Molecular engineering. Part 2.[1] Influence of side-chain substituents in lariat-type upper-rim calix[4]crowns on their binding properties and the reversal of these

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Cone-structured upper-rim 1,3-calix[4]crowns have been synthesized from the distal dibromo diol 6 which is itself regioselectively synthesized from *p*-bromocalix[4]arene hexyl ether by transmetallation, quenching with $B(OMe)_3$ and oxidation. The dibromo substituents in these calix[4]crowns have been transformed into hydrophobic or hydrophilic groups to give lariat-type hosts. Picrate extraction experiments show that alkylammonium ions bind more strongly than alkali-metal cations to hosts having hydrophobic side-arms such as bromo or *p*-methoxyphenyl, which means that the hydrophobic binding of the calix[4]arene unit and the hydrophilic binding of the crown unit synergistically increase the affinity of the calix[4]crowns for alkylammonium ions. ^{1}H NMR spectra also support the conformational change of the calix[4]crowns from pinched-cone to cone upon complexation. With amide or ester side-arms the affinity tendency is reversed. It is presumed that the hydrophilic side-arms have a high affinity for the charged part of the guest, which leads to a collapse of the hydrophobic cavity.

Introduction

Calixarenes have been used as hosts for cationic, anionic or neutral guests by providing a structural platform for the attachment of convergent binding groups at the upper or lower rim.[2] In particular, upper-rim functionalized calix[4]arenes which retain their cone structure have attracted considerable interest because their hydrophobic cavity can be manipulated for the purposes of molecular recognition.[3]

Calixcrowns[4] refer to the family of macropolycyclic hosts in which the cyclic structure of a calixarene is linked through a cyclic polyether moiety. Upper-rim calix[4]crowns in conformational mixtures were synthesized from distal bis(chloromethyl)calix[4]arene methyl ether, but no binding properties were reported.[5] Various lower-rim calix[4]crowns were also reported and have been shown to possess good binding properties toward alkali-metal cations[6] or alkyl ammonium ions.[7] Modified calix[4]crowns such as quinone derivatives have exhibited improved binding properties.[8]

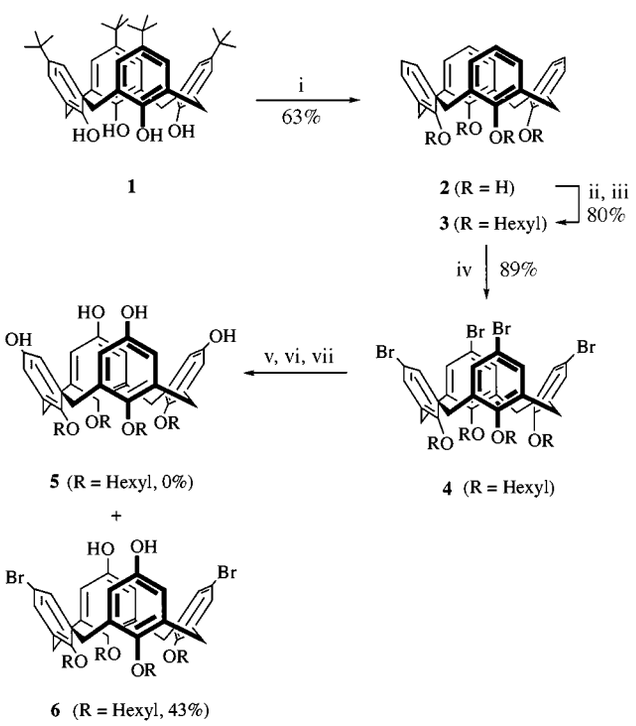
With this background, it was thought that conformationally stable, cone-structured upper-rim calix[4]crowns with both a hydrophobic cavity as well as a hydrophilic binding site would show interesting binding properties. Further, their binding properties could be tuned by modifying the other *para* functional groups which would act as side-arms of the lariat crown hosts.

Results and discussion

Regioselective synthesis of the distal dibromo diol 6

Regioselective functionalization on the upper-rim of calix[4]arenes has been achieved mainly by remote control exerted by a functionality on the lower-rim.[9] Direct regioselective functionalization on the upper rim was achieved *via* the *p*-bromocalix[4]arene hexyl ether **4** (Scheme 1).[10]

Calix[4]arene **2** was alkylated with 1-bromohexane to give a calix[4]arene hexyl ether **3** (80%). Subsequent treatment of this with NBS in methyl ethyl ketone (MEK) afforded the cone structured *p*-bromocalix[4]arene hexyl ether **4** (89%). Treatment of compound **4** with an excess of BuLi in dry THF at −78 °C followed by quenching with $B(OMe)_3$, oxidation with 3 M NaOH–28% H_2O_2 and then acidic hydrolysis gave the unexpected 5,17-dibromo-25,26,27,28-tetrahexyloxycalix[4]-arene-22,23-diol **6** (43% in isolated yield) instead of the tetrol **5**. It seems that the corresponding distal dilithiate is inactivated towards further lithiation at −78 °C. An increase in the reaction temperature or use of Bu^{s}Li or Bu^{t}Li decreased the yield of the diol **6**.



Scheme 1 *Reagents and conditions*: i, $AlCl_3$ benzene, 75 °C; ii, NaH, DMF, 70 °C; iii, 1-bromohexane; iv, NBS, MEK, RT; v, BuLi (8 equiv.)/ −78 °C; vi, $B(OMe)_3$; vii, 3 M aq. NaOH–28% H_2O_2

The splitting patterns in the ^{1}H NMR spectrum of **6** in $CDCl_3$ were consistent with those of known cone structure: *i.e.* two doublets for the bridging methylenes at 3.03 and 4.35 ppm (*J* 13.5 Hz) and two triplets for oxymethylenes at 3.60 and 3.90

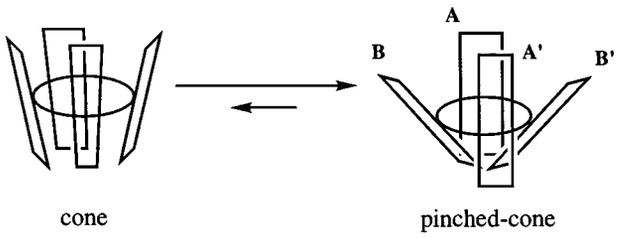
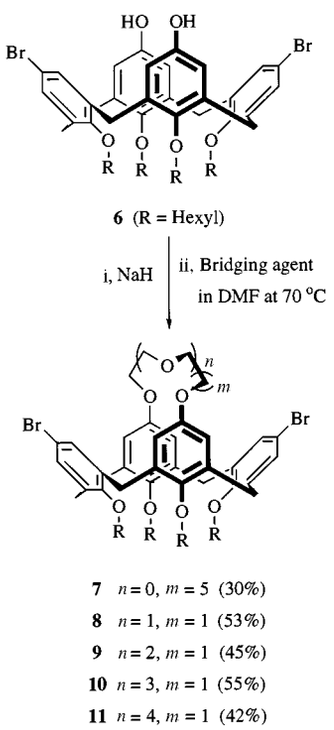


Fig. 1 Illustration of cone and piched-cone conformation

ppm. The solution conformation of the diol **6** as a pinched cone, was evidenced from the high upfield shift of the protons *ortho* to a hydroxy group (A and A′ in Fig. 1)[11] at 5.71 ppm compared with those *ortho* to a bromo group (B and B′) at 7.16 ppm in $CDCl_3$ on ^{1}H NMR spectrum. The corresponding *ortho* proton signals of 4-hexyloxyphenol and 4-bromophenetole are known to be at 6.76 and 7.34 ppm, respectively, in the same solvent.

Synthesis of upper-rim calix[4]crowns

From the distal diol **6** the conformationally stable host **7** and calix[4]crowns **8**–**11** were synthesized by introducing alkylene or oligoether bridges on the upper-rim (Scheme 2).[12] Hosts **7**, **8**, **9**, **10** and **11** were obtained in 30, 53, 45, 55 and 42% yield, respectively, by high-dilution reactions between the diol **6** treated with NaH and 1,10-dibromodecane or the corresponding oligoethylene glycol di-*p*-tosylate in DMF solution.



Scheme 2

The ^{1}H NMR spectrum of **10** shows two singlets for the aromatic protons at δ 5.80 and 7.26, and two doublets (J_{AB} 13.3 Hz) for the bridging methylene protons at δ 3.07 (H_{exo}) and 4.39 (H_{endo}). Similar patterns were observed for all the other calix[4]crowns, which indicates that calix[4]arene moiety is in a pinched-cone conformation.

The two versatile bromo substituents of the host **10** were used to prepare the lariat-type calix[4]crowns **12**, **14** and **15** (Scheme 3). The host **12** having an enlarged hydrophobic cavity was obtained in 51% yield using Pd^0-catalysed Suzuki reaction between the host **10** and *p*-methoxyphenylboronic acid.[13] Introduction of hydrophilic side-arms host into **10** was achieved by transforming it to the dihydroxycalix[4]crown **13** (43%) under similar conditions to those for the synthesis of the diol **6**. Compound **13** was then treated with ethyl bromoacetate in a DMF–NaH mixture at 80 °C or with *N*,*N*-diethyl-2-chloroacetamide in refluxing Me_3CN–NaI–K_2CO_3 mixture to give the calix[4]crowns **14** (64%) or **15** (66%).

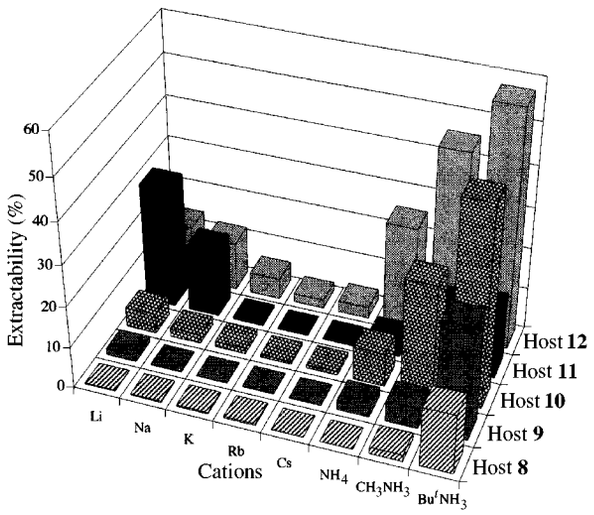
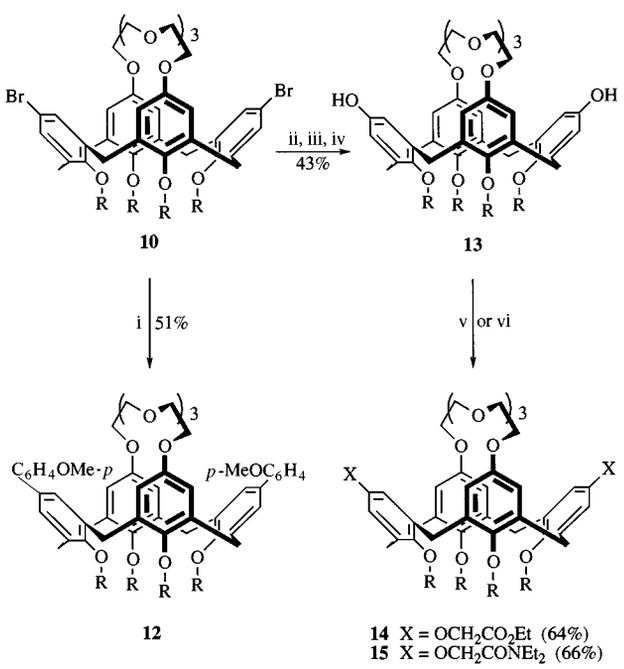


Fig. 2 Liquid–solid extractability spectra of calix[4]crowns **8**, **9**, **10**, **11** and **12**



Scheme 3 *Reagents and conditions* (R = Hexyl): i, *p*-methoxyphenylboronic acid, $Pd(PPh_3)_4$; ii, excess BuLi/−78 °C; iii, $B(OMe)_3$; iv, 3 M aq. NaOH–28% H_2O_2; v, $BrCH_2CO_2Et$, NaH, DMF, 80 °C; vi, $ClCH_2CONEt_2$, NaI, K_2CO_3, Me_3CN, reflux

The ^{1}H NMR spectrum of the calix[4]crown **14** shows a typical AB pattern of two doublets at δ 2.99 and 4.35 (J_{AB} 13.1 Hz) for the bridging methylene protons and two singlets of δ 5.76 and 6.67 for the aromatic protons, which indicates its pinched-cone conformation. The calix[4]crowns **12**, **13** and **15** show similar spectral features.

Complexation study using picrate extraction

The molecular recognition properties of calix[4]crowns **8**–**12** were studied by solid–liquid extraction of solid alkali-metal, ammonium, or alkylammonium picrates into a $CDCl_3$ solution of the host at 25 °C. A liquid–liquid extraction experiment of these hosts gave no binding evidence, which means that binding ability is rather weak.

Fig. 2 shows the extractability spectra of calix[4]crowns

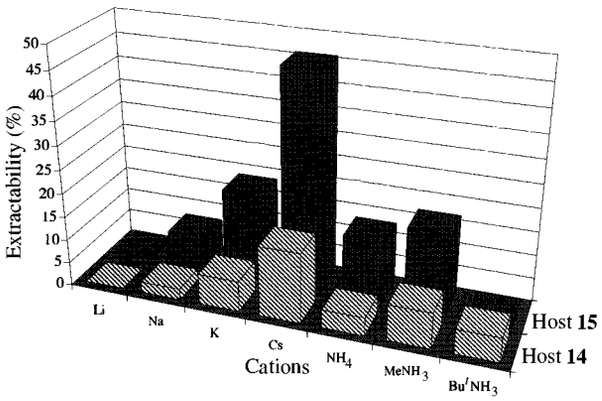


Fig. 3 Liquid–liquid extractability spectra of calix[4]crowns **14** and **15** of alkali-metal and alkylammonium picrates ([Host] = 5.0×10^{-4} mol dm^{-3} in $CHCl_3$, $[G^+Pic^-] = 1.0 \times 10^{-4}$ mol dm^{-3}, [GCl] = 0.5 mol dm^{-3} in water at 25 °C)

8, **9**, **10**, **11** and **12**. Each of these hosts except **11** had a higher affinity for primary alkylammonium ions than for alkali-metal cations. As the size of crown unit increases, the affinity of calix[4]crowns for alkylammonium ions increases, with the extractability increasing in order of $NH_4^+ < MeNH_3^+ < Bu^tNH_3^+$. These results suggest that the larger the crown unit the better able it is to sustain a cone-structured cavity in which to nest the larger alkyl ammonium ions; this, accordingly, emphasizes the importance of size–fit hydrophobic binding. For the host **11** the affinity shifted in favour of alkali-metal cations, especially for Li^+ (29%). It seems that the larger crown unit of the host **11**, because of its ability to coil, brings about collapse of the cavity to form a pseudocircular crown unit which can accommodate Li^+ or Na^+. The host **12** showed the largest affinity for alkylammonium ions. Because the host **12** has the large hydrophobic cavity fenced by two *p*-methoxyphenyls its hydrophobic binding effect seemed to be tuned to optimal (57% for $Bu^tNH_3^+$).

Fig. 3 shows the liquid–liquid extractability spectra of the calix[4]crowns **14** and **15**. Aqueous alkali-metal cations, ammonium, or alkylammonium picrate were extracted into chloroform solutions of the host at 25 °C. The host **15** having amide side-arms exhibited much higher extraction efficiency towards metal cations than that of the host **14** with ester side-arms; this is a result of the higher intrinsic affinity of the amide group for alkali-metal cations.[14] In particular, the host **15** whilst showing the highest extractability (46%) towards Cs^+ ion, scarcely extracted $Bu^tNH_3^+$ ion (< 5%). It implies that the side-arms interact with the guest significantly by charge–dipole interaction, thus reducing the significance of hydrophobic binding.

Spectroscopic and molecular mechanics study of the binding mode

To elucidate the binding mode of the host **10** complexed with Na^+, NH_4^+ or $Bu^tNH_3^+$ picrate and **15** complexed with Cs^+ picrate under the above-described solid–liquid extraction conditions, the ^{1}H (400 MHz) and ^{13}C (100.4 MHz) NMR spectra of the complexes were recorded. The results are summarized in Tables 1 and 2.

Table 1 shows that within the limits of experimental error the ^{1}H NMR chemical shifts of **10**·Na^+, apart from those of the crown-unit aryl protons, were unchanged from those of the free host. On the other hand, **10**·NH_4^+ and **10**·$Bu^tNH_3^+$ showed significantly different chemical shifts, which reflect conformational changes upon complexation. In particular, the large downfield shifts ($\Delta\delta = 11$ Hz for **10**·NH_4^+ and $\Delta\delta = 15$ Hz for **10**·$Bu^tNH_3^+$) of the crown-unit aryl protons and the small upfield shift ($\Delta\delta = -2$ Hz for **10**·$Bu^tNH_3^+$) of the bromoaryl protons upon complexation indicate that as the alkylammonium ion is bound to the cavity the pinched-cone conformation of the free host changes to a pseudo-cone conformation. Such a conformational change resulted in significant changes in chemical shifts for the corresponding aryl protons (29 and −14 Hz, respectively) of **15**·Cs^+. The alkyl part of the alkylammonium ion nests in the cavity whilst the ammonium function is directed towards the crown unit; this synergistically increases the affinity between host and guest. The sole cation–π interaction[16] appeared to be weaker than this synergistic interaction. No binding evidence for the host **7** supports this binding mode. Differences in chemical shift for the crown moiety of the host or the alkyl group of the guest could not be analysed because their signals overlapped with those of the oxymethylene or alkyl protons of the hexyloxy groups.

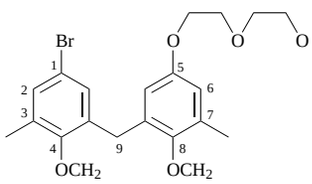
Table 2 shows the ^{13}C NMR induced shifts of **10** complexed with three picrate salts. In general, the better the guest the larger the chemical shifts induced in the host; this clearly implies a guest-induced conformational change in the host. The most striking downfield shifts (0.17, 0.37 and 1.31 ppm by Na^+, NH_4^+ and $Bu^tNH_3^+$, respectively) on one of the upper-rim oxymethylenes result, presumably, from the conformational change with the cation binding to its adjacent oxygen.

Table 1 ^{1}H NMR (400 MHz) induced shifts ($\Delta\delta$ in Hz) of calix[4]crown **10** and **15** complexed with alkali-metal and alkylammonium picrates[a]

Protons of host	$\Delta\delta$ (Hz) of complexed host[b]			
	10·Na^+	**10**·NH_4^+	**10**·$Bu^tNH_3^+$	**15**·Cs^+
ArH[c]	0.7	0.5	−2.2	−14
ArH[d]	4.2	11	15	29
endo-ArCH	0.5	2.3	2.7	2.0
exo-ArCH	0.9	2.1	1.4	4.0

[a] [**10**] = [**15**] = 6.8×10^{-3} mol dm^{-3} in $CDCl_3$ at 25 °C. The solid guests (0.01 mmol) were added. [b] $\Delta\delta = \delta_{complexed} - \delta_{free}$. [c] Bromoaryl or diethylcarbamoylmethoxy aryl proton. [d] Crown ether bridged aryl proton.

Table 2 ^{13}C NMR (100.4 MHz) induced shifts ($\Delta\delta$ in ppm) of several carbons on calix[4]crown **10** complexed with sodium and alkylammonium picrates[a]



Carbons[b] of host	$\Delta\delta$ (ppm) of complexed host[c]		
	Na^+	NH_4^+	$Bu^tNH_3^+$
C-1	0.01	0.11	0.68
C-2	0.00	−0.05	−0.09
C-3	0.05	0.09	0.31
C-4	0.01	−0.04	−0.06
C-5	0.08	0.17	0.64
C-6	0.13	0.31	0.40
C-7	0.01	0.02	0.04
C-8	0.02	−0.07	−0.03
C-9	0.01	0.01	−0.01
OCH_2 (lower)	0.01	0.04	0.15
	0.01	0.02	0.03
OCH_2 (upper)	−0.10	−0.08	−0.19
	−0.07	−0.04	−0.28
	0.01	0.03	0.07
	0.17	0.37	1.31

[a] [**10**] = 3.8×10^{-2} mol dm^{-3} in $CDCl_3$ at 25 °C. The solid guests (0.05 mmol) were added. [b] The aryl carbons were assigned using the substituent additivity rule.[15] [c] $\Delta\delta = \delta_{complexed} - \delta_{free}$.

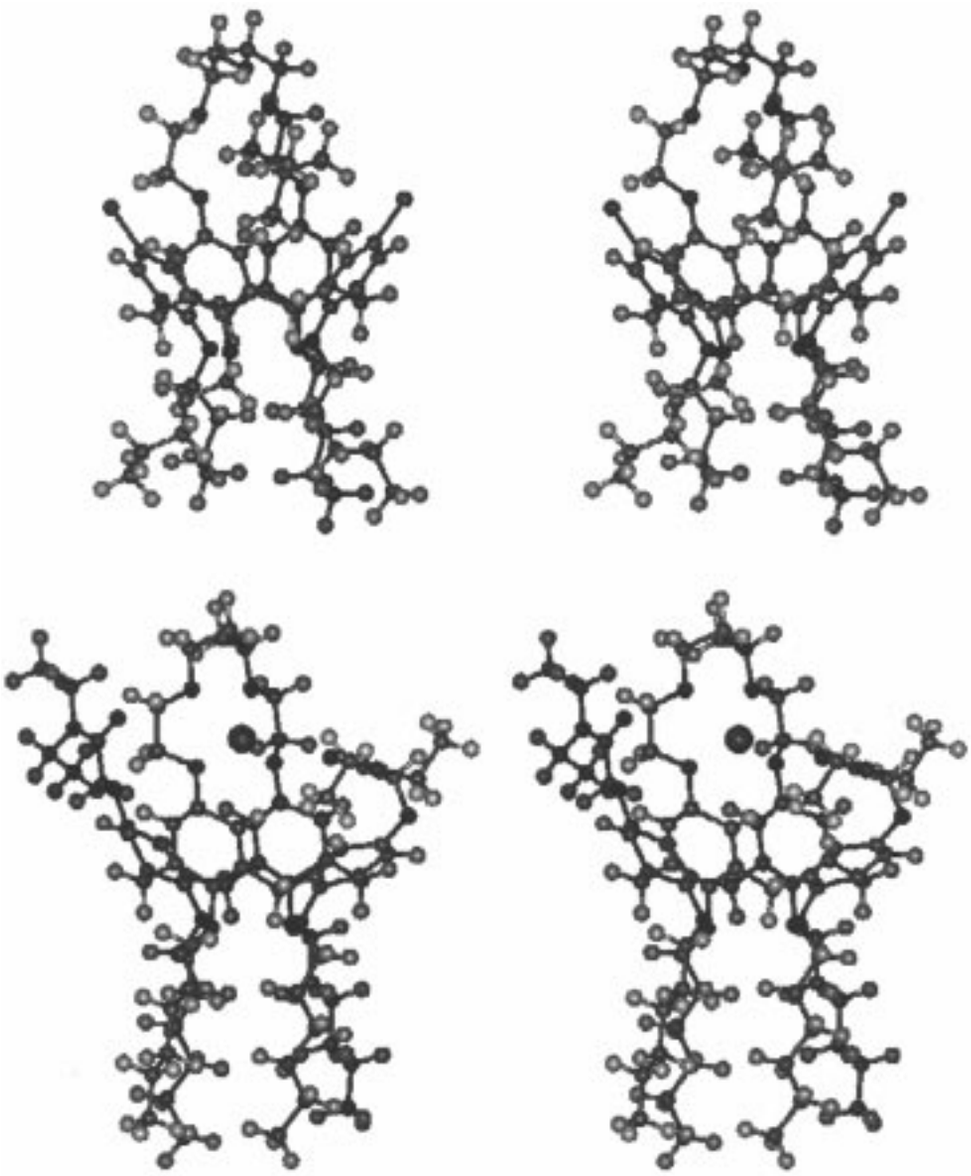


Fig. 4 Stereo views of the energy-minimized conformations of **10**·Bu^{t}NH$_3^+$(top) and **15**·Cs$^+$(bottom)

Fig. 4 shows energy-minimized stereoviews from molecular mechanics simulation (CVSS force field) of **10**·Bu^{t}NH$_3^+$ (upper) and **15**·Cs$^+$ (lower). The upper stereoview shows the proposed synergistic binding mode of **10**·Bu^{t}NH$_3^+$. The lower stereoview of **15**·Cs$^+$ shows that the Cs$^+$ was encircled by crown unit with the carbonyl oxygens of the amide groups directed towards the cation; this implies strong interaction between the cation and the amide side-arms.

Conclusions

Conformationally stable upper-rim calix[4]crowns have been efficiently synthesized and characterized. The binding mode greatly depends on the type of side-arms. Calix[4]crowns having hydrophobic side-arms have higher affinity for alkylammonium ions owing to their ability to simultaneously bind the polar and non-polar part of the guest. Calix[4]crowns having hydrophilic side-arms have higher affinity for alkali-metal cations as a result of strong charge–dipole interaction, which causes the cavity to collapse.

Experimental

General details

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. The ^{1}H NMR spectra were run on a Bruker Aw-80 (80 MHz), Gemini-300 (300 MHz) or JEOL lambda-400 (400 MHz) spectrometer. Spectra taken with TMS were referenced to internal reference at 0.00 ppm. Spectra taken in $CDCl_3$ were referenced to residual $CHCl_3$ at *ca.* 7.24 ppm. Mass spectra were run on a VG70-SEQ for EI mass or JMS-DX300 or VG 70-VSEQ for positive FAB mass using *m*-nitrobenzyl alcohol (NOBA) as a matrix. IR spectra were taken with a Mattson 3000 FT-IR spectrometer. UV spectra were obtained using a Shimadzu UV-3101PC spectrophotometer. Gravity column chromatography was performed on E. Merck silica gel 60 (70–230 mesh ASTM). Thin layer chromatography was done on plastic sheets silica gel 60 F_{254} (E. Merck, 0.2 mm). Elementary analyses were performed by Galbraith Laboratories (Knoxville, Tennessee).

Materials

All chemicals were reagent grades and used directly unless otherwise specified. THF was stored over calcium hydride for a week and was freshly distilled under N_2 from sodium benzophenone ketyl just prior to use. All anhydrous reactions were conducted under an argon atmosphere. Alkylammonium picrates were prepared by neutralization of the appropriate amine with picric acid in methanol and purified by recrystallization from methanol.[17]

Pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3(28),4,6,9(27),10,12,15(26),16,18,21(25),22-dodecaene-25,26,27,28-tetrol 2

Compound **2** was obtained by $AlCl_3$-catalysed removal of the *tert*-butyl groups from *p-tert*-butylcalix[4]arene **1**.[18]

25,26,27,28-Tetrahexyloxypentacyclo[19.3.1.1^{3,7}.1^{9,13}1^{15,19}]-octacosa-1(24),3(28),4,6,9(27),10,12,15(26),16,18,21(25),22-dodecaene 3

To a suspension of NaH [washed three times with hexane (30 cm^3); 5.8 g, 0.15 mol] in DMF (150 cm^3) was added calix-[4]arene **2** (3.0 g, 7.1 mmol). After the mixture had been stirred at 70 °C for 10 min, 1-bromohexane (11 cm^3, 77 mmol) was added to it and stirring continued for an additional 1 h at 70 °C. The mixture was then cooled to room temperature and quenched by the dropwise addition of methanol (6.8 cm^3). After removal of the solvent under reduced pressure the residue was treated with water (150 cm^3) and extracted with CH_2Cl_2. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was filtered through a short silica-gel gravity column using CH_2Cl_2 and recrystallized from CH_2Cl_2–MeOH to afford the product **3** (4.3 g, 80%) as white crystals, mp 94.4–94.8 °C; δ_H(80 MHz; $CDCl_3$) 0.90 (12 H, t, CH_3), 1.30 [24 H, m, $(CH_2)_3CH_3$], 1.90 (8 H, m, OCH_2CH_2), 3.15 (4 H, d, J_{AB} 13.6, *exo*-ArC*H*), 3.90 (8 H, t, *J* 7.2, OCH_2), 4.45 (4 H, d, J_{AB} 13.6 Hz, *endo*-ArC*H*) and 6.60 (12 H, m, Ar*H*); *m/z* (EI; 70 eV) 760.5 (M$^+$, 100%).

5,11,17,23-Tetrabromo-25,26,27,28-tetrahexyloxypentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3(28),4,6,9(27),10,12,15(26),16,18,21(25),22-dodecaene 4

To a solution of compound **3** (0.80 g, 1.1 mmol) in methyl ethyl ketone (50 cm^3) was added *N*-bromosuccinimide (3.0 g, 17 mmol) and the yellow mixture was stirred at room temperature for 3 days. It was then stirred with 10% aqueous $NaHSO_3$ (28 cm^3) for 1 h and extracted with CH_2Cl_2 (100 cm^3). The extract was washed with water and brine, dried ($MgSO_4$) and evaporated. Recrystallization of the residue from acetone–MeOH yielded product **4** (1.0 g, 89%) as white crystals, mp 109.7–111.2 °C; δ_H(80 MHz; $CDCl_3$), 0.90 (12 H, t, CH_3), 1.30 [24 H, m, $(CH_2)_3CH_3$], 1.90 (8 H, m, OCH_2CH_2), 3.10 (4 H, d, J_{AB} 13.5, *exo*-ArC*H*), 3.90 (8 H, t, *J* 7.2, OCH_2), 4.40 (4 H, d, J_{AB} 13.5, *endo*-ArC*H*) and 6.85 (8 H, s, Ar*H*); *m/z* (EI; 70 eV) 1076.2 (M$^+$, 100%).

11,23-Dibromo-25,26,27,28-tetrahexyloxypentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3(28),4,6,9(27),10,12,15(26),16,18,21(25),22-dodecane-5,17-diol 6

A stirred solution of the *p*-bromo compound **4** (5.0 g, 4.6 mmol) in dry THF (300 cm^3) under an argon atmosphere was cooled to −78 °C and treated dropwise with a solution of BuLi in hexane (1.6 M; 38 cm^3, 61 mmol). After the mixture had been stirred for 1.5 h it was quenched with $B(OMe)_3$ (9.5 cm^3, 84 mmol) at −78 °C and stirred for a further 2 h; after this 3 M aqueous NaOH–28% H_2O_2 (50 cm^3) was added to it. The mixture was then warmed to room temperature and stirred for 2 h. After careful addition of $Na_2S_2O_5{\cdot}5H_2O$ (31 g) to the mixture followed by removal of the THF *in vacuo*, the residue was extracted with CH_2Cl_2 and the extract washed with water. The organic phase was then dried (first with brine and then over $MgSO_4$) and evaporated to give the crude product. This was chromatographed on a silica-gel gravity column using 10% EtOAc in hexane as an eluent to yield the diol **6** (1.9 g, 43%), which was recrystallized from CH_2Cl_2–MeOH, mp 168–170 °C; ν_{max}(KBr)/cm^{-1} 3300 (OH); δ_H(300 MHz; $CDCl_3$) 0.90 (12 H, m, CH_3), 1.13–1.35 [24 H, m, $(CH_2)_3CH_3$], 1.82 (8 H, m, OCH_2CH_2), 3.04 (4 H, d, J_{AB} 13.5, *exo*-ArC*H*), 3.64 (4 H, t, *J* 7.3, OCH_2), 3.94 (4 H, t, *J* 7.3, OCH_2), 4.34 (4 H, d, J_{AB} 13.5, *endo*-ArC*H*), 5.71 (4 H, s, Ar*H*) and 7.16 (4 H, s, Ar*H*); δ_C(100.4 MHz; $CDCl_3$) 14.01, 14.11 (CH_3), 22.72, 22.87, 25.56, 26.19, 29.91, 30.35, 30.92, 31.90 (CH_2), 32.08 ($ArCH_2Ar$), 75.17, 75.38 (OCH_2), 114.29 (ArCH), 115.00 (ArCBr), 131.27, 133.95 (ArC), 138.75 (ArCH), 149.75 (ArCOH), 149.99 and 157.05 (ArC); *m/z* 950 (M$^+$, 15%) and 792 [(M − 2Br)$^+$, 10%].

General procedure for the synthesis of compounds 7–11

The diol **6** (0.50 g, 0.53 mmol) was dissolved in DMF (90 cm^3) and treated with NaH (0.25 g, 11 mmol). After the reaction mixture had been stirred at 70 °C for 10 min it was treated either with a solution of 1,10-dibromodecane or the corresponding oligoethylene glycol di-*p*-tosylate (1.1 equiv.) in DMF (100 cm^3), added from a dropping funnel over 10 h. The mixture was stirred at 70 °C for 2 h. After cooling, the mixture was acidified with 2 M aqueous HCl (200 cm^3) and extracted with CH_2Cl_2 (250 cm^3). The extract was washed with 2 M aqueous HCl and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by passage through a silica-gel gravity column using 50% CH_2Cl_2 in hexane as eluent for **7** or 10% EtOAc in hexane for **8**–**11**.

24,33-Dibromo-19,29,37,39-tetrahexyloxy-4,15-dioxahexacyclo[16.11.7.1^{3,28}.1^{16,20}.1^{22,26}.1^{31,35}]tetraconta-1,3(38),16,18,20-(40),22(39),23,25,28,31(37),32,34-dodecaene 7. Yield 30%; mp 88.3–89.6 °C; δ_H(300 MHz; $CDCl_3$) 0.90 (12 H, t, CH_3), 1.21–1.60 [36 H, m, $(CH_2)_3CH_3 + (CH_2)_6CH_2CH_2O$], 1.78–2.01 [12 H, m, $OCH_2CH_2(CH_2)_3 + (CH_2)_6CH_2CH_2O$], 3.06 (4 H, d, J_{AB} 13.5, *exo*-ArC*H*), 3.46 (4 H, t, OCH_2), 3.61 (4 H, t, lower OCH_2), 4.08 (4 H, t, lower OCH_2), 4.38 (4 H, d, J_{AB} 13.5, *endo*-ArC*H*), 5.80 (4 H, s, ArH) and 7.26 (4 H, s, ArH); δ_C(100.4 MHz; $CDCl_3$) 14.04, 14.13 (CH_3), 22.69, 22.96, 23.21, 24.54, 25.59, 26.21, 26.68, 27.96, 29.76, 30.48, 31.02, 31.92 (CH_2), 32.17 ($ArCH_2Ar$), 57.89 (bridged OCH_2), 75.13, 75.83 (OCH_2), 113.34 (ArCH), 114.29 (ArCBr), 131.24, 132.81 (ArC), 138.81 (ArCH), 149.12, 153.95 and 156.87 (ArC).

7,19-Dibromo-32,33,34,35-tetrahexyloxy-25,28,31-trioxahexacyclo[11.11.7.1^{3,23}.1^{5,9}.1^{11,15}.1^{17,21}]pentatriaconta-1,3(32),5,7,9(35),11,13,15(34),17,19,21(33),23-dodecaene 8. Yield 53%; mp 171.3–172.0 °C (Found: C, 65.72; H, 7.68. $C_{56}H_{76}O_7Br_2$ requires C, 65.88; H, 7.5%); δ_H(400 MHz; $CDCl_3$) 0.88 (12 H, m, CH_3), 1.18–1.55 [24 H, m, $(CH_2)_3CH_3$], 1.76–1.90 [8 H, m, $OCH_2CH_2(CH_2)_3$], 3.04 (4 H, d, J_{AB} 13.4, *exo*-ArC*H*), 3.58–3.63 (12 H, m, OCH_2 + lower OCH_2), 4.03 (4 H, t, lower OCH_2), 4.36 (4 H, d, J_{AB} 13.4, *endo*-ArC*H*), 5.70 (4 H, s, ArH) and 7.24 (4 H, s, ArH); δ_C(100.4 MHz; $CDCl_3$) 14.01, 14.11 (CH_3), 22.69, 22.92, 25.54, 26.25, 29.82, 30.45, 31.04, 31.89 (CH_2), 32.13 ($ArCH_2Ar$), 67.30, 69.49 (bridged OCH_2), 75.17, 75.55 (OCH_2), 113.31 (ArCH), 114.22 (ArCBr), 131.36, 133.37 (ArC), 139.05 (ArCH), 149.71, 152.56 and 157.09 (ArC); *m/z* 1020 [(M − H)$^+$, 100%].

22,31-Dibromo-17,27,35,37-tetrahexyloxy-4,7,10,13-tetraoxahexacyclo[14.11.7.1^{3,26}.1^{14,18}.1^{20,24}.1^{29,33}]octatriaconta-1,3(36),14,16,18(38),20(37),21,23,26,29(35),30,32-dodecaene 9. Yield 45%; mp 95.8–96.4 °C; δ_H(300 MHz; $CDCl_3$) 0.89 (12 H, m, CH_3), 1.21–1.61 [24 H, m, $(CH_2)_3CH_3$], 1.78–1.98 [8 H, m, $OCH_2CH_2(CH_2)_3$], 3.08 (4 H, d, J_{AB} 14.4, *exo*-ArCH), 3.56–3.72 (16 H, m, OCH_2 + lower OCH_2), 4.09 (4 H, t, lower OCH_2), 4.39 (4 H, d, J_{AB} 14.4, *endo*-ArC*H*), 5.87 (4 H, s, ArH) and 7.26 (4 H, s, ArH); δ_C(100.4 MHz; $CDCl_3$) 14.01, 14.10 (CH_3), 22.56, 22.94, 25.57, 26.19, 29.73, 30.45, 31.08, 31.89 (CH_2), 32.13 ($ArCH_2Ar$), 66.71 69.62, 70.12 (bridged OCH_2), 75.12, 75.83 (OCH_2), 113.28 (ArCH), 114.31 (ArCBr), 131.29, 132.89 (ArC), 138.75 (ArCH), 149.39, 153.84 and 156.89 (ArC); *m/z* 1064.8 (M$^+$, 100%).

25,34-Dibromo-20,30,38,40-tetrahexyloxy-4,7,10,13,16-pentaoxahexacyclo[17.11.7.1^{3,29}.1^{17,21}.1^{23,27}.1^{32,36}]hentetraconta-1,3(39),17,19,21(41),23(40),24,26,29,32(38),33,35-dodecaene 10. Yield 55%; mp 107.8–108.5 °C (Found: C, 65.01; H, 7.86. $C_{60}H_{84}O_9Br_2$ requires C, 65.07; H, 7.65%); δ_H(300 MHz; $CDCl_3$) 0.93 (12 H, t, CH_3), 1.21–1.59 [24 H, m, $(CH_2)_3CH_3$], 1.80–1.97 [8 H, m, $OCH_2CH_2(CH_2)_3$], 3.07 (4 H, d, J_{AB} 13.3, *exo*-ArC*H*), 3.57–3.69 (20 H, m, OCH_2 + lower OCH_2), 4.07 (4 H, t, lower

OCH_2), 4.39 (4 H, d, J_{AB} 13.3, *endo*-ArC*H*), 5.80 (4 H, s, ArH) and 7.26 (4 H, s, ArH); δ_C(100.4 MHz; $CDCl_3$) 14.00, 14.09 (CH_3), 22.66, 22.92, 25.55, 26.20, 29.76, 30.44, 31.01, 31.89 (CH_2), 32.12 ($ArCH_2Ar$), 67.91, 69.69, 70.19, 70.73 (bridged OCH_2), 75.11, 75.71 (OCH_2), 114.03 (ArCH), 114.27 (ArCBr), 131.27, 132.96 (ArC), 138.86 (ArCH), 149.59, 153.75 and 156.93 (ArC); *m/z* 1108.4 (M^+, 100%).

28,37-Dibromo-23,33,41,43-tetrahexyloxy-4,7,10,13,16,19-hexaoxahexacyclo[20.11.7.1^{3,32}.1^{20,24}.1^{26,30}.1^{35,39}]tetratetraconta-1,3(42),20,22,24,26(43),27,29,32,35(41),36,38-dodecaene 11. Yield 42%; mp 118.8–119.3 °C (Found: C, 64.62; H, 7.61. $C_{62}H_{88}O_{10}Br_2$ requires C, 64.67; H, 7.71%); δ_H(400 MHz; $CDCl_2$) 0.91 (12 H, t, CH_3), 1.19–1.52 [24 H, m, (CH_2)$_3$$CH_3$], 1.73–1.93 [8 H, m, $OCH_2CH_2(CH_2)_3$], 3.02 (4 H, d, J_{AB} 13.2, *exo*-ArC*H*), 3.54–3.67 (24 H, m, OCH_2 + lower OCH_2), 4.03 (4 H, t, lower OCH_2), 4.34 (4 H, d, J_{AB} 13.2, *endo*-ArCH), 5.73 (4 H, s, ArH) and 7.22 (4 H, s, ArH); δ_C(100.4 MHz; $CDCl_3$) 14.01, 14.11 (CH_3), 22.68, 22.83, 25.56, 26.22, 29.77, 30.45, 31.03, 31.89 (CH_2), 32.13 ($ArCH_2Ar$), 67.86, 69.76, 70.67, 70.72, 71.29 (bridged OCH_2), 75.13, 75.69 (OCH_2), 113.97 (ArCH), 114.26 (ArCBr), 131.27, 132.99 (ArC), 138.93 (ArCH), 149.62, 153.57 and 157.00 (ArC); *m/z* 1153 (M^+, 100%).

20,30,38,40-Tetrahexyloxy-25,34-di(4-methoxyphenyl)-4,7,10,13,16-pentaoxahexacyclo[17.11.7.1^{3,29}.1^{17,21}.1^{23,27}.1^{32,36}]hentetraconta-1,3(39),17,19,21(41),23(40),24,26,29,32(38),33,35-dodecaene 12

Compound **10** (0.20 g, 0.18 mmol) and tetrakis(triphenylphosphine)palladium(0) (18 mg) were dissolved in benzene (10 cm^3). 2 M Aqueous Na_2CO_3 (5 cm^3) and *p*-methoxyphenylboronic acid (0.16 g, 1.1 mmol) in ethanol (5 cm^3) were then added to the mixture after which it was refluxed under Ar for 2 days. After cooling of the reaction mixture to room temperature, the organic phase was separated and the aqueous phase was extracted with ether (20 cm^3). The combined organic phase and washings were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The crude residue was purified by column chromatography on silica gel using hexane–EtOAc (3:1, v/v) as the eluent. The major portion of the product was collected, concentrated and then recrystallized from CH_2Cl_2–methanol to yield **12** (0.11 g, 51%), mp 150.9–151.3 °C (Found: C, 76.21; H, 8.79. $C_{74}H_{98}O_{11}$ requires C, 76.37; H, 8.49); δ_H(400 MHz; $CDCl_3$) 0.92 (12 H, t, CH_3), 1.22–1.58 [24 H, m, (CH_2)$_3$$CH_3$], 1.82–2.02 [8 H, m, $OCH_2CH_2(CH_2)_3$], 3.15 (4 H, d, J_{AB} 13.1, *exo*-ArC*H*), 3.46–3.58 (16 H, m, OCH_2CH_2O), 3.65 (4 H, t, lower OCH_2), 3.87 (6 H, s, OCH_3), 4.12 (4 H, t, OCH_2), 4.46 (4 H, d, J_{AB} 13.1, *endo*-ArC*H*), 5.81 (4 H, s, ArH), 6.99 (4 H, d, *J* 6.6, CH_3OAr*H*), 7.31 (4 H, s, ArH) and 7.59 (4 H, d, *J* 6.6, CH_3OAr*H*); δ_C(100.4 MHz; $CDCl_3$) 14.06, 14.15 (CH_3), 22.72, 23.01, 25.67, 26.29, 29.97, 30.53, 31.44, 31.96 (CH_2), 32.24 ($ArCH_2Ar$), 55.37 (OCH_3), 67.83, 69.62, 70.17, 70.75 (bridged OCH_2), 75.16, 75.65 (OCH_2), 113.99, 114.08 (ArCH), 126.97, 127.92, 133.60 (ArC), 133.82 (ArCH), 134.31, 137.05 (ArCAr), 149.75, 153.62, 157.11 and 158.63 (ArC); *m/z* 1163 (M^+, 100%).

20,30,38,40-Tetrahexyloxy-4,7,10,13,16-pentaoxahexacyclo-[17.11.7.1^{3,29}.1^{17,21}.1^{23,27}.1^{32,36}]hentetraconta-1,3(39),17,19,21(41),23(40),24,26,29,32(38),33,35-dodecaene-25,34-diol 13

A stirred solution of compound **10** (0.90 g, 0.81 mmol) in anhydrous THF (50 cm^3) under an Ar atmosphere was cooled to −78 °C and treated dropwise with a solution of BuLi–hexane (1.6 M; 5.1 cm^3, 8.1 mmol). The mixture was stirred at −78 °C for 1.5 h and then quenched with trimethyl borate (1.4 cm^3, 12 mmol). The mixture was then warmed to room temperature and stirred for 2 h. After the mixture had been cooled again to −78 °C, 3 M aqueous NaOH–28% H_2O_2 (40 cm^3) was added to it; it was then slowly warmed to room temperature. After the mixture had been stirred for 2 h and $Na_2S_2O_3$·$5H_2O$ (10 g) was carefully added to it. Stirring was continued for 1 h, after which the mixture was evaporated *in vacuo*. The residue was then partitioned between 6 M aqueous HCl (150 cm^3) and ether (200 cm^3). The organic phase was separated and washed with water and brine, dried ($MgSO_4$) and evaporated *in vacuo*. The crude mixture was chromatographed on a silica-gel gravity column using hexane–EtOAc (3:2, v/v) as eluent. The major portion of the product was collected, concentrated and then recrystallized from acetone–hexane to give the diol **13** (0.34 g, 43%), mp 138.9–139.8 °C; ν_{max}(KBr)/cm^{-1} 3601 (OH); δ_H(400 MHz; $CDCl_3$) 0.89 (12 H, t, CH_3), 1.17–1.60 [24 H, m, (CH_2)$_3$$CH_3$], 1.76–1.94 [8 H, m, $OCH_2CH_2(CH_2)_3$], 2.96 (4 H, d, J_{AB} 12.9, *exo*-ArC*H*), 3.53–3.67 (20 H, m, OCH_2CH_2O + lower OCH_2), 3.96 (4 H, t, lower OCH_2), 4.33 (4 H, d, J_{AB} 12.9, *endo*-ArC*H*), 4.76 (2 H, br s, OH), 5.83 (4 H, s, ArH) and 6.58 (4 H, s, ArH); δ_C(100.4 MHz; $CDCl_3$) 14.04, 14.12 (CH_3), 22.69, 22.99, 25.67, 26.26, 29.73, 30.49, 31.11, 31.94 (CH_2), 32.23 ($ArCH_2Ar$), 67.99, 69.80, 70.06, 70.74 (bridged OCH_2), 75.04, 75.56 (OCH_2), 113.98, 115.40 (ArCH), 133.51, 137.47 (ArC), 149.76 (ArCOH), 150.09, 151.43 and 153.42 (ArC); *m/z* 982 [(M − H)$^+$, 28%].

Ethyl[34-(ethoxycarbonylmethoxy)-20,30,38,40-tetrahexyloxy-4,7,10,13,16-pentaoxahexacyclo[17.11.7.1^{3,29}.1^{17,21}.1^{23,27}.1^{32,36}]-hentetraconta-1,3(39),17,19,21(41),23(40),24,26,29,32(38), 33, 35-dodecaen-25-yloxy]acetate 14

A mixture of the diol **13** (0.10 g, 0.10 mmol), NaH (0.15 g, 0.61 mmol) and ethyl bromoacetate (0.06 cm^3, 0.51 mmol) in dry DMF (25 cm^3) was stirred at 80 °C for 5 h. The mixture was then allowed to cool at room temperature when it was thrice partitioned between CH_2Cl_2 (50 cm^3) and 2 M aqueous HCl (70 cm^3). The organic phase was separated, washed with water and brine, dried ($MgSO_4$) and evaporated *in vacuo.* The residue was chromatographed on a silica-gel gravity column using hexane–EtOAc (3:2, v/v) to give the product **14** (0.075 g, 64%), mp 62.2–63.1 °C; ν_{max}(KBr)/cm^{-1} 1750 (C=O); δ_H(400 MHz; $CDCl_3$) 0.89 (12 H, t, CH_3), 1.17–1.59 [30 H, m, (CH_2)$_3$$CH_3$ + OCH_2CH_3], 1.76–1.94 [8 H, m, OCH_2-$CH_2(CH_2)_3$], 2.99 (4 H, d, J_{AB} 13.1, *exo*-ArC*H*), 3.50 (4 H, t, OCH_2), 3.57 (4 H, t, OCH_2), 3.63–3.65 (12 H, m, OCH_2), 3.97 (4 H, t, OCH_2), 4.30 (4 H, q, $CO_2CH_2CH_3$), 4.35 (4 H, d, J_{AB} 13.1, *endo*-ArCH), 4.64 (4 H, s, OCH_2CO_2Et), 5.76 (4 H, s, ArH) and 6.67 (4 H, s, ArH); δ_C(100.4 MHz; $CDCl_3$) 14.04, 14.12, 14.24 (CH_3), 22.69, 22.99, 25.64, 26.24, 29.76, 30.45, 31.40, 31.93 (CH_2), 32.22 ($ArCH_2Ar$), 61.29, 66.03, 67.83, 69.84, 70.01, 70.79, 75.05, 75.51 (OCH_2), 113.77, 114.76 (ArCH), 133.29, 137.49, 149.62, 152.29, 152.37, 153.54 (ArC) and 169.31 (C=O); *m/z* 1155 (M^+, 100%), 1178 [(M + Na)$^+$, 35%] and 1287 [(M + Cs)$^+$, 20%].

***N*,*N*-Diethyl-2-[34-(diethylcarbamoylmethoxy)-20,30,38,40-tetrahexyloxy-4,7,10,13,16-pentaoxahexacyclo[17.11.7.1^{3,29}.1^{17,21}.1^{23,27}.1^{32,36}]hentetraconta-1,3(39),17,19,21(41),23(40),24,26,29,32(38),33,35-dodecaen-25-yloxy]acetamide 15**

To a refluxing mixture of the diol **13** (0.20 g, 0.20 mmol), sodium iodide (0.81 g, 1.2 mmol) and potassium carbonate (0.28 g, 2.0 mmol) in acetonitrile (120 cm^3) was added *N*,*N*-dimethyl-2-chloroacetamide (0.17 cm^3, 1.2 mmol). The reaction mixture was refluxed for 1 day, after which solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (100 cm^3). The solution was washed with water and brine, dried ($MgSO_4$) and evaporated *in vacuo*. The crude mixture was chromatographed on a silica-gel gravity column using hexane–EtOAc (1:4, v/v) to give the product **15** (0.16 g, 66%), mp 103.3–104.3 °C; ν_{max}(KBr)/cm^{-1} 1643 (C=O); δ_H(400 MHz; $CDCl_3$) 0.89 (12 H, t, CH_3), 1.15–1.28 (12 H, two t, NCH_2CH_3), 1.31–1.53 [24 H, m, (CH_2)$_3$(CH_3)], 1.77–1.95 [8 H, m, OCH_2-$CH_2(CH_2)_3$], 3.01 (4 H, d, J_{AB} 13.1, *exo*-ArC*H*), 3.44 (8 H, q, NCH_2), 3.49 (4 H, t, OCH_2), 3.57 (4 H, t, OCH_2), 3.62–3.67 (12 H, m, OCH_2), 3.98 (4 H, t, OCH_2), 4.36 (4 H, d, J_{AB} 12.9, *endo*-ArC*H*), 4.69 (4 H, s, OCH_2CONEt_2), 5.77 (4 H, s, ArH) and

6.70 (4 H, s, ArH); δ_C(100.4 MHz; $CDCl_3$) 12.80, 14.01, 14.09, 14.38 (CH_3), 22.65, 22.95, 25.61, 26.21, 29.72, 30.44, 31.36, 31.89 (CH_2), 32.18 ($ArCH_2Ar$), 40.22, 41.58 (NCH_2), 67.78, 68.14, 69.90, 69.97, 70.86, 74.34, 75.54 (OCH_2), 113.71, 114.65 (ArCH), 133.29, 137.44, 149.59, 152.16, 152.59, 153.59 (ArC) and 167.40 (C=O); *m/z* 1208 [$(M - H)^+$, 100%], 1231 [$(M + Na)^+$, 17%] and 1341 [$(M + Cs)^+$, 9%].

Liquid–solid extraction experiments

Solutions of each host (5×10^{-4} mol dm^{-3}) in chloroform were prepared. Solid guests were used as the picrate of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $MeNH_3^+$ and $Bu^tNH_3^+$. Into each of eight test tubes were added the appropriate picrate salts (0.01 mmol) and a portion of the host–chloroform solution (5 cm^3) with a volumetric pipette. The tubes were covered immediately to prevent evaporation and then stirred for 18 h. The chloroform solution of each complex was filtered and the concentration of the picrate ion was determined by UV absorption spectrophotometry at 25 °C. A blank test was performed by extraction of each picrate salt into pure chloroform. The extraction percentage was given by the following expression:

$$\text{Extractability (\%)} = \frac{[\text{Host}]_{\text{comp}}}{[\text{Host}]_{\text{o}}} \times 100$$

where $[Host]_o$ is the initial host concentration in chloroform and $[Host]_{comp}$ is the host–guest complex concentration in chloroform; the latter was determined by subtracting the concentration of picrate ion measured in the blank test from that of the picrate ion extracted into the chloroform solution containing the host.

Liquid–liquid extraction experiments

A two-phase liquid–liquid extraction experiment was carried out between an aqueous solution (1.0 cm^3, [GPic] = 1.0×10^{-4} mol dm^{-3}, [GCl] = 0.50 mol dm^{-3}) and a chloroform solution (1.0 cm^3, [Host] = 5.0×10^{-4} mol dm^{-3}). The two-phase mixture in a tightly-stoppered centrifuge tube was shaken with a Vortex-Genie for 1 min at 25 °C and then centrifuged at 1500 rpm for 1 min. The extractability was determined spectrophotometrically from the decrease in the absorbance of the picrate ion in the aqueous phase.

^1H and ^{13}C NMR experiments

An aliquot of $CDCl_2$ solution (0.7 cm^3) of host (6.8×10^{-3} mol dm^{-3} for ^1H, 3.8×10^{-2} mol dm^{-3} for ^{13}C) was treated with the solid guest (0.1 mmol for ^1H, 0.05 mmol for ^{13}C) of sodium, caesium, ammonium or *tert*-butylammonium picrate. The mixture was shaken for 18 h at room temperature and the resulting changes in the NMR spectra were monitored.

Molecular mechanics calculation

The molecular mechanics calculation was carried out with a CVFF force field.[19] The conjugate gradient minimization was used to minimize the energies with 1000 steps. Conformer searches were based on a simulated annealing method. Temperature annealing was achieved by decreasing the temperature gradually during the course of the simulations. The temperature was gradually reduced by 50 K per 1 ps from 1000 K to 300 K. At each temperature, MD simulation was carried out for 1 ps with a time step of 1 fs in the solution phase. After simulated annealing, MD simulation was carried out for 30 ps at 300 K. Periodic boundary conditions (25 Å × 25 Å × 25 Å) were used to solvate with $CHCl_3$. The cut-off distance was 10 Å for non-bonding interactions. All molecular mechanics was performed using the Discover 2.9.5 program. The visualization of the structures was aided with the Insight II (Molecular Simulation Inc., 1995, version 950) on INDIGO silicon graphics workstation in CAMD laboratory.

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