40	49	38	47	36	33	94
1,4-*alternate*-**3**	27	22	26	53	9	9	3	3	3	3	13	5	14

[a] 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%.

existence of two metal binding sites there are several possibilities for the metal complexation mode as shown in Figure 3. Thus, a 1:1 and a 2:1 metal complexation of the 1,4-alternate conformer of the tetrakis(dialkyl) amides **2** might be possible.

In fact, the chemical shifts of the Ar*CH*$_2$Ar methylene protons of tetrakis(diethyl) amide **2b** were altered by titration with KSCN in $CDCl_3$—CD_3OD (1:1 v/v): i.e., a 1:1 mixture of **2b** and KSCN showed a completely different ^{1}H NMR spectrum with sharp lines becoming evident for these protons. The methylene proton peaks of the Ar*CH*$_2$Ar methylene protons were shifted to downfield at δ 3.37 and 4.39 (J_{AB} = 12.7 Hz) as a pair of doublets in comparison to those in the metal free spectrum (δ 3.30 and 4.72, J_{AB} = 13.2 Hz). The ^{1}H NMR titration experiment clearly indicates a 1:1 stoichiometry for the KSCN complex with **2b**, since all signals remain essentially unchanged after the tetrakis(diethyl) amide **2b**/KSCN ratio has reached a value of unity. In addition to this observation, the signals for the aromatic protons slightly shifted to downfield and the phenoxy methylene protons and the protons of ethyl groups also showed different chemical shifts, respectively. 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 **2b** were observed. These results strongly suggest that the original C_{2v}-symmetry might remain after the complete metal cation complexation as shown in Figure 5. Thus the K^+ ion might exist in either the complexation mode **B** or **D** (Figure 3). 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. In spite of lowering the temperature to −80 °C, no clear evidence for the intramolecular hopping behaviour was obtained as with biscalix[4]arenes [21, 22].

More detailed examination of the chemical shift change in the ^{1}H NMR titration experiment of tetrakis(diethyl) amide **2b** with KSCN suggests that K^+ should be bound to the ionophoric cavity, which is composed of four phenolic oxygens, four oxygens of carbonyl groups and four benzene rings because the different chemical shifts were observed for the neighboring methylene protons of ArO*CH*$_2$CONEt$_2$ ($\Delta\delta$ + 0.13 and −0.29 ppm), Ar*CH*$_2$Ar [$\Delta\delta$ −0.33 (axial) and +0.07 (equatorial) ppm] and the large downfield shifts were observed for the aromatic protons ($\Delta\delta$ from +0.16 to +0.38 ppm). As mentioned above, $\Delta\delta$ between H_{ax} and H_{eq} of the Ar*CH*$_2$Ar methylene protons in calix[4]arene serves as a measure of the 'flattening'. $\Delta\delta_H$ decreases from δ 1.42 ppm to 1.02 ppm in **2b** in the binding of K^+. These findings implied that **2b** flattens when K^+ is complexed because K^+ was encapsulated into the cavity formed by four aromatic rings and amide groups.

Similar findings of the chemical shift change in the ^{1}H NMR titration experiment were observed in the corresponding tetrakis(dimethyl) amide **2a** and tetrakis[(piperidinocarbonyl)methoxy] derivative **2c**. Although tetrakis[(piperidinocarbonyl)methoxy] derivative **2c** shows a different behaviour in the extraction experiment and the loss of selectivity in comparison with **2a–b**, from the present available data we have not yet established the complete explanation for the different extractability arising from the size of the amide alkyl groups. Further experiments on these metal complexations are currently in progress in our laboratory.

Conclusion

An attempted *O*-alkylation of the flexible macrocycle 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]MCP **1** with *N*,*N*-dialkylchloroacetamides in the presence of NaH, K_2CO_3 or Cs_2CO_3 gave only one pure stereoisomer, 1,4-alternate conformer **2a–c**, while other possible isomers were not observed. Only when the template metal ion can hold the amide group(s) and the oxide group(s) on the different side of the propane bridges of the [3.1.3.1]MCP is the conformation immobilized to the thermodynamically stable 1,4-alternate conformer.

The two-phase solvent extraction data indicated that tetrakis(diethyl) amide **2b** shows a strong Li^+, Na^+ and K^+ affinity comparable with that for the cryptand 222 and the extractabilities are much higher than that for the corresponding calix[4]arene tetraethyl ester **4** and [3.1.3.1]MCP tetraethyl ester **3**. However, no significant high ion selectivity for alkali metal cations was observed in tetraamide **2b**. ^{1}H-NMR titration of tetraamide **2b** with KSCN clearly demonstrates that a 1:1 complex is formed with retention of

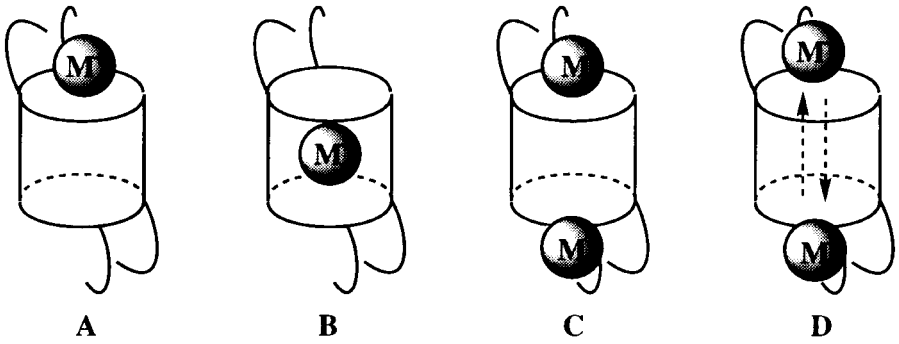


Figure 3. Possible metal complexations for [3.1.3.1]MCP tetrakis(diethyl) amide **2b**.

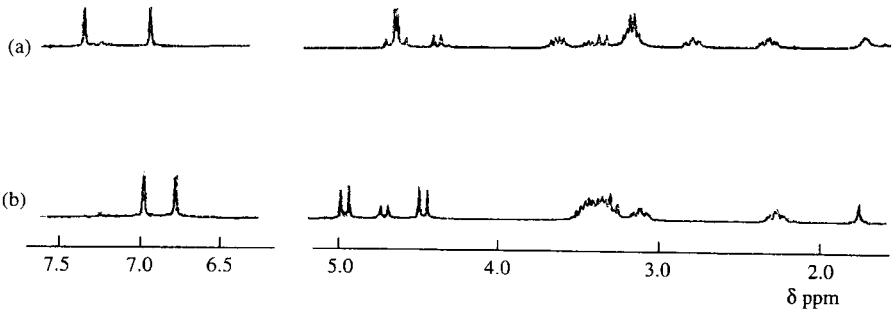


Figure 4. Partial ^{1}H NMR titration spectra of tetrakis(diethyl) amide **2b** (5×10^{-4} M) with KSCN in $CDCl_3$:CD_3OD = 1:1 v/v, 270 MHz. (a) in the presence of KSCN (5×10^{-4} M) and (b) in the absence of KSCN.

the original symmetry to be conformationally frozen on the NMR time scale.

We have demonstrated for the first time that the derivatives of the propane-bridged homocalixarenes formed by *O*-alkylation with *N*,*N*-dialkylchloroacetamides give ionophores with promising complexation properties and interesting stereochemistry. While to date only one stereoisomer has been obtained, variation of the alkylation conditions and reagents could lead to derivatives with the cone-conformation, which will serve as interesting building blocks for larger potential host molecules.

Experiment section

All mps (Yanagimoto MP-S_1) are uncorrected. NMR spectra were determined at 270 MHz with a Nippon Denshi JEOL FT-270 NMR spectrometer with $SiMe_4$ as an internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets or a liquid film on NaCl plates in a Nipon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by a Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system through GLC. Elemental analysis: Yanaco MT-5.

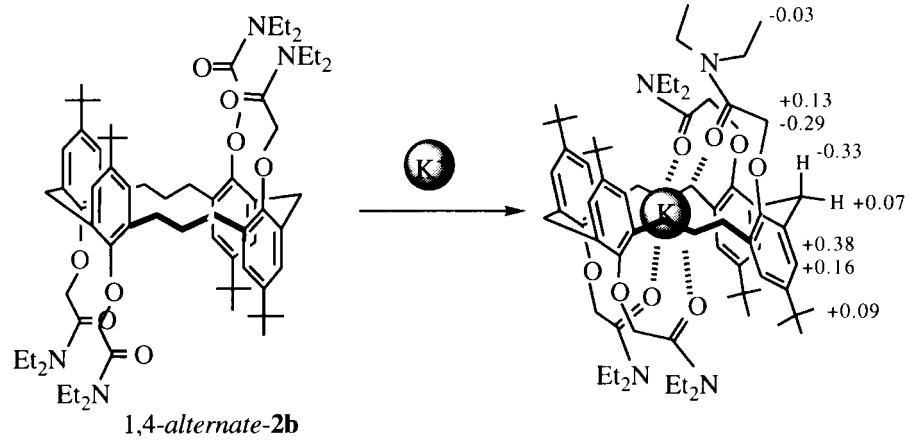
Materials

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]-metacyclophane **1** was prepared according to the literature [12].

Synthesis

Alkylation of **1** *with N,N-diethylchloroacetamide in the presence of NaH to afford 6,13,22,29-tetra-tert-butyl-9,16,25,32-tetrakis[(N,N-diethylaminocarbonyl)methoxy][3.1.3.1]metacyclophane (***2b***)*

A mixture of **1** (400 mg, 0.567 mmol) and NaH (640 mg, 16.0 mmol) in dry tetrahydrofuran (36 mL) was heated at reflux for 1 h under N_2. Then *N*,*N*-diethylchloroacetamide (1.94 mL, 14.18 mmol) was added and the mixture heated at reflux for an additional 3 h. After cooling the reaction mixture to room temperature, it was poured into ice-water (30 mL) and extracted with CH_2Cl_2 (2×30 mL). 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 reduced pressure to remove the excess unreacted *N*,*N*-diethylchloroacetamide using a Kugelrohr apparatus. The residue was treated with petroleum ether (10 mL) affording 460 mg (70%) of **2b** as a colorless solid. Recrystallization from benzene gave **2b** as colorless prisms; m.p. 239–241 °C; ν_{max} (KBr)/cm^{-1} 2965, 2868, 1662 (C=O), 1481, 1463, 1433, 1363, 1295, 1288, 1237, 1221, 1195, 1124, 1060; δ_H ($CDCl_3$) 1.13 (12 H, t, *J* 7.3, NCH_2CH_3), 1.15 (36 H, s, t-Bu), 1.11–1.24 (4 H, m, $ArCH_2CH_2CH_2Ar$), 1.21 (12 H, t, *J* 7.3, NCH_2CH_3), 2.23–2.35 (4 H, m, $ArCH_2CH_2CH_2Ar$), 3.08–3.19 (4 H, m, $ArCH_2CH_2CH_2Ar$), 3.29–3.40 (8 H, m, NCH_2CH_3), 3.30 (2 H, d, *J* 13.2, $ArCH_2Ar$), 3.43–3.53 (8 H, m, NCH_2CH_3), 4.48 (4 H, d, *J* 14.2, OCH_2CO), 4.72 (2 H, d, *J* 13.2, $ArCH_2Ar$), 4.97 (4 H, d, *J* 14.2, OCH_2CO), 6.80 (4 H, d, *J* 2.2, ArH), 6.99 (4 H, d, *J* 2.2, ArH); *m/z*: 1157 (M^+);



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

Figure 5. Metal complexation mode of [3.1.3.1]MCP tetrakis(diethyl) amide **2b**. Chemical shift changes of 1,4-*alternate*-**2b** induced in the presence of KSCN in $CDCl_3$-[D_4]methanol (1:1 v/v) at 27 °C; [1,4-*alternate*-**2b**] = 5.0×10^{-2} M, [KSCN] = 5.0×10^{-2} M; (+) denotes the down-field and (-) denotes the up-field shift.

Found: C, 74.45; H, 9.19; N, 4.94. *Calcd*. for $C_{72}H_{108}N_4O_8$: C, 74.70; H, 9.40; N, 4.84%.

Alkylation of **1** *with N,N-diethylchloroacetamide in the presence of alkali metal carbonate to afford* **2b***: Typical procedure*

A mixture of **1** (400 mg, 0.567 mmol) and cesium carbonate (3.70 g, 11.4 mmol) in dry acetone (36 mL) 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 3 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 hexane (10 mL) and the precipitate was filtered to give 482.2 mg (81%) of **2b** as a colorless solid. The solid was extracted with CH_2Cl_2 (2 × 30 mL), washed with water, dried with Na_2SO_4 and concentrated. The residue was treated with petroleum ether (10 mL) affording 440 mg (67%) of **2b** as a colorless solid.

Alkylation of **1** *with N,N-dimethylchloroacetamide in the presence of K_2CO_3 to afford 6,13,22,29-tetra-tert-butyl-9,16,25,32-tetrakis[(N,N-dimethylaminocarbonyl)methoxy][3.1.3.1]metacyclophane (***2a***)*

A mixture of **1** (400 mg, 0.567 mmol) and potassium carbonate (1.57 g, 11.4 mmol) in dry acetone (36 mL) was heated at reflux for 1 h under N_2. Then *N,N*-dimethylchloroacetamide (2.35 g, 14.2 mmol) was added and the mixture heated at reflux for an additional 3 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*-dimethylchloroacetamide using a Kugelrohr apparatus. The residue was treated with hexane (10 mL) and the precipitate was filtered to give 528 mg (89%) of **2a** as a colorless solid. Recrystallization from benzene gave **2b** as colorless prisms; m.p. 118–120 °C; λ_{max} (KBr)/cm^{-1} 2958, 2865, 1667 (C=O), 1481, 1463, 1416, 1400, 1361, 1295, 1266, 1199, 1124, 1055, 1024, 1008, 878; δ_H ($CDCl_3$) 1.17 (36 H, s, t-Bu), 1.86–1.98 (4 H, m, ArCH$_2$*CH*$_2$CH$_2$Ar), 2.26–2.38 (4 H, m, Ar*CH*$_2$CH$_2$*CH*$_2$Ar), 3.07–3.19 (4 H, m, Ar*CH*$_2$CH$_2$*CH*$_2$Ar), 2.99 (12 H, s, N*CH*$_3$), 3.08 (12 H, s, N*CH*$_3$), 3.33 (2 H, d, *J* 13.2, Ar*CH*$_2$Ar), 4.46 (4 H, d, *J* 13.9, O*CH*$_2$CO), 4.66 (2 H, d, *J* 13.2, Ar*CH*$_2$Ar), 4.99 (4 H, d, *J* 13.9, O*CH*$_2$CO), 6.84 (4 H, d, *J* 2.2, ArH), 7.06 (4 H, d, *J* 2.2, ArH); *m/z*: 1045 (M^+); *Found*: C, 73.53; H, 8.87; N, 5.36. *Calcd*. for $C_{64}H_{92}N_4O_8$: C, 73.38; H, 8.59; N, 5.12%.

Alkylation of **1** *with piperidinylchloroacetamide to afford 6,13,22,29-tetra-tert-butyl-9,16,25,32-tetrakis[(N,N-piperidinocarbonyl)methoxy][3.1.3.1]metacyclophane (***2c***): Typical procedure*

A mixture of **1** (400 mg, 0.567 mmol) and cesium carbonate (3.70 g, 11.4 mmol) in dry acetone (36 mL) was heated at reflux for 1 h under N_2. Then 1-chloroacetylpiperidine (1.6 mL, 11.3 mmol) was added and the mixture heated at reflux for an additional 3 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 1-chloroacetylpiperidine using a Kugelrohr apparatus. The residue was extracted with CH_2Cl_2 (2 × 30 mL). The CH_2Cl_2 extract was washed with water, dried with Na_2SO_4 and concentrated to give a colorless solid. The solid was treated with hexane (10 mL) and the precipitate was filtered to give 525 mg (80%) of **2c** as a colorless solid. Recrystallization from benzene gave **2c** as colorless prisms; m.p. 233–235 °C; ν_{max} (KBr)/cm^{-1} 2950, 2857, 1667 (C=O), 1480, 1445, 1392, 1361, 1280, 1255, 1228, 1195, 1124, 1064, 1010, 988, 852; δ_H ($CDCl_3$) 1.14 (36 H, s, t-Bu), 1.20-1.33 (4 H, m, ArCH$_2$*CH*$_2$CH$_2$Ar), 1.56–1.63 (24 H, m, piperidine-H), 2.31–2.45 (4 H, m, Ar*CH*$_2$CH$_2$*CH*$_2$Ar), 2.93–3.06 (4 H, m, Ar*CH*$_2$CH$_2$*CH*$_2$Ar), 3.35 (2 H, d, *J* 13.2, Ar*CH*$_2$Ar), 3.42–3.75 (16 H, m, piperidine-H), 4.59 (4 H, d, *J* 14.2, OCH$_2$CO), 4.75 (2 H, d, *J* 13.2, Ar*CH*$_2$Ar), 4.92 (4 H, d, *J* 14.2, O*CH*$_2$CO), 6.81 (4 H, d, *J* 2.4, ArH), 7.05

(4 H, d, *J* 2.4, ArH); m/z: 1205 (M^+); *Found*: C, 74.77; H, 8.93; N, 4.43. *Calcd*. for $C_{76}H_{108}N_4O_8 \cdot H_2O$: C, 74.59; H, 9.06; N, 4.58%.

Estimation of the association constants (K)

The association constants (*K*) could be readily determined from the absorption spectral change of alkal picrates in THF using the Benesi–Hildebrand equation [23] for a 1:1 complex according to the literature [6]. The absorption maxima (λ_{max}) of alkali picrates shift to longer wavelength with an isosbestic point on increasing the ionophore concentrations. From a plot of the absorbance for the new λ_{max} vs. ionophore concentration the association constant (*K*) for the 1:1 complex could be determined (by the Benesi–Hildebrand plot). The plots well satisfied the Benesi–Hildebrand equation with the correlation coefficients > 0.99.

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 was sufficient to attain the distribution equilibrium. This was repeated 3 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 [24].

^1H NMR complexation experiment

To a $CDCl_3$ solution (5×10^{-4} M) of tetradiethyl amide **2b** in the NMR tube was added a [D_4]methanol solution (5×10^{-4} M) of KSCN. The spectrum was recorded after addition and the temperature of the NMR probe kept constant at 27 °C.

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrakis[(*N*,*N*-diethylaminocarbonyl)methoxy][3.1.3.1]metacyclophane (**2b**)-KSCN complex: ^1H NMR ($CDCl_3$: [D_4]methanol 1:1 v/v): δ_H 1.15 (12 H, t, *J* 7.3, NCH_2CH_3), 1.18 (12 H, t, *J* 7.3, NCH_2CH_3), 1.24 (36 H, s, t-Bu), 1.20–1.31 (4 H, m, $ArCH_2CH_2CH_2Ar$), 2.28–2.37 (4 H, m, $ArCH_2CH_2CH_2Ar$), 2.77–2.85 (4 H, m, $ArCH_2CH_2CH_2Ar$), 3.15–3.24 (8 H, m, NCH_2CH_3), 3.37 (2 H, d, *J* 12.7, $ArCH_2Ar$), 3.61–3.69 (8 H, m, NCH_2CH_3), 4.39 (2 H, d, *J* 12.7, $ArCH_2Ar$), 4.61 (4 H, d, *J* 14.2, OCH_2CO), 4.68 (4 H, d, *J* 14.2, OCH_2CO), 6.96 (4 H, d, *J* 2.4, ArH), 7.37 (4 H, d, *J* 2.4, ArH).

References

1. (a) A. Arduini, A. Pochini, S. Reverberi, R. Ungaro, G. D. Andreetti and F. Ugozzoli: *Tetrahedron* **42**, 2089 (1986). (b) S. K. Chang and I. Cho: *J. Chem. Soc., Perkin Trans. 1* 1986, 211. (c) M. A. McKervey, E. M. Seward, G. Ferguson, B. Ruhl and S. Harris: *J. Chem. Soc., Chem. Commun.* 1985, 388. (d) F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. Harris, J. B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. Ruhl, M. J. Schwing-Weill and E. M. Seward: *J. Am. Chem. Soc.* **111**, 8681 (1989). (e) F. Calestani, F. Ugozzoli, A. Arduini, E. Ghidini and R. Ungaro: *J. Chem. Soc., Chem. Commun.* 1987, 344; (f) A. Arduini, E. Ghidini, A. Pochini, R. Ungaro, G. D. Andreetti, G. Calestani and F. Ugozzoli: *J. Incl. Phenom.* **6**, 119 (1988). (g) F. Arnaud-Neu, M. J. Schwing-Weill, K. Ziat, S. Cremin, S. J. Harris and M. A. McKervey: *New. J. Chem.* **15**, 33 (1991).
2. (a) T. Arimura, H. Kawabata, T. Matsuda, T. Muramatsu, H. Satoh, K. Fujio, O. Manabe and S. Shinkai: *J. Org. Chem.* **56**, 301 (1991). (b) A. Ikeda, T. Nagasaki and S. Shinkai: *J. Phys. Org. Chem.* **5**, 699 (1992). (c) A. Casnati, P. Minari, A. Pochini, R. Ungaro, W. F. Nijenhuis, F. de Jong and D. N. Reinhoudt: *Isr. J. Chem.* **32**, 79 (1992). (d) E. Nomura, H. Tanuguchi, K. Kawaguchi and Y. Otsuji: *J. Org. Chem.* **58**, 4709 (1993). (e) A. Barrett, M. A. McKervey, J. F. Malone, A. Walker, F. Arnaud-Neu, L. Guerra, M. J. Schwing-Weill, C. D. Gutsche and D. R. Stewart: *J. Chem. Soc., Perkin Trans. 2* 1993, 1475. (f) D. R. Stewart, M. Krawiec, R. P. Kashyap, W. H. Watson and C. D. Gutsche: *J. Am. Chem. Soc.* **117**, 586 (1995). (g) Z. Goren and S. E. Biali: *J. Chem. Soc., Perkin Trans. 1* 1990, 1484.
3. (a) C. Alfieri, E. Dradi, A. Pochini, R. Ungaro and G. D. Andreetti, *J. Chem. Soc. Chem., Commun.* 1983, 1075. (b) G. D. Andreetti, O. Ori, F. Ugozzoli, C. Alfieri, A. Pochini and R. Ungaro: *J. Incl. Phenom.* **6**, 523 (1988). (c) E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, A. Abu El-Fadl and D. N. Reinhoudt: *J. Am. Chem. Soc.* **112**, 6979 (1990). (d) A. Casnati, P. Jacopozzi, A. Pochini, F. Ugozzoli, R. Cacciapaglia, L. Mandolini and R. Ungaro: *Tetrahedron* **51**, 591 (1995). (e) Z. Asfari, R. Abidi, F. Arnaud and J. Vicens: *J. Incl. Phenom. Mol. Recogn.* **13**, 163 (1992). (f) Z. Asfari, S. Pappalardo and J. Vicens: *J. Incl. Phenom. Mol. Recogn.* **14**, 189 (1992). (g) D. Kraft, R. Arnecke, V. Böhmer and W. Vogt: *Tetrahedron* **27**, 6019 (1993).
4. (a) D. N. Reinhoudt, P. J. Dijkstra, P. J. A. in't Veld, K. E. Bugge, S. Harkema, R. Ungaro and E. Ghidini: *J. Am. Chem. Soc.* **109**, 4761 (1987). (b) P. J. Dijkstra, J. A. J. Brunink, K. E. Bugge, D. N. Reinhoudt, S. Harkema, R. Ungaro, F. Ugozzoli and E. Ghidini: *J. Am. Chem. Soc.* **111**, 4761 (1989). (c) J.-D. van Loon, D. Kraft, M. J. K. Ankoné, W. Verboom, S. Harkema, W. Vogt, V. Böhmer and D. N. Reinhoudt: *J. Org. Chem.* **55**, 5176 (1990). (d) S. Kanamathareddy and C. D. Gutsche: *J. Am. Chem. Soc.* **115**, 6572 (1993). (e) W. I. Iwerma Bakker, M. Haas, C. Khoo-Beattie, R. Ostaszewski, S. M. Franken, H. J. den Hertog, Jr., W. Verboom, D. de Zeeuw, S. Harkema and D. N. Reinhoudt: *J. Am. Chem. Soc.* **116**, 123 (1994). (f) D. Kraft, V. Böhmer, W. Vogt, G. Ferguson and J. F. Gallagher: *J. Chem. Soc., Perkin Trans. 1* 1994, 1221.
5. (a) S. Shinkai: *Tetrahedron* **49**, 8933 (1993). (b) V. Böhmer: *Angew. Chem. Int. Ed. Engl.* **34**, 713 (1995). (c) M. Takeshita and S. Shinkai: *Bull. Chem. Soc. Jpn.* **68**, 1088 (1995). (d) A. Ikeda and S. Shinkai: *Chem. Rev.* **97**, 1713 (1997).
6. T. Arimura, M. Kubota, T. Matsuda, O. Manabe and S. Shinkai: *Bull. Chem. Soc. Jpn.* **62**, 1674 (1989).
7. S. Shinkai, K. Fujimoto, T. Otsuka and H. L. Ammon: *J. Org. Chem.* **57**, 1516 (1992).
8. K. Iwamoto and S. Shinkai: *J. Org. Chem.* **57**, 7066 (1992).
9. K. Iwamoto, K. Araki and S. Shinkai: *J. Chem. Soc., Perkin Trans. 1* 1991, 1611.
10. C. D. Gutsche and P. A. Reddy: *J. Org. Chem.* **56**, 4783 (1991).
11. (a) J. D. van Loon, L. C. Groenen, S. S. Wijmenga, W. Verboom and D. N. Reinhoudt: *J. Am. Chem. Soc.* **113**, 2378 (1991). (b) L. C. Groenen, J. D. van Loon, W. Verboom, S. Harkema, A. Casnati, R. Ungaro, A. Pochini, F. Ugozzoli and D. N. Reinhoudt: *J. Am. Chem. Soc.* **113**, 2385 (1991). (c) K. Fujimoto, N. Nishiyama, H. Tsuzuki and S. Shinkai: *J. Chem. Soc., Perkin Trans. 2* 1992, 643. (d) K. Iwamoto, K. Araki and S. Shinkai: *Tetrahedron* **47**, 4325 (1991).
12. (a) T. Yamato, Y. Saruwatari, S. Nagayama, K. Maeda and M. Tashiro: *J. Chem. Soc., Chem. Commun.* 1992, 861. (b) T. Yamato, Y. Saruwatari and M. Yasumatsu: *J. Chem. Soc., Perkin Trans. 1* 1997, 1725. (c) T. Yamato, Y. Saruwatari and M. Yasumatsu: *J. Chem. Soc., Perkin Trans. 1* 1997, 1731. (d) T. Yamato, M. Haraguchi, T. Iwasa and H. Tsuzuki: *Anales Química Int. Ed.* **93**, 301 (1997). (e) T. Yamato, Y. Saruwatari, M. Yasumatsu and S. Ide: *Eur. J. Org. Chem.* 1998, 309.

13. (a) A. Arduini, E. Ghidini, A. Pochini, R. Ungaro, G. D. Andreetti, G. Calestani and F. Ugozzoli: *J. Incl. Phenom.* **6**, 119 (1988). (b) H. Matsumoto, S. Nishio, M. Takeshita and S. Shinkai: *Tetrahedron* **51**, 4647 (1995).
14. (a) For a comprehensive review of all aspects of calixarene chemistry, see: C. D. Gutsche: *Calixarenes*, Royal Society of Chemistry, Cambridge, 1989. (b) J. Vicens and V. Böhmer: *Calixarenes. A Versatile Class of Macrocyclic Compounds*, Kluwer Academic Publishers, Cambridge, 1990. (c) C. D. Gutsche: *Acc. Chem. Res.* **16**, 161 (1983).
15. (a) M. Tashiro, A. Tsuge, T. Sawada, T. Makishima, S. Horie, T. Arimura, S. Mataka and T. Yamato: *J. Org. Chem.* **55**, 2404 (1990). (b) T. Yamato, K. Hasegawa, Y. Saruwatari and L. K. Doamekpor: *Chem. Ber.* **126**, 1435 (1993). (c) T. Yamato, Y. Saruwatari, L. K. Doamekpor, K. Hasegawa and M. Koike: *Chem. Ber.* **126**, 2501 (1993). (d) T. Yamato, M. Yasumatsu, Y. Saruwatari and L. K. Doamekpor: *J. Incl. Phenom.* **19**, 315 (1994). (e) T. Sawada, A. Tsuge, T. Thiemann, S. Mataka and M. Tashiro: *J. Incl. Phenom.* **19**, 301 (1994). (f) G. Brodesser and F. Vögtle: *J. Incl. Phenom.* **19**, 111 (1994). (g) T. Yamato, L. K. Doamekpor, K. Koizumi, K. Kishi , M. Haraguchi and M. Tashiro: *Liebigs Ann.* 1995, 1259.
16. T. Yamato, Y. Saruwatari, M. Yasumatsu and H. Tsuzuki: *New. J. Chem.* 1998, 1351.
17. (a) M. F. Semmelhack, J. J. Harrison, D. C. Young, A. Gutiérrez, S. Rafii and J. Clardy: *J. Am. Chem. Soc*. **107**, 7508 (1985). (b) K. Kobiro, M. Takashi, N. Nishikawa, K. Kikuchi, Y. Tobe and Y. Odaira: *Tetrahedron Lett.* **28**, 3825 (1987). (c) K. Kurosawa, M. Suenaga, T. Inazu and T. Yoshino: *Tetrahedron Lett.* **23**, 5335 (1982). (d) T. Shinmyozu, Y. Hirai and T. Inazu: *J. Org. Chem.* **51**, 1551 (1986). (e) K. Sako, T. Hirakawa, N. Fujimoto, T. Shinmyozu, T. Inazu and H. Horimoto: *Tetrahedron Lett.* **29**, 6275 (1988). (f) T. Meno, K. Sako, M. Suenaga, M. Mouri, T. Shinmyozu, T. Inazu and H. Takemura: *Can. J. Chem.* **68**, 440 (1990). (g) K. Sako, T. Meno, H. Takemura, T. Shinmyozu and T. Inazu: *Chem. Ber.* **123**, 630 (1990). (h) K. Sako, T. Shinmyozu, H. Takemura, M. Suenaga and T. Inazu: *J. Org. Chem.* **57**, 6536 (1992).
18. (a) K. Araki, N. Hashimoto, H. Otsuka and S. Shinkai: *J. Org. Chem.* **58**, 5958 (1993). (b) N. Sato and S. Shinkai: *J. Chem. Soc., Perkin Trans. 1* 1993, 2621.
19. Y. Inoue, C. Fujikawa, K. Wada, A. Tai and T. Hakushi: *J. Chem. Soc., Chem. Commun.* 1987, 393.
20. M. Bourgoin, K. H. Wong, J. Y. Hui and J. Smid: *J. Am. Chem. Soc.* **97**, 3462 (1975).
21. Z. Asfari, R. Abidi, F. Arnaud and J. Vicens: *J. Incl. Phenom.* **13**, 163 (1992).
22. F. Ohseto and S. Shinkai: *Chem. Lett.* 1993, 2045.
23. H. A. Benesi and J. H. Hildebrand: *J. Am. Chem. Soc*. **71**, 2703 (1949).
24. C. J. Pedersen: *J. Am. Chem. Soc.* **89**, 2495 (1967).