Control of conformational flexibility in calix[6]arenes: synthesis and characterisation of triply bridged calix[6]arene—10,15-dihydro-5*H*-tribenzo [*a,d,g*]cyclononene conjugates

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A series of triply bridged symmetrical *tert*-butylcalix[6]arene—10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene conjugates have been synthesised in excellent yields. It has been observed that the synthesised multi-cavity molecular receptors retain the calix[6]arene and derivatised 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene units in their cone conformations in solution. While the employed alkyl spacers confer flexibility to the conjugate units at room temperature, the synthesised receptors have been observed to exist in flattened cone conformations at low temperatures as determined by variable temperature NMR measurements. It has been observed that **6b** shows a significant selectivity towards Ba^{2+} over other metal ions while compound **6c** shows selectivity towards NH_4^+ ions from amongst alkali, alkaline-earth and transition metal picrates. Alkali and transition metal ions are poorly extracted by the hosts **6a–c**. The extraction abilities of host molecules **5a–c** towards metal picrates were found to be much less than that of **6a–c**.

Keywords: calix[6]arene, 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene, conjugate receptors, extraction, recognition

The design and synthesis of molecular receptors represented by macrocyclic molecules containing hydrophobic or hydrophilic cavities has generated considerable interest in scientific community in recent years. Calixarenes, resorcinarenes, cyclodextrins, cyclotriveratrylenes and porphyrins are suitable macrocyclic building blocks.[1-7] Coupling of two or more building blocks via covalent linkages can provide artificial receptor molecules with large well defined structural motifs for useful applications. For example, synthetic receptors have been obtained by covalently linking calix[4]arenes, resorcinarenes,[8–10] β-cyclodextrins,[11] porphyrins,[12,13] cryptophans[14] and carbohydrates[15] to give 'conjugate molecules' for drug delivery, stabilisation of reactive intermediates, catalysis, ionic or molecular recognition and separations in the recent past. In this context, it was envisaged that if one could 'couple' calix[*n*]arenes (*n*>4) (Fig. 1) and 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene (Fig. 2), it would provide unique molecular architectures with distinct upper and lower rims with hydrophilic and hydrophobic regions. The linking spacer units can act as structural corridors that would present a third cavity or hollow space. Although such molecular scaffolds would adopt numerous conformations due to calix[*n*]arenes and nature of substitutents in derivatised 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene, they would provide an opportunity to encapsulate molecular and ionic species in a multitopic manner. We envisaged that out of three kinds of hollow spaces in their molecular architecture for encapsulating bioactive organic species, the seat of actual host guest complexation would depend upon the conformational mobility of such receptors that provide a judicious balance of hydrophobicity, hydrophilicity and flexibility necessary for an ideal molecular receptor. Additionally, the spacer units can in principle provide windows or gates for efficient applications.

Previous studies using mass spectrometry and X-ray diffraction techniques have amply demonstrated that the π-basic cavity of calix[4]arene is too small to accept biologically important organic molecules as guests while their higher homologues are too flexible for ionic/molecular recognition. It is also known that rotational freedom of calix[6]arenes and calix[8]arenes can be suppressed by anchoring them to different molecular scaffolds or by introduction of bulky substituents at their lower rim.[16,17]

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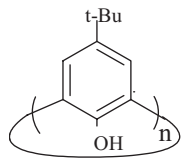


Fig. 1 *p*-tert butyl calix[n]arene (n = 2, 4, 6…20).

Likewise 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene are intrinsically rigid macrocycles that possess a shallow 3-fold symmetric core associated with functional groups at the upper rim. While calix[6]arenes possess numerous conformations that are difficult to control, the 10,15-dihydro-5*H*-tribenzo [*a,d,g*]cyclononene are known to be present in their cone or the saddle form (Fig. 3) which needs to be controlled. Such difficulties pose serious hurdles in the synthesis and characterisation of calix[6]arene—10,15-dihydro-5*H*-tribenzo [*a,d,g*]cyclononene conjugates for molecular recognition despite the fact that both calix[6]arene and 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene are known to form endo cavity inclusion complexes in solution.[18,19]

In such molecular scaffolds, it is understood that while the cavity size of 10,15-dihydro-5*H*-tribenzo[*a,d,g*]

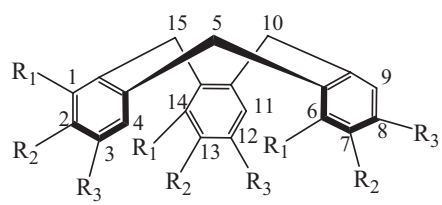


Fig. 2 Substituted 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene.

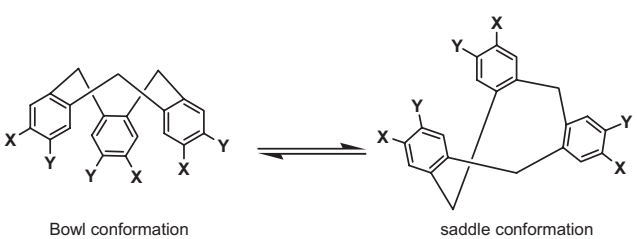


Fig. 3 Bowl and saddle conformation of 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene.

cyclononene and calix[6]arene would remain largely unchanged with reduced conformational flexibility, one can employ functionalised connecting corridors to provide different structural motifs for exploring molecular selectivities and allosteric sites in the multi cavity receptors. To the best of our knowledge, such calix[6]arene and 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene coupled molecular receptors have not been examined so far, possibly due to structural and conformational complexity as explained above and also because of difficulties in identification of guests at specific sites in the synthesised multi-cavity receptors.

In this paper, we discuss our attempts to immobilise calix[6] arene and 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene units and to couple them through variable alkyl spacer units. The resultant molecular scaffolds have three point linkages through alkyl (ethyl, propyl and 1,4-dimethyl phenyl) spacer units to provide a preorganised platform for wider binding sites. In order to obtain a fine host–guest complexation in such receptors, stepwise changes in the cross section of wall have been achieved by varying the length and structure of the linking bridges to produce receptors with varied binding abilities and allosteric properties. The synthesised multi cavity molecular receptors have been analysed for conformational analysis by NMR spectroscopy. They have also been examined for recognition of different metals and ammonium cations when they are present in the form of their picrates. Since target molecular scaffolds are complex chemical entities, one needs to achieve good yields and be able to identify specific spectral properties that can signal the recognition event. It has been observed that multicavity receptors **6a**–**c** can be obtained in good yield through the use of *p*-toluenesulfonic acid and trifluoroacetic acid as per reaction Scheme 2. This paper presents our initial efforts to achieve these objectives.

Results and discussion

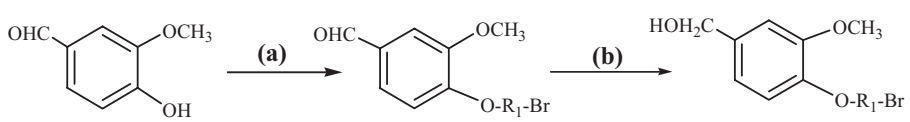
Vanillin **1** was alkylated with dibromoalkanes in refluxing acetone using K_2CO_3 as a base to provide **3a–c** in good yields (**3a**, 95%; **3b**, 92%; **3c**, 97%). **3a–c** were subjected to reduction with $NaBH_4$ in methanol to provide **4a-c** in more than 90% yield (Scheme 1). Symmetrical 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-trihydroxycalix[6]arene (prepared from hexa-*tert*-butylcalix[6]arene by reaction with methyl iodide and potassium carbonate under reaction conditions reported in the literature[20]) was then reacted with 4 equivalents of **4a–c** in refluxing anhydrous DMF using Cs_2CO_3 as a base to provide **5a–c** in excellent yields (Scheme 2) which on cyclisation gave **6a–c**.

It has been determined that cyclisation of **5a–c** to **6a–c** is an important key step for synthesis. The reaction was found to be markedly affected by the nature of acid used for cyclisation to provide varying yields of **6a–c**. For example, it was observed that cyclisation of **5a** in the presence of *p*-toluenesulfonic acid gave **6a** in moderate yield (62%) as compared to 25% yield obtained when cyclisation was carried out with 10% TFA in $CHCl_3$. Similarly when cyclisation of **5b** was effected with 10% TFA in $CHCl_3$, it provided **6b** in excellent yield (85%) as compared to when cyclisation was carried out with perchloric acid (yield 39%). Analogously cyclisation of **5c** gave **6c** in high yield (85%) in the selected solvent system. The use of other acids (H_2SO_4, HNO_3 and HCl) in acetic acid did not provide the target cyclised derivatives (Table 1).

Characterisation of the products

The formation of **6a–c** was confirmed by recording their ^{1}H NMR, ^{13}C NMR, DEPT-135 and Mass spectra. For instance, the ^{1}H NMR spectrum of **6a** gave distinct signals for *tert*-butyl and aromatic protons at δ 0.71, δ 1.31 and δ 6.64, δ 7.20 respectively indicating two types of O-substitutions in the calix[6]arene core. The protons of the methylene bridge of calix[6]arene appeared as a pair of doublets at δ 3.33 and δ 4.57 while the protons of the methylene bridge of 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene appeared as a pair of doublets at δ 3.49 and δ 4.69. It was observed that the chemical shift of the methoxy protons of calix[6]arene appeared at a higher field (δ 2.1) than the methoxy protons of the 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene core (δ 3.7). Two doublets at δ 7.3 and 7.46 could be assigned to the aromatic protons of the 1,4-dimethyl phenyl spacer unit. Two singlets at δ 6.73 and δ 6.91 could be ascribed to the aromatic protons of the 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene core. Two pairs of doublets between δ 4.79 and 5.25 could be attributed to the diastereotopic protons of the methylene group attached to the phenolic oxygen which was confirmed by recording the DQF-COSY spectrum of **6a**.

Likewise, the ^{1}H NMR spectra of **6b** exhibited the tertiary butyl protons as two singlets at δ 0.63 and δ 1.23. Protons of the methoxy group of calix[6]arene unit could be discerned at δ 1.57 while the methoxy protons of the 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene core appeared at δ 3.69 ppm plausibly due to the shielding of the methoxy group of calix[6]arene unit. Well defined two pairs of doublets for methylene bridge protons of calix[6]arene appeared at δ 3.19 and 4.46, δ 3.44 and 4.73. This was confirmed by its HSQC spectrum in which these pairs of doublets were correlated with three types of methylene carbons. The signals at δ 6.54, 6.66, 7.15 and 7.24 for aromatic protons of calix[6]arene and signals at δ 6.83 and δ 6.89 for aromatic protons of 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene core could be easily discerned in the ^{1}H NMR spectrum of **6b**. This was confirmed by recording its ^{13}C NMR spectrum which exhibited aromatic carbon signals at δ 112, 113, 126 and 128 which could be attributed to calix[6]arene unit and signals at δ 122.3, and 123.1 for aromatic carbons of 10,15-dihydro-5*H*-tribenzo [*a,d,g*]cyclononene unit. A pair of doublets at δ 3.57 and 4.83 could be assigned to the methylene bridge protons of 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene unit. Two triplets between δ 3.9–δ 4.0 and δ 4.38–δ 4.51 could be assigned to methylene protons of the spacer unit.



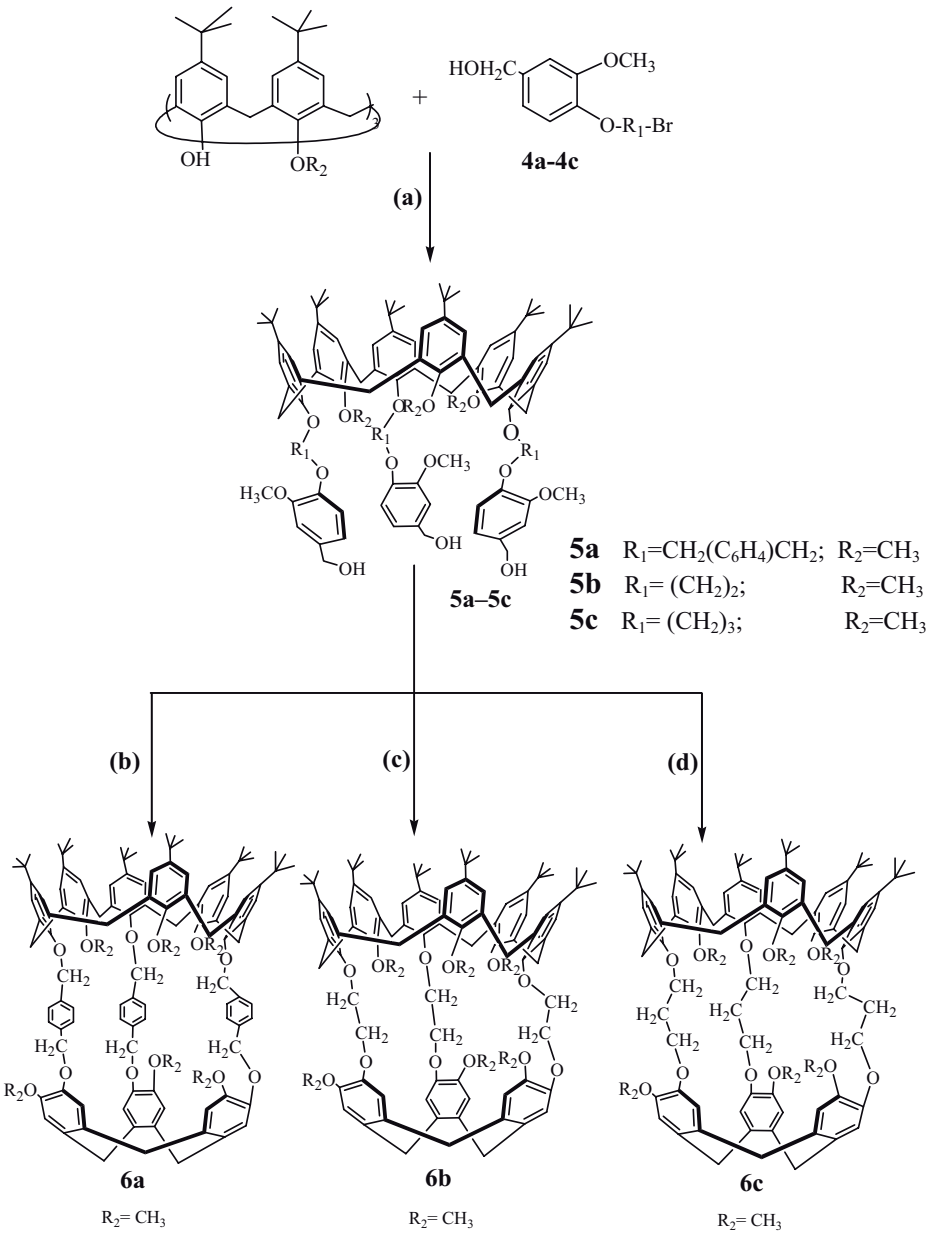
1 **3a–3c** **4a–4c**

3a, R_1 = $–CH_2(C_6H_4)CH_2–$ **4a,** R_1 = $–CH_2(C_6H_4)CH_2–$

3b, R_1 = $–(CH_2)_2–$ **4b,** R_1 = $–(CH_2)_2–$

3c, R_1 = $–(CH_2)_3–$ **4c,** R_1 = $–(CH_2)_3–$

Scheme 1 Synthesis of **4a–c**; reagents: (a) α,α′-dibromo-*p*-xylene/dibromoethane/dibromopropane, acetone, K_2CO_3, reflux, 5–12 h. (b) $NaBH_4$, methanol: dichloromethane (2:1), 0°C, 4 h.



Scheme 2 Synthesis of **6a–c**; Reagents and reaction conditions: (a) Cs_2CO_3, Dry DMF, 90°C, 72 h. (b) *p*-toluene sulfonic acid, $CHCl_3$, r.t, 96 h. (c) 10% TFA in $CHCl_3$, r.t., 48 h. (d) 10% TFA in $CHCl_3$, r.t, 72 h.

The identification of **6c** could be achieved by detailed analysis of its ^{1}H NMR and ^{13}C NMR spectrum. The tertiary butyl protons appeared as two singlets at δ 0.67 and δ 1.32. The methoxy protons of calix[6]arene core could be observed at δ 1.94 while methoxy protons of 10,15-dihydro-5*H*-tribenzo [*a,d,g*]cyclononene core appeared at δ 3.73. A doublet and a singlet at δ 6.45 and δ 7.18 respectively could be assigned to aromatic protons of calix[6]arene core while two singlets observed at δ 6.88 and δ 6.92 could be ascribed to the aromatic protons of 10,15-dihydro-5*H*-tribenzo[*a,d,g*] cyclononene unit. The protons of methylene bridge of calix[6]arene could be observed as a triplet and a doublet at δ 3.25 and δ 4.32 respectively while protons of methylene bridge of 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene moiety appeared as a pair of doublets at δ 3.49 and δ 4.69. Two broad signals at δ 2.23 and δ 3.73 – δ 4.26 could be assigned to spacer methylene protons.

Variable temperature NMR studies

The ^{1}H NMR spectrum of receptor **6c** has been recorded at different temperatures varying between 223 and 298 K in deuterated chloroform. It was observed that the position

Table 1 Percentage yield (%) of compound **6a–c** in various conditions

Entry No.	Reactant	Acids	Solvent	Temperature	Product	Percentage yield/%
1.	**5a**	*p*-toluenesulfonic acid	$CHCl_3$	0°C	**6a**	62%
2.	**5a**	10% TFA in $CHCl_3$	$CHCl_3$	R.T.	**6a**	25%
3.	**5b**	10% TFA in $CHCl_3$	$CHCl_3$	R.T.	**6b**	85%
4.	**5b**	$HClO_4$	CH_3COOH	0°C	**6b**	39%
5.	**5c**	10% TFA in $CHCl_3$	$CHCl_3$	0°C	**6c**	85%

of a pair of doublets for ArCH_2Ar protons of calix[6]arene and 10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene appeared consistently between –40°C and 25°C while a portion of signals for spacer protons between δ 3.73 and 3.99 (methylene protons attached to phenolic oxygen of calix[6]arene and 10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene platforms) displayed a splitting to different extents in the proton NMR spectrum of **6c** between –40°C and 25°C. On the other hand a broad signal of –CH_2–CH_2–CH_2– at δ 2.23 got broadened in the above temperature range as shown in Fig. 4. This splitting of spacer methyl protons observed at low temperatures in **6c** could be attributed to the freezing of the spacer unit while calix[6]arene and 10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene units remained stable in their cone conformations at all temperatures in the studied range. In the case of **6a** and **6b**, no spectral changes were observed in their proton NMR spectrum. Different NMR signals that can be used for identification of plausible recognition event are summarised in Table 2.

Discussion

The methylene bridge protons of 10,15-dihydro-5*H*-tribenzo [*a,d,g*]cyclononene unit were observed as a pair of doublets in ^{1}H NMR spectrum. One signal for methylene carbon in its ^{13}C NMR spectrum suggested that the conformation of 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene unit does not alter after its attachment with calix[6]arene and it retains its cone conformation with C_{3V} symmetry intact in **6a–c.** These observations strongly favour the trimerisation mechanism for preparation of **6a–c** for which derivatives of benzyl alcohol have been used as the starting materials. These derivatives of benzyl alcohol provide a significant advantage of generation of a single benzylic cation in the first step (Scheme 3) to eventually lead to the formation of a single 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene analogue having C_3 symmetry as described previously.[21] Although 10,15-dihydro-5*H*-tribenzo [*a,d,g*]cyclononene is known to exist in the bowl and saddle conformation, the saddle conformation could not be detected in the reaction mixture. On the other hand, a clear splitting of methylene protons (Table 2) for calix[6]arene in **6a–c** was found to be significantly different from that of the parent trimethoxy calix[6]arene which showed only one singlet for methylene protons due to conformational flexibility. Spectral analysis thus indicated that flexibility of calix[6]arenes is suppressed when they get connected to 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene in **6a–c.**

The methylene bridge protons of calix[6]arene in **6a** appeared as a pair of doublets. A significant upfield shift of methoxy group as compared to trimethoxycalix[6]arene[20] (δ 2.1, Δδ = 1.37) revealed that **6a** is present in its flattened cone conformation. In **6b**, the methoxy protons shifted more upfield (δ 1.5) in its ^{1}H NMR spectrum indicating that the anisole units are more flattened in **6b** than in **6a**. Two pairs of doublets for methylene bridge protons in ^{1}H NMR, three signals for methylene bridge carbons in the ^{13}C NMR and no spectral change at different temperatures (between 223 and 298 K) suggested that the angle of flattening of anisole moieties in calix[6]arene is different in **6b.**

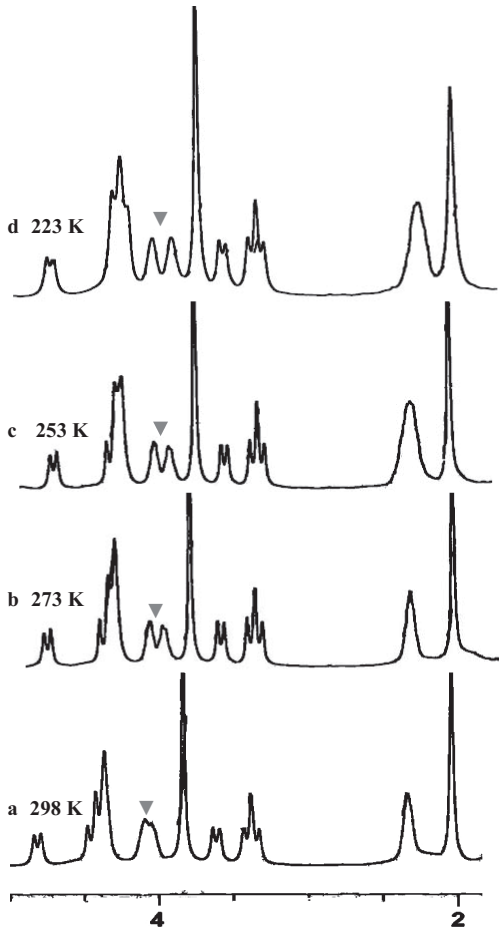


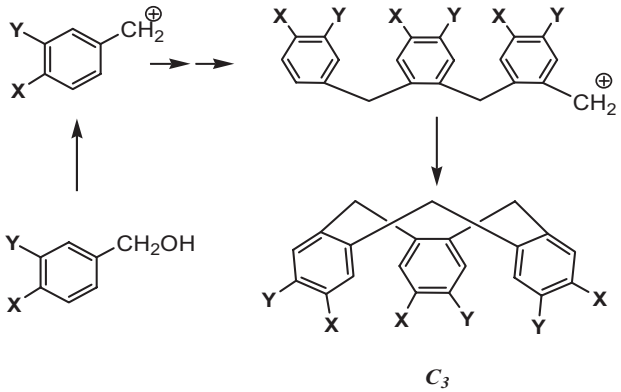
Fig. 4 Temperature dependence of protons of methylene region (shown by ▼) of **6c** in $CDCl_3$ at (a) 298 K, (b) 273 K, (c) 253 K and (d) 223 K.

Since chemical shift of methoxy group shifted upfield to δ 1.94 and typical signals of other conformations were not observed,[22] it appears that the calix[6]arene unit in **6c** predominantly exists in a flattened cone conformation. This was supported by the HSQC spectrum which exhibited correlating cross peaks of axial and equatorial protons connected to methylene bridge carbons of calix[6]arene with one methylene bridge carbon at δ 29.4 (shown in Fig. 5). It was further observed that the axial proton of the methylene bridge carbon of calix[6]arene exhibited

Table 2 ^{1}H NMR for methylene protons and ^{13}C NMR data for methylene carbons (δ, 300 MHz, 25°C) of synthesised molecular receptors **6a–c**

Product	^{1}H NMR values for ArCH_2Ar protons		^{13}C NMR values for ArCH_2Ar carbons	
	calix[6]arene	tbc	calix[6]arene	tbc
6a	3.33 (6H, d, *J* = 14.8 Hz) 4.57 (6H, d, *J* = 14.8 Hz)	3.49 (3H,d, *J* = 13.4 Hz) 4.69 (3H,d, J = 13.4 Hz)	29.3	36.4
6b	3.19(4H, d, *J* = 13.9 Hz) 4.46 (4H,d, *J* = 13.9 Hz) 3.44 (2H, d, *J* = 14.0 Hz) 4.73 (2H, d, *J* = 14.0 Hz)	3.57 (3H, d, *J* = 16.1 Hz) 4.83 (3H, d, *J* = 16.1 Hz)	28.0, 28.8, 29.2	36.6
6c	3.25 (6H, t, *J* = 15.3 Hz) 4.32 (6H, d, *J* = 15.3 Hz)	3.49 (3H,d, *J* = 13.5 Hz) 4.69 (3H, d, *J* = 13.5 Hz)	29.4	36.0

tbc = 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene.



Scheme 3

a strong correlation with the aromatic proton of calix [6]arene. On the other hand, it has been observed that methoxy protons of 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene unit have a weak connectivity with its aromatic protons through space as revealed from the NOESY spectrum of **6c (**Fig. 6).

Two-phase solvent extraction

The synthesised molecular receptors **6a–c** and **5a–c** were examined for their efficiency in extraction of alkali, alkaline-earth, transition metals and ammonium ion picrates. The results of extraction of metal ions in the organic phase as well as aqueous phase are summarised in Table 3. It has been observed that **6b** shows a significant selectivity towards Ba^{2+} as compared with other metal ions while compound **6c** shows selectivity towards NH_4^+ ions from amongst alkali, alkaline-earth, and transition metal picrates. Alkali and transition metal ions are poorly extracted by the hosts **6a–c**. The extraction abilities of host molecules of **5a–c** towards metal picrates were found to be much less as compared to those of **6a–c**, which may be explained by the 10,15-dihydro-5*H*-tribenzo [*a,d,g*]cyclononene capping the lower rim of calix[6]arenes to adopt a more convenient cone conformation suitable for the complexation event.

Conclusion

It has been observed that better yields of **6a, 6b** and **6c** are obtained from **5a**, **5b** and **5c** when cyclisation step was accomplished by *p*-toluenesulfonic acid or trifluroacetic acid as compared to when cyclisation is effected by using other acids ($HClO_4$, HCl and H_2SO_4). The ^{1}H NMR studies

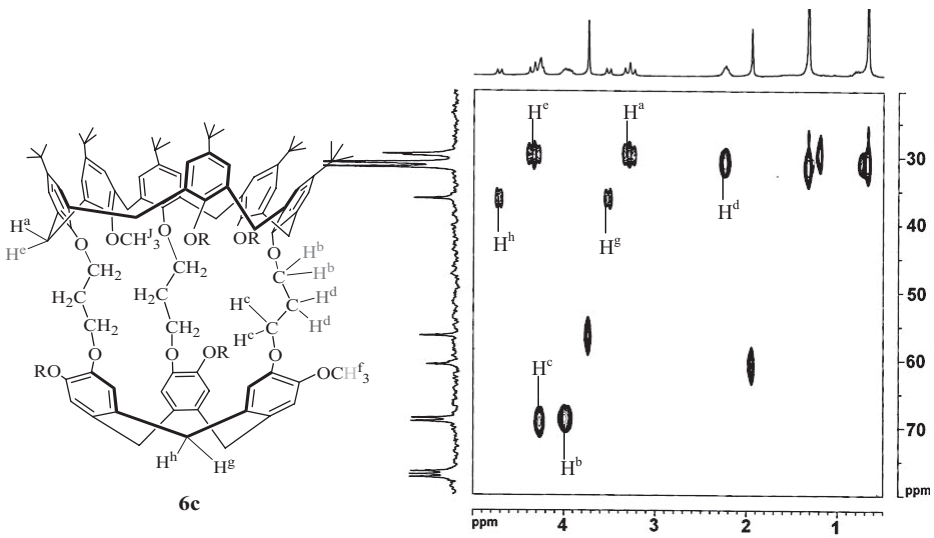


Fig. 5 Two-dimensional HSQC spectrum of compound **6c** in $CDCl_3$ in 298 K.

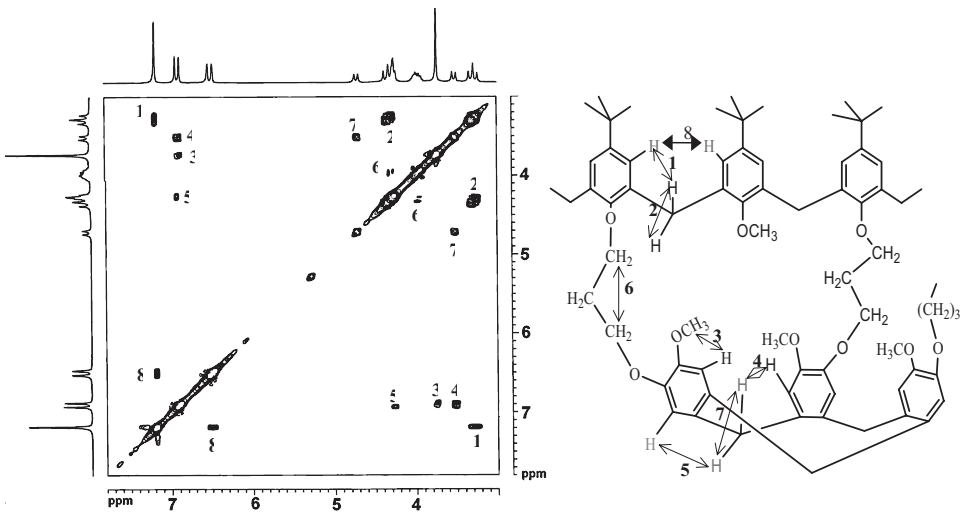


Fig. 6 Partial NOESY spectrum of compound **6c** in $CDCl_3$ at 298 K (shown by arrow).

Table 3 Percentage extraction (%E) of metal picrates (2.5×10^{-5} M) by host **5b–5c, 6b–6c** (2.5×10^{-5} M) from water into dichloromethane

	% Extraction			
Metals	5b	6b	5c	6c
Li^+	ne	3	ne	5
Na^+	ne	4	ne	3
K^+	ne	2	ne	ne
Rb^+	ne	4	ne	4
Cs^+	ne	5	ne	ne
Mg^{2+}	ne	ne	ne	ne
Ca^{2+}	ne	ne	ne	ne
Sr^{2+}	ne	ne	ne	ne
Ba^{2+}	ne	**33**	ne	3
Fe^{2+}	ne	2	ne	4
Co^{2+}	ne	3	ne	2
Ni^{2+}	ne	ne	ne	ne
Cu^{2+}	ne	ne	ne	ne
Cd^{2+}	ne	ne	ne	4
Pb^{2+}	3	ne	5	ne
NH_4^+	ne	ne	ne	**52**
$CH_3NH_3^+$	ne	ne	ne	8
n-$PrNH_3^+$	ne	ne	ne	ne

ne = No extraction.

demonstrated that the a 10,15-dihydro-5*H*-tribenzo[*a,d,g*] cyclononene cap at the lower rim of calix[6]arene can immobilise the conformation of calix[6]arene. It has been determined that the calix[6]arene and 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene units remain stable in their cone conformation in **6a** and **6c.** The alkyl spacers in **6c** are able to confer flexibility at room temperature which can be suppressed by lowering the temperature. The cavities provided by these receptors are rigid and conformationally defined to be used for ionic and molecular recognition.

Experimental

All the regents used in the experiments were purchased from Sigma-Aldrich or Merck and were chemically pure. The solvents were distilled and dried. Column chromatography was performed on silica gel (60–120 mesh) obtained from Merck. ^{1}H and ^{13}C NMR, DEPT-135, HSQC, DQF-COSY, NOESY spectra were recorded on a 300 MHz Brucker DPX 300 instrument at different temperatures using tetramethylsilane (TMS) at δ 0.00 as internal standard. IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr disks while CHN analysis was obtained by using a Perkin-Elmer 240C elemental analyser. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer/Data System using Argon/Xenon (6 kV, 10 mA) as the FAB gas. Melting points were determined on an electrothermal Toshniwal melting point apparatus and were uncorrected.

General procedure for synthesis of **3a–c**

A solution of vanillin (5.0 g, 0.32 mol) and K_2CO_3 (18.2 g, 0.13 mol) in 25 ml of anhydrous acetone was refluxed for 10 min and then a solution of alkyl dibromide (**2a–2c**, 1.5 equivalents) in acetone (10 ml) was introduced. After refluxing for 18 h, the solvent was removed under reduced pressure and the resulting mixture dissolved in chloroform and washed with water (25 ml). The organic layer was separated and the aqueous layer extracted with $CHCl_3$ (20 × 3 ml). The organic extracts were combined, washed with water and dried over anhydrous Na_2SO_4. It was filtered to give a crude product (**3a–c**) which was then purified by column chromatography (silica gel) to give pure **3a–c**.

General procedure for synthesis of **4a–c**

A solution of **3a–c** (4.0 g, 0.015 mol) in anhydrous methanol-dichloromethane (2:1) was cooled at 0°C for 20 min. $NaBH_4$ (1.8 g, 0.046 mol) was slowly added at 0°C within 1 h. It was stirred at the same temperature for 5 h and then chloroform (20 ml) was added and the organic layer washed with water (25 ml). The organic layer was separated and dried over anhydrous Na_2SO_4 followed by evaporation of the solvent under reduced pressure to yield **4a–c** as a white solid.

General procedure for synthesis of **5a–c**

A solution of trimethoxycalix[6]arene (0.5 g, 0.038 mmol) and Cs_2CO_3 (0.962 g, 2.3 mmol) in 20 ml of anhydrous DMF. The reaction mixture was heated at 70°C for 30 min, compounds **4a–c** (4.5 equivalents) were added to it and heated at 70°C for 72 h. The reaction mixture was diluted with $CHCl_3$ (40 ml) and water (20 ml) was added to it. The organic layer was separated and the aqueous layer extracted again with $CHCl_3$ (20 × 3 ml). The organic extracts were combined, washed with water and dried over anhydrous Na_2SO_4. After filtration and removal of solvent under reduced pressure, the resulting crude products **5a–c** were purified by column chromatography (silica gel) to give **5a–c**.

3a: Column chromatography of the crude product by using hexane-ethyl acetate (7:3) as an eluent to afford **3a** as a white solid (9.13 g, 95%), m.p. 92–94°C. (Found: C 57.2, H 4.6%. $C_{16}H_{15}O_3Br$ requires C 57.3 H 4.5%.) ν_{max} (KBr pellet)/cm^{-1} 1720 (CO). δ_H (300 MHz, $CDCl_3$, 25°C) 9.83 (1H, s, C*H*O), δ 7.7–7.3 (6H, m, Ar*H*), 6.95 (1H, d, *J* = 8.1 Hz, Ar*H*), 5.22 (2H, s, CH_2Br), 4.48 (2H, s, OCH_2), 3.94 (3H, s, OCH_3). δ_C (75 MHz, $CDCl_3$, 25°C) 173, 147.9, 147, 146, 134, 119.3, 117.2, 113.6, 112, 111, 65.7, 64.1, 54.8. FAB- MS *m/z*: 336 (M^+).

4a: White solid (3.16 g, 90%), m.p. 83–85°C. (Found: C 56.7, H 5.2%. $C_{16}H_{17}O_3Br$ requires C 57.0 H 5.1%.) ν_{max} (KBr pellet)/cm^{-1} 3344 (OH). δ_H (300 MHz, $CDCl_3$, 25°C) 7.39–7.30 (6H, m, Ar*H*), 6.18 (1H, d, *J* = 8.1 Hz, Ar*H*), 5.22 (2H, s, CH_2Br), 4.60 (2H, s, CH_2OH), 4.44 (2H, s, OCH_2), 3.89 (3H, s, OCH_3), 1.25 (1H, s, O*H*). δ_C (75 MHz, $CDCl_3$, 25°C) 148, 147.4, 146.3, 118.4, 134, 117.8, 113.5, 112, 111, 65.3, 64.3, 54.3, 31.3. FAB-MS *m/z*: 338 (M^+).

5a: Column chromatography of the crude reaction mixture by using hexane-ethyl acetate (7:3) as an eluent afforded **5a** as a white solid (7.9 g, 90%), m.p. 293–297°C. (Found: C 78. 7, H 7.7%. $C_{117}H_{138}O_{15}$ requires C 78.8 H 7.8%) ν_{max} (KBr pellet)/cm^{-1} 3354 (OH). δ_H (300 MHz, $CDCl_3$, 25°C) 7.55–7.52 (6H, d, *J* = 7.2 Hz, dimethyl phenyl Ar*H*), 7.44–7.42 (6H, d, *J* = 7.2 Hz, Ar*H*), 7.27 (6H, s, calixarene Ar*H*), 6.93 (3H, s, Ar*H*), 6.81–6.76 (6H m, dimethyl phenyl Ar*H*), 6.68 (6H, s, calixarene Ar*H*), 5.19 (6H, s, ArOCH_2Ar), 4.94 (6H, s, ArOCH_2Ar), 4.63 (6H, s, CH_2OH), 4.63–4.57 (6H, bs, calixarene ArCH_2Ar), 3.88 (9 H, s, OCH_3), 3.42–3.37 (6H, d, *J* = 14.5 Hz, calixarene ArCH_2Ar), 2.23 (9H, s, calixarene OCH_3), 1.63 (3H, s, O*H*), 1.37 (27H, s, *t*-butyl), 0.81 (27H, s, *t*-butyl). δ_C (75 MHz, $CDCl_3$, 25°C) 133.6, 133, 127, 126, 123, 119, 118, 117, 113.4, 113, 111.8, 111, 108, 73, 71, 69, 64, 58, 54, 31.2, 31, 29.3. FAB-MS *m/z*: 1782 (M^+).

6a: A solution of **5a** (100 mg, 0.0056 mmol) and *p*-toluene sulfonic acid (70 mg, 0.0036 mmol) in 15 ml of dry $CHCl_3$ was stirred at room temperature in the presence of molecular sieves (4 Å) for 3 days. After filtration of the reaction mixture, it was diluted with $CHCl_3$ (40 ml) and water (25 ml) was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (20 × 3 ml). The organic extracts were combined, washed with water and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the resulting crude product **6a** was purified by column chromatography using ethyl acetate-hexane, (1:4) as an eluent to give **6a** as a white solid (44 mg, 62%), m.p. 287–290°C. (Found: C 80.9, H 7.3%. $C_{117}H_{132}O_{12}$ requires C 81.2, H 7.7%.) δ_H (300 MHz, $CDCl_3$, 25°C) 7.46 (6H, d, *J* = 7.2 Hz, dimethyl phenyl Ar*H*), 7.31 (6H, d, *J* = 7.2 Hz, dimethyl phenyl Ar*H*), 7.20 (6H, s, calixarene Ar*H*), 6.91 (3H, s, tbc Ar*H*), 6.73 (3H, s, tbc Ar*H*), 6.64 (6H, s, calixarene Ar*H*), 5.25–5.12 (6H, m, ArOCH_2Ar), 4.98–4.79 (6H, m, ArOCH_2Ar), 4.69 (3H, d, *J* = 13.4 Hz, tbc ArCH_2Ar), 4.57 (6H, d, *J* = 14.8 Hz, calixarene ArCH_2Ar), 3.7 (9H, s, tbc OCH_3), 3.49 (3H, d, *J* = 13.4 Hz, tbc ArCH_2Ar), 3.33 (6H, d, *J* = 14.8 Hz, calixarene ArCH_2Ar), 2.1 (9H, s, calixarene OCH_3), 1.31 (27H, s, *t*-butyl), 0.71 (27H, s, *t*-butyl). δ_C (75 MHz, $CDCl_3$, 25°C) 155.2, 151.2, 149.6, 147.5, 145, 133.8, 133.7, 133.3, 133.1, 132.9, 132.6, 131.3, 129.8, 129, 127, 123, 116, 114, 67.7, 67.4, 60.3, 55.4, 36.4, 30.8, 29.4, 29.3. FAB-MS *m/z*: 1728 (M^+).

3b: Column chromatography of the crude reaction mixture by using hexane-ethyl acetate (7:3) as an eluent afforded **3b** as a white solid (7.9 g, 92%), m.p. 89–91°C. (Found: C 46.5, H 4.2%. $C_{10}H_{11}O_3Br$ requires C 46.4 H 4.3%.) ν_{max} (KBr pellet)/cm^{-1} 1731 (CO). δ_H (300 MHz, $CDCl_3$, 25°C) 9.86 (1H, s, C*H*O), 7.46–7.42 (2H, bs, Ar*H*), 7.02–6.99 (1H, d, *J* = 8.0 Hz, Ar*H*), 4.4–4.0 (2H, t, *J* = 6.7 Hz, CH_2Br), 3.94 (3H, s, OCH_3), 3.73–3.68 (2H, t, *J* = 6.7 Hz, OCH_2) δ_C (75 MHz, $CDCl_3$, 25°C) 164, 149.7, 147, 134, 119.3, 113.6, 111, 66.8, 65.1, 55.8, 32.3. FAB-MS *m/z*: 259 (M^+).

4b: White solid (3.6 g, 90%), m.p. 84–87°C. (Found: C 45.8, H 5.1%. $C_{10}H_{13}O_3Br$ requires C 46.0 H 5.0%.) ν_{max} (KBr pellet)/cm^{-1} 3364 (OH). δ_H (300 MHz, $CDCl_3$, 25°C) 6.9 (1H, s, Ar*H*) 6.8 (2H, bs, Ar*H*), 4.6 (2H, s, CH_2OH), 4.34–4.30 (2H, t, *J* = 6.6 Hz, CH_2Br), 3.88 (3H, s, OCH_3), 3.67–3.62 (2H, t, *J* = 6.6 Hz, OCH_2), 1.67 (1H,

bs, O*H*). δ_C (75 MHz, $CDCl_3$, 25°C) 149.7, 147, 134, 119.3, 113.6, 111, 66.8, 32.3, 55.8, 65.1, 29.7. FAB-MS *m/z*: 260.9 (M^+).

5b: Column chromatography of the crude product by using hexane-ethyl acetate (1:4) as an eluent gave **5b** as a white solid (8.2 g, 89%), m.p. 284–287°C. (Found: C 76.4, H 8.1%. $C_{99}H_{126}O_{15}$ requires C 76.4 H 8.2%) ν_{max} (KBr pellet)/cm^{-1} 3341 (OH). δ_H (300 MHz, $CDCl_3$, 25°C) 7.24 (6H, s, calixarene Ar*H*), 6.89 (9H, bs, Ar*H*), 6.62 (6H, s, calixarene Ar*H*), 4.64 (6H, s, CH_2OH), 4.60–4.49 (12H, m, ArOCH_2 + calixarene ArCH_2Ar), 4.28 (6H, t, *J* = 12.0 Hz, ArOCH_2), 3.70 (9H, s, OCH_3), 3.38 (6H, d, *J* = 14.8 Hz, calixarene ArCH_2Ar), 2.1 (9H, s, calixarene OCH_3), 1.61 (3H, bs, O*H*), 1.37 (27H, s, *t*-butyl), 0.77 (27H, s, *t*-butyl). δ_C (75 MHz, $CDCl_3$, 25°C) 154.4, 145.7, 134.4, 133.9, 133.6, 127, 126, 123, 119.8, 119, 111.8, 111, 71, 68, 65, 59, 55, 31, 30.3, 29.5. FAB-MS *m/z*: 1555 $(M)^+$.

6b: A solution of 10% TFA and in $CHCl_3$ (10 ml) was cooled and stirred at 0°C temperature for 30 min. Compound **5b** (200 mg, 0.12 mmol) dissolved in $CHCl_3$ (2.0 ml) was added drop wise (within 2 h) to it. After 12 h stirring, the reaction mixture was diluted with $CHCl_3$ (40 ml) and water (20 ml) was added to it. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (20 × 3 ml). The organic extracts were combined, washed with water and dried over anhydrous Na_2SO_4. After filtration and removal of solvent under reduced pressure, the crude product was purified by column chromatography using ethyl acetate and hexane (2:4) as the eluent to give pure **6b** as a white solid (83 mg, 85%), m.p. 292–294°C. (Found: C 79.4, H 8.3%. $C_{99}H_{120}O_{12}$ requires C 79.2, H 8.1%.) δ_H (300 MHz, $CDCl_3$, 25°C) 7.24–7.11 (6H, m, calixarene Ar*H*), 6.89 (3H, s, tbc Ar*H*), 6.83 (3H, s, tbc Ar*H*), 6.66 (3H, s, calixarene Ar*H*), 6.54 (3H, s, calixarene Ar*H*), 4.95–4.7 (5H, m, calixarene ArCH_2Ar + tbc ArCH_2Ar), 4.42–4.51 (10H, m, calixarene ArCH_2Ar + ArOCH_2), 4.0–3.9 (6H, m, ArOCH_2), 3.69 (9H, s, tbc OCH_3), 3.57 (3H, d, *J* = 16.1 Hz, tbc ArCH_2Ar), 3.44(2H, d, *J* = 14.0 Hz, calixarene ArCH_2Ar), 3.19 (4H, d, *J* = 13.9 Hz, calixarene ArCH_2Ar), 1.57 (9H, bs, calixarene OCH_3), 1.23 (27H, s, *t*-butyl), 0.63 (27H, s, *t*-butyl). δ_C (75 MHz, $CDCl_3$, 25°C) 154, 149, 148, 147, 145, 144, 133.6, 133, 132, 131, 130, 128, 126, 123.01, 122.3, 113, 112, 71, 67, 58, 54, 31.1, 36.6, 30.4, 29.2, 28.8, 28.0. FAB-MS *m/z* 1501 (M^+).

3c: Column chromatography of the crude product by using hexane-ethyl acetate 7:3 as an eluent afforded **3c** as a white solid (7.8 g, 97%), m.p. 94–96°C. (Found: C 48.6, H 4.7%. $C_{11}H_{13}O_3Br$ requires C 48.4, H 4.8%.) ν_{max} (KBr pellet)/cm^{-1} 1723 (CO). δ_H (300 MHz, $CDCl_3$, 25°C) 9.86 (1H, s, C*H*O), 7.46–7.42 (2H, m, Ar*H*), 7.02–6.99 (1H, d, *J* = 8.0 Hz, Ar*H*), 4.27–4.23 (2H, t, *J* = 5.8 Hz, CH_2Br), 3.92 (3H, s, OCH_3), 3.65–3.60 (2H, t, *J* = 6.24 Hz, OCH_2CH_2), 2.45–2.17 (2H, quint, CH_2CH_2CH_2). δ_C (75 MHz, $CDCl_3$, 25°C) 172, 149.8, 147, 136, 116.4, 115.6, 112.2, 66.8, 63.1, 53.8. FAB-MS *m/z*: 273 (M^+).

4d: White solid (3.56 g, 93%), m.p. 82–87°C. (Found: C 48.21, H 5.65%. $C_{11}H_{15}O_3Br$ requires C 48.02, H, 5.50%.), ν_{max} (KBr pellet)/cm^{-1} 3349 (OH). δ_H (300 MHz, $CDCl_3$, 25°C) 6.83–6.86 (3H, m, Ar*H*), 4.5 (2H, s, CH_2OH), 4.09–4.06 (2H, t, *J* = 5.8 Hz, CH_2Br), 3.79 (3H, s, OCH_3), 3.57–3.53 (2H, t, *J* = 6.2 Hz, OCH_2CH_2), 2.3–2.2 (2H, quint, CH_2CH_2CH_2), 1.68 (1H, s, O*H*). δ_C (300 MHz, $CDCl_3$, 25°C) 149.7, 148, 135, 119.4, 114.6, 111.2, 65.8, 63.1, 54.8,31.3. FAB-MS *m/z*: 274 (M^+).

5c: Column chromatography of the crude reaction mixture by using hexane-ethyl acetate (2:8) as the eluent gave **5c** as a white solid (8.2 g, 98%), m.p. 278–284°C. (Found: C 76.8, H 7.9%. $C_{102}H_{132}O_{15}$ requires C, 76.7 H, 8.3%.), ν_{max} (KBr pellet)/cm^{-1} 3419 (OH). δ_H (300 MHz, $CDCl_3$, 25°C) 7.16 (6H, s, calixarene Ar*H*), 6.89–6.75 (9H, m, Ar*H*), 6.53 (6H, s, calixarene Ar*H*), 4.49 (6H, s, CH_2OH), 4.43–4.32 (12H, m, ArOCH_2 + calixarene ArCH_2Ar), 4.32 (6H, bs, ArOCH_2), 3.75 (9H, s, OCH_3), 3.31–3.26 (6H, d, *J* = 14.8 Hz, calixarene ArCH_2Ar), 2.33 (6H, bs, CH_2CH_2CH_2), 2.06 (9H, s, calixarene OCH_3), 1.63 (3H, s, O*H*), 1.31 (27H, s, *t*-butyl), 0.69 (27H, s, *t*-butyl). δ_C (75 MHz, $CDCl_3$, 25°C) 155, 151.1, 149.5, 147.6, 145.2, 133.4, 133, 132.9, 132, 131, 126, 127.8, 123, 118, 113, 68.9, 68.4, 64.5, 60, 56, 31.2, 30.4, 29.4, 29. FAB-MS *m/z*: 1597 (M^+).

6c: A solution of 10% TFA and in $CHCl_3$ (10.0 ml) was cooled and stirred at 0°C temperature for 30 min and compound **5c** (300 mg, 0.18 mmol) dissolved in $CHCl_3$ (7 ml) was added drop wise (within 1 h) to it. After 12 h stirring, the reaction mixture was diluted with $CHCl_3$ (40 ml) and water (25 ml) was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (20 × 3 ml). The organic extracts were combined, washed with water and dried over anhydrous Na_2SO_4. After filtration and removal of solvent under reduced pressure, the resulting crude product **6c** was purified by column chromatography using ethyl acetate and hexane (1:4) as the eluent to provide **6c** as a white solid (82 mg, 85%), m.p. 295–299°C. (Found: C 79.6, H 8.0%. $C_{102}H_{126}O_{12}$ requires C 79.3 H 8.2%.) δ_H (300 MHz, $CDCl_3$, 25°C) 7.18 (6H, s, calixarene Ar*H*), 6.92 (3H, s, tbc Ar*H*), 6.88 (3H, s, tbc Ar*H*), 6.45 (6H, d, *J* = 18 Hz, calixarene Ar*H*), 4.69 (3H, d, *J* = 13.5 Hz, tbc ArCH_2Ar), 4.37–4.2 (12H, m, ArOCH_2 + calixarene ArCH_2Ar), 3.9 (6H, m, ArOCH_2), 3.73 (9H, s, tbc OCH_3), 3.49 (3H, d, *J* = 13.5 Hz, tbc ArCH_2Ar), 3.25 (6H, t, *J* = 15.3 Hz, calixarene ArCH_2Ar), 2.23 (6H, bs, CH_2CH_2CH_2), 1.94 (9H, s, calixarene OCH_3), 1.31 (27H, s, *t*-butyl), 0.67 (27H, s, *t*-butyl), δ_C (75 MHz, $CDCl_3$, 25°C) 155, 151, 149.5, 147.6, 145.2, 133.3, 132.6, 131.3, 128, 127.6, 123.2, 119.5, 114.9, 68.9, 68.4, 60.5, 56.5, 36.0, 31.4, 30.8, 29.8, 29.4. FAB-MS *m/z*: 1542 (M^+).

Solvent extraction

The general extraction procedures employed were similar to those described previously[23]. Distilled dichloromethane and demineralised water were used. The solvents were saturated with each other before use in order to prevent volume changes of the phase during extraction. Equal volumes (5 ml) of dichloromethane solution of the respective host **6a–c** as well as **5a–c** (2.5×10^{-5} M) and of an aqueous solution of the corresponding metal picrate (2.5×10^{-5} M) were stirrered for 10 h at 25°C in a round bottom flask. The mixture was then allowed to stand for at least half an hour at that temperature for complete phase separation. The extractability was determined spectrophotometrically from the decrease in the absorbance of picrate ion in the aqueous phase. In control runs, no detectable amounts of picrates were extracted into the organic phase in the absence of host molecules.

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