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Synthesis and complexing properties of 1,5:3,7-doubly bridged calix[8]arenes with mixed spanning elements

Luisa Gregoli,[a] Laura Russo,[a] Ivan Stefio,[a] Carmine Gaeta,[a] Françoise Arnaud-Neu,[b] Véronique Hubscher-Bruder,[b] Poupak Khazaeli-Parsa,[b] Corrada Geraci[c] and Placido Neri[a,*]

[a]*Dipartimento di Chimica, Università di Salerno, Via S. Allende 43, I-84081 Baronissi (Salerno), Italy*
[b]*Laboratoire de Chimie Physique, UMR 7512 (CNRS-ULP), Ecole Européenne de Chimie Polymères et Matériaux, 25, rue Becquerel, 67087 Strasbourg Cedex 2, France*
[c]*Istituto di Chimica Biomolecolare—Sezione di Catania, CNR, Via del Santuario 110, I-95028 Valverde (CT), Italy*

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Abstract—Two different bridges were introduced at the 1,5:3,7-positions of *p-tert*-butylcalix[8]arene **1** using a two-step alkylation procedure. A probable cation template effect in the introduction of the second bridge was evidenced. The obtained bis-bridged derivatives **3** possess encapsulating properties toward alkali cations modulated by the length and nature of the bridges.

Among the 'major' calix[*n*]arenes[1] ($n=4$, 6, 8) the larger octamers[2] have been much less studied because prospecting a more intricate chemistry joined to a higher conformational mobility. However, their large dimensions make them somewhat attractive for the synthesis of molecular receptors for medium-sized compounds and, indeed, interesting complexing properties toward C_{60}-fullerene[3] and photolabile cholinergic ligands[4] have been reported. In these instances, the guest-directed fit of the calix[8]arene macrocycle or the host–guest mutually-induced fit is observed, respectively.

An alternative approach to calix[8]arene-based hosts relies on intramolecular bridging to effectively preorganize the macrocycle. One of the most interesting results of this approach has been the preparation, by both Shinkai[5] and our[6] groups, of highly preorganized D_{2d}-symmetrical 1,5:3,7-doubly-bridged calix[8]arenes (compounds **3** with X=Z). As predicted by molecular mechanics calculations and demonstrated by X-ray diffractometry,[6b] these derivatives possess a structure composed of four 3/4-cone clefts with a central polyhedral cavity apt to encapsulate cations with a size-dependent selectivity. In fact, highly selective cesium ionophores were obtained using two identical *o*-xylylene[5b] or diethylene-glycol bridges.[6a]

It is conceivable that introduction of bridges of different or mixed nature could give rise to derivatives with diverse or improved selectivity. Therefore, we decided to investigate this aspect and we wish to report here the first examples of calix[8]arene derivatives 1,5:3,7-doubly-bridged with mixed spanning elements.

The synthesis of these compounds, originally devised by us for the homogenous 1,5:3,7-double bridging,[6] was based on two distinct alkylation steps, which allow the introduction of two different bridges (Scheme 1).

The first step makes use of Cs_2CO_3, in nonanhydrous DMF, to promote 1,5-mono-bridging of *p-tert*-butylcalix[8]arene **1** with short spacers.[7] It has already been exploited by us for the preparation of calix[8]arenes 1,5-bridged with the following spanning elements: tetramethylene **2a** (68% yield),[7b] crown-2 **2b** (88%),[7a] crown-3 **2c** (78%),[7a] *o*-xylylene **2d** (50%),[7c] *m*-xylylene **2e** (80%).[7c]

In the second step, the introduction of a further bridge at the 3,7-positions of compounds **2a**–**e** is obtained in

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* Corresponding author. Tel.: +39-089-965262; fax: +39-089-965296; e-mail: neri@unisa.it

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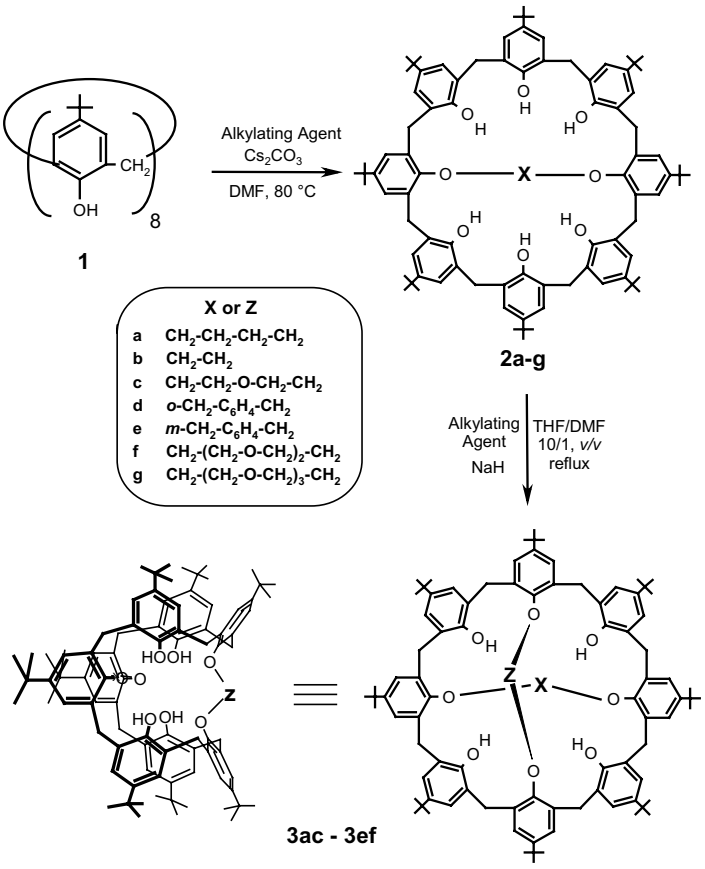

Scheme 1.

the presence of NaH in anhydrous THF/DMF (10:1, v/v) at reflux.[6] As reported in Table 1, the selected alkylating agents allowed the introduction of crown-4 and crown-5 bridges, in addition to the above ones. All combinations of these bridges were examined, also by considering the alternative order of bridging. In particular, 1,5-tetramethylene bridged **2a** was reacted with all alkylating agents to give derivatives **3ac**–**ag** in 35–99% yield (Table 1, entries 1–5).[8] In a similar way, 1,5-crown-2 **2b** led to the preparation of hetero-bridged derivatives **3bc**–**be** in 15–93% yield (entries 6–8).

Starting from 1,5-calix[8]crown-3 **2c**, *ortho*-, and *meta*-xylylene-bridged derivatives **3cd** and **3ce** were obtained (entries 9 and 10) in almost quantitative yield (98% and 94%, respectively), while the corresponding crown-4 derivative **3cf** was formed only in a 10% yield (entry 11). A mixed *meta*- and *ortho*-xylylene bridged derivative **3ed** was obtained in excellent yield (94%) by using 1,5-*m*-xylylene-bridged **2e** as starting substrate (entry 12). In contrast, the same substrate gave the crown-4-bridged derivative **3ef** (entry 14) in a lower yield (10%). It is worthy to note that this two-step procedure allowed also the synthesis of the two *meta*- and *ortho*-xylylene homo-bridged derivatives **3ee** and **3dd**[9] (entries 13 and 15) in excellent yield (98%).

The high yield observed in the insertion of the second bridge could be explained by the previously described cation templation in 1,5-bridged derivatives[7b] that folds the calix[8]arene skeleton in the 'tub-shaped' conformation[10] more suitable to bridging with short spacers. On the basis of this hypothesis we tested the effect of an additional cation in some low-yielding reactions. Thus, simple addition of 5 equiv of Cs_2CO_3 in the reaction leading to **3ae** improves the yield from 37% (entry 3) to 85% (entry 16) due to a probable Cs^+-template effect. In a similar way, addition of 5 equiv of Li_2CO_3 increases the yield of **3bc** from 15% (entry 6) to 55% (entry 17) indicating that the smaller cavity of **2b** gives a better fitting with the smaller Li^+ cation. On this ground, obviously, the other high-yielding reactions would rely on an effective Na^+ templating effect.

Compounds **3** were readily characterized by spectroscopic methods.[11] In particular, homo-bridged derivatives **3xx** gave very simple ^1H NMR spectra characterized by two *t*-Bu singlets and one $ArCH_2Ar$ AX system, typical of their D_{2d}-symmetry.[5,6] Correspondingly, hetero-bridged compounds **3xz** gave three 1:2:1 *t*-Bu singlets and two $ArCH_2Ar$ AX systems indicative of their lower C_{2v}-symmetry.

As anticipated, preliminary ^1H NMR experiments showed interesting cation complexing properties for bis-bridged calix[8]arenes **3**. Typically, upon addition of solid alkali picrate to a $CDCl_3$ solution of hosts **3** a new set of signal emerged due to the $\mathbf{M^+}\subset\mathbf{3}$ complex formation, whose 1:1 stoichiometry was determined by spectral integration. Because of the heterogenous condi-

Table 1. Yield of 1,5:3,7-doubly bridged calix[8]arenes **3** in alkylation of 1,5-bridged derivatives **2** with bis-electrophiles in the presence of NaH (10 equiv) in anhydrous THF/DMF (10:1, v/v)

Entry	2	Electroph. (equiv)	Time (h)	Isolated compd (yield%)
1	**2a**	$TsO(CH_2CH_2O)_2Ts$ (3)	26	**3ac** (50)
2	**2a**	*o*-$C_6H_4(CH_2Br)_2$ (1)	26	**3ad** (99)
3	**2a**	*m*-$C_6H_4(CH_2Br)_2$ (3)	48	**3ae** (37)[a]
4	**2a**	$TsO(CH_2CH_2O)_3Ts$ (10)	28	**3af** (43)[a]
5	**2a**	$TsO(CH_2CH_2O)_4Ts$ (1)	30	**3ag** (35)
6	**2b**	$TsO(CH_2CH_2O)_2Ts$ (2)	72	**3bc** (15)
7	**2b**	*o*-$C_6H_4(CH_2Br)_2$ (1)	40	**3bd** (93)
8	**2b**	*m*-$C_6H_4(CH_2Br)_2$ (2)	40	**3be** (92)
9	**2c**	*o*-$C_6H_4(CH_2Br)_2$ (1)	40	**3cd** (98)
10	**2c**	*m*-$C_6H_4(CH_2Br)_2$ (1)	40	**3ce** (94)
11	**2c**	$TsO(CH_2CH_2O)_3Ts$ (1)	72	**3cf** (10)
12	**2e**	*o*-$C_6H_4(CH_2Br)_2$ (1)	72	**3de** (94)
13	**2e**	*m*-$C_6H_4(CH_2Br)_2$ (1)	72	**3ee** (98)
14	**2e**	$TsO(CH_2CH_2O)_3Ts$ (1)	72	**3ef** (10)
15	**2d**	*o*-$C_6H_4(CH_2Br)_2$ (1)	27	**3dd** (98)
16	**2a**	*m*-$C_6H_4(CH_2Br)_2$ (1)	38	**3ae** (85)[b]
17	**2b**	$TsO(CH_2CH_2O)_2Ts$ (2)	90	**3bc** (55)[c]

[a] 20 equiv of NaH were used.
[b] Cs_2CO_3 (5 equiv) was added in the reaction mixture.
[c] Li_2CO_3 (5 equiv) was added in the reaction mixture.

tions a slow complexation kinetic was usually observed as illustrated by hetero-bridged *o*-xylylene/crown-3 derivative **3cd** (Fig. 1). In particular, this behavior also demonstrated that the complex is kinetically stable in the $CDCl_3$ phase (Fig. 1b). However, under homogenous conditions ($CD_3CN/CDCl_3$, 9:1 *v*/*v*) a complete complexation occurred within the time of sample preparation. In these instances, titration experiments demonstrated the kinetic lability of the complex in the homogenous $CD_3CN/CDCl_3$ phase.

The complexation-induced shifts (Fig. 1) clearly demonstrated that in the $\mathbf{M}^+\subset\mathbf{3}$ complex the cation is encapsulated inside the spheroidal cavity delimitated by the eight calix[8]arene oxygens and by the two bridging elements (Fig. 2).

The cation extraction selectivity was estimated by standard two-phase picrate extraction experiments.[12] The results, summarized in Table 2, indicate that **3cd** shows the best extraction for cesium cation, but **3ac** appears also selective for it. A preference for rubidium cation is shown by compounds **3ae**, **3bd**, **3ce**, and **3ee**. A significant extraction of K^+ is observed with **3be** with absence of selectivity. A shift of preference toward Na^+ is given by **3cf** and **3de**.

1,5:3,7-Doubly-bridged calix[8]arenes were found not to be soluble enough in dissociating solvents like methanol and acetonitrile, frequently used for complexation studies. Some of them were more soluble in dimethylformamide where complexation equilibria revealed to be very sluggish. However their higher solubility in apolar chloroform allowed the determination of the association constant K_{ass} in this solvent according to the method described by Cram.[13] Table 3 gives K_{ass} values of complexes of cesium and sodium picrates with ligands **3af**, **3ad**, **3be**, **3cd**, and **3de**.[14] **3cd** displays a selectivity for cesium over sodium of 6.3 (expressed as the ratio of the association constants) in agreement with the extraction results. The other ligands show a slight preference for sodium, although the values of K_{ass} are close taking into account the experimental error.

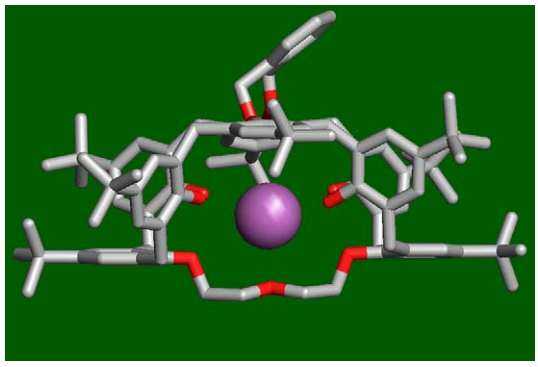

Figure 2. Computer model of the $Cs^+\subset$**3cd** complex. For clarity reasons the Cs^+ cation was drawn as a sphere of smaller dimension.

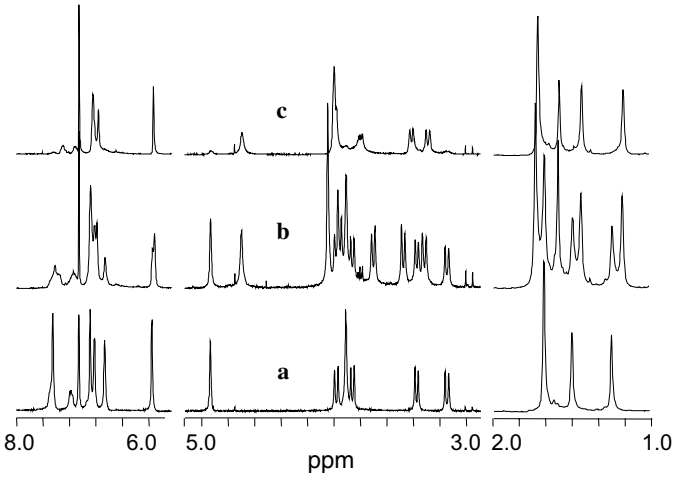

Figure 1. ^1H NMR spectra (400 MHz, $CDCl_3$, 25 °C) of **3cd** upon addition of excess solid cesium picrate: (a) free host **3cd**; (b) 48 h, and (c) 96 h after the addition of CsPic.

Table 2. Extraction percentages of alkali metal picrates from water into CH_2Cl_2 for bis-bridged calix[8]arene **3** ($T = 20\,°C$; $C_{Pic} = C_{Lig} = 5.5\times10^{-5}$ M)[a]

Compd **3**	Cs^+	Rb^+	K^+	Na^+	Li^+
3ac	10	3	3	2	⩽1
3af	9	6	7	13	6
3ad	8	8	9	10	7
3ae	⩽1	5	⩽1	⩽1	⩽1
3bd	⩽1	4	⩽1	⩽1	⩽1
3be	13	12	14	15	8
3cf	7	8	6	12	8
3cd	15	11	5	4	9
3ce	⩽1	4	⩽1	⩽1	⩽1
3de	10	8	10	14	6
3ee	6	14	7	⩽1	⩽1

[a] Standard deviation of at least three experiments: ⩽1.

Table 3. Logarithms of association constants of cesium and sodium picrates complexes with selected ligands **3** in $CHCl_3$ saturated with H_2O at 25 °C

Compd **3**	Cs^+ ($\log K_{ass}$)[a]	Na^+ ($\log K_{ass}$)[a]
3af	5.4	5.7
3ad	5.1	5.5
3be	5.7	5.9
3cd	5.6	4.8
3de	5.5	5.8

[a] Standard deviation of at least three experiments: 0.1–0.2.

In conclusion, we have synthesized the first examples of 1,5:3,7-doubly-bridged calix[8]arenes with mixed spanning elements, which possess encapsulating properties toward alkali metal cations. Experimental support for a probable cation template effect in the introduction of the second bridge were obtained. As anticipated, the length and nature of the bridges allow a modulation of cation preference from Cs^+ to Na^+. A more detailed evaluation of complexation properties of these compounds is currently in progress in our laboratory.

Acknowledgements

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8. *Synthesis of 1,5:3,7-bis-bridged calix[8]arenes* **3**: To a solution of **2** (0.037 mmol) in dry THF/DMF (10:1, v/v, 10 mL) NaH (0.37 mmol) was added. The mixture was kept at reflux under stirring for 1 h and then a solution of alkylating agent (see Table 1) dissolved in THF/DMF (3 mL) was added in several aliquots. The reaction mixture was stirred under reflux for 26–90 h (see Table 1). After concentration under vacuum, the residue was triturated with 1 N HCl (30 mL), collected by filtration, washed with MeOH, and dried. Analytically pure samples were obtained by crystallization or by column chromatography on silica gel.
9. Bis(*o*-xylylene)-bridged calix[8]arene **3dd** was previously obtained in 19% yield by Shinkai and co-workers, by direct alkylation of **1** in the presence of NaH (see Ref. 5a).
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11. Satisfactory microanalytical and spectral data were obtained for all new compounds. *Compound* **3ac**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.16, 1.18, 1.24 (s, $(CH_3)_3$, 18H, 18H, 36H), 2.09 (s, OCH_2CH_2, 4H), 3.43 and 4.30 (AX, $J = 14.4$ Hz, $ArCH_2Ar$, 8H), 3.44 and 4.30 (AX, $J = 14.3$ Hz, $ArCH_2Ar$, 8H), 3.88 (s, OH_2CH_2, 4H), 4.07 (m, $O(CH_2CH_2O)_2$, 8H), 6.96, 7.04, 7.11, 7.14 (br s, ArH, 8H, 4H, 4H), 7.23 (s, OH, 4H). *Compound* **3ad**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.06, 1.18, 1.32 (s, $(CH_3)_3$, 18H, 18H, 36H), 2.29 (s, OCH_2CH_2, 4H), 3.13 and 4.23 (AX, $J = 14.4$ Hz, $ArCH_2Ar$, 8H), 3.42 and 4.24 (AX, $J = 13.3$ Hz, $ArCH_2Ar$, 8H), 4.14 (s, OCH_2CH_2, 4H), 5.75 (s, *o*-Xyl-CH_2O, 4H), 6.85 (s, Ar, 4H), 7.10 (d, $J = 2.2$ Hz, ArH, 4H), 7.12 (s, ArH, 4H), 7.16 (d, $J = 2.2$ Hz, ArH, 4H), 7.29 (m, *o*-Xyl-H, 2H), 7.36 (br s, *o*-Xyl-H, 2H), 7.64 (s, OH, 4H). *Compound* **3ae**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.21, 1.22 (s, $(CH_3)_3$, 18H, 54H), 2.18 (s, OCH_2CH_2, 4H), 3.45 and 4.27 (AX, $J = 13.9$ Hz, $ArCH_2Ar$, 8H), 3.49 and 4.33 (AX, $J = 14.2$ Hz, $ArCH_2Ar$, 8H), 4.06 (s, OCH_2CH_2, 4H), 4.84 (s, *m*-Xyl-CH_2O, 4H), 6.74 (s, ArH, 4H), 7.02 (d, $J = 1.8$ Hz, ArH, 2H), 7.07 (d, $J = 1.8$ Hz, ArH, 2H), 7.11 (s, ArH, 4H), 7.17 (s, ArH, 4H), 7.20–7.38 (m, *m*-Xyl-H, 4H), 7.40 (s, OH, 4H). *Compound* **3af**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.16, 1.17, 1.33 (s, $(CH_3)_3$, 18H, 18H, 36H), 2.22 (s, OCH_2CH_2, 4H), 3.48 and 4.41 (AX, $J = 14.9$ Hz, $ArCH_2Ar$, 8H), 3.51 and 4.31 (AX, $J = 14.3$ Hz, $ArCH_2Ar$, 8H), 3.64 (s, OCH_2CH_2, 4H), 3.93 (br s, $O(CH_2CH_2O)_3$, 6H), 4.15 (br s, $O(CH_2CH_2O)_3$, 6H), 7.05, 7.06, 7.18 (br s, ArH, 4H, 8H, 4H), 7.44 (s, OH, 4H). *Compound* **3ag**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.18, 1.21, 1.26 (s, $(CH_3)_3$, 16H, 16H, 36H), 2.00 (s, OCH_2CH_2, 4H), 3.71 (s, OCH_2CH_2, 4H), 3.49 and 4.33 (AX, $J = 14.1$ Hz, $ArCH_2Ar$, 4H), 3.77 and 4.15 (AX, $J = 15.7$ Hz, $ArCH_2Ar$, 4H), 3.84, 3.96, 4.15 (br s, $O(CH_2CH_2O)_4$, 8H, 4H, 4H), 7.01 (s, ArH, 4H), 7.04 (d,

$J = 1.2$ Hz, ArH, 4H), 7.15 (s, ArH, 4H), 7.17 (d, $J = 1.2$ Hz, ArH, 4H), 7.44 (s, OH, 4H). *Compound* **3bc**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.11, 1.20, 1.31 (s, $(CH_3)_3$, 18H, 18H, 36H), 3.42 and 4.40 (AX, $J = 14.5$ Hz, $ArCH_2$, Ar, 8H), 3.47 and 4.20 (AX, $J = 13.5$ Hz, $ArCH_2Ar$, 8H), 4.21 (m, OCH_2CH_2O, 2H), 4.29 (m, $O(CH_2CH_2O)_2$, 4H) 4.95 (s, OCH_2CH_2O, 2H), 6.94 (s, $O(CH_2CH_2O)_2$, 4H), 7.12–7.17 (m, ArH, 16H), 7.66 (s, OH, 4H). *Compound* **3bd**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.10, 1.16, 1.30 (s, $(CH_3)_3$, 18H, 18H, 36H), 3.34 and 4.23 (AX, $J = 13.3$ Hz, $ArCH_2Ar$, 8H), 3.43 and 4.29 (AX, $J = 13.9$ Hz, $ArCH_2Ar$, 8H), 4.99 (s, *o*-Xyl-CH_2O, 4H), 5.76 (s, OCH_2CH_2O, 4H), 6.94, 7.06, 7.01, 7.11 7.12 (br s, ArH, 4H, 4H, 4H, 4H), 7.15 (m, *o*-Xyl-H, 2H), 7.32 (m, *o*-Xyl-H, 2H), 7.43 (s, OH, 4H). *Compound* **3be**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.11, 1.17, 1.32 (s, $(CH_3)_3$, 18H, 18H, 36H), 3.36 and 4.31 (AX, $J = 14.3$ Hz, $ArCH_2$-Ar, 8H), 3.51 and 4.39 (AX, $J = 13.4$ Hz, $ArCH_2Ar$, 8H), 4.78 (s, *m*-Xyl-CH_2O, 4H), 5.08 (s, OCH_2CH_2O, 4H), 6.92 (s, ArH, 4H), 6.99 (s, *m*-Xyl-H, 1H), 7.10, 7.15, 7.24 (br s, ArH, 4H, 4H, 4H), 7.30 (t, $J = 7.6$ Hz, *m*-Xyl-H, 1H), 7.44 (d, $J = 7.6$ Hz, *m*-Xyl-H, 2H), 7.52 (s, OH, 4H). *Compound* **3cd**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.04, 1.20, 1.30 (s, $(CH_3)_3$, 18H, 18H, 36H), 3.14 and 4.26 (AX, $J = 15.0$ Hz, $ArCH_2Ar$, 8H), 3.45 and 4.09 (AX, $J = 13.6$ Hz, $ArCH_2Ar$, 8H), 4.14 (br d, $J = 4.1$ Hz, $O(CH_2CH_2O)_2$, 4H), 4.17 (br d, $J = 4.1$ Hz, $O(CH_2CH_2O)_2$, 4H), 5.54 (s, *o*-Xyl-CH_2O, 4H), 6.73 (s, ArH, 4H), 7.07 (d, $J = 2.0$ Hz, ArH, 4H), 7.14 (d, $J = 2.0$ Hz, ArH, 4H), 7.18 (s, ArH, 4H), 7.31 (m, *o*-Xyl-H, 2H), 7.43 (s, OH, 4H), 7.44 (m, *o*-Xyl-H, 2H). *Compound* **3ce**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.16, 1.18, 1.20 (s,$(CH_3)_3$, 18H, 18H, 36H), 3.46 and 4.28 (AX, $J = 14.4$ Hz, $ArCH_2Ar$, 16H), 4.07 (br d, $J = 3.8$ Hz, $O(CH_2CH_2O)_2$, 4H), 4.12 (br d, $J = 4.4$, $O(CH_2CH_2O)_2$, 4H), 4.76 (s, *m*-Xyl-CH_2O, 4H), 6.74, 6.99, 7.02 (br s, ArH, 4H, 4H, 4H), 7.07 (d, $J = 2.1$ Hz, ArH, 4H), 7.13 (m, *m*-Xyl-H, 2H), 7.34 (m, *m*-Xyl-H, 2H), 7.52 (s, OH, 4H). *Compound* **3cf**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.01, 1.06, 1.20 (s, $(CH_3)_3$, 18H, 18H, 36H), 3.32 and 4.40 (AX, $J = 13.1$ Hz, $ArCH_2Ar$, 8H), 3.40–4.27 (m, OCH_2, 10H) 3.46 and 4.38 (AX, $J = 14.3$ Hz, $ArCH_2Ar$, 8H), 5.10 (br s, OCH_2, 10H), 6.93 (s, ArH, 4H), 7.10 (d, $J = 2.1$ Hz, ArH, 4H), 7.15, 7.65 (br s, ArH, 4H, 4H), 8.02 (s, OH, 4H). *Compound* **3ed**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.07, 1.16, 1.30 (s, $(CH_3)_3$, 18, 18H, 36H), 3.14 and 4.47 (AX, $J = 14.9$ Hz, $ArCH_2Ar$, 8H), 3.48 and 4.18 (AX, $J = 13.6$ Hz, $ArCH_2Ar$, 8H), 5.02, 5.46 (s, Xyl-CH_2O, 4H, 4H), 6.78, 7.04, 7.09 (s, ArH, 4H, 4H, 4H), 7.16 (d, $J = 1.8$ Hz, ArH, 4H), 7.24–7.30 (m, Xyl-H, 3H), 7.34 (d, $J = 6.4$ Hz, *m*-Xyl-H, 2H), 7.35 (s, *m*-Xyl-H, 1H), 7.41 (d, $J = 7.5$ Hz, *o*-Xyl-H, 2H), 8.05 (s, OH, 4H). *Compound* **3ee**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.16, 1.22 (s, $(CH_3)_3$, 36H, 36H), 3.47 and 4.34 (AX, $J = 14.7$ Hz, $ArCH_2Ar$, 16H), 4.89 (s, *m*-Xyl-CH_2O, 8H), 7.01, 7.07 (s, ArH, 8H, 8H), 7.22 (t, $J = 7.6$ Hz, *m*-Xyl-H, 2H), 7.41 (d, $J = 7.6$ Hz, *m*-Xyl-H, 4H), 7.56 (s, *m*-Xyl-H, 2H), 7.56 (s, OH, 4H). *Compound* **3ef**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.07, 1.16, 1.30 (s, $(CH_3)_3$, 18H, 18H, 36H), 3.14 and 4.18 (AX, $J = 14.9$ Hz, $ArCH_2Ar$, 8H), 3.48 and 4.41 (AX, $J = 13.6$ Hz, $ArCH_2Ar$, 8H), 3.75–4.10 (br m, $O(CH_2CH_2O)_3$, 8H), 5.02 (br s, $O(CH_2CH_2O)_3$, 4H), 5.46 (s, *m*-Xyl-CH_2O, 4H), 6.78 (s, ArH, 4H), 7.04 (d, $J = 2.1$ Hz, ArH, 4H), 7.09 (s, ArH, 4H), 7.16 (d, $J = 2.1$ Hz, ArH, 4H), 7.28 (m, *m*-Xyl-H, 1H), 7.33 (s, *m*-Xyl-H, 1H), 7.41 (d, $J = 7.4$ Hz, *m*-Xyl-H, 2H), 8.05 (s, OH, 4H).

12. Equal volumes (5 mL) of solution at equal concentration (5.5×10^{-5} M) of compounds **3** (in CH_2Cl_2) and alkali metal picrate (in H_2O) were magnetically stirred for 48 h at 20 °C The two phases were separated and the extraction percentage ($A_0-A/A_0\times100$) was determined by measuring the absorbance (A) of aqueous phase at 356 nm and the corresponding absorbance (A_0) of a blank experiment.
13. (a) Moore, S. S.; Tarnowski, T. L.; Newcomb, N.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398; (b) Helgeson, R. C.; Weisman, G. R.; Toner; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928.
14. Association constants were calculated from the equation $K_{ass} = K_{ex}/K_d$ where K_{ex} and K_d are the extraction and the distribution constants, respectively according to Ref. 13 a. The experimental conditions were the following: K_d was determined by shaking (3 min with a vortex and 30 min magnetically) 50 mL of aqueous picrate solution (10^{-2} M) with 75 mL of $CHCl_3$ saturated with water. After phase separation, the $CHCl_3$ layer was evaporated at 60 °C under vacuum; the residue was then diluted in 5 mL CH_3CN and its absorbance measured at 375 nm at 25 °C. K_{ex} was determined by shaking 2 mL of an aqueous picrate solution (5×10^{-3} M) and 2 mL of a 10^{-3} M calixarene solution in $CHCl_3$. After separation of the two phases, 1 mL or 0.5 mL of the $CHCl_3$ solution were diluted in 5 mL CH_3CN. The absorption of this solution was measured against the appropriate blank solution at 375 nm at 25 °C.