Syntheses of and metal cation oscillation in ionophoric biscalix[4]arenes

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A series of biscalix[4]arenes ($\mathbf{2}_n$) doubly-bridged with oxyethylene chains at the lower rim have been synthesized. As in conventional ionophoric monocalix[4]arene derivatives, these compounds showed ion selectivity towards Na^+. The ^1H NMR spectroscopic studies established that Na^+ and K^+ ions complexed with $\mathbf{2}_n$ oscillate intramolecularly between two calix[4]arene ionophoric sites. Two coalescence temperatures were found in the temperature-dependent ^1H NMR spectra in the presence of these metal cations: the coalescence for the intermolecular metal exchange appears at a high temperature region whereas the coalescence for the intramolecular metal oscillation appears at a low temperature region. These two processes could be discriminated by the difference in the concentration dependence: the intermolecular process is concentration-dependent whereas the intramolecular process is concentration-independent. This is a unique dynamic system in which metal cations jump from one ionophoric site to another ionophoric site in biscalix[4]arenes in the NMR time-scale.

Calix[4]arenes which are cyclic tetramers made up of phenols and formaldehydes provide new, fascinating platforms not only for metal recognition but also for molecular recognition.[1–3] For example, it has been well established that ester derivatives of *cone*-calix[4]arene show a remarkably high affinity as well as remarkably high selectivity towards Na^+.[1–7] When the oxygen-through-the-annulus rotation of each phenyl unit is suppressed, one can isolate four different conformational isomers, cone, partial cone, 1,2-alternate and 1,3-alternate.[8–14] It was recently shown that a selectivity for different metal cations can be realized by using these conformational isomers.[8–11]

Meanwhile, a few groups have been devoting their research efforts towards the molecular design of higher-order supramolecular systems containing more than one calix[*n*]arene. For example, Böhmer *et al.*[15] and Ungaro *et al.*[16] synthesized a few biscalix[4]arenes in which the upper edges confront each other. McKervey *et al.*[17] synthesized a biscalix[4]arene in which two calix[4]arenes are linked by a single chain. The synthesis of a biscalix[6]arene was also reported.[18] Reinhoudt *et al.*[19] showed the synthesis of 'giant cavities' consisting of two calix[4]arenes and two calix[4]resorcinarenes. On the other hand, Vicens *et al.*[20] succeeded in the isolation of biscalix[4]arenes with a 1,3-alternate conformation. To the best of our knowledge, however, dynamic properties of biscalix[4]arene functions originating from the characteristic structure of biscalix[4]arenes have never been reported.

Previously, we synthesized a series of biscalix[4]arene derivatives ($\mathbf{1}_n$) consisting of two calix[4]arene tetraesters linked with one alkyl chain.[21] The temperature-dependent ^1H NMR spectra of the $\mathbf{1}_n$·metal complexes and the corresponding monocalix[4]arene·metal complexes showed that the metal exchange rates in the $\mathbf{1}_n$ complexes are much faster than those in the monocalix[4]arene complexes. We thus presumed that the intramolecular metal exchange process which is faster than the intermolecular metal one is involved in $\mathbf{1}_n$.

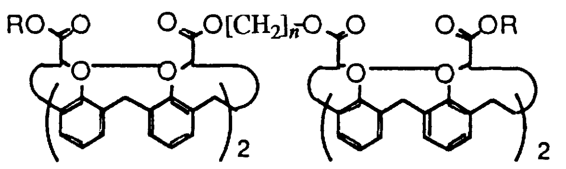
In the ^1H NMR spectra of $\mathbf{1}_n$, however, the intramolecular metal exchange process and the intermolecular metal exchange process could not be observed separately. We considered that the intramolecular metal exchange rate would be selectively facilitated if the two metal binding sites are linked with an 'ionophoric tube'. With this idea in mind we synthesized a new series of biscalix[4]arenes ($\mathbf{2}_n$) in which two calix[4]arenes are bridged by two ionophoric oxyethylene chains.[22] On the basis of the detailed ^1H NMR spectroscopic studies we obtained unequivocal evidence for intramolecular metal oscillation between two metal binding sites (as shown in Fig. 1).

Results and discussion

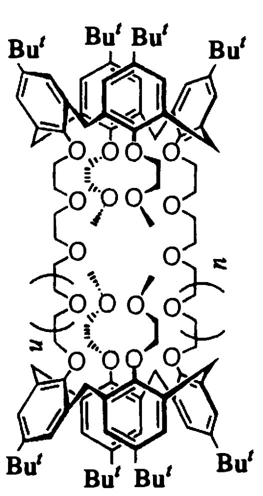
Syntheses

Compounds $\mathbf{2}_n$, doubly-bridged ionophoric biscalix[4]arenes were synthesized according to Scheme 1. As described in the introduction, calix[4]arenes can be immobilized into four different conformers.[8–14] Vicens *et al.*[20] synthesized biscalix[4]-crowns with a 1,3-alternate conformation by the one-pot reaction of *p*-*tert*-butylcalix[4]arene and poly(oxyethylene) ditosylate. The results suggest that a possible reaction route to a biscalix[4]arene with a cone conformation and with two calix[4]arenes confronting each other at the lower rim is the immobilization of calix[4]arenes to the cone conformation (as the first step) followed by the coupling of these two components (as the second step).

Compounds $\mathbf{5}_n$ which has two methoxyethoxy groups and two tetrahydropyran (THP)-protected oxyethylene chains were synthesized from **3**. After deprotection of THP the terminal OH groups were converted to the tosylate groups. It was confirmed by ^1H NMR spectroscopy that the conformation of two intermediates, $\mathbf{6}_n$ and **7**, is fixed in as a cone because the $ArCH_2Ar$ protons appear as a pair of doublets (see Experimental section). As seen in Scheme 1, one can prepare **7** from $\mathbf{6}_n$ in one step and $\mathbf{2}_n$ results from the coupling reaction of $\mathbf{6}_n$ and **7**. The coupling reaction between $\mathbf{6}_n$ and tosylate **7** was carried out under high dilution conditions in dehydrated tetrahydrofuran (THF) in the presence of NaH. The addition of $NaClO_4$ was effective to enhance the yield probably because it acted as a template metal. After purification by flash column chromatography and recyclable gel permeation chromatography, we could isolate three ionophoric biscalix[4]arenes $\mathbf{2}_0$, $\mathbf{2}_1$ and $\mathbf{2}_2$ in 23%, 35% and 31% yield, respectively. The structures were identified by IR, ^1H NMR (Fig. 2), mass spectroscopy (SIMS mode) and elemental analyses. Two pairs of doublets at 3.1 and 4.4 ppm in the ^1H NMR spectra establish that the calix[4]arenes are immobilized in a cone conformation. As shown in Fig. 2, $\mathbf{2}_n$ gives two resonance peaks for aromatic protons, one assignable



$\mathbf{1}_n$



$\mathbf{2}_n$

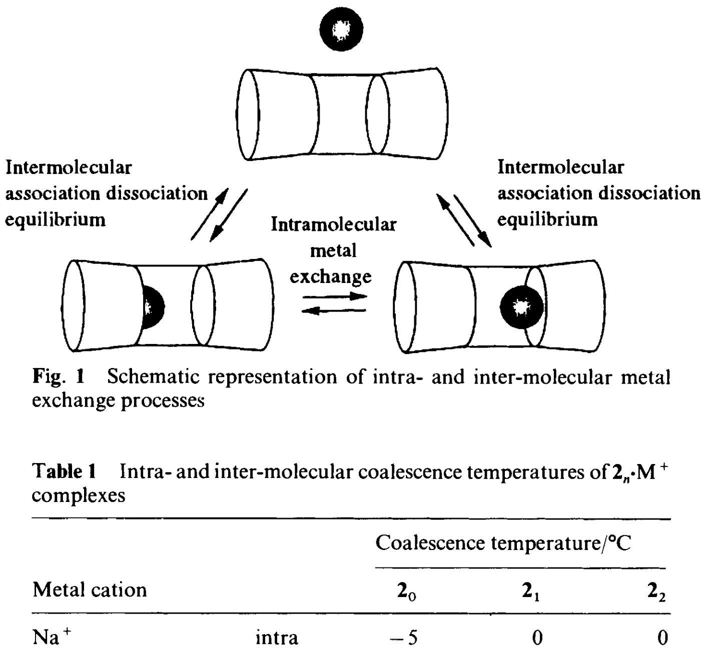


Fig. 1 Schematic representation of intra- and inter-molecular metal exchange processes

Table 1 Intra- and inter-molecular coalescence temperatures of $\mathbf{2}_n\cdot M^+$ complexes

Metal cation		Coalescence temperature/°C		
		$\mathbf{2}_0$	$\mathbf{2}_1$	$\mathbf{2}_2$
Na^+	intra	−5	0	0
	inter	>35	25	30
K^+	intra		−25	
	inter		25	

to bridged phenyl units (higher magnetic field) and the other assignable to non-bridged phenyl units (lower magnetic field). Interestingly, with decreasing the number *n* the peak at the higher magnetic field moves more and more to higher magnetic field and that at the lower magnetic field to lower magnetic field. This implies that with decreasing the number *n* the bridged phenyl units gradually stand up whereas the non-bridged phenyl units are gradually flattened.

Metal selectivity

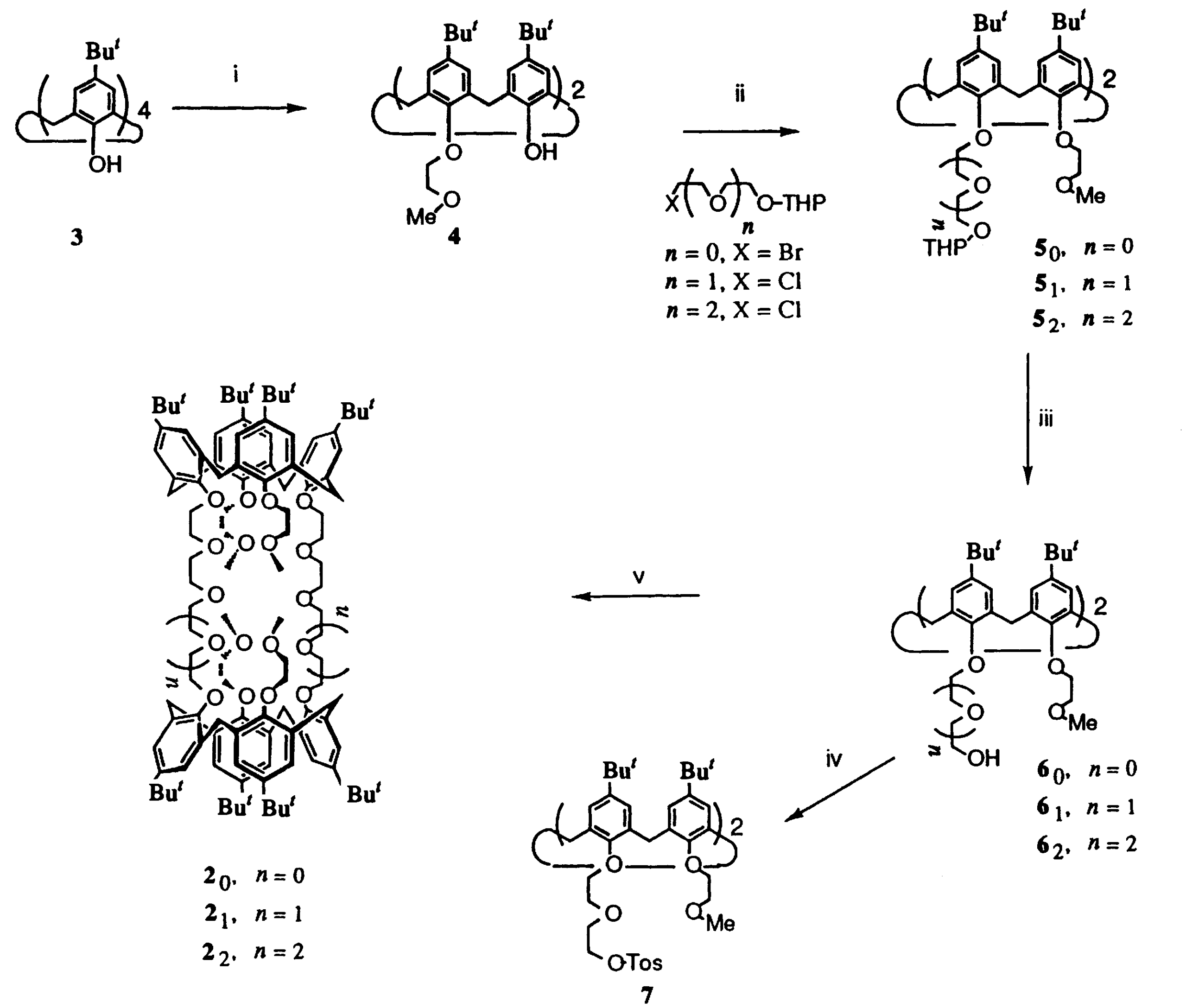
We first estimated the metal selectivity of $\mathbf{2}_n$ by two-phase solvent extraction. As shown in Fig. 3, $\mathbf{2}_n$ shows selectivity for the Na^+ ion among alkali metal cations. This selectivity is the same as that of conventional monocalix[4]arene tetraester or tetraether derivatives.[1-7] Generally, it is known that the extraction ability of monocalix[4]arene tetraether derivatives (*e.g.*, **8**[23]) is lower than that of tetraester derivatives because of the flexibility inherent to $ROCH_2CH_2O$ groups. On the other hand, the molecular motion of $\mathbf{2}_n$ is significantly suppressed by two bridge units connecting two calix[4]arenes. It is seen from Fig. 3 that the extraction ability of $\mathbf{2}_n$ is much higher than that of **8**.

The stoichiometry of the Na^+ and K^+ complexes was estimated from ^1H NMR titration.[22] Fig. 4 shows plots of two chemical shifts (ppm) of aromatic protons versus $[MSCN]/[\mathbf{2}_1]$ above the coalescence temperature. A break-point commonly appears at $[MSCN]/[\mathbf{2}_1] = 2.0$, indicating that $\mathbf{2}_1$ forms a 1:2 complex (*i.e.*, one M^+ per one calix[4]arene) with alkali metal cations. Interestingly, the difference between the two chemical shifts becomes smaller with increasing M^+ concentration and in the NaSCN system they are inverted above the break-point. This implies that the C_2 symmetry adopted in $\mathbf{2}_n$ in the absence of metal cations is changed to nearly C_4 symmetrical conformation when M^+ ions are bound to the calix[4]arene cavities. Fig. 5 shows the partial ^1H NMR spectra of $\mathbf{2}_1$ below the coalescence temperature. At $[NaSCN]/[\mathbf{2}_1] = 0.5:1.0$ new peaks assignable to the Na^+ complex appear: in Fig. 5 *cc* corresponds to the aromatic protons in the Na^+-complexed calix[4]arene and *cf* corresponds to those in the Na^+-uncomplexed calix[4]arene in the $\mathbf{2}_1\cdot Na^+$ complex. At $[NaSCN]/[\mathbf{2}_1] = 2.1:1.0$ the peaks assignable to free $\mathbf{2}_1$ (*f*) disappear, indicating that the $Na^+/\mathbf{2}_1$ stoichiometry is 2:1.

Intramolecular metal oscillation in biscalix[4]arenes

When one metal cation is bound to a ditopic ionophore {*e.g.*, bis(crown ether)s and biscalix[4]arenes}, it is considered that the metal cation jumps between the two binding-sites.[24] This phenomenon is interesting in relation to the behaviour of metal cations moving in the ion channel. This process may be monitored by the measurement of the temperature-dependent NMR spectra if the rate is comparable to the NMR time-scale. In artificial ditopic ionophores, however, the intermolecular exchange process frequently overlaps with the intramolecular exchange process and therefore the discrimination becomes difficult. In the present system we could successfully discriminate between these two processes by ^1H NMR spectroscopy.

Fig. 6 shows the temperature-dependent ^1H NMR spectra of $\mathbf{2}_n$ (1.0 equiv.) in the presence of NaSCN (0.5 equiv.) in CD_2Cl_2. For $\mathbf{2}_1$, for example, we can count three inequivalent ArH protons at −25 °C. They are assignable to two free calix[4]arenes in free $\mathbf{2}_1$ (*f* at 6.60 and 6.96 ppm), one free calix[4]arene in $\mathbf{2}_1\cdot Na^+$ (*cf* at 6.53 and 6.89 ppm) and one complexed calix[4]arene in $\mathbf{2}_1\cdot Na^+$ (*cc* at 7.15 and 7.20 ppm). The peaks of *cf* and *cc* broadened with the rising temperature and coalesced at 0 °C without any influence on the peaks of *f*. Coalescence temperatures are summarized in Table 1. In $\mathbf{2}_2$, *cf* (appearing



Scheme 1 *Reagents:* i, $CH_3OCH_2CH_2Br$, K_2CO_3, THF; ii, NaH, KI, THF; iii, H_2SO_4, MeOH; iv, toluene-*p*-sulfonyl chloride, pyridine; v, **7**, NaH, $NaClO_4$, THF

as shoulder peaks at 6.83 and 6.93 ppm) and *cc* (7.45 and 7.65 ppm) coalesce at 0 °C. In $\mathbf{2}_0$, *cf* (appearing as shoulder peaks at 7.03 and 6.77 ppm) and *cc* (broad peak at 7.06 ppm) coalesce at −5 °C. In $\mathbf{2}_1$ and $\mathbf{2}_2$ the *cc*–*cf* coalesced peak coalesces again with the *f* peaks (6.70 and 6.93 ppm for $\mathbf{2}_1$ and 6.84 and 6.92 ppm for $\mathbf{2}_2$) at 25 °C and 30 °C, respectively. In $\mathbf{2}_0$, on the other hand, the coalescence with the *f* peaks (6.78 and 7.02 ppm) is incomplete even at 35 °C.

As a summary of the foregoing findings one can propose that the low-temperature coalescence is ascribed to the intramolecular metal oscillation and the high-temperature coalescence is ascribed to the intermolecular metal exchange: that is, a metal cation oscillates between two ionophoric sites in $\mathbf{2}_n$ and the rate is comparable with the ^1H NMR time-scale. This is a unique system in which the intra- and the inter-molecular metal exchange processes can be observed separately.

To corroborate further the assignment of the low-temperature T_c and the high-temperature T_c we measured the T_c as a function of the $\mathbf{2}_1$ concentration (Fig. 7) because the intramolecular metal oscillation process should be concentration-independent whereas the intermolecular metal exchange process should be concentration-dependent. It is seen from Fig. 7 that in both NaSCN and KSCN systems the low-temperature T_c is unaffected by the $\mathbf{2}_1$ concentration whereas the high-temperature T_c decreases with increasing $\mathbf{2}_1$ concentration. It is reasonable that the rate of the intermolecular metal exchange becomes faster at high $\mathbf{2}_1$ and MSCN concentrations. The results clearly indicate that the assignment of the two T_c values is correct. The similar phenomenon was also observed for the $K^+\cdot\mathbf{2}_1$ complex (spectra not shown here). The low-temperature coalescence of *cc* (7.05 and 7.12 ppm) and *cf* (6.58 and 6.98 ppm) was observed at −25 °C and the high-temperature coalescence with *f* (6.70 and 6.85 ppm) at 25 °C (Table 1). From the ^1H NMR spectral data we can calculate the rate of the intramolecular metal exchange (k_c) and the free energy of activation ($\Delta_c G^\ddagger$) at the coalescence temperature.[25] The results are summarized in Table 2. In the Na^+ oscillation system the k_c value (at 5 °C) for $\mathbf{2}_0$ is apparently larger than those (at 0 °C) for $\mathbf{2}_1$ and $\mathbf{2}_2$. This may be attributed to the short distance between the two metal-binding sites in $\mathbf{2}_0$. However, the difference is not large enough to change the $\Delta_c G^\ddagger$ term. The T_c value for the K^+ oscillation is −25 °C. This implies that the energy barrier for the K^+ jump is much lower than that for the Na^+ jump. We previously found that the similar metal cation oscillation occurs through the π-basic cavity of 1,3-*alternate*-calix[4]arenes.[26] Generally, the high T_c values were observed for 1,3-*alternate*-calix[4]arenes with high metal affinity.[26] The results suggest that when the metal complexed initial state is stabilized, the rate of the metal cation oscillation is suppressed. As shown in Fig. 3, $\mathbf{2}_n$ shows the highest selectivity towards Na^+. Hence, the initial state for the K^+ jump should be more destabilized than that for the Na^+ jump and the rate should

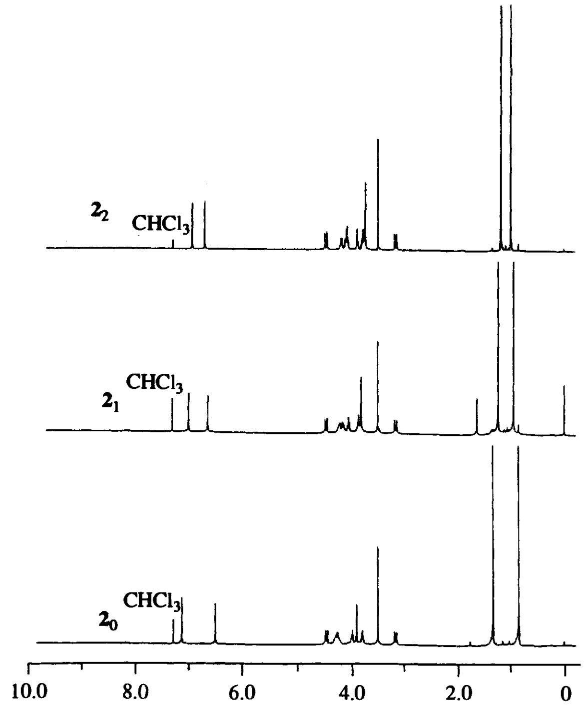


Fig. 2 ^{1}H NMR spectra of 2_n in CDCl$_3$ at 20 °C: 300 MHz, Me$_4$Si (internal standard)

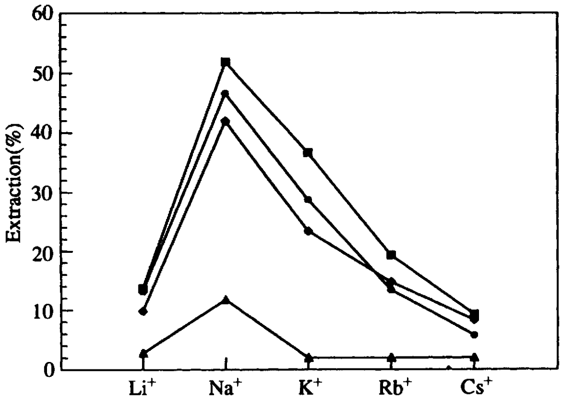
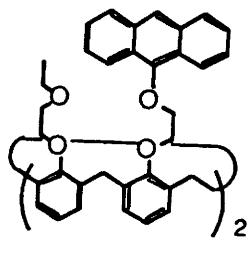


Fig. 3 Metal selectivities obtained from two-phase solvent extraction of alkali metal picrates. Conditions for extraction are described in the experimental section and ref. 23. (●) 2_0; (■) 2_1; (◆) 2_2; (▲) 8.

become faster. These considerations allow us to conclude that the rate of the intramolecular metal oscillation is controlled by the distance between the two metal-binding sites and the stability of the metal complexes.

Conclusions

This paper demonstrates the synthesis of novel biscalix[4]-arenes bearing lower-rim ionophoric sites confronting each other and unique metal cation oscillation properties that can be monitored by ^{1}H NMR spectroscopy. It was shown that the rate of the intramolecular metal oscillation is controllable by the distance between the two ionophoric sites and the stability of the metal complexes. This dynamic system is readily applicable as a component to design artificial ion channels and provides useful information to control the rate of ion transport. Further investigations are currently continued in this laboratory.



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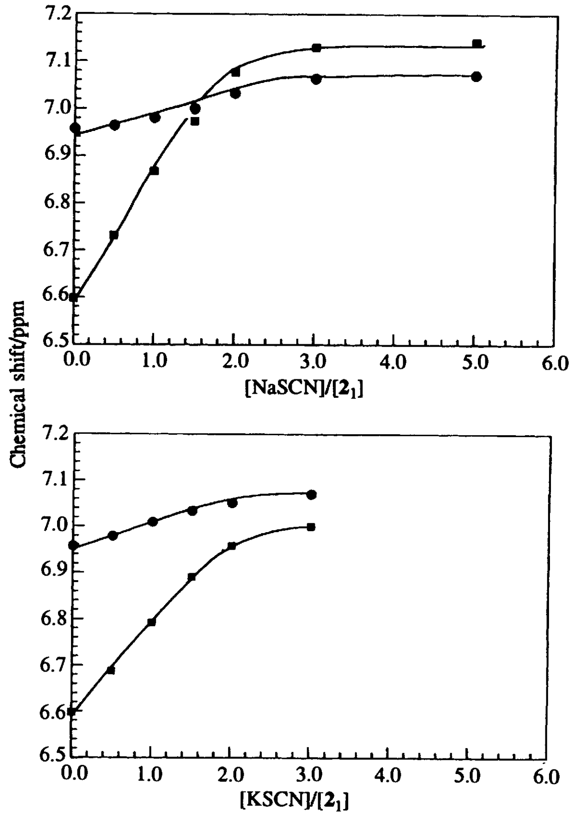

Fig. 4 ^{1}H NMR titration of 2_1 with NaSCN or KSCN in CDCl$_3$ at 20 °C. [2_1] = 2.1 × 10^{-2} mol dm^{-3}: two aromatic protons are monitored: (■) chemical shifts of protons on bridged phenyl units; (●) chemical shifts of protons on non-bridged phenyl units.

Experimental

^{1}H NMR spectra were recorded on a Bruker ARX-300 (300 MHz) spectrometer. Mass spectrometry was performed on a Hitachi M-2500 instrument using a SIMS mode. IR spectra were obtained using a Shimadzu FT-IR 8100 spectrometer. Melting points were determined on a Yanaco MP-500D micro melting point apparatus.

Materials

The syntheses of 2_n were conducted according to Scheme 1. Here, we mainly describe the methods used for the preparation of 2_1. The methods used for the preparation of 2_0 and 2_2 are similar, so that we only record the analytical data.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-methoxyethoxy)-26,28-dihydroxycalix[4]arene (4). *p-tert*-Butylcalix[4]arene **3** (50 g, 77.2 mmol), bromoethyl methyl ether (50 g, 360 mmol) and K$_2$CO$_3$ (25 g) were mixed in acetone (200 cm^3) and the mixture was refluxed for 3 days under a nitrogen atmosphere. After cooling the precipitate formed from the reaction mixture was filtered off, and the filtrate was concentrated to dryness.

The residue was dissolved in $CHCl_3$ (300 cm^3) and the solution was washed with water several times and dried (Na_2SO_4). The filtrate was concentrated to dryness again. MeOH (300 cm^3) was added to the residue to precipitate the crude product. The solid was collected by suction and recrystallized from $CHCl_3$–MeOH: (44.7 g, 75.8%), mp 228 °C (Found: C, 78.4; H, 8.9. $C_{50}H_{68}O_6$ requires C, 78.49; H, 8.96%); ν_{max}/cm^{-1} 3450 (OH); δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.18 (2 H, s, OH), 7.04 (4 H, s, ArH), 6.77 (4 H, s, ArH), 4.38 (4 H, d, J = 12.6 Hz, $ArCH_2Ar$), 4.15 (6 H, br t, $\mathrm{OC}H_2\mathrm{CH_2O}$), 3.88 (6 H, br t, $\mathrm{OCH_2C}H_2\mathrm{O}$), 3.53 (6 H, s, Me), 3.28 (4 H, d, J = 12.6 Hz, $ArCH_2Ar$), 1.28 (18 H, s, Bu^t) and 0.93 (18 H, s, Bu^t); m/z 765 (M + 1).

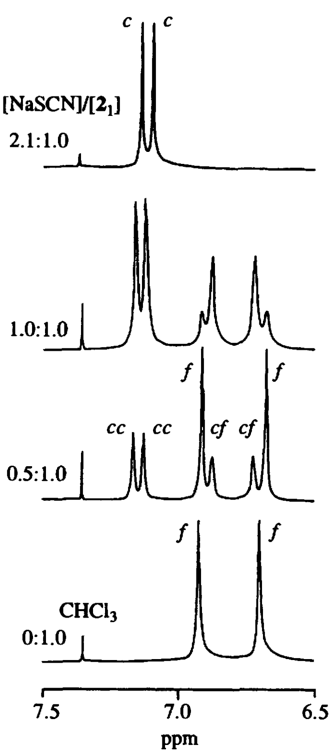

Fig. 5 ^1H NMR spectra of $\mathbf{2}_1$ in the presence of NaSCN in $CDCl_3$: [$\mathbf{2}_1$] = 2.1 × 10^{-2} mol dm^{-3}, −25 °C (6.5–7.5 ppm). *cc*: ArH protons of the complex site in the $\mathbf{2}_1 \cdot M^+$ complex species. *cf*: ArH protons of the uncomplex site in the $\mathbf{2}_1 \cdot M^+$ complex species. *c*: ArH protons of the $\mathbf{2}_1 \cdot (M^+)_2$ complex species. *f*: ArH protons of the free species.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-methoxyethoxy)-26,28-bis{2-[2-(tetrahydropyran-2-yloxy)ethoxy]ethoxy}-calix[4]arene (5_1). 5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-methoxyethoxy)-26,28-dihydroxycalix[4]arene (**4**) (15 g, 19.7 mmol) was dissolved in THF (400 cm^3) and then NaH (60% in oil, 2.5 g, 62.5 mmol) was added at room temperature. After 30 min, tetrahydropyran-2-ylethyl chloroethyl ether (12.3 g, 58.9 mmol) was added and the mixture was allowed to react for 2 weeks with stirring at refluxing temperature. The precipitate was removed by filtration, the filtrate being concentrated to dryness. The residue was dissolved in diethyl ether (300 cm^3) and washed with water several times. The ether layer was dried (Na_2SO_4) and concentrated again. The residue was purified by column chromatography (silica gel, $CHCl_3$–MeOH 9 : 1 v/v): oil (17.0 g, 79.5%), δ_H(300 MHz; $CDCl_3$; Me_4Si) 6.80 (4 H, s, ArH), 6.74 (4 H, s, ArH), 4.62 (2 H, br t, CH), 4.44 (4 H, d, J = 12.6 Hz, $ArCH_2Ar$), 3.68–4.12 (28 H, m, OCH_2–), 3.45 (6 H, s, Me), 3.10 (4 H, d, J = 12.6 Hz, $ArCH_2Ar$), 1.50–1.71 (12 H, m, –CH_2–), 1.09 (18 H, s, Bu^t) and 1.05 (18 H, s, Bu^t).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-methoxyethoxy)-26,28-bis[2-(tetrahydropyran-2-yloxy)ethoxy]calix[4]arene (5_0). Oil, δ_H(300 MHz; $CDCl_3$; Me_4Si) 6.79 (4 H, s, ArH), 6.76 (4 H, s, ArH), 4.64 (2 H, br t, CH), 4.43 (4 H, d, J = 12.6 Hz, $ArCH_2Ar$), 3.76–4.18 (20 H, m, OCH_2–), 3.42 (6 H, s, Me), 3.12 (4 H, d, J = 12.6 Hz, $ArCH_2Ar$), 1,50–1.75 (12 H, m, –CH_2–), 1.09 (18 H, s, Bu^t) and 1.07 (18 H, s, Bu^t).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-methoxyethoxy)-26,28-bis[9-(tetrahydropyran-2-yloxy)-1,4,7-trioxanonyl]-calix[4]arene (5_2). Oil, δ_H(300 MHz; $CDCl_3$; Me_4Si) 6.81 (4

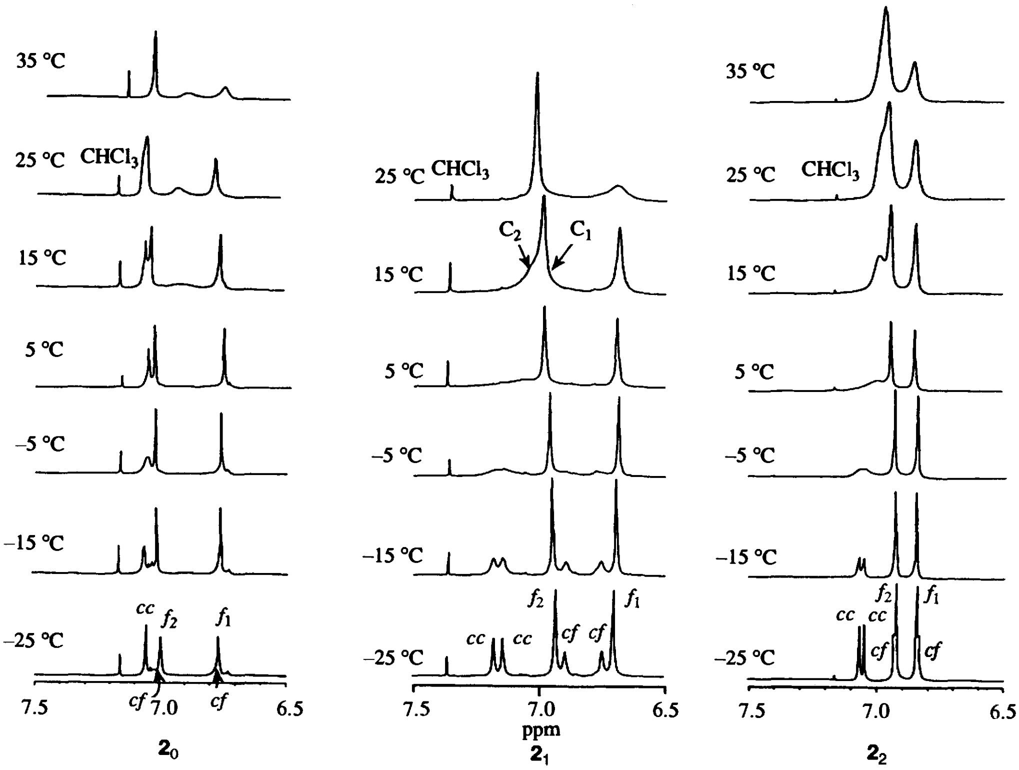

Fig. 6 Temperature-dependent ^1H NMR spectra of $\mathbf{2}_n$ in the presence of Na^+ cation. [$\mathbf{2}_n$] = 2.1 × 10^{-2} mol dm^{-3}, [NaSCN] = 1.0 × 10^{-2} mol dm^{-3}, CD_2Cl_2, 300 MHz. Taking the spectra of $\mathbf{2}_1$, for instance, *cc* and *cf* coalescence to give c_1 (bridged aromatic protons: the chemical shift overlaps with f_2) and c_2 (non-bridged aromatic protons), which subsequently coalesce with f_1 and f_2, respectively.

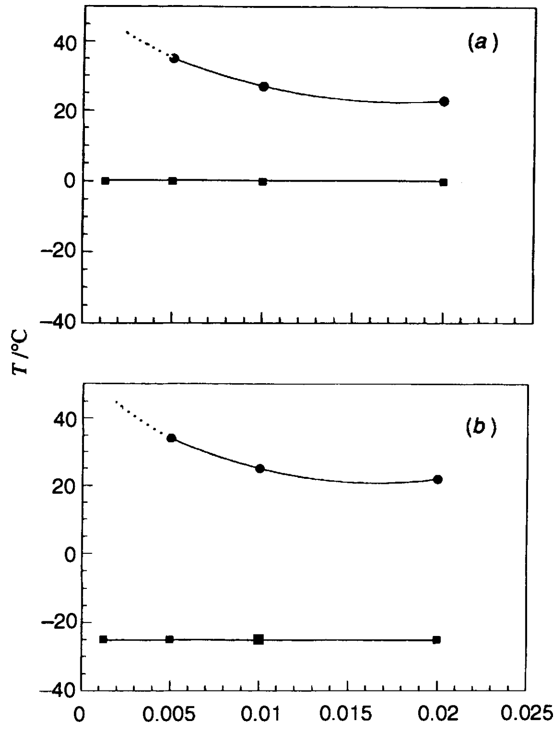

Fig. 7 Concentration dependence of low- and high-temperature coalescences of $\mathbf{2_1}$ plus MSCN. The ratio of $\mathbf{2_1}$/M$^+$ was maintained constant (1.0–0.5): (*a*) NaSCN, (*b*) KSCN.

H, s, ArH), 6.73 (4 H, s, ArH), 4.62 (2 H, br t, CH), 4.44 (4 H, d, J = 12.6 Hz, ArCH$_2$Ar), 3.61–4.10 (36 H, m, OCH$_2$), 3.44 (6 H, s, Me), 3.10 (4 H, d, J = 12.6 Hz, ArCH$_2$Ar), 1.50–1.71 (12 H, m, -CH$_2$-), 1.10 (18 H, s, Bu^t) and 1.04 (18 H, s, Bu^t).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-methoxyethoxy)-26,28-bis[2-(2-hydroxyethoxy)ethoxy]calix[4]arene (6_1). Sulfuric acid (2 cm^3) was carefully added to MeOH (300 cm^3) at room temperature. A methanol solution (70 cm^3) of $\mathbf{5_1}$ (15.1 g, 12.8 mmol) was added dropwise to the acidic methanol solution and the solution was stirred at room temperature for 3 h. The solution was neutralized with aq. Na$_2$CO$_3$ solution and poured into water (500 cm^3). The solution was extracted with CHCl$_3$ (250 cm^3, twice), the CHCl$_3$ layer being separated and dried (Na$_2$SO$_4$). The filtrate was concentrated to dryness and the residue was purified by column chromatography (silica gel, CHCl$_3$: MeOH 9 : 1 v/v): (10.5 g, 93.5%), mp 146 °C (Found: C, 73.75; H, 8.95. C$_{58}$H$_{84}$O$_{10}$ requires C, 74.01; H, 8.99%); ν_{max}/cm^{-1} 3444 (OH); δ_H(300 MHz; CDCl$_3$; Me$_4$Si) 6.76 (8 H, s, ArH), 4.56 (4 H, d, J = 12.6 Hz, ArCH$_2$Ar), 3.61–417 (24 H, m, CH$_2$-), 3.45 (6 H, s, Me), 3.43 (2 H, s, OH), 1.06 (18 H, s, Bu^t) and 1.05 (18 H, s, Bu^t); *m/z* 942 (M + 1).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-methoxyethoxy)-26,28-bis(2-hydroxyethoxy)calix[4]arene (6_0). Mp 234 °C (Found: C, 76.2; H, 9.15. C$_{54}$H$_{76}$O$_8$ requires C, 76.02; H, 8.98%); ν_{max}/cm^{-1} 3446 (OH); δ_H(300 MHz; CDCl$_3$; Me$_4$Si) 7.12 (4 H, s, ArH), 6.49 (4 H, s, ArH), 4.43 (4 H, d, J = 12.6 Hz), 3.68–4.25 (16 H, m, OCH$_2$-), 3.38 (6 H, s, Me), 3.15 (4 H, d, J = 12.5 Hz, ArCH$_2$Ar), 1.32 (18 H, s, Bu^t) and 0.81 (18 H, s, Bu^t); *m/z* 854 (M + 1).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-methoxyethoxy)-26,28-bis([9-hydroxy-1,4,7-trioxanonyl]calix[4]arene (6_2). Mp 133 °C (Found: C, 72.05; H, 9.0. C$_{62}$H$_{92}$O$_{12}$ requires C, 72.34; H, 9.01%); ν_{max}/cm^{-1} 3444 (OH); δ_H(300 MHz; CDCl$_3$; Me$_4$Si) 6.4 (4 H, s, ArH), 6.72 (4 H, s, ArH), 4.42 (4 H, d, J = 12.6 Hz), 3.59–4.15 (32 H, m, OCH$_2$-), 3.45 (6 H, s, Me), 3.12 (4 H, d, J = 12.5 Hz, ArCH$_2$Ar), 1.12 (18 H, s, Bu^t) and 1.02 (18 H, s, Bu^t); *m/z* 1029 (M + 1).

Table 2 Spectral parameters, coalescence temperatures (T_c), exchange rates (k_c) and free energies of activation ($\Delta_cG^\ddagger$) for the intramolecular metal oscillation[a]

2_n·M$^+$	$\Delta\nu^b$/Hz	$T_c{}^c$/°C	$k_c{}^d$/s^{-1}	$\Delta_cG^{\ddagger\,e,f}$/kcal mol^{-1}
2_0·Na	180.7	5	401	12.923
2_1·Na	118.8	0	264	12.908
2_2·Na	125.9	0	280	12.876
2_1·K	148.4	−25	329	11.570

[a] These data are calculated from the peaks of aromatic protons. [b] Difference of the chemical shifts between complexed and uncomplexed species. [c] Coalescence temperature. [d] Exchange rate at the coalescence temperature. [e] Free energy of activation at the coalescence temperature calculated from T_c and k_c using the Eyring's equation.

$$k_c = \pi\Delta\nu/\sqrt{2} = (kT/h)\exp(-\Delta_cG^\ddagger/RT)$$
$$\Delta_cG^\ddagger = 2.303RT_c(10.319 - \log_{10}k_c + \log_{10}T_c)$$

[f] 1 cal = 4.184 J.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-methoxyethoxy)-26,28-bis-{2-[2-(toluene-*p*-sulfonyloxy)ethoxy]ethoxy}-calix[4]arene (7). Compound $\mathbf{6_1}$ (4 g, 4.3 mmol) was dissolved in pyridine (10 cm^3) and tosyl chloride (1.8 g, 9.45 mmol) was added at 5 °C. The solution was allowed to stand overnight with stirring at room temperature, and was then poured into water containing crushed ice and extracted with CHCl$_3$. The CHCl$_3$ layer was washed with dil. HCl to remove pyridine. After being dried (Na$_2$SO$_4$), the organic layer was passed through a silica gel bed to remove polar impurities and the filtrate was concentrated to dryness: (3.5 g, 65.9%). This intermediate was used for the next step without further purification: δ_H(300 MHz; CDCl$_3$; Me$_4$Si) 7.75 (4 H, d, J = 10.2 Hz, ArH), 7.28 (4 H, d J = 10.2 Hz, ArH), 6.82 (4 H, s, ArH), 6.70 (4 H, s, ArH), 4.35 (4 H, d, J = 12.6 Hz, ArCH$_2$Ar), 3.70–4.19 (24 H, m, OCH$_2$-), 3.37 (6 H, s, Me), 3.09 (4 H, d, J = 12.6 Hz, ArCH$_2$Ar), 2.39 (6 H, s), 1.11 (18 H, s, Bu^t) and 0.95 (18 H, s, Bu^t).

Biscalix[4]arene (2_1). A THF solution (50 cm^3) containing $\mathbf{6_1}$ (753 mg, 0.8 mmol) and **7** (1.0 g, 0.8 mmol) was added dropwise to a refluxing THF (160 cm^3) solution containing NaH (60% in oil, 150 mg, 3.75 mmol) and NaClO$_4$ (160 mg); this operation took 24 h. The reaction was continued at reflux temperature for 24 h and then stopped by adding a small amount of water. The reaction mixture was concentrated to dryness. The residue was dissolved in diethyl ether and the solution was washed with water. The ether solution was dried (Na$_2$SO$_4$), treated with charcoal and concentrated to dryness. The residue was purified by column chromatography (silica gel, CHCl$_3$). The product was finally recrystallized from CHCl$_3$–MeOH (3 : 7 v/v): (35%), white powder, mp 274–275 °C (Found: C, 76.4; H, 8.9. C$_{116}$H$_{164}$O$_{18}$ requires C, 76.50; H, 8.94%); δ_H(300 MHz; CDCl$_3$; Me$_4$Si) 6.96 (8 H, s, ArH), 6.60 (8 H, s, ArH), 4.42 (8 H, d, J = 12.6 Hz, ArCH$_2$Ar), 4.16 (8 H, br t, OCH$_2$-), 4.10 (8 H, br t, OCH$_2$-), 4.00 (8 H, br t, OCH$_2$-), 3.82 (8 H, br t, OCH$_2$-), 3.77 (16 H, s, OCH$_2$CH$_2$O), 3.46 (12 H, s, Me), 3.11 (8 H, d, J = 12.6 Hz, ArCH$_2$Ar), 1.21 (36 H, s, Bu^t) and 0.93 (36 H, s, Bu^t); *m/z* 1868 (M + Na$^+$).

Biscalix[4]arene 2_0. (23%), Mp 270–271 °C (Found: C, 75.4; H, 8.8. C$_{112}$H$_{156}$O$_{18}$ requires C, 75.45; H, 8.95); δ_H(300 MHz; CDCl$_3$; Me$_4$Si) 7.12 (8 H, s, ArH), 6.50 (8 H, s, ArH), 4.42 (8 H, d, J = 12.6 Hz, ArCH$_2$Ar), 4.18–4.30 (16 H, m, OCH$_2$CH$_2$O), 4.22 (8 H, br t, OC*H*$_2$CH$_2$O), 3.82 (8 H, s, OCH$_2$CH$_2$O), 3.76 (8 H, br t, OCH$_2$C*H*$_2$O), 3.13 (8 H, d, J = 12.6 Hz, ArCH$_2$Ar), 1.34 (36 H, s, Bu^t) and 0.83 (36 H, s, Bu^t); *m/z* 1756 (M + Na$^+$).

Biscalix[4]arene 2_2. (31%), Mp 275–276 °C (Found: C, 74.4; H, 8.8. C$_{120}$H$_{172}$O$_{20}$ requires C, 74.50; H, 8.96%); δ_H(300 MHz; CDCl$_3$; Me$_4$Si) 6.89 (8 H, s, ArH), 6.66 (8 H, s, ArH), 4.42 (8 H, d, $J = 12.6$ Hz, $ArCH_2Ar$), 3.72–4.17 (48 H, m, OCH_2CH_2O), 3.69 (16 H, s, OCH_2CH_2O), 3.42 (12 H, s, Me), 3.11 (8 H, d, $J = 12.6$ Hz, $ArCH_2Ar$), 1.16 (36 H, s, Bu^t) and 0.98 (36 H, s, Bu^t); m/z 1954 ($M + Na^+$).

Two-phase solvent extraction

A dichloromethane solution (5 cm^3) of biscalix[4]arene (8.02×10^{-5} mol dm^{-3}) and aq. metal hydroxide (0.1 mol dm^{-3}; 5 cm^3), metal chloride (0.5 mol dm^{-3}) and picric acid (2.75×10^{-5} mol dm^{-3}) were placed in a sample tube and the mixture was shaken for 5 min at room temperature. The mixture was then left for 5 min at room temperature to complete the phase separation. The concentration of the picrate in the aqueous phase was determined spectrophotometrically using the molar absorptivity [$\lambda_{max}(H_2O)$ 354 nm (ε 15 000 dm^3 mol^{-1} cm^{-1})].

References

1 C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge 1989.

2 J. Vicens and V. Bömer, ed., *Calixarenes*, Kluwer Academic Express, Dordrecht, 1991.

3 S. Shinkai, *Tetrahedron*, 1993, **49**, 8933.

4 A. Arduini, A. Pochini, S. Reverberi, R. Ungaro, G. D. Andreetti and F. Ugozzoli, *Tetrahedron*, 1986, **42**, 2089; G. D. Andreetti, G. Calestani, F. Ugozzoli, A. Arduini, E. Ghidini, A. Pochini and R. Ungaro, *J. Incl. Phenom.*, 1987, **5**, 123.

5 S.-K. Chang and I. Cho, *J. Chem. Soc.*, *Perkin Trans. 1*, 1986, 211.

6 F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M. J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.*, 1989, **111**, 8681.

7 S. Shinkai, S. Edamitsu, T. Arimura and O. Manabe, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 1674; T. Sakaki, H. Harada, G. Deng, H. Kawabata, Y. Kawahara and S. Shinkai, *J. Incl. Phenom.*, 1992, **14**, 285.

8 K. Iwamoto, A. Yanagi, K. Araki and S. Shinkai, *Chem. Lett.*, 1991, 473.

9 K. Iwamoto, K. Araki and S. Shinkai, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 1661.

10 K. Iwamoto, K. Araki and S. Shinkai, *J. Org. Chem.*, 1991, **56**, 4955.

11 K. Iwamoto and S. Shinkai, *J. Org. Chem.*, 1992, **57**, 7006.

12 M. Igbal, T. Mangiafico and C. D. Gutsche, *Tetrahedron*, 1987, **43**, 4917.

13 C. D. Gutsche, B. Dhawan, J. A. Levine, K. H. No and L. J. Bauer, *Tetrahedron*, 1983, **39**, 409.

14 C. D. Gutsche and P. A. Reddy, *J. Org. Chem.*, 1991, **56**, 4783.

15 V. Bömer, H. Goldmann, W. Vogt, J. Vicens and Z. Asfari, *Tetrahedron Lett.*, 1989, **30**, 1391.

16 A. Arduini, G. Manfredi, A. Pochini, A. R. Sicuri and R. Ungaro, *J. Chem. Soc.*, *Chem. Commun.*, 1991, 936.

17 M. A. McKervey, M. Owens, H.-R. Schulten, W. Vogt and V. Böhmer, *Angew. Chem.*, *Int. Ed. Engl.*, 1990, **29**, 280.

18 T. Arimura, S. Matsumoto, O. Teshima, T. Nagasaki and S. Shinkai, *Tetrahedron Lett.*, 1991, **32**, 5111.

19 P. Timmerman, K. G. A. Nierop, E. A. Brinks, W. Verboom and D. N. Reinhoudt, paper presented at 18th International Symposium on Macrocyclic Chemistry (18th ISMC), Enschede, 1993, B-85.

20 Z. Asfari, R. Abidi, F. Arnaud and J. Vicens, *J. Incl. Phenom.*, 1992, **13**, 163.

21 F. Ohseto, T. Sakaki, K. Araki and S. Shinkai, *Tetrahedron Lett.*, 1993, **34**, 2149. The synthesis of the similar compounds was also reported by McKervey *et al.* (see ref. 17).

22 Preliminary communication: F. Ohseto and S. Shinkai, *Chem. Lett.*, 1993, 2045.

23 G. Deng, T. Sakaki, K. Nakashima and S. Shinkai, *Chem. Lett.*, 1992, 1287; G. Deng, T. Sakaki, Y. Kawahara and S. Shinkai, *Supramol. Chem.*, 1993, **2**, 71.

24 J. M. Lehn and M. E. Stubbs, *J. Am. Chem. Soc.*, 1974, **96**, 4012.

25 I. C. Calder and P. J. Garratt, *J. Chem. Soc. B*, 1967, 660.

26 A. Ikeda and S. Shinkai, *J. Am. Chem. Soc.*, 1994, **116**, 3102.

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