Synthesis, Structures and Inclusion Properties of [(Arenylaminocarbonyl) methoxy] hexahomotrioxacalix [3] arenes

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Synthesis, Structures and Inclusion Properties of [(Arenylaminocarbonyl)methoxy]hexahomotrioxacalix[3]arenes

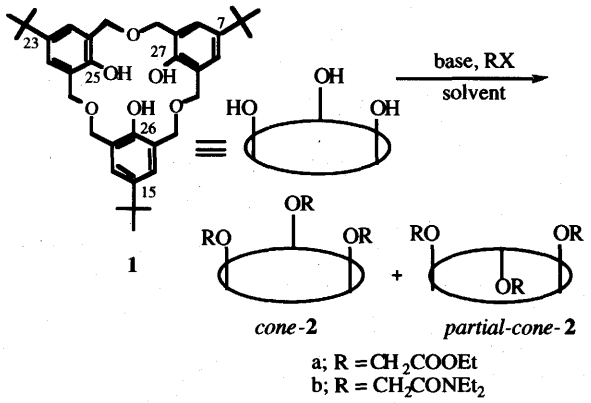
Takehiko Yamato* and Fenglei Zhang

The lower rim functionalized homotrioxacalix[3]arene **4a** and **4b** were synthesized from triol **1** by a stepwise reaction. Extraction data for metal and ammonium picrates from water into dichloromethane are discussed. Due to the strong intramolecular hydrogen bonding between the neighboring NH and CO groups, their affinities as an ionophore to metal cations decreased. *cone*-**4a** shows single selectivity to *n*-$BuNH_3^+$ while *partial-cone*-**4a** almost has no affinity to cations. *cone*-**4b** has high selectivity and affinity to Ag^+ cation. The complex mode of *cone*-**4a** with *n*-$BuNH_3Cl$ and *cone*-**4b** with Ag^+ was demonstrated by ^1H NMR titration in $CDCl_3$, respectively. A good Job plot proves 1:1 coordination of *cone*-**4b** with Ag^+ cation.

Introduction

Calixarene and related macrocycles have received considerable attention for their host-guest chemistry as ionophoric receptors[1-4] and potential enzyme mimics in biology.[5] Chemical modification of calixarene represents a simple though versatile way of producing receptors with high selective cation binding properties.[6-10] When larger alkyl groups were introduced onto the phenolic oxygens of calixarene, which can not pass each by oxygen-through-the-annulus rotation, there exist four possible conformational isomers in calix[4]arene (*i.e.* cone, partial-cone, 1,2-alternate and 1,3-alternate)[11] and five conformational isomers for [3.1.3.1]metacyclophane adding 1,4-alternate due to the propane bridge.[12] However, there are only two possible conformers in homotrioxacalix[3] arene (*i.e.* cone and partial-cone), because of the three substituents having on phenolic oxygen positions.[13-15]

Scheme 1



Recently, Shinkai and co-workers have reported the complexation of alkali metals to derivatives of the homotrioxacalix[3]arene with alkylated phenolic oxygens.[14,15]

On the other hand, hydrogen bonding plays an important role in the self-assembly of molecular recognition and has been attracted interesting in calixarene systems. Shinkai *et al.* reported that a hydrogen-bonded duplex was formed through the interaction between a calix[4]arene with four carboxyl groups and a calix[4]-arene with stilbazole moieties.[16] Recently, Pochini *et al.* described the formation of a hydrogen-bonded dimer in $CDCl_3$ based on the self-complementarity of carboxylic acid.[17] The intramolecular hydrogen-bonding was also formed between opposite urea groups, which can bind with anion species, in calix[4]arene.[18] However, very little effort has been devoted to the C_3-symmetrical homotrioxacalix[3]arene on this aspect of noncovalent aggregation processes.

In the present paper, we describe the synthesis, structures, and metal and ammonium ion complexation properties of the cone and partial-cone toluidinylamide derivatives as well as 2-pyridylamide derivatives of hexahomotrioxacalix[3]arene tricarboxylic acid, which are supposed to have encapsuled ionophoric cavities.

Results and Discussion

Partial-cone hexahomotrioxacalix[3]arene triethyl ester **2a** was prepared by alkylation of hexahomotrioxacalix[3]arene **1**[19] with ethyl bromoacetate in the presence of cesium carbonate as a base in refluxing acetone in 90% yield.[14]

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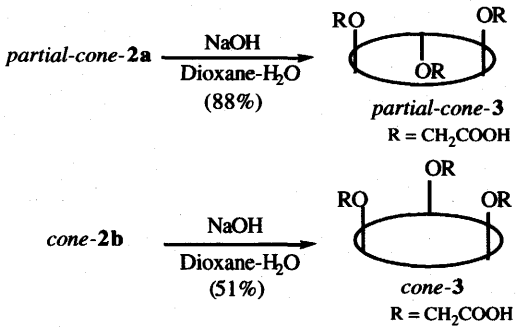
Dedicated to Professor Masashi Tashiro on the occasion of his retirement.
Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Saga-shi, Saga 840
This paper is submitted through Professor Shuntaro Mataka.

Scheme 2

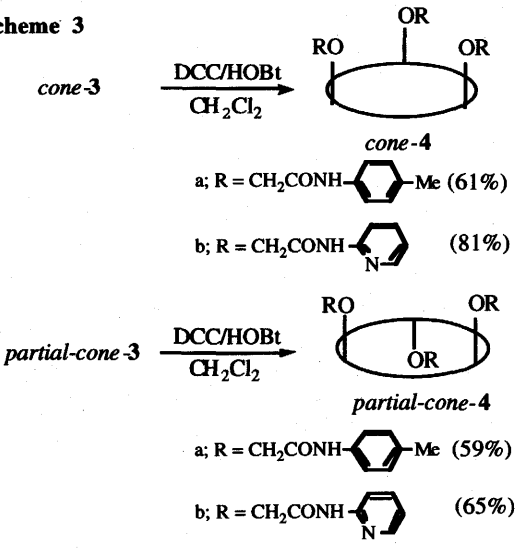


Hydrolysis of *partial-cone*-**2a** in a mixture of dioxane and water using NaOH as a base at room temperature afforded the corresponding partial-cone-hexahomotrioxacalix[3]arene tricarboxylic acid **3** in 88% yield. Although it is easy to get cone triacid **3** by the same reaction from triethyl ester *cone*-**2a**, the yield is lower than 20% to get cone conformation of triethyl ester **2a** in the alkylation process. On the other hand, it is almost quantitative to get cone amide derivative of **2b** through the *O*-alkylation of triol **1** with *N,N*-diethylchloroacetamide in the presence of NaH in refluxing THF.[15] Hydrolysis of cone amide **2b** in refluxing a mixture of dioxane and water afforded cone triacid **3** in 51% yield in the presence of NaOH. Although this method required much longer time and evaluate the reaction temperature compared to that of ester derivative, it was more efficient and effective to get enough amount of cone triacid **3**. ^{1}H-NMR spectra of **3** showed a single peak at δ 1.14 ppm for *tert*-butyl protons in *cone*-**3** and two single peak at δ 0.9 ppm and 1.08 ppm (intensity 2:1) for *tert*-butyl protons in *partial-cone*-**3**, which are in agreement with their conformations.

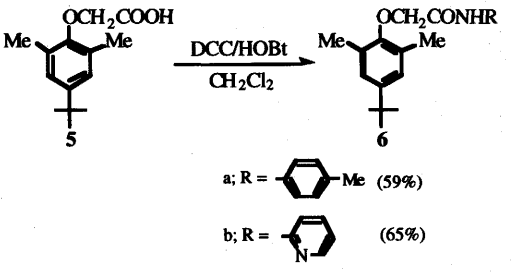
Reaction of triacid **3** with *p*-toluidine in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) in CH_2Cl_2 afforded the corresponding compound **4a** in a yield of 61% for *cone*-**4a** and 59% for *partial -cone*-**4a**, respectively. From the singlet peaks for *cone*-**4a** and the splitting patterns with a 1:2 integral intensity ratio for *partial-cone*-**4a** in their ^{1}H NMR spectra, the original conformations were retained in the desired compounds **4a**. In order to investigate the conformation of **4a** in detail, a reference compound **6a** was synthesized from 4-*tert*-butyl-2,6-dimethylphenoxyacetic acid **5** by similar method of the preparation of **4a** (Scheme 4).

Conformation assignments for the new amino homooxacalix[3]arenes **4a** followed from analysis of their ^{1}H NMR spectra. The *cone*-**4a** is firmly established by the presence of AB quartets for the bridging methylene protons with a Δδ separation between H_{ax} and H_{eq} of 0.60 ppm. In the calix[4]arenes the Δδ values of the ArCH_2Ar protons have been correlated to the orientation of adjacent aromatic rings, *i.e.* Δδ >1 with cone conformation or syn orientation, Δδ about 0.5 with flattened cone or out orientation, Δδ at 0 ppm with 1,3-

Scheme 3



Scheme 4



alternate or anti orientation.[20,21] Similar findings were observed in hexahomotrioxacalixarenes.[14a] Thus, we can deduce that *cone*-**4a** prefers to a flattened cone conformation, in which hydrogen bonding can form. On comparison with the chemical shift of relative protons between *cone*-**4a** and the reference compound **6a**, we can observe that proton NH in *cone*-**4a** is dramatically shifted to downfield (δ 0.83 ppm) so that the intramolecular hydrogen bonding was formed between NH and the neighboring C=O moieties. On the other hand, *partial-cone*-**4a** exhibits two singlet for the *tert*-butyl protons at δ 0.94 and 1.08 ppm (integral intensity 2:1), a singlet for ArOCH_2CO methylene protons at δ 3.35 and 4.37 ppm, these signals are consistent with the structure of *partial-cone*-**4a** having a C_2-symmetrical structure. The two substituents were pointed up to the aromatic rings while the other one was inverted and tightly accommodated inside the hydrophobic cavity generated by the diaryl moieties, in a sort of self-inclusion complex. Intramolecular hydrogen bond was also formed between the two pointed-up substituents so that a downfield shift of NH proton (Δδ = 0.79 ppm) was observed compared to **6a**. Dramatic upfield shifts for diastereotopic ArOCH_2CO proton (Δδ = -1.04 ppm) and for NH (Δδ = -0.44 ppm) were observed in the inverted substituent, which strongly suggested that the inverted substituent was folded into the hydrophobic cavity

Table 1. Extraction (%) of metal and ammonium picrates in CH_2Cl_2[a)]

Ionophore	Na^+	K^+	Ag^+	Cu^{2+}	Al^{3+}	n-$BuNH_3^+$	i-$BuNH_3^+$	t-$BuNH_3^+$
cone-**2b**	93.0	71.6	90.4	27.5	19.0	97.8	48.0	35.4
partial-cone-**2b**	27.9	72.9	77.1	24.0	8.9	93.2	36.8	14.2
cone-**4a**	0	0	0	0	0	18.7	0	0
partial-cone-**4a**	0	0	0	0	0	0	0	0
cone-**4b**	0	0	76.9	16.6	11.5	38.1	1.9	0.8
partial-cone-**4b**	0	0	31.1	3.1	2.6	2.2	0.4	0.4

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

formed by two aromatic rings. Therefore, same self-inclusion phenomenon was observed in partial-cone structure like in other calix[4]arenes[22)] and homocalix-[3]arenes.[23)]

However, even minor changes in the regioselective functionalization[24)] or conformation[25)] of the chemically modified calixarene can be associated with drastic changes in the complexation properties. N-heterocyclic reagents, such as pyridine moieties, or dipyridine moieties, have been introduced into calixarene in order to form ligands for both hard and soft metal ions, which should exhibit some superior to amide and ester structures because of a high stability in a wide pH range.[26,27)] Compound **4b** and its reference compound **6b** were prepared from the reaction of triacid **3** and **5** with 2-aminopyridine similar to that of compound **4a**, respectively. Like *cone*-**4a**, *cone*-**4b** has a C_3-symmetrical conformation, which has a AB patterns for ArCH_2O bridged protons with a $\Delta\delta$ separation of δ 0.42 ppm between H_{ax} and H_{eq}. The intramoleclar hydrogen bond was formed between neighboring NH and CO groups which induce a large downfield shift for NH proton ($\Delta\delta$ = +0.45 ppm) in *cone*-**4b** compared to compound **6b**.

Due to the repulsion among the nitrogen atoms in pyridine rings between the dibenzylether linkage, nitrogens in all of the pyridine rings were oriented outwards the cyclophane cavity, whereas the protons in pyridine rings were subjected to the ring current shielding effects from the mutual pyridine rings. The protons were accordingly shifted to the high magnetic field compared to those in a single unit of *cone*-**4b**, reference compound **6b**. On the other hand, the intramolecular hydrogen bond makes the free-fold chain, OCH_2CONH, approach each other so that the orientation of pyridine rings is twisted. Therefore, proton H_3 is located more closer in space than other protons in pyridine rings and the most upfield shift has been observed ($\Delta\delta$ = -0.4 ppm). A similar trendency is also found for *partial-cone*-**4b**. Intramolecular hydrogen bonding was formed in the two pointed-up substituents, the nitrogen atoms in pyridine rings were orientated outward against the cavity and a large upfield shift was observed for H_3 ($\Delta\delta$ = -0.27 ppm) in pyridine rings. The inverted substituent was folded down to the cavity rings formed by diaryl moieties. In comparison with compound **6b**, in the inverted substituent, proton of diastereomethylene, NH and H_3 in pyridine ring were largely shifted to upfield with δ 1.55, 0.50 and 0.25 ppm, respectively, while other protons in pyridine ring have a little change. This observation indicates that the nitrogen atom is also orientated outward even in the inverted substituent.

The *O*-alkylated calixarenes can bind the metal cations to form the complex, which had been investigated by several groups through different types of calixarenes. Extraction studies were conducted by the standard two phase procedure whereby dilute solutions of each calixarene derivative in dichloromethane were shaken with neutral aqueous metal picrate solutions, following which the equilibrium distribution of the picrate was measured spectrophotometrically.[8)]

Interestingly, amides **4a** and **4b** show a low efficiency for metal cations compared to *N,N*-diethylamide derivatives **2b**.[14a,15)] Although the ionophoric activity of compound **4a** was almost absent, *cone*-**4a** shows moderate affinity and high selectivity to *n*-butyl ammonium cation because of the C_3-symmetrical structure. The ionophores usually formed a loose ion pairs with metal picrates, which showed the maximum absorption peak at 377nm.[28)] As to Cu^{2+} and Al^{3+}, they form a contact ion pairs with *partial-cone*-**2b** and *cone*-**4b**, which showed the maximum absorption peak at 365nm. Interestingly, *cone*-**4a** also form a contact ion pairs with n-$BuNH_3^+$ and showed the maximum absorption peak at 365 nm. As to *partial-cone*-**4b**, a contact ion pair was formed with Ag^+. In comparison with *cone*-**4a**, *cone*-**4b** has high affinity to transition metal ions, Ag^+, Cu^{2+} and Al^{3+}. These findings clearly indicate that the lower-rim side chains having pyridyl groups play a significant role on the complexation with transition metal cations. Thus, the cations might be encapsulated into the cavity formed by pyridine rings. Due to the strong hydrogen bonding formed between NH and neighboring CO groups in *cone*-**4a**, it shows no affinity to either hard or soft metal

Table 2. Chemical shift changes of *cone*-**4a** induced in the presence of *n*-$BuNH_3Cl$ [a)]

compd.	Ph		Ph-CH_3	NH	$ArOCH_2$	$ArCH_2O$	Ar-H	t-Bu
	Ha	Hb						
cone-**4a**	7.44	6.95	2.25	9.43	4.39	4.27, 4.86	6.92	1.14
cone-**4a** +*n*-$BuNH_3Cl$	7.53	6.90	2.21	10.52	5.14	4.30, 5.50	7.22	1.23
$\Delta\delta$ [b)]	+0.09	-0.05	-0.04	+1.09	+0.75	+0.03, +0.64	+0.30	+0.09

[a)] $\Delta\delta$ Values are the difference of the chemical shift of *cone*-**4a** (5×10^{-3} M) induced in the presence of *n*-$BuNH_3Cl$ (5×10^{-4} M) in $CDCl_3$ at 27 °C. [b)] A plus sign (+) denotes a shift to lower magnetic field, whereas a minus sign (-) denotes a shift to higher magnetic field.

cations. On the other hand, *cone*-**4b** can bind transition metal cations because of having the pyridine groups which can bind with soft metal cations.

The present bonding mode can be demonstrated more clearly by using ^1H NMR spectroscopy. There are two modes for *cone*-**4a** to bind with *n*-butyl ammonium cation, *i.e.* from the lower rim through substituents moieties or from the upper rim through the π-cavity formed by three aromatic rings. As listed in Table 2 the chemical shifts of *cone*-**4a** changed in the absence and presence of *n*-butyl ammonium cation. After adding an equivalent of *n*-$BuNH_3Cl$ into *cone*-**4a** ($5x10^{-3}$ mol/L) in $CDCl_3$ at 25°C, protons on aromatic rings, $ArCH_2O$, $ArOCH_2$ were dramatically shifted to lower magnetic field, which indicate that the binding mode occurred through the π-cavity formed by three aromatic rings. This binding is attributed to the π-effect of aromatic rings because both the host and the guest molecules have a C_3-symmetrical conformation. With excess of *n*-$BuNH_3Cl$, the free guest molecule and the encapsulated molecule were clearly observed by the proton ^1H NMR spectroscopy, in which the encapsulated one was shifted to upfield, CH_3 (0.95 to 0.26, $\Delta\delta$ = -0.69 ppm), CH_3CH_2 (1.45 to 0.30, $\Delta\delta$ = -1.05 ppm), $CH_3CH_2CH_2$ (1.77 to 0.30, $\Delta\delta$ = -1.45 ppm) and CH_2N (3.00 to -0.25, $\Delta\delta$ = -3.25 ppm). The chemical shift of NH proton in *cone*-**4a** was shifted to lower magnetic field (δ 9.43 to 10.52; $\Delta\delta$ = +1.09 ppm) while NH in *n*-$BuNH_3Cl$ was shifted to upper field (δ8.30 to 5.93; $\Delta\delta$ = -2.37 ppm). Intramolecular hydrogen bonding in *cone*-**4a** decreases the affinity of *cone*-**4a** to metal cations which was encapsulated through the lower rim of homotrioxacalix-[3]arene derivative. When *cone*-**4a** was complexed with *n*-$BuNH_3^+$ through π-cavity, the conformation of *cone*-**4a** was changed and intramolecular hydrogen bonding was impossible in this conformation, the NH protons in *cone*-**4a** was shifted to lower magnetic field indicates complexation of the anionic guest, Cl^-, through hydrogen bonding (Figure 1).[29)] Addition of *n*-Bu_4NI and $PhMe_3NCl$ to a solution of *cone*-**4a** in $CDCl_3$ ($5x10^{-3}$ mol/L), no complexation of halide anions was observed. Due to the stronger intramolecular hydrogen bonding, the anion binding site is blocked.

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 ^1H NMR titration experiment.[30)] In the present systems, due to the existence of three metal-binding sites of pyridine moiety, there are several possibilities for metal complexation mode. Thus, a 1:1 and a 2:1 metal complexation of *cone*-**4b** might be possible.

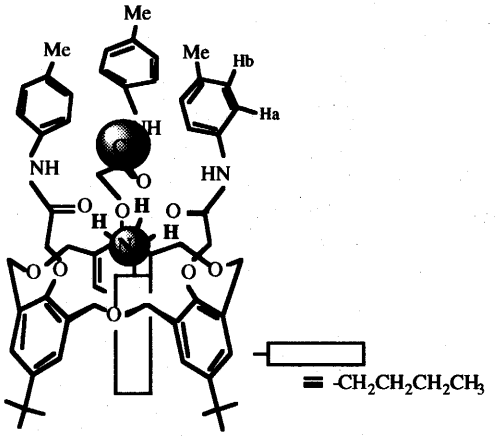


Figure 1. Binding mode of tris[(4-methylphenyl)amino-carbonyl)methoxy]hexahomotrioxacalix[3]arenes*cone*-**4a** and *n*-$BuNH_3Cl$

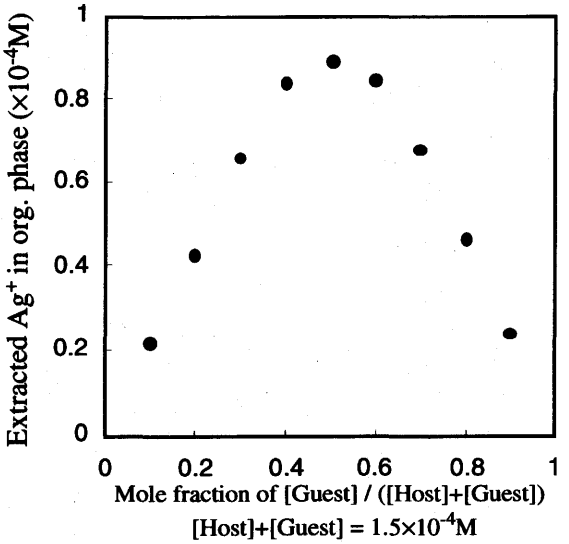
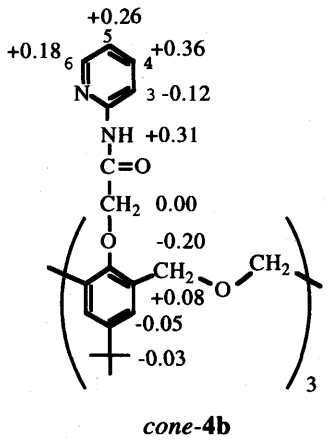


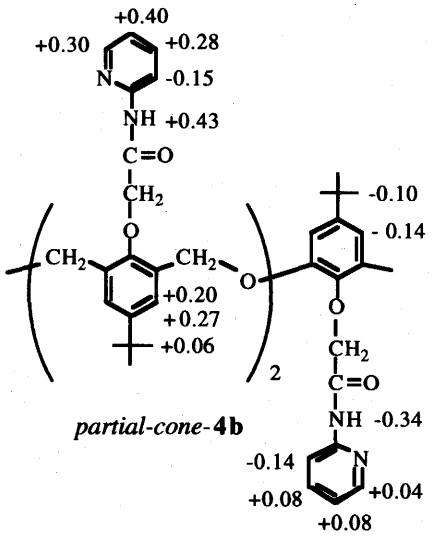
Figure 2. Job plots of the extractions of Ag^+ with host *cone*-**4b**

As shown in Figure 2, the percent extractions reach maximum at 0.5 mole fraction for this cation. The fact clearly indicates that Ag^+ forms 1:1 complex with *cone*-**4b**. Thus we could prove the synergism of the cyclophane moiety and three pyridine-arms at the complexation. It was also found that the corresponding *cone*-**4a** hardly extracted Ag^+ cation in this experimental conditions (extaraction %: less than 1%).

In order to prove the synergism between cyclophane moiety and three lower-rim side chains having pyridyl groups, we examined the ^{1}H NMR chemical shift differences between those before and after the addition of an equimolar $AgSO_3CF_3$, and composition of the ion-ionophore complex. After titration with an equivalent of $AgSO_3CF_3$, the protons in pyridine rings in *cone*-**4b** were shifted to lower magnetic field except H_3 shifted to upper field ($\Delta\delta$ = -0.12 ppm). This indicates that the nitrogen atoms turned to inside of the cavity and interact with Ag^+, which make great downfield shift for H_4, H_5 and H_6 induced by the inductive effect arising for the N$\cdots$$Ag^+$ interaction present around this cavity. After



cone-**4b**



partial-cone-**4b**

Figure 3 Chemical shift changes of*cone*-**4b** and *partial-cone*-**4b** induced in the presence of $AgSO_3CF_3$; + denotes the down-field and - denotes the up-field shi

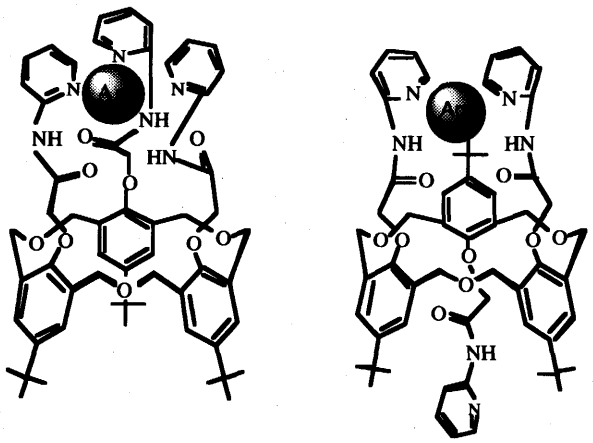


Figure 4. Binding mode of tris[(2-pyridylaminocarbonyl)-methoxy]hexahomotrioxacalix[3]arenes *cone*-**4b**, and *partial-cone*-**4b** and Ag^+

complexation with Ag^+, *cone*-**4b** still retains the C_3-symmetrical conformation and NH proton is also shifted to lower field due to the increased intramolecular hydrogen bonding formed with the neighboring C=O group.

Similar results were obtained when *partial-cone*-**4b** was titrated with an equivalent of $AgSO_3CF_3$, the nitrogen atoms in the pyridine rings of the two pointed-up substituents turned to inside of the cavity and coordinated with Ag^+ (Figure 4), as well as much stronger hydrogen bonding formed between NH protons and C=O (a lower magnetic field shift of $\Delta\delta$ = +0.43 ppm for NH proton). Protons in pyridine rings shifted to lower magnetic field except H_3 shifted to upper field ($\Delta\delta$ = -0.15 ppm). The complexation of *partial-cone*-**4b** with Ag^+ makes the flatten aromatic rings stand up whereas the shielding effect formed by diaryl rings become more strong. In the inverted substituent, both NH proton and H_3 in pyridine ring were shifted to upfield ($\Delta\delta$ = -0.34 ppm for NH and -0.14 ppm for H_3, respectively) because they were under the shielding current caused by diaryl rings. Due to the complicated patterns of diastereomethylene protons with bridge methylene protons in the presence of Ag^+, as well as lower solubility of the complex in $CDCl_3$, it seems difficult to detected the changes of these methylene protons in the inverted substituent in the complex with Ag^+ cation. As mentioned above, $\Delta\delta$ between H_{ax} and H_{eq} of the ArCH_2Ar methylene protons in Calix[4]arene serves as a measure of the 'flattening'. $\Delta\delta$ H increases from δ 0.60 ppm to 1.20 ppm in *cone*-**4a** in the binding of *n*-BuNH_3^+ and from δ 0.42 ppm to 0.69 ppm in *cone*-**4b** in the binding of Ag^+, respectively. These findings implies that *cone*-**4** stands up when the guest is included because n-BuNH_3^+ enters into the cavity from π-cavity formed by three aromatic rings. On the other hand, Ag^+ was encapsulated into the cavity formed pyridine rings.

Conclusion

For the first time, the relationship of properties of host as ionophores and its intramolecular hydrogen bonding was taken into account in C_3-symmetrical conformation. Due to the intramolecular hydrogen bonding, the affinities of ionophores **4a** and **4b** to metal ions decreased, they do not bind with alkali and alkaline earth metal cations because the binding site was blocked. Both *cone*-**4a** and *cone*-**4b** can bind with *n*-butyl ammonium cation through the π-cavity formed by triaryl rings, which can provide functional moieties in biologic system with a good affinity and high selectivity. Amides **4b** can bind with Ag^+ cation and the complexation mode were elucidated clearly in this paper. After complexation of amides **4b** with Ag^+, the original C_3-symmetry and C_2-symmetry have been retained for *cone*-**4b** and *partial-cone*-**4b**, respectively. The nitrogen atom in pyridine ring turned from outward against the cavity to inside of the cavity to interact with Ag^+ while the inverted substituent in *partial-cone*-**4b** still retained. The oxygen in ethereal linkage did not take part in the complex procedure.

Experimental

All mps (Yanagimoto MP-S_1) are uncorrected. NMR spectra were determined at 270MHz 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 Nippon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75eV using a direct-inlet system through GLC.

Materials: *partial-cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(ethoxycarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*partial-cone*-**2a**) and *cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris[(*N,N*-diethylaminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**2b**) were prepared according to the literature. [14, 15]

Preparation of *cone*-hexahomotrioxacalix-[3]arene triacetic acid (*cone*-3). To a mixture of *cone*-**2b** (1.0 g, 1.14 mmol) in dioxane (30 cm^3) was added 1N NaOH aqueous solution (30 cm^3). After the mixture was refluxed for three days, it was condensed under reduced pressure, then acidified to pH 1-2. The dispersion was extracted with ethyl acetate (2 x 30 cm^3). The combined extracts were washed with water (2 x 20 cm^3), saturated brine (20 cm^3), dried (Na_2SO_4) and condensed under reduce pressure. The residue was washed with small amount of diethyl ether to give the crude *cone*-**3** as a colorless solid. Recrystallization from methanol gave *cone*-**3** (440 mg, 51.2%) as colorless powder; mp 227-229 °C; υ_{max} (KBr)/ cm^{-1} 3400, 2975, 2915, 2867, 1758, 1483, 1456, 1363, 1234, 1199, 1094 and 1058; δ_H ($CDCl_3$) 1.12 (27 H, s, *t*-Bu), 4.44 (6 H, d, *J* 12.7, ArCH_2O), 4.92 (6 H, d, *J* 12.7, ArCH_2O), 4.46 (6 H, s, ArOCH_2) and 6.95 (6 H, s, Ar-H); *m/z* 750 (M^+) (Found C, 67.36; H, 7.40. $C_{42}H_{54}O_{12}$ requires C, 67.18; H, 7.25%).

Preparation of *partial-cone*-hexahomotrioxacalix[3]arene triacetic acid (*partial-cone*-3). To a mixture of *partial-cone*- **2a** (1.0 g, 1.20 mmol) in dioxane (30 cm^3) was added 1N NaOH aqueous solution (30 cm^3). After the mixture was stirred for 1 h at room temperature, it was condensed under reduced pressure, then acidified to pH 1-2. The dispersion was extracted with ethyl acetate (2 x 30 cm^3). The combined extracts were washed with water (2 x 20 cm^3), saturated brine (20 cm^3), dried (Na_2SO_4) and condensed under reduce pressure. The residue was washed with small amount of hexane to give the crude *partial-cone*-**3** as a colorless solid. Recrystallization from methanol gave *partial-cone*-**3** (790 mg, 87.8%) as colorless powder; mp 158-160 °C; υ_{max} (KBr)/ cm^{-1} 3400, 2961, 2873, 1786, 1738, 1365, 1195, 1065, 1056 and 886; δ_H ($CDCl_3$) 1.29 (18 H, s, *t*-Bu), 1.33 (9 H, s, *t*-Bu), 2.61 (2 H, s, ArOCH_2), 3.15, 4.27, 4.34, 4.45, 4.95, 5.17 (each 2 H, d, *J* 12.7, ArCH_2O), 4.60 (4 H, s, ArOCH_2), 7.30 (2 H, d, *J* 2.4, Ar-H), 7.38 (2 H, d, *J* 2.4, Ar-H) and 7.43 (2 H, s, Ar-H); *m/z* 750 (M^+) (Found C, 67.32; H, 7.35. $C_{42}H_{54}O_{12}$ requires C, 67.18; H, 7.25%).

Preparation of *cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris[(4-methylphenylaminocarbonyl) methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-4a). To a solution of *cone*-**3** (100 mg, 0.133 mmol), *p*-toluidine (130 mg, 1.17 mmol) and HOBt (23mg, 0.17 mmol) in CH_2Cl_2 (12 cm^3) was added dropwise a solution of DCC(171 mg) in CH_2Cl_2 (5 cm^3) at 0 °C. After the mixture was stirred for 15h at room temperature, it was condensed under reduced pressure. The residue was extracted with ethyl acetate (2 x 30 cm^3). The combined extracts were washed with 10% citric acid (2 x 20 cm^3), 5% sodium bicarbonate (20 cm^3), water (20 cm^3), saturated brine (20 cm^3), dried (Na_2SO_4) and condensed under reduce pressure. The residue was recrystallized from methanol gave *cone*-**4a** (83mg, 61.2%) as colorless prisms; mp 234-236 °C; υ_{max} (KBr)/ cm^{-1} 3333, 2921, 2860, 1632, 1580, 1539, 1437, 1312, 1244, 1230, 1089, 1068, 1045, 1020, 802, 657 and 641; δ_H ($CDCl_3$) 1.14 (27 H, s, *t*-Bu), 2.25 (9 H, s, Ph-CH_3), 4.27 (6 H, d, *J* 12.7, ArCH_2O), 4.39 (6 H, s, ArOCH_2), 4.86 (6 H, d, *J* 12.7, ArCH_2O), 6.92 (6 H, s, Ar-H), 6.95 (6 H, d, *J* 8.8,Ph-Hb), 7.44 (6 H, d, *J* 8.8,Ph-Ha) and 9.42 (3 H, s, NH); m/z 1018 (M^+) (Found C, 74.52; H, 7.53; N, 4.30. $C_{63}H_{75}O_9N_3$ requires C,74.31; H, 7.42; N, 4.13%).

Similarly, *partial-cone*-**4a**, *cone*-**4b** and *partial-cone*-**4b** were prepared in 59.0, 80.1 and 65.2% yields, respectively.

***partial-cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(4-methylphenylaminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*partial-cone*-4a)**: Colorless prisms (from methanol); mp 254-255 °C; υ_{max} (KBr)/ cm^{-1} 3362, 3322, 2962, 2867, 1696, 1606, 1526, 1483, 1458, 1407, 1312, 1249, 1197, 1060, 885 and 817; δ_H ($CDCl_3$) 0.94 (18 H, s, *t*-Bu), 1.07(9 H, s, *t*-Bu), 2.32 (6 H, s, Ph-CH_3), 2.34 (3 H, s, Ph-CH_3), 3.35(2 H, s, ArOCH_2), 4.01, 4.38, 4.45, 4.53, 4.87, 4.92 (each 2 H, d, *J* 12.7, ArCH_2O), 4.37 (4 H, s, ArOCH_2), 6.98 (2 H, d, *J* 8.8,Ph-Hb), 7.08 (4 H, d, *J* 8.8, Ph-Hb), 7.14, 7.27 (each 2 H, d, *J* 2.4, Ar-H), 7.35 (2 H, s, Ar-H), 7.46 (2 H, d, *J* 8.8, Ph-Ha), 7.49 (4 H, d, *J* 8.8, Ph-Ha), 7.95 (1 H, s, NH) and 9.40 (2 H, s, NH); m/z 1018 (M^+) (Found C, 74.59; H, 7.40; N,3.98. $C_{63}H_{75}O_9N_3$ requires C,74.31; H, 7.42; N, 4.13%).

***cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris-[(2-pyridylaminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-4b)**: Colorless prisms (from methanol); mp 124-126 °C; υ_{max} (KBr)/ cm^{-1} 3395, 3304, 2957, 2909, 1701, 1696, 1595, 1575, 1516, 1483, 1461, 1433, 1303, 1196, 1094 and 777; δ_H ($CDCl_3$) 1.15 (27 H, s, *t*-Bu), 4.53 (6 H, d, *J* 12.7, ArCH_2O), 4.49 (6 H, s, ArOCH_2), 4.94 (6 H, d, *J* 12.7, ArCH_2O), 6.99 (6 H, s, Ar-H), 6.89 (3 H, m, pyridine-H5), 7.45 (3 H, m, pyridine-H4), 7.89 (3 H, d, *J* 8.8, pyridine-H3), 8.18(3 H, m, pyridine-H6) and 9.71 (3 H, s, NH); m/z 979 (M^+) (Found C,69.65; H,6.73; N,8.30. $C_{57}H_{66}O_9N_6$ requires C,69.92; H,6.79; N, 8.58%).

***partial-cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(2-pyridylaminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*partial-cone*-4b)**: Colorless prisms (from methanol); mp 216-218 °C; υ_{max} (KBr)/ cm^{-1} 3326, 2918, 2851, 1702, 1628, 1577, 1524, 1483, 1460, 1433, 1302, 1197, 1086, 1052 and 779; δ_H ($CDCl_3$) 0.92 (18 H, s, *t*-Bu), 1.10 (9 H, s, *t*-Bu), 2.86 (2 H, s, ArOCH_2), 3.99, 4.40, 4.57, 4.62, 5.00, 5.08 (each 2 H, d, *J* 12.7, ArCH_2O), 4.42 (4 H, s, ArOCH_2), 6.98 (2 H, m, pyridine-H5), 7.03 (1 H, m, pyridine-H5'), 7.12 (2 H, d, *J* 2.4, Ar-H), 7.35 (2 H, d, *J* 2.4, Ar-H), 7.43 (2 H, s, Ar-H), 7.58 (2 H, m, pyridine-H4), 7.62 (1 H, m, pyridine-H4'), 8.03 (2 H, d, *J* 8.8, pyridine-H3), 8.06 (1 H, d, *J* 8.8, pyridine-H3'), 8.31 (2 H, m, pyridine-H6), 8.46 (1 H, m, pyridine-H6'), 8.76 (1 H, s, NH) and 9.42 (2 H, s, NH); m/z 979 (M^+) (Found C,69.77; H,6.91; N,8.34. $C_{57}H_{66}O_9N_6$ requires C,69.92; H,6.79; N, 8.58%).

Preparation of 4-*tert*-butyl-2,6-dimethyl-[(4-methylphenyl)aminocarbonyl)methoxy]-benzene (6a). To a solution of (4-*tert*-butyl-2,6-dimethyl)phenoxyacetic acid (100 mg, 0.43 mmol), *p*-toluidine (137 mg, 1.28 mmol) and HOBt (75 mg, 0.17 mmol) in CH_2Cl_2 (12 cm^3) was added dropwise a solution of DCC(560 mg) in CH_2Cl_2 (5 cm^3) at 0 °C. After the mixture was stirred for 7h at room temperature, it was condensed under reduced pressure. The residue was extracted with ethyl acetate (2 x 30 cm^3). The combined extracts were washed with 10% citric acid (2 x 20 cm^3), 5% sodium bicarbonate (20 cm^3), water (20 cm^3), saturated brine (20 cm^3), dried (Na_2SO_4) and condensed under reduce pressure. The residue was recrystallized from methanol gave the *title compound* **6a** (81 mg, 59%) as colorless prisms; mp 204-206 °C; υ_{max} (KBr)/ cm^{-1} 3277, 2950, 2928, 2865, 1667, 1533, 1515, 1484, 1458, 1443, 1408, 1360, 1322, 1310, 1195, 1124, 1050, 870, 819 and 753; δ_H ($CDCl_3$) 1.30 (9 H, s, *t*-Bu), 2.30 (6 H, s, Ph-CH_3), 2.35 (3 H, s, Ph-CH_3), 4.39 (2 H, s, ArOCH_2), 7.05 (2 H, s, Ar-H), 7.18 (2 H, d, *J* 8.8, Ph-Hb), 7.52 (2 H, d, *J* 8.8, Ph-Ha) and 8.60 (1 H, s, NH); *m/z* 325 (M^+) (Found C, 77.36; H, 8.33; N, 4.27. $C_{21}H_{27}O_2N$ requires C,77.50; H,8.36; N, 4.31%).

Similarly, compound **6b** was prepared in 65.3% yield.

4-*tert*-Butyl-2,6-dimethyl[(2-pyridylaminocarbonyl)methoxy]benzene (6b): colorless prisms; mp 118-120 °C; υ_{max} (KBr)/ cm^{-1} 3397, 3323, 2926, 2851, 1714, 1703, 1627, 1572, 1518, 1435, 1310, 1304, 1244, 1047 and 774; δ_H ($CDCl_3$) 1.30 (9 H, s, *t*-Bu), 2.30 (6 H, s, Ph-CH_3), 4.41 (2 H, s, ArOCH_2), 7.04 (2 H, s, Ar-H), 7.10 (1 H, m, pyridine-H5), 7.75 (1 H, m, pyridine-H4), 8.31(1 H, d, *J* 8.8, pyridine-H3), 8.35(1 H, m, pyridine-H6) and 9.25 (1 H, s, NH); *m/z* 312 (M^+) (Found C, 73.23; H, 7.35; N, 8.72. $C_{19}H_{47}O_2N_2$ requires C,73.05; H,7.74; N, 8.97%).

References

1. (a) Gutsche, C. D., *Prog. Macrocyclic Chem.*, **1987**, *3*, 93; (b) Xu, B., Svager, T. M., *J. Am. Chem. Soc.*, **1993**, *115*, 1159; (c) Bott, S. G., Coleman, A. W., Atwood, J. L., *J. Chem. Soc., Chem. Commun.*, **1986**, 610.
2. Anduni, A., Pochini, A., Reverber, S., Ungaro, R., Andretti, G. D., Ugozzoli, F., *Tetrahedron*, **1986**, *42*, 2089.
3. Chang, S. K., Cho, I., *J. Chem. Soc., Perkin Trans. 1*, **1986**, 211.
4. (a) Zerr, P., Mussrabi, M., Vicens, J., *Tetrahedron Lett.*, **1991**, *32*, 1879; (b) Gutsche, C. D., Bauer, L. J., *J. Am. Chem. Soc.*, **1985**, *107*, 6052.
5. (a) Shinkai, S., *Tetrahedron*, **1993**, *49*, 8933; (b) Lehn, J. M., *Angew. Chem., Int. Ed. Engl.*, **1988**, *27*, 89; (c)

Cram, D. J., *Angew. Chem., Int. Ed. Engl.*, **1988**, *27*, 1009.
6. Bocchi, V., Foina, D., Pochini, A., Ungaro, R., *Tetrahedron*, **1982**, *38*, 373.
7. Ferguson, G., Kaitner, B., Mckervey, M. A., Seward, E. M., *J. Chem. Soc., Chem. Commun.*, **1987**, 584.
8. Arnaud-Neu, F., Schwing-Weill, M.-J., Ziat, K., Cremin, S., Harris, S. J., Mckervey, M. A., *New J. Chem.*, **1991**, *15*, 33.
9. (a) Andreetti, G. D., Calestani, G., Ugozzoli, F., Arduini, A., Ghidini, E., Pochini, A., Ungaro, R., *J. Inclusion Phenom.*, **1987**, *5*, 123; (b) Chang, S. K., Cho, I., *Chem. Lett.*, **1987**, 947.
10. (a) Ghidini, E., Ugozzoli, F., Ungaro, R., Harkema, S., El-Fadl, A. Abu, Reinhoudt, D. N., *J. Am. Chem. Soc.*, **1990**, 112, 6979; (b) Arduini, A., Ghidini, E., Pochini, A., Ungaro, R., Andreetti, G. D., Calestani, G., Ugozzoli, F., *J. Inclusion Phenom.*, **1988**, *6*, 119.
11. (a) Böhmer, V., *Angew. Chem., Int. Ed. Engl.*, **1995**, *34*, 713; (b) Gutsche, C. D., *Calixarene*, Royal Society of Chemistry, Cambridge, **1989**.
12. (a) Yamato. T., Saruwatari, Y., Nagayama, S., Maeda, K., Tashiro, M., *J. Chem. Soc., Chem. Commun.*, **1992**, 861; (b) Yamato, T., Doamekpor, L. K., Tsuzuli, H. Tashiro, M., *Chem. Lett.*, **1995**, 89; (c) Yamato, T., Saruwatari, Y., Yasumatsu, M., *J. Chem. Soc. Perkin Trans. 1*, **1997**, 1725; (d) Yamato, T., Saruwatari, Y., Yasumatsu, M., *J. Chem. Soc. Perkin Trans. 1*, **1997**, 1731; (e) Yamato, T., Doamekpor, L. K., Tsuzuki, H., *Liebigs Ann.*, **1997**, 1537; (f) Yamato, T. Haraguchi, M., Iwasa, Tsuzuki, H., T., Ide, *Anales de Quimica, Int. Ed.*, in press; (g) Yamato, T., Saruwatari, Y., Yasumatsu, M., Ide, S., *Liebigs Ann.*, accepted for publication; (h) Yamato, T., Saruwatari, Y., Yasumatsu, M., Tsuzuki, H., *Tetrahedron*, accepted for publication.
13. Hampton, P. D., Bencze, Z., Tong, W., Daitch, C. E., *J. Org. Chem.*, **1994**, *59*, 4838.
14. (a) Araki, K., Hashimoto, N., Otsuka, H., Shinkai, S., *J. Org. Chem.*, **1993**, *58*, 5958; (b) Takeshita, M., Shinkai, S., *Chem. Lett.*, **1994**, 125.
15. Matsumoto, H., Nishio, S., Takeshita, M., Shinkai, S., *Tetrahedron*, **1995**, *51*, 4647.
16. Koh, K., Araki, K., Shinkai, S., *Tetrahedron Lett.*, **1994**, *35*, 8255.
17. Arduini, A., Fabbi, M., Mantovani, M., Mirone, L., Pochini, A., Secchi, A., Ungaro, R., *J. Org. Chem.*, **1995**, *60*, 1454.
18. (a) Scheerder, J., Duynhoven, J. P. M. van, Engbersen, J. F. J., Reinhoudt, D. N., *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 1090; (b) Rudevich, D. M., Verboom, W., Reinhoudt, D. N., *J. Org. Chem.*, **1994**, *59*, 3683; (c) Scheerder, J., Vreekamp, R. H., Engbersen, J. F. J., Verboom, W., Duynhoven, J. P. M. van, Reinhoudt, D. N., *J. Org. Chem.*, **1996**, *61*, 3476.
19. Ninagawa, H., Matsuda, H., *Makromol. Chem. Rapid Commun.*, **1982**, *3*, 65.
20. Kanamathareddy, S., Gutsche, C. D., *J. Org. Chem.*, **1992**, *57*, 2160.
21. Cunsolo, F., Piattelli, M., Neti, P., *J. Chem. Soc., Chem. Commun.*, **1994**, 1977.
22. (a) Pappalardo, S., Giunta, L., Foti, M., Ferguaon, F., Gallagher, J. F., Kaitmer, B., *J. Org. Chem.*, **1992**, *57*, 2611; (b) Ferguson, G., Gallagher, J. F., Giunta, L., Neri, P., Pappalardo, S., Parisi, M., *J. Org. Chem.*, **1994**, *59*, 42.
23. (a) Yamato, T., Doamekpor, L. K., Koizumi, K. Kishi, K. Haraguchi, M. Tashiro, M., *Liebigs Ann.*, **1995**, 1259; (b) Yamato, T., *J. Inclusion Phenom.*, in press; (c) Yamato, T. Haraguchi, M., Nishikawa, J., Ide, S., *J. Chem. Soc., Perkin Trans. 1*, accepted for publication; (d) Yamato, T., Haraguchi, M., Nishikawa, J., Ide, S., Tsuzuli, H., submitted to *Liebigs Ann.*
24. Brunink, J. A. J., Verboom, W., Engbersen, J. F. J., Harkema, S., Reinhoudt, D. N., *Recl. Trav. Chim.* Pays-Bas, **1992**, *111*, 511.
25. Ungaro, R., Casnati, A., Ugozzoli, F., Pochini, A., Dozol, J. F., Hill, C., Rouquette, H., *Angew. Chem., Int. Ed. Engl.*, **1994**, *33*, 1506.
26. (a) Shinkai, S., Otsuka, T., Araki, K., Matsuda, T., *Bull Chem. Soc. Jpn.*, **1989**, *62*, 4055; (b) Bottino, F., Giunta, L., Pappalardo, S., *J. Org. Chem.*, **1989**, *54*, 5407.
27. Canevet, C., Libman, J., Shanzer, A., *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 2657.
28. Kita, K., Kida, T., Nakatsuji, Y., Ikeda, I., *Chem. Lett.*, **1997**, 405.
29. (a) Scheerder, J., Fochi, M., Engbersen, J. F. J., Reinhoudt, D. N., *J. Org. Chem.*, **1994**, *59*, 7815; (b) Scheerder, J., Engbersen, J. F. J., Casnati, A., Ungaro, R., Reinhoudt, D. N., *J. Org. Chem.*, **1995**, *60*, 6448.
30. Iwamoto, K., Shinkai, S., *J. Org. Chem.*, **1992**, *57*, 7066.