J Incl Phenom Macrocycl Chem (2010) 68:423–429
DOI 10.1007/s10847-010-9802-8

ORIGINAL ARTICLE

Intramolecular cyclization strategy: synthesis of 1,3- and 1,2-calix[4]crown-7 and calix[4]crown-9 cone conformers

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Received: 26 March 2010 / Accepted: 4 May 2010 / Published online: 20 May 2010

Abstract 1,3- and 1,2-calix[4]crown-7 and calix[4]-crown-9 cone conformers were synthesized in acceptable yields by sequential introduction of two distal or proximal polyethylene glycolic chains with terminal hydroxyls at the lower rim, monotosylation, and intramolecular ring closure reaction. According to the two-phase extraction experiment, the title compounds showed mediocre affinity for alkali and alkaline earth metal picrates. The 1,2-calix[4]-crown-9 extracted Sr^{2+} selectively among other alkaline earth metal cations.

Keywords Calix[4]crown-7 · Calix[4]crown-9 · Intramolecular cyclization strategy · Synthesis · Monotosylation

Introduction

Calix[4]crowns represent a wide range of peculiar synthetic ionophores which possess both versatile calix[4]arene skeletons and crown ether moieties. Intense investigation has revealed that specific calix[4]crowns exhibit efficient and selective binding ability towards alkali metal, alkaline earth metal and ammonium cations, depending on the conformation of the calix skeleton, the size of the crown ether loop, the identity of donor atoms on the crown ether moiety, and the coordination-assisting groups deployed around the crown ether moiety [1–3]. Apart from serving as macrocyclic ionophores for ion recognition, nowadays the utilization of calix[4]crowns containing large crown ether loops has been expanded to the construction of calix-based rotaxanes [4] and catenanes [5], which have potential application in molecular devices.

Regarding the synthesis of calix[4]crowns, intramolecular cyclization strategy has been widely applied. In this context, the most popular method features the direct condensation of calix[4]arenes and oligoethylene glycol ditosylates in the presence of appropriate base and solvent via nucleophilic substitution reaction. A newly developed alternative opened a new perspective for the synthesis of calix[4]crown by the reaction of calix[4]arenes with oligoethylene glycols under the Mitsunobu protocol using the diethyl azodicarboxylate (DEAD)/triphenylphosphine (TPP) system [6, 7]. Generally, the intermolecular cyclization strategy worked well in the case of 1,3- and 1,2-calix[4]crowns containing 3–6 ethereal oxygen atoms. However, in some cases, where the syntheses of a 1,3-calix[4]crown-7 analogue [8], 1,3-calix[4]crown-9 and crown-11 analogues utilized as donor rings to assemble calix[4]arene[2]catenanes [9], and 1,2-calix[4]monocrown-7 [10] were involved, the yields proved to be rather poor, presumably due to the disfavor of entropy or/and the lack of efficient metal template effect during the ring closure process.

Intramolecular cyclization strategy has been less applied in this regard and rarely seen in calixarene chemistry. The first example of a calix[4]arene bridged at the 1,3-position of the upper rim with a very short CH_2OCH_2 group was derived from an intramolecular cyclization process by chance rather than by design [11]. Recently, ring-closing metathesis (RCM) reaction as an efficient approach to

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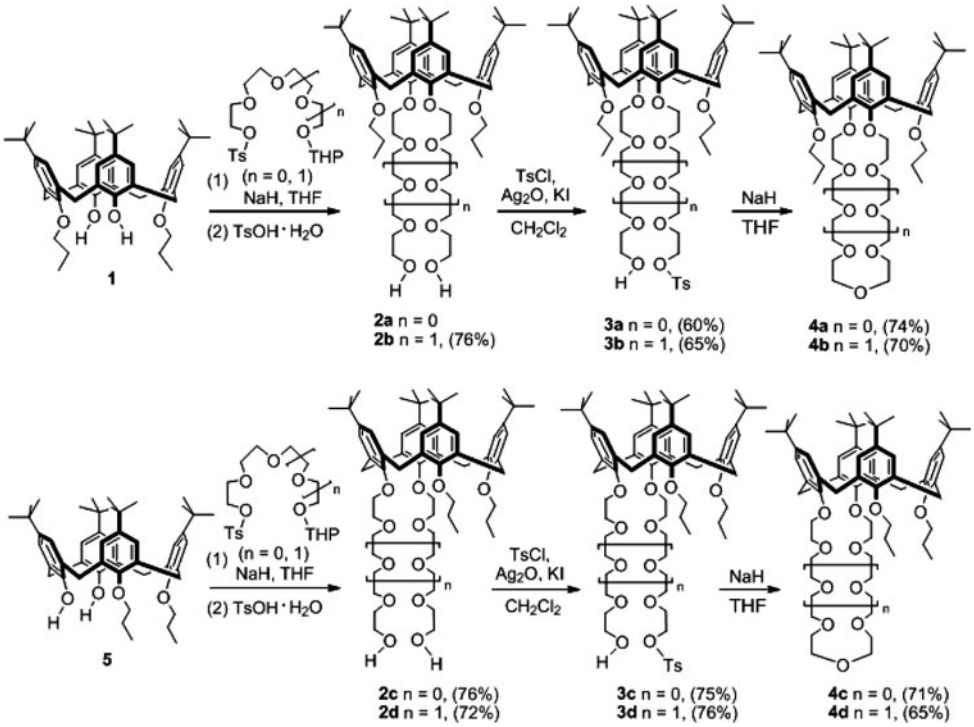
macrocyclic systems via intramolecular formation of carbon–carbon double bonds has also been used for the synthesis of novel calix[4]crowns [12]. In fact, by proper design, the imaginable advantages of intramolecular cyclization strategy may involve: (i) the readiness of ring closure because of less entropy disfavor and the less dependence on the template effect; (ii) the easy availability of the reagents for the synthesis of calixcrowns containing large size crown ether moieties, where the preparation of long polyethylene glycols or corresponding ditosylates as the ring formation segments is avoided. Based on our preliminary work [13], herein we report a general method for the synthesis of distally- and proximally-substituted calix[4]crown cone conformers by an intramolecular cyclization strategy via simple nucleophilic substitution reaction. In view of the scarcity of the reports on the properties of calix[4]crowns containing more than 6 oxygen atoms in the crown ether units, their binding properties towards alkali and alkaline earth metal picrates have also been evaluated by two-phase extraction experiment.

Results and discussion

We initially synthesized the 1,3-calix[4]crown-7 and calix[4]crown-9 cone conformers by a four-step sequence as depicted in Scheme 1. The treatment of 25,27-dipropoxy-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arene **1** with readily available THP-protected oligoethylene glycol monotosylates in the presence of NaH in THF afforded corresponding tetra-*O*-alkylated derivatives, followed by the removal of the THP protecting groups with $TsOH{\cdot}H_2O$ to give diol compounds **2**. As such, two oligoethylene glycolic chains with terminal hydroxyls were introduced into the calix[4]-arene skeleton at the lower rim. Efficient monotosylation of diol compounds **2** is a guarantee of the feasibility of the whole scheme. In 2002, Bouzide and Sauvé reported the Ag_2O mediated highly selective monotosylation of symmetrical diols, the high selectivity being explained on the basis of the difference in acidity between the two hydroxyl groups which undergo an intramolecular hydrogen bonding [14]. Application of this synthetic protocol to substrates **2a** and **2b**, which contain two hydroxyl groups at the lower rim, led to the formation of **3a** and **3b**, respectively, in good yields. Subsequent intramolecular cyclization was smoothly achieved in the presence of NaH in THF to furnish 1,3-calix[4]crown-7 **4a** and calix[4]crown-9 **4b**.

The successful synthesis of the 1,3-calix[4]crown-7 and calix[4]crown-9 derivatives prompted us to synthesize their 1,2-calix[4]crown counterparts for the purposes of (i) investigating the generality of this four-step sequence for the synthesis of calixcrowns with large crown ether loops and (ii) providing more examples for the less studied 1,2-calix[4]crowns [15–18]. Thus, 25,26-dipropoxy-27,28-dihydroxy-*p*-*tert*-butylcalix[4]arene **5** as the starting material was subjected to the same procedure aforementioned and the key steps of monotosylation and intramolecular ring closure worked well under similar conditions to afford 1,2-



Scheme 1 Synthesis of 1,3-calix[4]crown-7 cone conformer 4a, 1,3-calix[4]crown-9 cone conformer 4b, 1,2-calix[4]crown-7 cone conformer 4c and 1,2-calix[4]crown-9 cone conformer 4d

calix[4]crown-7 **4c** and 1,2-calix[4]crown-9 **4d** in good yields. It is worth noting that monotosylation of 1,2-dipropyl diol compounds **2c** and **2d** afforded **3c** and **3d**, respectively, as inherently chiral calix[4]arenes of AABC substitution pattern at the lower rim.

The structures of all new compounds were fully confirmed by NMR, ESI-MS and HRMS data. 1,3-calix[4]-crowns and their 1,2-counterparts showed obvious structural differences, which was reflected from the NMR spectra of typical compounds **4b** and **4d**. For **4b**, the two singlets attributable to the aromatic protons, a pair of doublets assignable to the $ArCH_2Ar$ methylene bridge protons (in a ratio of 1:1) and the two singlets attributable to the *tert*-butyl groups are in agreement with its molecular symmetry. For **4d**, which has only one plane of symmetry, three pairs of doublets are assignable to the $ArCH_2Ar$ methylene bridge protons (in a ratio of 1:1:2, partially overlapped). In view of the differences of the chemical shift values of the aromatic protons (6.97 ppm and 6.57 ppm) as well as that of the *tert*-butyl protons (1.23 ppm and 0.91 ppm), combining with the signals arising from the $ArCH_2Ar$ methylene bridge carbons at around 30.9 ppm, 1,3-calix[4]crown **4b** was believed to adopt a pinched cone conformation. 1,2-Calix[4]crown **4d** also adopts a cone conformaiton, which could be deduced from the $ArCH_2Ar$ methylene bridge carbons appearing at 31.0 ppm. By comparison, the resonances of its aromatic protons and *tert*-butyl protons centered at 6.77 ppm and 1.07 ppm, indicating a regular cone conformation (Fig. 1).

The complexation ability of **4a–d** towards alkali and alkaline earth metal ions was evaluated by liquid–liquid extraction experiment. According to the results (Table 1), 1,3-dipropyl calix[4]crown-7 (**4a**) extracted all the alkali metal cations with mediocre efficiency and selectivity, the highest extraction percentage occurring in the case of Na^+ (7.5%). Similarly, its crown-9 counterpart (**4b**) and 1,2-counterpart (**4c**) showed mediocre efficiency and selectivity towards alkali metal cations, with the highest extraction percentage of 7.2% for K^+ and 8.9% for Na^+, respectively. Comparatively, 1,2-dipropyl calix[4]crown-9 (**4d**) had the lowest affinity towards alkali metal cations, the highest extraction percentage occurring in the case of Cs^+ (3.1%). Generally, **4a–d** extracted alkaline earth metal cations less efficiently than alkali metal cations. Compounds **4b** and **4c** didn't extract Mg^{2+}, Ba^{2+} and Mg^{2+}, Ca^{2+}, respectively. Compound **4d** proved to be most selective for Sr^{2+} because no extraction was detected for all other alkaline earth metal cations.

Though the title compounds did not show pronounced extraction efficiency and selectivity towards alkali metal and alkaline earth metal cations, it is conceivable that by replacing the lower rim propyl groups with coordinating

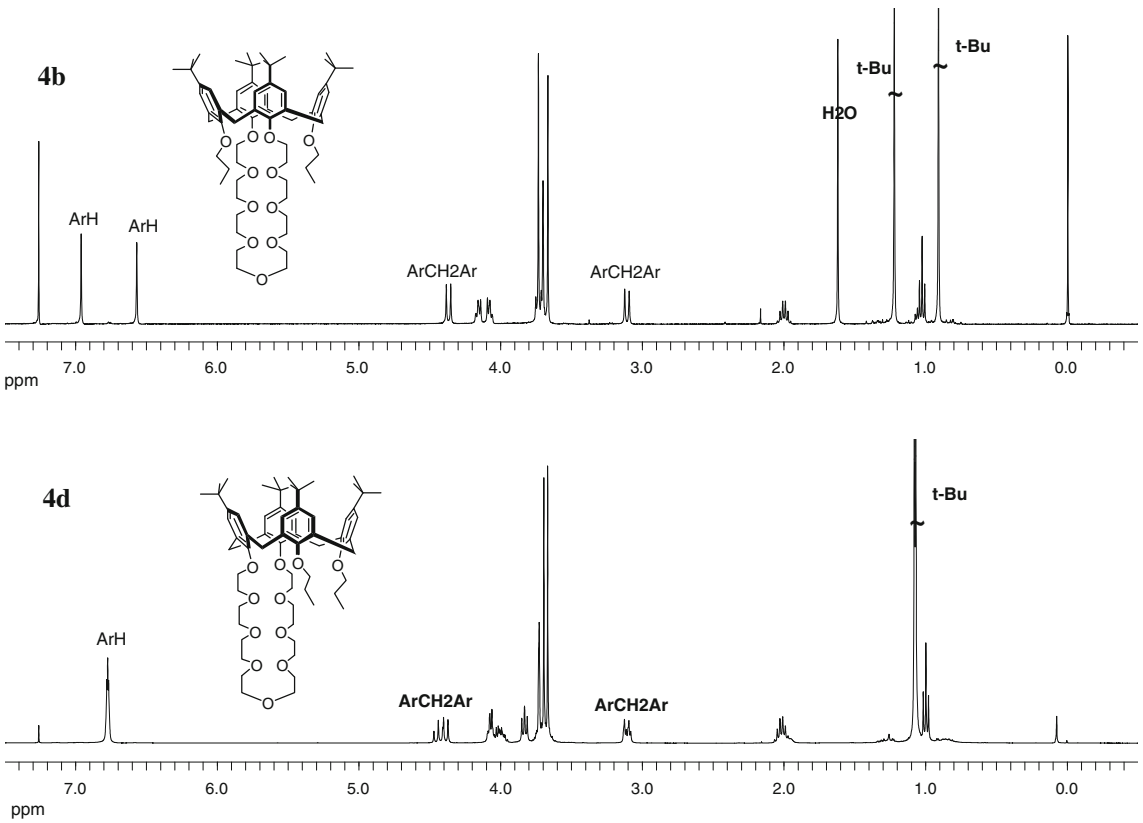


Fig. 1 ^1H NMR spectra of **4b** and **4d** (400 MHz, $CDCl_3$, 25 °C)

Table 1 Extraction percentage of alkali metal and alkaline earth metal picrates by **4a–d**, from water to dichloromethane, at 16 ± 2 °C

c4aalix[4] crowns	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
4a	4.2	7.5	2.2	1.5	4.1	1.6	3.9	6.1	4.0
4b	6.1	6.3	7.2	2.4	2.4	0	2.8	2.7	0
4c	3.1	8.9	4.1	4.0	2.8	0	0	1.4	2.1
4d	1.7	1.4	1.5	0	3.1	0	0	5.0	0

groups such as ester groups, amide groups and proton-ionizable groups [15, 16], the binding efficiency and selectivity should be enhanced.

Conclusion

We have offered a general approach to 1,3- and 1,2-calix[4]crown-7 and calix[4]crown-9 cone conformers by an intramolecular cyclization strategy in acceptable yields, which may complement the traditional intermolecular cyclization strategy for the synthesis of calixcrowns, especially that of large crown ether loops. The 1,3-calix[4]crowns in question adopt the pinched cone conformation and the 1,2-counterparts adpot the regular cone conformaiton according to NMR data analysis. Currently, we are engaged in exploring the possibility of applying our method to the design and synthesis of topologically interesting calixcrowns which could not be prepared otherwise.

Experimental

Melting points were measured on a Beijing Taike X-5 apparatus and uncorrected. NMR spectra were recorded on a Bruker Av-400 spectrometer with $CDCl_3$ as a solvent and TMS as an internal standard. ESI-MS spectra were recorded on an LCQ Deca XP mass spectrometer. High resolution mass spectra were recorded on a Waters Q-Tof micro mass spectrometer. UV–Vis spectra were recorded by an SP-756PC UV–Vis spectrophotometer. Compounds **1** [19], **2a** [20], **5** [21], 1-tosyl-10-(tetrahydropyran-2-yl)-1,4,7,10-tetraoxadecane, 1-tosyl-13-(tetrahydro pyran-2-yl)-1,4,7,10,13-penta oxatridecane [22] and Ag_2O [23] were prepared as described in pertinent literatures. THF was freshly distilled from Na-benzophenone prior to use. The syntheses of **2b**, **3b** and **4b** have been reported by us previously [13].

General procedure for the syntheses of diol compounds **2c** and **2d**

A solution of 25,26-dipropoxy-27,28-dihydroxy-*p*-*tert*-butylcalix[4]arene **5** (1.86 g, 2.54 mmol) in THF (40 mL) was stirred at room temperature in the presence of NaH (487 mg, 8.0 equiv) for 30 min, followed by addition of a solution of 1-tosyl-10-(tetrahydro pyran-2-yl)-1,4,7,10-tetraoxadecane or 1-tosyl-13-(tetrahydro pyran-2-yl)-1,4,7,10,13-penta oxatridecane (3.0 equiv) in THF (30 mL). The reaction mixture was refluxed under N_2 for 3d. Methanol was added dropwise to quench the reaction (caution!). After evaporation of the solvent under reduced pressure, the residue was partitioned between water (50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over Na_2SO_4. Subsequent purification by column chromatography (SiO_2, petroleum ether/acetone 4:1) gave corresponding tetra-*O*-alkylated intermediates, which was further treated with $TsOH{\cdot}H_2O$ (1.0 equiv) in 95% ethanol (50 mL) under reflux for 3 h. Aqueous NaOH (1 N, 3 mL) was added to quench the reaction. After evaporation of the solvent under reduced pressure, the residue was partitioned between aqueous HCl (1 N, 50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over Na_2SO_4. Subsequent purification by column chromatography furnished compounds **2c** or **2d** as a colorless solid.

Compound **2c**: Column chromatography (SiO_2, petroleum ether/acetone 3:1). Yield 76%. Mp 62–64 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.79–6.76 (m, 8H, ArH), 4.46 (d, 1H, J = 12.8 Hz, $ArCH_2Ar$), 4.42 (d, 1H, J = 12.8 Hz, $ArCH_2Ar$), 4.38 (d, 2H, J = 12.8 Hz, $ArCH_2Ar$), 4.11–3.94 (m, 8H, OCH_2CH_2O), 3.85–3.81 (m, 4H, $ArOCH_2CH_2CH_3$), 3.75–3.70 (m, 12H, OCH_2CH_2O), 3.61–3.59 (m, 4H, OCH_2CH_2O), 3.43 (t, 2H, J = 6.4 Hz, OH), 3.11 (d, 3H, J = 12.4 Hz, $ArCH_2Ar$), 3.10 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 2.06–1.96 (m, 4H, $ArOCH_2CH_2CH_3$), 1.08 (s, 18H, $C(CH_3)_3$), 1.07 (s, 18H, $C(CH_3)_3$), 1.00 (t, 6H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 153.2, 144.6, 144.3, 133.83, 133.76, 133.7, 125.0, 124.9, 77.2, 72.8, 72.6, 70.5, 70.43, 70.40, 61.7, 33.82, 33.79, 31.43, 31.41, 31.01, 30.96, 23.3, 10.4. ESI-MS *m*/*z* 1019.6 [M + Na^+], 1035.6 [M + K^+]. HRMS calcd for $C_{62}H_{92}O_{10}Na$ [M + Na^+] 1019.6588; found 1019.6591.

Compound **2d**: Column chromatography (SiO_2, petroleum ether/acetone 3:1). Yield 72%. Mp 66–70 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.77–6.76 (m, 8H, ArH), 4.43 (d, 1H, J = 12.2 Hz, $ArCH_2Ar$), 4.41 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 4.39 (d, 2H, J = 12.3 Hz, $ArCH_2Ar$), 4.14–3.94 (m, 8H, OCH_2CH_2O), 3.82 (t, 4H, J = 7.8 Hz, $ArOCH_2CH_2CH_3$), 3.72–3.57 (m, 24H, OCH_2CH_2O), 3.113 (d, 1H, J = 12.5 Hz, $ArCH_2Ar$), 3.106 (d, 2H, J = 12.6 Hz, $ArCH_2Ar$), 3.10 (d, 1H, J = 12.7 Hz, $ArCH_2Ar$), 2.97 (s, 2H, OH), 2.01 (sextet, 4H, J = 7.8 Hz, $ArOCH_2CH_2CH_3$), 1.075 (s, 18H, $C(CH_3)_3$), 1.067 (s, 18H, $C(CH_3)_3$), 1.00 (t, 6H, J = 7.8 Hz, $ArOCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.6, 153.3, 144.6, 144.3, 133.8, 133.7, 124.94, 124.89, 72.8, 72. 7, 70.7, 70.6, 70.5,

70.41, 70.38, 61.7, 33.82, 33.80, 31.5, 31.4, 31.1, 31.0, 23.3, 10.4. ESI-MS *m/z* 1107.8 [M + Na^+]. HRMS calcd for $C_{66}H_{100}O_{12}Na$ [M + Na^+] 1107.7112; found 1107.7106.

General procedure for the monotosylation of **2** to afford **3a–d**

To a solution of **2** (0.37 mmol) in CH_2Cl_2 (40 mL) were added Ag_2O (128 mg, 1.5 equiv), KI (12 mg, 0.2 equiv) and TsCl (84 mg, 1.2 equiv). The reaction mixture was stirred overnight at room temperature. After filtration and evaporation of the solvent under reduced pressure, the residue was directly subjected to column chromatography to give **3** as colorless solids.

Compound **3a**: Column chromatography (SiO_2, petroleum ether/acetone 5:1). Yield 60%. Mp 92–95 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, J = 8.3 Hz, SO_2ArH), 7.32 (d, 2H, J = 8.3 Hz, SO_2ArH), 6.85 (d, 2H, ArH), 6.84 (d, 2H, ArH), 6.69 (d, 4H, ArH), 4.382 (d, 2H, J = 12.5 Hz, $ArCH_2Ar$), 4.378 (d, 2H, J = 12.5 Hz, $ArCH_2Ar$), 4.16–3.60 (m, 24H, OCH_2CH_2O), 3.78 (t, 4H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$), 3.12 (d, 2H, J = 12.5 Hz, $ArCH_2Ar$), 3.11 (d, 2H, J = 12.5 Hz, $ArCH_2Ar$), 2.43 (s, 3H, SO_2ArCH_3), 2.00 (sextet, 4H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$), 1.145 (s, 9H, $C(CH_3)_3$), 1.133 (s, 9H, $C(CH_3)_3$), 1.01 (s, 18H, $C(CH_3)_3$), 0.99 (t, 6H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.50, 153.48, 153.3, 144.8, 144.71, 144.67, 144.2, 134.2, 133.2, 133.0, 129.8, 128.0, 125.0, 124.8, 77.2, 72.6, 72.44, 72.35, 70.8, 70.6, 70.47, 70.46, 70.3, 69.2, 68.8, 61.8, 33.9, 33.7, 31.5, 31.4, 31.0, 23.4, 21.6, 10.5. ESI-MS *m/z* 1173.8 [M + Na^+]. HRMS calcd for $C_{69}H_{98}O_{12}SNa$ [M + Na^+] 1173.6677; found 1173.6680.

Compound **3c**: Column chromatography (SiO_2, petroleum ether/acetone 4:1). Yield 75%. Mp 89–90 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, J = 8.0 Hz, SO_2ArH), 7.32 (d, 2H, J = 8.0 Hz, SO_2ArH), 6.79–6.75 (m, 8H, ArH), 4.41 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 4.40 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 4.39 (d, 2H, J = 12.4 Hz, $ArCH_2Ar$), 4.16–3.93 (m, 10H, OCH_2CH_2O), 3.81 (t, 4H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$), 3.70–3.59 (m, 14H, OCH_2CH_2O), 3.11 (d, 2H, J = 12.4 Hz, $ArCH_2Ar$), 3.10 (d, 2H, J = 12.4 Hz, $ArCH_2Ar$), 2.58 (s, 1H, OH), 2.43 (s, 3H, SO_2ArCH_3), 2.00 (sextet, 4H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$), 1.09 (s, 9H, $C(CH_3)_3$), 1.08 (s, 9H, $C(CH_3)_3$), 1.06 (s, 18H, $C(CH_3)_3$), 0.99 (t, 3H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$), 0.98 (t, 3H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.6, 153.5, 153.3, 153.2, 144.8, 144.63, 144.56, 144.30, 144.27, 133.9, 133.78, 133.75, 133.7, 133.6, 133.0, 129.8, 128.0, 125.0, 124.92, 124.85, 72.7, 72.61, 72.56, 70.8, 70.52, 70.49, 70.41, 70.37, 69.2, 68.8, 61.8, 33.82, 33.79, 33.77, 31.44, 31.42, 31.40, 31.04, 30.98, 23.32, 23.28, 21.62, 10.40, 10.36. ESI-MS *m/z* 1173.7 [M + Na^+]. HRMS calcd for $C_{69}H_{98}O_{12}SNa$ [M + Na^+] 1173.6677; found 1173.6672.

Compound **3d**: Column chromatography (SiO_2, petroleum ether/acetone 5:1). Yield 76%. Mp 81–83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, J = 8.2 Hz, SO_2ArH), 7.33 (d, 2H, J = 8.2 Hz, SO_2ArH), 6.77 (s, 8H, ArH), 4.41 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 4.40 (d, 3H, J = 12.5 Hz, $ArCH_2Ar$), 4.16–3.93 (m, 10H, OCH_2CH_2O), 3.81 (t, 4H, J = 7.4 Hz, $ArOCH_2CH_2CH_3$), 3.70–3.56 (m, 22H, OCH_2CH_2O), 3.11 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 3.104 (d, 1H, J = 12.6 Hz, $ArCH_2Ar$), 3.097 (d, 2H, J = 12.6 Hz, $ArCH_2Ar$), 2.63 (s, 1H, OH), 2.44 (s, 3H, SO_2ArCH_3), 2.01 (sextet, 4H, J = 7.4 Hz, $ArOCH_2CH_2CH_3$), 1.08 (s, 9H, $C(CH_3)_3$), 1.07 (s, 18H, $C(CH_3)_3$), 1.06 (s, 9H, $C(CH_3)_3$), 0.99 (t, 3H, J = 7.4 Hz, $ArOCH_2CH_2CH_3$), 0.98 (t, 3H, J = 7.4 Hz, $ArOCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.6, 153.5, 153.32, 153.30, 144.8, 144.5, 144.3, 133.83, 133.79, 133.77, 133.75, 133.70, 133.0 129.8, 128.0, 124.93, 124.89, 77.2, 72.8, 72.7, 72.5, 70.8, 70.7, 70.63, 70.58, 70.44, 70.39, 70.37, 69.2, 68.7, 61.8, 33.81, 33.80, 31.45, 31.43, 31.1, 31.0, 23.3, 21.6, 10.4. ESI-MS *m/z* 1261.8 [M + Na^+]. HRMS calcd for $C_{73}H_{106}O_{14}SNa$ [M + Na^+] 1261.7201; found 1261.7203.

General procedure for intramolecular ring closure to afford **4a–d**

A solution of 3 (0.16 mmol) in THF (55 mL) was refluxed in the presence of NaH (45 mg, 12.0 equiv) under N_2 for 1d. Methanol was added dropwise to quench the reaction (caution!). After evaporation of the solvent under reduced pressure, the residue was partitioned between water (50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over Na_2SO_4. Subsequent purification by column chromatography gave **4** as colorless solids.

Compound **4a**: Column chromatography (SiO_2, petroleum ether/acetone 2:1). Yield 74%. Mp 214–216 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (s, 4H, ArH), 6.45 (s, 4H, ArH), 4.36 (d, 4H, J = 12.5 Hz, $ArCH_2Ar$), 4.26–4.14 (m, 8H, OCH_2CH_2O), 3.77 (s, 8H, OCH_2CH_2O), 3.71 (s, 8H, OCH_2CH_2O), 3.68 (t, 4H, J = 7.4 Hz, $ArOCH_2CH_2CH_3$), 3.12 (d, 4H, J = 12.5 Hz, $ArCH_2Ar$), 1.96 (sextet, 4H, J = 7.4 Hz, $ArOCH_2CH_2CH_3$), 1.32 (s, 18H, $C(CH_3)_3$), 1.04 (t, 6H, J = 7.4 Hz, $ArOCH_2CH_2CH_3$), 0.82 (18H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 152.4, 145.0, 144.0, 135.5, 131. 9, 125.4, 124.5, 77.7, 72.0, 71.2, 70.7, 70.5, 70.4, 69.8, 34.1, 33.6, 31.7 31.1, 30.9, 23.5, 10.7. ESI-MS *m/z* 1001.8 [M + Na^+]. HRMS calcd for $C_{62}H_{90}O_9Na$ [M + Na^+] 1001.6483; found 1001.6478.

Compound **4c**: Column chromatography (SiO_2, petroleum ether/acetone 7:1). Yield 71%. Mp 131–134 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.78–6.77 (m, 8H, ArH), 4.50 (d, 1H, J = 12.8 Hz, $ArCH_2Ar$), 4.42 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 4.38 (d, 2H, J = 12.4 Hz, $ArCH_2Ar$), 4.13–3.94 (m, 8H, OCH_2CH_2O), 3.83 (t, 4H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$), 3.75–3.68 (m, 16H, OCH_2CH_2O), 3.12 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 3.11 (d, 2H, J = 12.4 Hz, $ArCH_2Ar$), 3.10 (d, 1H, J = 12.8 Hz, $ArCH_2Ar$), 2.02 (sextet, 4H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$), 1.08 (s, 18H, $C(CH_3)_3$), 1.07 (s, 18H, $C(CH_3)_3$), 1.00 (t, 6H, J = 7.6 Hz, $ArOCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.6, 153.3, 144.5, 144.2, 133.9, 133.8, 133.7, 125.0, 124.89, 124.87, 77.2, 73.0, 70.73, 70.68, 70.6, 70.4, 33.81, 33.78, 31.44, 31.43, 31.0, 30.9, 23.3, 10.4. ESI-MS m/z 1001.7 [M + Na^+]. HRMS calcd for $C_{62}H_{90}O_9Na$ [M + Na^+] 1001.6483; found 1001.6487.

Compound **4d**: Column chromatography (SiO_2, petroleum ether/acetone 3:1). Yield 65%. Mp 129–133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.78–6.76 (m, 8H, ArH), 4.45 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 4.42 (d, 1H, J = 12.4 Hz, $ArCH_2Ar$), 4.38 (d, 2H, J = 12.5 Hz, $ArCH_2Ar$), 4.09–3.95 (m, 8H, OCH_2CH_2O), 3.83 (t, 4H, J = 7.5 Hz, $ArOCH_2CH_2CH_3$), 3.75–3.63 (m, 24H, OCH_2CH_2O), 3.11 (d, 3H, J = 12.5 Hz, $ArCH_2Ar$), 3.09 (d, 1H, J = 12.6 Hz, $ArCH_2Ar$), 2.06–1.97 (m, 4H, $ArOCH_2CH_2CH_3$), 1.08 (s, 18H, $C(CH_3)_3$), 1.07 (s, 18H, $C(CH_3)_3$), 1.00 (t, 6H, J = 7.5 Hz, $ArOCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 153.3, 144.5, 144.2, 133. 9, 133.8, 133.7, 124.92, 124.89, 124.88, 124.84, 72.8, 70.80, 70.78, 70.7, 70.64, 70.58, 70.3, 33.78, 33.76, 31.42, 31.40, 30.94, 23.3, 10.4. ESI-MS m/z 1089.9 [M + Na^+]. HRMS calcd for $C_{66}H_{98}O_{11}Na$ [M + Na^+] 1089.7007; found 1089.7004.

Two-phase solvent extraction experiment

The binding properties of 1,3-calix[4]crown-7 **4a**, 1,3-calix[4]crown-9 **4b**, 1,2-calix[4]crown-7 **4c** and 1,2-calix[4]crown-9 **4d** towards alkali and alkaline earth metal picrates were investigated by liquid–liquid extraction experiment at 16 ± 2 °C. An 8×10^{-5} M of aqueous alkali metal picrate solution (6 mL) and an 8×10^{-5} M solution of calix[4]crown **4** in CH_2Cl_2 (6 mL) were vigorously stirred in a stoppered flask for 2 h, followed by standing for an additional 1 h. The concentration of the picrate ion remaining in the aqueous phase was then determined spectrophotometrically at 356 nm. Blank experiments showed that no picrate extraction occurred in the absence of **4**. The percentage extraction ($E\%$) was calculated as $E\% = [(A_0 - A)/A_0] \times 100$, where A_0 and A were the initial and final absorbance of pictrates before and after the extraction, respectively. For the extraction experiment of alkaline earth metal picrates, 4×10^{-5} M of the calixarenes and alkaline earth metal picrates was used. All data were obtained as the average of at least three independent experiments.

Acknowledgments The authors are grateful to Project Aurora (ChénGuāng) of Wuhan Science and Technology Bureau for Young Scholars (No. 200750731267) and National Natural Science Foundation of China (No. 20902029) for financial support.

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