Crown ether derivatives of calix[5]arenes: synthesis and complexation properties

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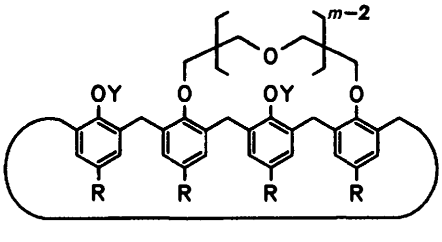
Several crown ether derivatives of calix[5]- and *tert*-butylcalix[5]-arene have been synthesized and converted into their trimethyl ethers as neutral ligands. For selected examples extraction studies have been carried out with alkali metal picrates in the system water–dichloromethane and stability constants have been determined by UV spectroscopy in methanol. All ligands show a more or less pronounced preference for the larger alkali cations. The selectivity for Cs$^+$ over Na$^+$ is highest for the crown-5 derivative of *tert*-butylcalix[5]arene (S = 630). Calorimetric titrations show that the complexation is enthalpically and entropically driven.

Introduction

Calixarenes are macrocyclic compounds which are not only easily available on a large scale, but also offer nearly boundless possibilities for chemical modification.[1] This makes them highly attractive as building blocks for more sophisticated and elaborate host molecules. Among the numerous 'tailor made' ligands for a large variety of metal cations crown ether derivatives of calixarenes (calixcrowns) represent not only some of the earliest examples[2] but also elegantly demonstrate the potential of these compounds.[3]

Remarkable and hitherto unknown selectivities based on a delicate balance of factors such as ring size and conformation have been found for 1,3-crown ether derivatives **1** of calix[4]arenes. While the crown-4 derivatives **1a** show the highest Na$^+$ over K$^+$ selectivity (the partial cone conformer being slightly better than the cone conformer),[4] K$^+$ over Na$^+$ selectivity is found for *tert*-butyl calix[4]crown-5 derivatives **1b** fixed in the partial cone conformation.[5] If the corresponding crown-5 derivative **1c** of the unsubstituted calix[4]arene is fixed in the 1,3-alternate conformation the K$^+$/Na$^+$ selectivity is even higher than that of valinomycin.[6] Finally, crown-6 derivatives **1d** fixed in the 1,3-alternate conformation[7] show Cs$^+$ over Na$^+$ selectivities of 10^5 or higher. The same is true for the double crown-6 derivatives **2** in which pairs of opposite oxygen functions are connected by two oligoether chains, which requires the 1,3-alternate conformation of the calixarene skeleton.[8] The selectivities for the softer cations K$^+$ or Cs$^+$ over the harder Na$^+$ cation are, at least in part, due to cation-π interactions with the inverted phenolic units acting as π-bases.



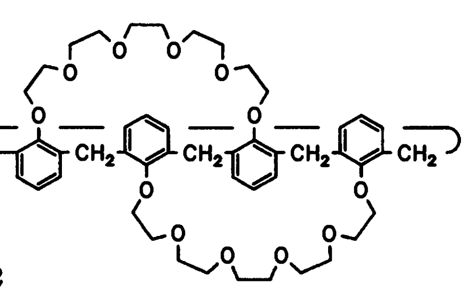
Y = H, alkyl

1a $m = 4$ R = C(CH$_3$)$_3$

1b $m = 5$ R = C(CH$_3$)$_3$

1c $m = 5$ R = H

1d $m = 6$ R = H



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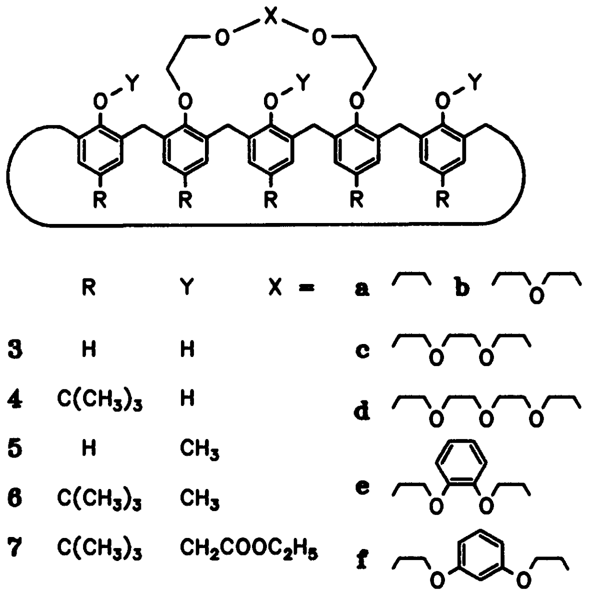
Calixcrowns are macrobicyclic (or bi-macrocyclic) molecules, and it seems reasonable to assume that a preference for larger cations may be achieved not only by enlarging the crown ether part, as shown by the examples mentioned above, but also by enlarging the macrocyclic part formed by the calixarene. Although some crown ether derivatives have been prepared from calix[5]-,[9] calix[6]-,[10] and even calix[8]-arenes,[11] very little is known about their complexation behaviour towards metal cations. Results obtained with a chromoionophore derived from calix[5]crown-5 support this idea.[12]

We report in the following the synthesis of several new crown ether derivatives from calix[5]- and *tert*-butylcalix[5]-arene and a study of the extraction and complexation properties of their trimethylethers.

Syntheses

All the new crown ether derivatives **3** and **4** were prepared by reaction of calix[5]arene or *tert*-butylcalix[5]arene (1 mol) with the appropriate ditosylate (1 mol) in refluxing acetonitrile in the presence of CsF (5 mol), using exactly the same procedure as described previously for **4b–d**.[9] Pure compounds were easily obtained by flash chromatography in reasonable to excellent yield (39–88%), with the exception of the crown-7 derivative **3d**



(11% only). In general yields are somewhat lower for **3**, derived from calix[5]arene, than for **4** derived from *tert*-butylcalix[5]arene, and higher for the benzocrown ethers (**3e**, **4e**,**f**) in comparison with the more flexible derivatives **3b–d** and **4a–d**.

All crown ethers were checked for purity by TLC and identified on the basis of their mass and NMR spectra. In principle the macrocyclization may lead to two isomeric monocrown ethers in which two adjacent (1,2) or two distal (1,3) oxygen functions are connected. Both isomers possess a mirror plane as the only symmetry element. In contrast to the corresponding derivatives of calix[4]arenes their distinction by ^{1}H NMR spectroscopy is possible only indirectly, based on the chemical shift of the phenolic OH-protons. In all cases the signal integrating for two OH-protons appears at lower field (δ 7.65–7.95 in $CDCl_3$), due to intramolecular OH–OH hydrogen bonding, than the signal for the single OH-group (δ 6.65–7.30). For a 1,2-crown ether, with three adjacent OH-groups, the signal for one OH-group (central) would be expected at lower field than the signal for the other two OH-groups. The molecular structure of **3** and **4** seems sufficiently confirmed by this spectroscopic evidence, although a definite proof by single crystal X-ray analysis has not yet been possible. It should be mentioned, however, that the structure of a 1,2-crown ether obtained by reaction of mono-*O*-α-picolyl *tert*-butylcalix[5]arene with tetraethylene glycol ditosylate has been confirmed by a single crystal X-ray analysis.[13]

The remaining hydroxy groups in crown ethers **3** and **4** could be completely methylated by reaction with excess methyl iodide in tetrahydrofuran (THF) in the presence of sodium hydride as base. The trimethyl ethers **5** and **6** were thus obtained in yields of 57–89% after purification by flash chromatography. Again the formation of a single product was based mainly on the basis of the NMR spectra. For instance two singlets for OMe protons (ratio 1:2) were found in all cases and three singlets for Bu^t protons (ratio 1:2:2) for compounds **6**. The formation of a single methylation product is most probably due to the fact that the methoxy group can pass through the macrocyclic ring.[14] Attempts to attach larger residues at the oxygens led to inseparable product mixtures, which most probably consist of conformational isomers. The triester derivative **7b**, described previously,[9] therefore remains the only pure product of this type. It should be mentioned, however, that the selective *O*-alkylation of one of the adjacent hydroxy groups in **4b** was possible in the presence of very weak bases,[13] which represents additional support for its 1,3-crown structure.

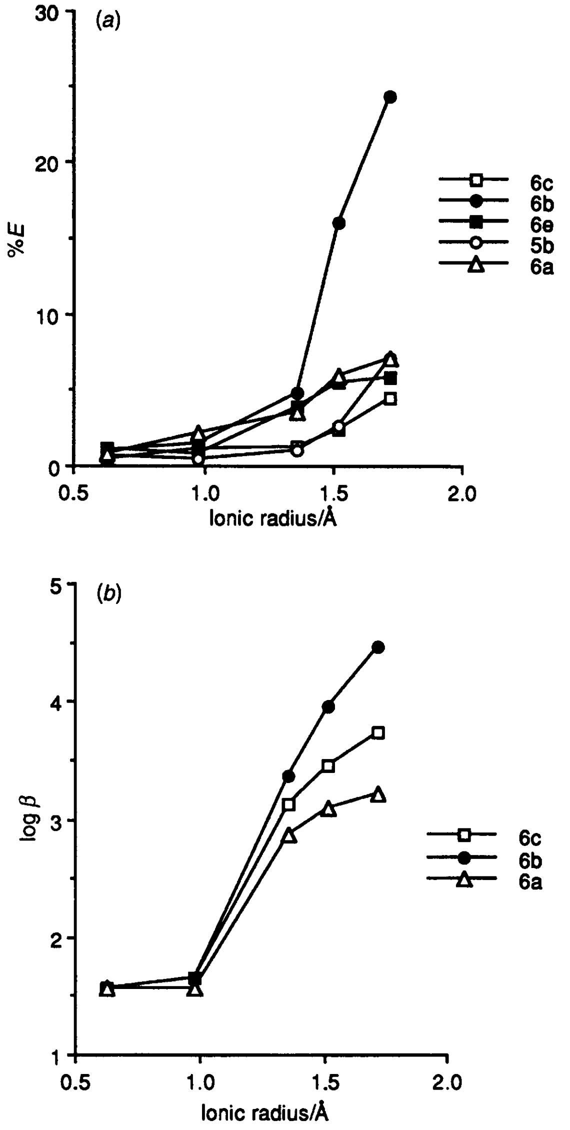


Fig. 1 Plot of percentage extraction (upper part) and stability constant (lower part) *versus* the ionic radii of the alkali cations Li^+ to Cs^+

Extraction and complexation studies

The extraction of alkali and alkaline earth picrates from aqueous solution into dichloromethane was studied with selected crown ether derivatives **5** to **7**. Stability constants for the complexation of alkali cations were additionally determined for **6b–d** in homogeneous phase (methanol). The extraction and complexation data for alkali cations are given in Tables 1 and 2 and illustrated in Fig. 1.

Extraction efficiency

All the compounds except the calix[5]crown-7, **6d**, which does not extract any of the alkali cations, extract caesium preferentially. For trimethoxy *p*-*tert*-butylcalix[5]crown-*x*, the efficiency towards all alkalis decreases from $x = 5$, to $x = 4$ as well as to $x = 6$ and 7. The replacement of the alkyl groups on the unbridged positions by an ester functional group (compound **7b**) leads to an overall increase in extraction and to greater extraction power, especially for Li^+ and Cs^+, than the related unbridged *p*-*tert*-butylcalix[5]arene pentaethylester.[15]

Calix[5]crowns **5** which are unsubstituted at the upper rim show lower extraction efficiencies than their *tert*-butyl analogues **6**. For instance, the percentage Cs^+ extracted decreases from 23.9 with **6b** to 6.7 with **5b**.

Replacing the crown chain by a benzocrown chain leads to an increased extraction efficiency for Cs^+ in the case of the 1,2-

Table 1 Percentage extraction (% E) of alkali picrates (C_M = 2.5 × 10^{-4} mol dm^{-3}) from water to dichloromethane, by various calix[5]crowns at 20 °C[a]

Ligands	Li^+	Na^+	K^+	Rb^+	Cs^+
5b	0.2 ± 0.1	N.d.	0.6 ± 0.1	2.2 ± 0.1	6.7 ± 0.2
5e	N.d.	N.d.	0.3 ± 0.1	1.2 ± 0.2	3.1 ± 0.1
6a	0.4 ± 0.1	1.7 ± 0.1	3.1 ± 0.1	5.5 ± 0.1	6.7 ± 0.1
6b	0.6 ± 0.1	1.0 ± 0.1	4.4 ± 0.1	15.5 ± 0.3	23.9 ± 0.2
6c	N.d.	0.7 ± 0.1	0.8 ± 0.1	1.9 ± 0.6	4.0 ± 0.8
6d	*b*	*b*	*b*	*b*	*b*
6e	0.7 ± 0.2	0.3 ± 0.1	3.5 ± 0.1	5.0 ± 0.1	5.4 ± 0.1
6f	N.d.	N.d.	0.3 ± 0.1	0.6 ± 0.1	2.2 ± 0.1
7b	28.5 ± 0.7	39 ± 1	47.8 ± 0.3	60 ± 1	69.5 ± 0.7

[a] Standard deviation σ_{N-1} on the arithmetic mean of N experiments ($N \geq 4$). [b] Not detectable.

Table 2 Logarithms of the stability constants (log β ± σ_{N-1}) of alkali complexes of some calix[5]crowns in methanol [T = 25 °C, I = 0.01 mol dm^{-3} (Et_4NCl)][a]

Ligands	Li^+	Na^+	K^+	Rb^+	Cs^+
6a	≤1.5	≤1.5	2.82 ± 0.06	3.03 ± 0.03	3.16 ± 0.06
6b	≤1.5	1.6 ± 0.1	3.3 ± 0.1	3.90 ± 0.06	4.40 ± 0.09
6c	≤1.5	1.6 ± 0.2	3.06 ± 0.05	3.4 ± 0.1	3.68 ± 0.08

[a] Standard deviation σ_{N-1} on the arithmetic mean of N experiments ($N \geq 3$).

benzocrown **6e** whereas the 1,3-benzocrown **6f** shows, not unexpectedly, a lower extraction ability.

Among all the calix[5]crowns studied, only the ester derivative **7b** showed a significant extraction level for alkaline earth picrates. However, with extraction values E ranging from 17.9% for Sr^{2+} to 18.3% for Ca^{2+}, 18.9% for Ba^{2+} and 19.9% for Mg^{2+}, under the conditions described in Table 1, no particular selectivity is observed along the series.

Selectivity

Crown-5 **6b** shows the greatest Cs^+ over Na^+ selectivity in extraction and complexation, followed by crown-6 **6c** and crown-4 **6a**. These observations differ from those made with calix[4]crowns, for which the nature of the selectivity depends strongly on the chain length.[4–7,16] With calix[5]crowns the preference is always in favour of Cs^+, but the efficiency depends on the crown size. It seems that the influence of the macrocyclic ring size defined by the five aromatic units, which actually should be better adapted to larger cations like Cs^+ than to the smaller ones like Na^+, is predominant over the influence of the crown size. This could be also an indication for the localization of the cation in the complex which might penetrate deeper in the circle formed by the phenolic oxygens of the calix[5]crowns than in the case of the calix[4]crowns.

Comparison with similar receptors

The selectivity $S = \beta(Cs^+)/\beta(Na^+)$ = 630 found for ligand **6b** is somewhat lower but still comparable to that for 21-crown-7, which shows the best Cs^+/Na^+ selectivity in the family of simple crown ethers (S = 2.5 × 10^3).[17] It is, however, much lower than that of diisopropoxycalix[4]crown-6, fixed in the 1,3-alternate conformation, which has been shown to be the most Cs^+ selective compound among calix[4]crowns, with $S = \beta(Cs^+)/\beta(Na^+) = 10^5$ in methanol.[7b] If this comparison is restricted to the dimethoxy-calix[4]crowns-6, which display a conformational mobility as the trimethoxy-calix[5]crowns, similar results are observed: dimethoxy *p*-*tert*-butylcalix[4]crown-6 shows a Cs^+/Na^+ selectivity of 1250 and its *para*-dealkylated counterpart a selectivity of 500.[7b]

In contrast to these calix[4]arene analogues there is obviously no larger conformational change upon complexation with the calix[5]crowns. For instance **6b** forms a Cs^+-complex stable on the ^1H NMR timescale in solvents like $CDCl_3$ or CD_2Cl_2 with two broad signals for the aromatic protons at δ 7.27 and 7.24 or δ 7.4 and 7.3 ppm, respectively. These values are not too different from the signals found in the free ligand, which are δ 7.13 (2 H), 7.06 (4 H), 6.96 (2 H) and 6.79 (2 H) in $CDCl_3$ and δ 7.12 (4 H), 7.07 (2 H), 7.01 (2 H) and 6.88 (2 H) in CD_2Cl_2. Furthermore, there is apparently only one pair of doublets for the Ar–CH_2–Ar protons (δ 4.34 and 3.37 in $CDCl_3$, δ 4.30 and 3.43 in CD_2Cl_2). This suggests that the calix[5]arene part assumes a more or less regular (eventually time averaged) cone conformation in this complex, while the 1,3-alternate conformation is present in Cs^+ complexes of calix[4]crown-6 derivatives.

Thermodynamics of complexation

In order to understand better the alkali cations complexation process, a calorimetric study has been carried out with compounds **6a–c**. The results are given in Table 3. Compounds **6b** and **6c** behave similarly; $-\Delta H_c$ decreases from Cs^+ to K^+ whereas $T\Delta S_c$ increases. With **6a**, for which only the complexation of Cs^+ and Rb^+ has been studied, the trend is reversed. In addition, for a given cation $-\Delta H_c$ and $T\Delta S_c$ values of **6b** and **6c** are the same within experimental error.

The variations of the thermodynamic parameters in the series are less important than those observed with calix[4]crowns-6.[7] All the complexes are both enthalpically and entropically stabilized. Since **6c** possesses one additional oxygen atom on its crown part with respect to **6b**, the similarity between ΔH_c values for both ligands and a given cation suggests that not all the oxygen atoms participate in the complexation of the metal ions, even of Cs^+. With **6a** possessing a shorter crown part $-\Delta H_c$ is lower than with **6c** and **6b**.

High values for ΔS_c may be explained by desolvation of the ligand and/or the cation. However, a desolvation of the ligand seems unlikely here, since the NMR spectra do not show appreciable conformational variations upon complexation. This contrasts with what was observed with the dimethoxy *p*-*tert*-butylcalix[4]crown-6.[7b] One could assume that, due to the larger size of the calix[5]arene, the Cs^+ cation is pulled more deeply into the circle of the phenolic oxygens as already suggested above. High values observed for $T\Delta S_c$ could thus be interpreted in terms of remaining conformational freedom of the crown part in the complex. The fact that $T\Delta S_c$ increases when the crown part becomes shorter is consistent with a more pronounced desolvation of the cations in order to fit the smaller cavity.

Table 3 Thermodynamic parameters of complexation in methanol, at 25 °C ΔH_c (kJ mol^{-1}), ΔG_c (kJ mol^{-1}), $T\Delta S$ (kJ mol^{-1}) and ΔS_c (J K^{-1} mol^{-1})[a]

Ligands		K$^+$		Rb$^+$		Cs$^+$	
6a[c]	log β	(2.8)[b]		(3.0)[b]		(3.2)[b]	
	$-\Delta G_c$	16.1		17.1		18.2	
	$-\Delta H_c$	*d*		15.7[c]		10.9[c]	
	$T\Delta S_c$	—		1.4		7.3	
	ΔS_c	—		5		24	
6b	log β	3.4 ± 0.1	(3.3)[b]	4.0 ± 0.2	(3.9)[b]	(4.4)[b]	
	$-\Delta G_c$	18.8 ± 0.6		22.2 ± 0.6		25.1 ± 0.6	
	$-\Delta H_c$	10 ± 3		16 ± 2		21.3 ± 0.8	
	$T\Delta S_c$	9 ± 4		6 ± 3		4 ± 1	
	ΔS_c	30 ± 10		20 ± 10		13 ± 3	
6c	log β	3.2 ± 0.2	(3.1)[b]	3.5 ± 0.1	(3.4)[b]	3.8 ± 0.1	(3.7)[b]
	$-\Delta G_c$	17.4 ± 0.3		19.4 ± 0.6		21.0 ± 0.5	
	$-\Delta H_c$	14 ± 1		17.9 ± 0.8		19.6 ± 0.6	
	$T\Delta S_c$	3 ± 1		1 ± 1		1 ± 1	
	ΔS_c	10 ± 3		3 ± 3		3 ± 3	

[a] Standard deviation σ_{N-1} on the mean of N experiments ($N \geqslant 2$). [b] Spectrophotometric determination. [c] One determination only. [d] Not detectable.

Experimental

Syntheses

Mps were determined with a Büchi melting point apparatus and are uncorrected.

^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Bruker AM 400 spectrometer using CDCl$_3$ as solvent in all cases. Coupling constants *J* are given in Hz. FD MS were recorded with a Finnigan MAT 90 (5 kV/10 mA min^{-1}). Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh ASTM, 0.04–0.063 mm) with a N$_2$ pressure of 0.1–0.5 bar.

THF was dried over Na–benzophenone and distilled freshly before use. Acetonitrile (p.a. quality) was dried over molecular sieves (4 Å). CsF was heated for 1 h *in vacuo* at 100 °C before use. All reactions were carried out under dry argon or nitrogen.

All starting materials (*tert*-butylcalix[5]arene,[18] calix[5]arene[19] and the ditosylates of di- to hexa-ethylene glycol[20] and the benzo-analogues of pentaethylene glycol[21]) were prepared as described in the literature.

General procedure for the synthesis of the crown ether derivatives 3 and 4. A suspension of the calix[5]arene (1 mmol) and CsF (5 mmol) in CH$_3$CN (40 ml) was refluxed for 1 h. Then a solution of the required oligoethylene glycol-ditosylate (1 mmol) in MeCN (40 ml) was slowly added over an 8 h period. The mixture was refluxed for another 15 h before the solvent was removed. The residue was taken up in CHCl$_3$ and brine. The organic layer was separated and dried (MgSO$_4$). The crude product obtained after evaporation of the solvent was purified by flash chromatography (CH$_2$Cl$_2$–acetone).

Calix[5]*crown*-5 **3b**.—Yield 51%, mp 132 °C; δ_H 7.91 (s, 2 H, OH), 7.20 (d, ^3J 7.5, 2 H, ArH), 7.19 (dd, ^3J 7.5, ^4J 1.6, 2 H, ArH), 7.14 (dd, ^3J 7.5, ^4J 1.6, 2 H, ArH), 7.03 (d, ^3J 7.5, 4 H, ArH), 6.97 (s, 1 H, OH), 6.83 (t, ^3J 7.5, 2 H, ArH), 6.78 (t, ^3J 7.5, 2 H, ArH), 6.82 (t, ^3J 7.5, 1 H, ArH), 4.54 (d, ^2J 14.2, 2 H, ArCH$_2$Ar), 4.41 (d, ^2J 14.0, 2 H, ArCH$_2$Ar), 4.28–3.96 (m, 16 H, OCH$_2$CH$_2$O and 1 H, ArCH$_2$Ar), 3.47 (d, ^2J 14.0, 1 H, ArCH$_2$Ar), 3.44 (d, ^2J 14.2, 2 H, ArCH$_2$Ar), 3.43 (d, ^2J 14.0, 2 H, ArCH$_2$Ar); δ_C 153.2, 152.0, 151.8 (C_{Ar}O), 132.8, 132.7, 129.6, 129.4, 129.8, 128.7, 128.4, 127.4, 126.8, 126.7, 125.2, 120.1, 118.9 (Ar–C), 75.2 (ArO*C*H$_2$), 72.2, 70.9, 69.8 (O*C*H$_2$*C*H$_2$O), 30.8, 30.1, 29.7 (Ar*C*H$_2$Ar); *m*/*z* (FD) 689.5 (M$^+$. Calc. for $C_{43}H_{44}O_8$: M, 688.8).

Calix[5]*crown*-6 **3c**.—Yield 39%, mp 102 °C; δ_H 7.77 (s, 2 H, OH), 7.11–7.23 (m, 6 H, ArH), 6.73–6.96 (m, 9 H, ArH), 6.67 (s, 1 H, OH), 4.56 (d, ^2J 14.4, 2 H, ArCH$_2$Ar), 4.45 (d, ^2J 14.0, 2 H, ArCH$_2$Ar), 3.64–4.25 (m, 20 H, OCH$_2$CH$_2$O and 2 H, ArCH$_2$Ar), 3.42 (d, ^2J 14.0, 2 H, ArCH$_2$Ar), 3.40 (d, ^2J 14.4, 2 H, ArCH$_2$Ar); δ_C 153.0, 152.4, 151.9 (C_{Ar}O), 132.9, 132.7, 129.8, 129.7, 129.4, 128.4, 128.3, 127.4, 127.3, 127.0, 125.0, 120.1, 119.0 (Ar-C), 74.7 (ArO*C*H$_2$), 71.7, 71.3, 71.1, 70.3 (O*C*H$_2$*C*H$_2$O), 30.1, 29.8, 29.4 (Ar*C*H$_2$Ar); *m*/*z* (FD) 732.8 (M$^+$. Calc. for $C_{46}H_{48}O_9$: 732.9).

Calix[5]*crown*-7 **3d**.—Yield 11%, mp 85 °C; δ_H 7.95 (br s, 2 H, OH), 6.68–7.19 (m, 15 H, ArH and 1 H, OH), 4.64 (d, ^2J 14.3, 2 H, ArCH$_2$Ar), 4.39 (d, ^2J 14.1, 2 H, ArCH$_2$Ar), 4.37 (d, ^2J 14.3, 1 H, ArCH$_2$Ar), 3.94 (t, ^3J 8.5, 4 H, ArOC*H*$_2$CH$_2$O), 3.87 (d, ^2J 14.3, 1 H, ArCH$_2$Ar), 3.55–3.81 (m, 20 H, OCH$_2$CH$_2$O), 3.43 (d, ^2J 14.1, 2 H, ArCH$_2$Ar), 3.42 (d, ^2J 14.3, 2 H, ArCH$_2$Ar); δ_C 154.1, 151.7, 151.0 (C_{Ar}O), 134.2, 133.7, 129.5, 129.0, 128.90, 128.85, 127.7, 127.6, 124.1, 120.2, 120.7 (Ar-C), 73.3 (ArO*C*H$_2$-), 71.0, 70.9, 70.8, 70.7, 70.5 (O*C*H$_2$*C*H$_2$O), 31.9, 31.0, 30.9 (Ar*C*H$_2$Ar); *m*/*z* (FD) 776.7 (M$^+$. Calc. for $C_{47}H_{52}O_{10}$: 776.9).

Calix[5]*benzocrown*-6 **3e**.—Yield 62%, mp 95 °C; δ_H 7.85 (s, 2 H, OH), 7.18 (d, ^3J 7.5, 2 H, ArH), 7.13 (d, ^3J 7.5, 4 H, ArH), 6.99 (d, ^3J 8.0, 2 H, ArH), 6.97 (d, ^3J 9.7, 2 H, ArH), 6.95 (s, 1 H, OH), 6.91 (m, 4 H, ArH, bridge), 6.82 (t, ^3J 7.1, 1 H, ArH), 6.81 (t, ^3J 7.6, 2 H, ArH), 6.76 (t, ^3J 7.5, 2 H, ArH), 4.48 (d, ^2J 14.1, 2 H, ArCH$_2$Ar), 4.47 (d, ^2J 14.0, 2 H, ArCH$_2$Ar), 4.29–4.12 (m, 18 H, OCH$_2$CH$_2$O), 3.81 (d, ^2J 14.1, 2 H, ArCH$_2$Ar), 3.43 (d, ^2J 14.1, 2 H, ArCH$_2$Ar), 3.41 (d, ^2J 14.0, 2 H, ArCH$_2$Ar); δ_C 152.8, 152.4, 151.7, 149.3 (C_{Ar}O), 133.0, 129.6, 129.5, 129.3, 128.7, 128.5, 127.4, 127.0, 126.8, 125.1, 121.9, 120.0, 119.2, 115.7 (Ar-C), 75.0, 70.8, 70.5, 69.8 (O*C*H$_2$*C*H$_2$O), 30.7, 30.1, 29.9 (Ar*C*H$_2$Ar); *m*/*z* (FD) 781.6 (M$^+$. Calc. for $C_{49}H_{48}O_9$: 780.9).

p-tert-*Butylcalix*[5]*crown*-4 **4a**.—Yield 47%, mp 166 °C; δ_H 7.65 (s, 2 H, OH), 7.17 (d, ^4J 2.2, 2 H, ArH), 7.16 (d, ^4J 2.4, 2 H, ArH), 7.16 (s, 2 H, ArH), 7.15 (s, 1 H, OH), 7.13 (d, ^4J 2.3, 2 H, ArH), 7.10 (d, ^4J 2.2, 1 H, ArH), 4.77 (d, ^2J 13.7, 2 H, ArCH$_2$Ar), 4.23–3.38 (m, 20 H, ArCH$_2$Ar and OC*H*$_2$C*H*$_2$O), 1.24 (s, 18 H, Bu^t), 1.20 (s, 9 H, Bu^t), 1.15 (s, 18 H, Bu^t); δ_C 151.0, 149.0, 148.5 (C_{Ar}O), 146.8, 143.0, 142.8, 132.6, 132.3, 127.2, 127.1, 126.8, 126.4, 125.9, 125.7, 125.6, 125.5 (Ar–C), 73.9, 70.9, 69.5 (O*C*H$_2$*C*H$_2$O), 34.2, 33.8 (Ar*C*H$_2$Ar), 32.5, 31.8 [C(*C*H$_3$)$_3$], 31.1, 28.4 (*C*Me$_3$); *m*/*z* (FD) 925.6 (M$^+$. Calc. for $C_{61}H_{80}O_7$: 925.3).

p-tert-*Butylcalix*[5]*benzocrown*-6 **4e**.—Yield 88%, mp 134 °C; δ_H 7.82 (s, 2 H, OH), 7.31 (s, 1 H, OH), 7.18–7.14 (m, 10 H, ArH), 7.00–6.92 (m, 4 H, ArH), 4.44 (d, ^2J 13.7, 2 H, ArCH$_2$Ar), 4.39–4.18 (m, 19 H, ArCH$_2$Ar and OCH$_2$CH$_2$O), 3.98 (d, ^2J 13.9, 1 H, ArCH$_2$Ar), 3.39 (d, ^2J 13.7, 2 H, ArCH$_2$Ar), 3.29 (d, ^2J 13.9, 2 H, ArCH$_2$Ar), 1.33 (s, 9 H, Bu^t), 1.27 (s, 18 H, Bu^t), 1.10 (s, 18 H, Bu^t); δ_C 150.3, 150.2, 149.6, 149.1, 147.1, 142.4, 141.6, 132.5, 132.4, 127.0, 126.5, 126.3, 126.0, 125.90, 125.85, 125.7, 125.3, 122.1, 116.3 (Ar–C), 75.1, 71.0, 70.7, 70.4 (O*C*H$_2$*C*H$_2$O), 34.1, 33.8 (*C*Me$_3$), 31.7, 31.6, 31.2

[C(*C*H$_3$)$_3$], 30.2, 30.1, 29.8 (Ar*C*H$_2$Ar); *m*/*z* (FD) 1060.4 (M$^+$. Calc. for C$_{69}$H$_{88}$O$_9$: 1061.5).

p-tert-*Butylcalix*[5]*benzocrown*-6 **4f**.—Yield 71%, mp 136 °C; δ_H 7.64 (s, 2 H, OH), 7.21 (d, ^4J 2.3, 2 H, ArH), 7.20 (s, 2 H, ArH), 7.15 (d, ^4J 2.3, 2 H, ArH), 7.10–6.96 (m, 4 H, ArH), 6.97 (s, 1 H, OH), 6.53 (d, ^4J 2.3, 2 H, ArH), 6.51 (d, ^4J 2.2, 1 H, ArH), 4.78 (d, ^2J 14.2, 2 H, ArCH$_2$Ar), 4.40–3.36 (m, 24 H, ArCH$_2$Ar and OCH$_2$CH$_2$O), 1.36 (s, 9 H, Bu^t), 1.28 (s, 18 H, Bu^t), 0.95 (s, 18 H, Bu^t); δ_C 160.2, 150.3, 150.1, 149.2, 147.1, 142.5, 132.2, 129.5, 127.1, 126.6, 126.2, 126.1, 125.8, 125.4, 124.9, 108.9 (Ar–C), 74.8 (ArO*C*H$_2$), 70.4, 69.9, 68.2 (O*C*H$_2$*C*H$_2$O), 34.0, 33.9, 33.8 (Ar*C*H$_2$Ar), 31.7, 31.6, 31.0 [C(*C*H$_3$)$_3$], 30.8, 30.7, 29.9 [*C*(Me$_3$)$_3$]; *m*/*z* (FD) 1060.7 (M$^+$. Calc. for C$_{69}$H$_{88}$O$_9$: 1061.5).

General procedure for the synthesis of the trimethyl ether derivatives 5 and 6. A mixture of the crown ether **3** or **4** (0.2 mmol) and NaH (5 mmol) in THF (10 ml) was stirred for 30 min at room temp. Then methyl iodide (12 mmol) was added and the stirring was continued for 9 h. The reaction mixture was poured into 0.5 M HCl (40 ml) and extracted with CHCl$_3$. The organic phase was dried, evaporated and the crude product obtained was purified by flash chromatography (diethyl ether–light petroleum).

Trimethyl ether **5b**.—Yield 57%, mp 91 °C; δ_H 7.24–6.71 (m, 15 H, ArH), 4.56 (d, ^2J 13.9, 2 H, ArCH$_2$Ar), 4.50 (d, ^2J 13.6, 2 H, ArCH$_2$Ar), 4.41 (d, ^2J 15.0, 1 H, ArCH$_2$Ar), 4.03–3.79 (m, 16 H, OCH$_2$CH$_2$O), 3.48 (d, ^2J 15.6, 1 H, ArCH$_2$Ar), 3.39 (d, ^2J 13.9, 2 H, ArCH$_2$Ar), 3.32 (d, ^2J 14.0, 2 H, ArCH$_2$Ar), 3.19 (s, 6 H, OMe), 2.90 (s, 3 H, OMe); δ_C 157.4, 156.9, 155.0 (C_{Ar}O), 135.1, 134.6, 134.5, 134.4, 129.1, 128.9, 128.8, 128.7, 123.4, 122.9, 122.8 (Ar–C), 73.1 (ArO*C*H$_2$), 71.8, 71.0, 70.4 (O*C*H$_2$*C*H$_2$O), 61.1, 60.9 (O*C*H$_3$), 30.3, 29.7, 29.6 (Ar*C*H$_2$Ar); *m*/*z* (FD) 730.6 (M$^+$. Calc. for C$_{46}$H$_{54}$O$_8$: 730.9).

Trimethyl ether **5e**.—Yield 58%, mp 84 °C; δ_H 7.06–6.59 (m, 14 H, ArH), 4.53 (d, ^2J 14.7, 2 H, ArCH$_2$Ar), 4.45 (d, ^2J 14.6, 2 H, ArCH$_2$Ar), 4.27–3.91 (m, 17 H, OCH$_2$CH$_2$O and ArCH$_2$Ar), 3.54 (d, ^2J 15.0, 1 H, ArCH$_2$Ar), 3.39 (d, ^2J 14.6, 2 H, ArCH$_2$Ar), 3.29 (d, ^2J 14.7, 2 H, ArCH$_2$Ar), 3.04 (s, 3 H, OMe), 3.00 (s, 6 H, OMe); δ_C 157.0, 156.9, 155.1, 149.3 (C_{Ar}O), 134.7, 134.6, 134.50, 134.45, 134.3, 129.0, 128.9, 128.7, 127.6, 123.2, 122.9, 122.7, 121.6, 115.3 (Ar–C), 73.1 (ArO*C*H$_2$), 70.7, 70.2, 69.4 (O*C*H$_2$*C*H$_2$O), 61.0, 60.7 (O*C*H$_3$), 30.7, 30.6, 30.0 (Ar*C*H$_2$Ar); *m*/*z* (FD) 823.6 (M$^+$. Calc. for C$_{52}$H$_{54}$O$_9$: 823.0).

Trimethyl ether **6a**.—Yield 83%, mp 108 °C; δ_H 7.18 (d, ^4J 2.7, 2 H, ArH), 7.15 (s, 2 H, ArH), 7.06 (d, ^4J 2.5, 2 H, ArH), 6.93 (d, ^4J 2.4, 2 H, ArH), 6.90 (d, ^4J 2.6, 2 H, ArH), 4.80 (d, ^2J 13.8, 2 H, ArCH$_2$Ar), 4.63 (d, ^2J 13.9, 2 H, ArCH$_2$Ar), 4.30–3.33 (m, 18 H, OCH$_2$CH$_2$O and ArCH$_2$Ar), 3.00 (s, 3 H, OMe), 2.89 (s, 6 H, OMe), 1.23 (s, 9 H, Bu^t), 1.20 (s, 18 H, Bu^t), 1.16 (s, 18 H, Bu^t); δ_C 154.2, 152.3, 145.4, 145.0, 134.3, 133.8, 133.5, 133.1, 126.5, 126.2, 125.8, 124.8 (Ar–C), 72.9, 71.90, 71.85, 71.3, 70.9 (O*C*H$_2$*C*H$_2$O, O*C*H$_3$), 34.3, 34.2, 33.8 (Ar*C*H$_2$Ar), 34.1, 34.0, 33.9 [C(*C*H$_3$)], 31.6, 31.4, 29.8 (CMe$_3$); *m*/*z* (FD) 967.0 (M$^+$. Calc. for C$_{64}$H$_{86}$O$_7$: 966.6).

Trimethyl ether **6b**.—Mp 125 °C (the formerly[9] reported value of 225 °C is erroneous); δ_C 154.5, 152.7, 145.3, 145.0, 134.2, 133.8, 133.5, 126.0, 125.2, 125.4 (Ar–C), 73.3, 71.9, 70.7, 70.5 (O*C*H$_2$*C*H$_2$, O*C*H$_3$), 34.10, 34.05 (Ar*C*H$_2$Ar), 33.8, 31.5 [C(*C*H$_3$)$_3$], 31.8, 30.8, 29.8 (*C*Me$_3$).

Trimethyl ether **6c**.—Mp 117 °C (the formerly[9] reported value of 217 °C is erroneous); δ_C 154.3, 152.3, 145.4, 145.0, 144.6, 134.2, 134.0, 133.7, 133.6, 133.0, 126.9, 126.3, 126.2, 125.6, 124.7 (Ar–C), 72.8, 72.0, 71.9, 71.2, 70.9, 70.5, 60.2 (O*C*H$_2$*C*H$_2$O, O*C*H$_3$), 34.5, 34.4 (Ar*C*H$_2$Ar), 34.1, 34.0, 33.9 [C(*C*H$_3$)$_3$], 31.6, 31.3, 29.7 (*C*Me$_3$).

Trimethyl ether **6d**.—Yield 68%, mp 129 °C; δ_H 7.21 (d, ^4J 2.7, 2 H, ArH), 7.16 (s, 2 H, ArH), 7.10 (d, ^4J 2.5, 2 H, Ar), 6.93 (d, ^4J 2.5, 2 H, ArH), 6.90 (d, ^4J 2.6, 2 H, ArH), 4.66 (d, ^2J 13.8, 2 H, ArCH$_2$Ar), 4.29–3.33 (m, 32 H, OCH$_2$CH$_2$O and Ar–CH$_2$–Ar), 2.99 (s, 3 H, OMe), 2.90 (s, 6 H, OMe), 1.24 (s, 9 H, Bu^t), 1.155 (s, 18 H, Bu^t), 1.150 (s, 18 H, Bu^t); δ_C 153.9, 152.2, 145.5, 144.9, 135.3, 134.1, 133.7, 133.0, 126.8, 126.3, 125.8, 124.8, 124.7, 124.0 (Ar–C), 73.1, 72.8, 71.7, 71.6, 71.2, 70.9 (O*C*H$_2$*C*H$_2$O, O*C*H$_3$), 34.4, 34.3, 34.2 (Ar*C*H$_2$Ar), 34.1, 34.0, 33.9 [C(*C*H$_3$)$_3$], 32.02, 31.5, 29.9 (*C*Me$_3$); *m*/*z* (FD) 1100.1 (M$^+$. Calc. for C$_{70}$H$_{98}$O$_{10}$: 1099.5).

Trimethyl ether **6e**.—Yield 78%, mp 130 °C; δ_H 7.13 (d, ^4J 2.2, 2 H, ArH), 7.05 (s, 2 H, ArH), 7.03 (d, ^4J 2.2, 2 H, ArH), 7.00 (d, ^4J 2.2, 2 H, ArH), 6.84 (d, ^4J 2.2, 2 H, ArH), 6.82 (br s, 4 H, ArH), 4.45 (d, ^2J 14.0, 2 H, ArCH$_2$Ar), 4.18–3.63 (m, 19 H, OCH$_2$CH$_2$O and ArCH$_2$Ar), 4.10 (d, ^2J 14.0, 2 H, ArCH$_2$Ar), 3.55 (d, ^2J 14.0, 1 H, ArCH$_2$Ar), 3.18 (d, ^2J 14.0, 2 H, ArCH$_2$Ar), 2.99 (s, 3 H, OMe), 2.76 (s, 6 H, OMe), 1.22 (s, 9 H, Bu^t), 1.24 (s, 18 H, Bu^t), 1.06 (s, 18 H, Bu^t); δ_C 154.5, 152.5, 149.1 (C_{Ar}O), 145.3, 145.1, 144.7, 133.9, 133.8, 133.7, 133.6, 133.5, 126.4, 126.2, 125.7, 125.3, 121.4, 114.7 (Ar–C), 73.2, 70.9, 70.4, 68.8 (O*C*H$_2$*C*H$_2$O), 61.1, 60.2 (O*C*H$_3$), 34.10, 34.05, 29.7 (Ar*C*H$_2$Ar and *C*Me$_3$), 31.6, 31.4 [C(*C*H$_3$)$_3$]; *m*/*z* (FD) 1102.5 (M$^+$. Calc. for C$_{72}$H$_{94}$O$_9$: 1103.5).

Trimethyl ether **6f**.—Yield 79%, mp 126 °C; δ_H 7.27 (s, 1 H, ArH), 7.19 (d, ^4J 2.2, 2 H, ArH), 7.16–6.97 (m, 5 H, ArH), 6.63 (d, ^4J 2.1, 2 H, ArH), 6.43 (d, ^4J 2.2, 2 H, ArH), 6.38 (s, 2 H, ArH), 4.47 (d, ^2J 14.4, 2 H, ArCH$_2$Ar), 4.17–3.54 (m, 22 H, OCH$_2$CH$_2$O and ArCH$_2$Ar), 3.17 (d, ^2J 14.5, 2 H, ArCH$_2$Ar), 2.84 (s, 6 H, OMe), 2.35 (s, 3 H, OMe), 1.38 (s, 9 H, Bu^t), 1.29 (s, 18 H, Bu^t), 0.99 (s, 18 H, Bu^t); δ_C 159.8, 154.8, 152.2, 145.4, 144.9, 134.2, 133.9, 133.6, 133.3, 127.3, 133.0, 126.3, 125.7, 124.2, 107.4 (Ar–C), 72.3, 70.9, 69.5, 67.3, 60.3 (O*C*H$_2$*C*H$_2$O, O*C*H$_3$), 34.9, 34.1, 33.9 (Ar*C*H$_2$Ar), 31.9, 31.6, 31.4 [C(*C*H$_3$)$_3$], 31.0, 29.7, 29.4 (*C*Me$_3$); *m*/*z* (FD) 1103.9 (M$^+$. Calc. for C$_{72}$H$_{94}$O$_9$: 1103.5).

Extraction and complexation studies

Materials. The solvents methanol (Carlo Erba, water content < 0.1%) and dichloromethane (Fluka, or SDS, purex for syntheses) used in physicochemical measurements have been used without further purification.

The metallic salts used for the spectrophotometric measurements were chlorides: LiCl (Fluka, puriss.), NaCl (Prolabo, Normapur), KCl (Merck, p.a.), RbCl (Fluka, puriss.) and CsCl (Merck, puriss).

Alkali picrates used in extraction experiments have been synthesized by reaction of picric acid with hydroxides (for Na$^+$, K$^+$, Rb$^+$ and Cs$^+$) or with carbonate (for Li$^+$) according to methods previously described by Kirch.[22] Alkaline earth picrates have been obtained after addition of the metal carbonates in excess to aqueous solutions of picric acid according to the method of Selim.[23] After filtration of the excess carbonate, and cooling the solution at 0 °C, the salts precipitated. They were all recrystallized from water, washed rapidly with ether and dried under vacuum for 12 h. They were protected from light and moisture when stored.

Picrate extraction measurements. Picrate extraction experiments were performed following Pedersen's procedure,[24] which consisted in mixing 5 ml of a 2.5×10^{-4} mol dm^{-3} aqueous solution of metal picrate and 5 ml of a 2.5×10^{-4} mol dm^{-3} solution of calixarene in dichloromethane. The experimental details have been published elsewhere.[7b]

Complexation studies. The stability constants *b*, defined as the concentration ratio [ML$^+$]/([M$^+$][L]) (M$^+$ = cation and L = ligand), have been determined in methanol [T = 25 °C, I = ionic strength = 0.01 mol dm^{-3} (Et$_4$NCl)] by UV absorption spectrophotometry according to a procedure already described.[25] The ligand concentrations ranged between 10^{-4} and 2×10^{-4} mol dm^{-3} and the spectra were recorded between 210 and 250 nm. The experimental data were treated using the program SIRKO.[26]

The complexation enthalpies, ΔH_c have been determined in the same solvent using an isoperibol titration calorimeter (Tronac 450, Orem, Utah). The experimental details have been previously described.[27] The ligand concentrations were 4×10^{-4} to 7×10^{-4} mol dm^{-3}, and the metal concentrations between 0.03 and 0.06 mol dm^{-3}. In most cases, ΔH_c and log β were refined simultaneously by the program SIRKO. The values thus obtained are in excellent agreement with those obtained from spectrophotometric measurements. In the case of the more stable Cs^+ complex with **6b**, ΔH_c was refined alone, the β value for this complex, obtained by spectrophotometry, being settled as constant. The corresponding complexation entropies, ΔS_c, were derived from the equation: $\Delta G_c = \Delta H_c - T\Delta S_c$, knowing $\Delta G_c = -RT \ln \beta$.

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