Shape Recognition of Alkylammonium Ions by 1,3-Bridged Calix[5]arene Crown-6 Ethers: *Endo*- vs *Exo*-Cavity Complexation

Gabriella De Salvo,[†] Giuseppe Gattuso,[†] Anna Notti,[†] Melchiorre F. Parisi,*[,†] and Sebastiano Pappalardo*[,‡]

Dipartimento di Chimica Organica e Biologica, Università di Messina, Salita Sperone 31, I-98166 Messina, Italy and Dipartimento di Scienze Chimiche, Università di Catania, Viale A. Doria 6, I-95125 Catania, Italy

mparisi@unime.it

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A series of tri-*O*-substituted 1,3-bridged calix[5]arene crown-6 ethers bearing alkyl, arylalkyl, alkoxyalkyl, and alkoxycarbonylmethyl residues at the lower rim and either ^{t}Bu or H substituents at the upper rim have been synthesized. ^{1}H NMR studies have shown that *p*-*tert*-butylcalix[5]-crowns, irrespective of the size and nature of their lower rim pendant groups, adopt preorganized conelike conformations, whereas *p*-H-calix[5]crowns with bulky substituents preferentially exist in solution as partial cone conformers (C_1 symmetry). Calix[5]crown derivatives behave as mono- or ditopic receptors for isomeric butylammonium ions, forming *endo*-cavity (inside the calixarene cup) and/or *exo*-cavity (at the crown ether moiety) 1:1 complexes according to the shape of the guest. These two binding modes can be clearly distinguished and monitored by ^{1}H NMR titration experiments.

Introduction

Calixcrowns[1] are macrobicyclic molecules in which two phenolic oxygens of the calixarene[2] substructure are linked together by a polyether moiety. Ungaro and co-workers, back in 1983, reported the synthesis of (1,3)-*p*-*tert*-butylcalix[4]crown-6-diol as the first example of this class of compounds.[3] After that, synthetic strategies for the attainment of regio (1,2- and 1,3-bridged),[4] conformational (cone, partial cone, 1,2-, and 1,3-alternate),[5] and even chiral[6] calixcrown isomers swiftly developed. Calix[4]crown derivatives are probably the most potent and size-selective synthetic receptors for alkali metal ions known to date.[7] They also recognize and bind amines,[8] amino acids,[9] and organic ammonium ions.[10] These remarkable host−guest properties are related to the calix[4]arene backbone which provides a highly preorganized three-dimensional platform on which crown ether moieties of different length can be assembled to create converging binding sites.

Although the selective introduction of polyether intra-bridging provides nowadays a useful tool by which the more flexible cavity of larger calix[*n*]arenes (n = 5,[11] 6,[12] and 8[13]) can be rigidified and preorganized, the binding potentials of the resulting calixcrowns have received less attention. It is known that calix[5]crowns are able to bind

* Fax: +39 090 393895.
[†] Università di Messina.
[‡] Università di Catania.

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large alkali metal ions[11b,14] and a number of organic ions;[11d,15] similarly calix[6]crowns are quaternary alkylammonium ion[12a] selective.

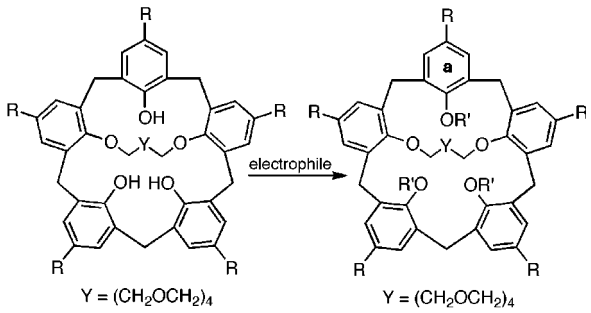
Not long ago we started investigating the molecular recognition properties of (1,3)-calix[5]arene crown-6 ethers, arguing that these molecules are potentially heteroditopic receptors which combine within their macrobicyclic structure both a hydrophilic and a hydrophobic binding site. The first site is defined by the intrabridging crown ether chain, the second one is provided by the five aryl rings which generate a π-electron-rich cavity. These structural features make calix[5]crowns particularly attractive as host molecules not only for inorganic cations and neutral molecules but also, and more interestingly, for organic ions. These compounds, because of the size[16] of their cavity (assuming this is preorganized in a conelike arrangement) and their crown-6 ether moiety (which is known to bind NH_3^+ ions effectively),[17] are ideal molecular receptors for alkylammonium ions. Selective recognition of differently shaped ions can either be provided by increasing steric hindrance of the substituents attached at the upper rim and/or rely on two topologically different regions around the polyether chain, featuring one or two lower rim pendant groups. Preliminary studies along this route have shown that tri-*O*-substituted (1,3)-bridged *p-tert*-butylcalix[5]arene crown-6 ethers, bearing alkyl or arylalkyl[18] and alkoxycarbonylmethyl[19] functionalities at the lower rim, behave as mono- or ditopic receptors for isomeric alkylammonium ions. These receptors generally form *endo*-cavity (inside the calixarene cup) and/or *exo*-cavity (at the crown ether moiety) 1:1 complexes according to the shape of the guest. We now provide a full account of the synthesis, conformational features, and molecular recognition properties of this family of compounds.

Results and Discussion

Syntheses. All calix[5]arene crown-6 ethers described in this study were synthesized according to Scheme 1.

The two calix[5]crown-6 triol precursors **3a**[11a] and **4a**,[11a,b] prepared from the corresponding parent *p-tert*-butyl-calix[5]arene **1**[20] and *p*-H-calix[5]arene **2**[16,21] by the method of Böhmer, were subjected to an excess of K_2CO_3 and the appropriate electrophile in refluxing CH_3CN (DMF at 60−70 °C in the case of **3d**) to afford (1,3)-*p-tert*-butyl- and (1,3)-*p*-H-calix[5]arene crown-6 ether derivatives **3c**−**k** and **4c**,**d**, respectively. Calixcrowns **3b**[11a] and **4b** were obtained by using MeI/NaH in anhydrous THF. Although the exhaustive alkylation of a given (1,3)-bridged calix[5]crown triol can in principle produce the six extreme conformational isomers shown in Figure 1, under our reaction conditions single products were always obtained, except in the case of **3a** where two conformational isomers **3j** and **3k** were isolated after reaction with $BrCH_2CO_2{}^tBu$. The remarkable selectivity found for the calixcrown derivatives immobilized in the cone conformation (**3c**−**f** and **3i**; see below) suggests a pronounced template effect by the potassium ion, which ensures the formation of a calixcrown anion intermediate preferentially held in the cone conformation.

Scheme 1. Syntheses of (1,3)-Calix[5]arene Crown-6 Ether Derivatives 3, 4[a−d]



3a: R = ^{t}Bu
4a: R = H

3b–k: R = ^{t}Bu
4b–d: R = H

compd	R	R'	electrophile[a]	Yield (%)[b]
3b	^{t}Bu	Me	MeI	65[c]
3c	^{t}Bu	Bn	BnBr	48
3d	^{t}Bu	α-Pic	α-PicCl·HCl	68[d]
3e	^{t}Bu	$(CH_2)_3CH(CH_3)_2$	$TsO(CH_2)_3CH(CH_3)_2$	64
3f	^{t}Bu	$(CH_2)_2OCH(CH_3)_2$	$TsO(CH_2)_2OCH(CH_3)_2$	88
3g	^{t}Bu	CH_2CO_2Me	$BrCH_2CO_2Me$	57
3h	^{t}Bu	CH_2CO_2Et	$BrCH_2CO_2Et$	47
3i	^{t}Bu	$CH_2CO_2{}^iPr$	$BrCH_2CO_2{}^iPr$	70
3j	^{t}Bu	$CH_2CO_2{}^tBu$	$BrCH_2CO_2{}^tBu$	62
3k	^{t}Bu	$CH_2CO_2{}^tBu$	$BrCH_2CO_2{}^tBu$	9
4b	H	Me	MeI	62
4c	H	Bn	BnBr	84
4d	H	$CH_2CO_2{}^tBu$	$BrCH_2CO_2{}^tBu$	76

[a] See Experimental Section for conditions. [b] Isolated yield. [c] Data from ref 11a. [d] Data from ref 11d.

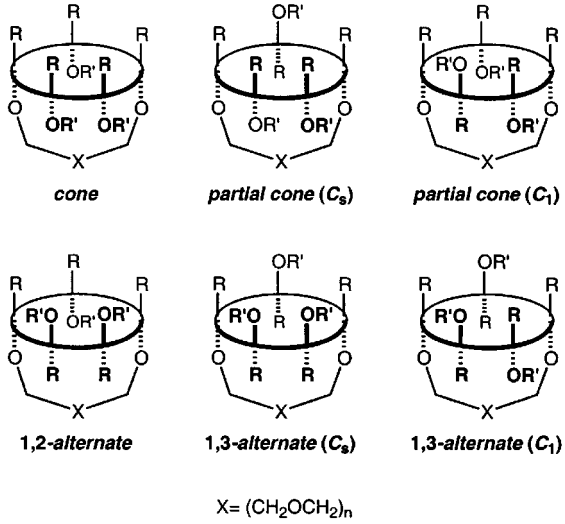


Figure 1. Schematic representation of the six extreme conformations of 1,3-bridged calix[5]arene crown ethers.

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Table 1. (1,3)-Calix[5]arene Crown-6 Ether Derivatives 3, 4: Conformations, Percentages of *Endo*-Cavity Complexation with $^{n}BuNH_3^+$ Ions, and Association Constants

compd	conformation	%[a]	K_a (M^{-1})[b]
3a	cone	*c*	
3b	cone-out	25	86
3c	cone-in	40	222
3d	cone-in	24	83
3e	cone-in	45	298
3f	cone-in	41	236
3g	cone[d]/noncone	50	
3h	cone[d]/noncone (C_1)	51	
3i	cone	55	
3j	cone	54	
3k	1,2-alternate	*c*	
4a	cone	*c*	
4b	cone-out	*c*	
4c	partial cone (C_1)[d]	*c*	
4d	partial cone (C_1)[d]	*c*	

[a] Values refer to equimolar (5×10^{-3} M) host−guest mixtures. [b] Only K_a values of hosts that show a single binding mode are reported, percentage of standard error ≤10%. [c] Not observed. [d] Predominant conformer.

Analytically pure compounds were easily recovered by column chromatography or direct crystallization and their structures established by ^{1}H and ^{13}C NMR spectroscopy, FAB (+) MS spectrometry, and elemental analysis.

Conformational Features. A simple correlation, similar to the one used by Gutsche for *p-tert*-butylcalix[5]arenes,[22] based on symmetry considerations and expected NMR patterns of diagnostic moieties (ArH, $ArCH_2$-Ar, and ^{t}Bu) (table provided in the Supporting Information), allowed us to directly assess the room temperature conformation present in solution ($CDCl_3$) of all *tert*-butylated compounds **3b**−**k**. On the other hand, derivatives **4b**−**d** required additional 2D-NMR studies (Table 1).

The ^{1}H NMR spectra of derivatives **3b**−**j** are consistent with calix[5]arene structures with a C_s symmetry[23] in a cone conformation. The ^{t}Bu, $ArCH_2Ar$, and ArH hydrogens give rise to sets of three singlets, three AX systems, and one singlet and two AB systems, respectively, all of them in a 1:2:2 ratio. Furthermore, the three signals due to the carbons of the bridging methylene groups resonate in the expected δ 28.6−30.8 ppm range.[24]

Triether derivatives **3b**−**f** adopt distorted cone conformations. In the case of the trimethyl ether **3b** a time-averaged cone-out conformation is observed. The methoxy group of the 'isolated' aryl ring (labeled as **a** in Scheme 1) is pointing into the calixarene annulus (while its ^{t}Bu substituent is tilted away), and consequently its ^{1}H NMR resonance is upfield shifted (δ 1.99 ppm) in comparison with the one (δ 2.86 ppm) of the two remaining methoxy groups (Figure 2).[25] Conversely, derivatives **3c**−**f** preferentially adopt a cone-in conformation in which the

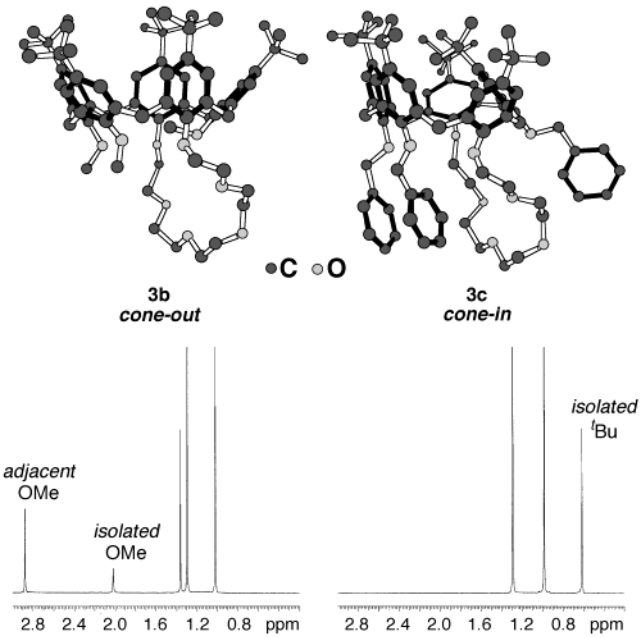

Figure 2. CS Chem3D molecular models of derivatives **3b** and **3c** with relevant regions of their ^{1}H NMR spectrum (300 MHz, $CDCl_3$) showing the preferred cone-out and cone-in conformations.

p-tert-butylphenyl moiety of the isolated aryl ring is leaning into the calixarene cup, while its substituent at the lower rim has moved away from the crown-6 moiety. Because of this structural arrangement, high-field singlets are observed for the pertinent ^{t}Bu (δ 0.48−0.74 ppm, see Figure 2 for **3c**) and aromatic (δ 6.31−6.62 ppm) hydrogens.

The conformational features of triester derivatives **3g**−**k** are also influenced by the size of the lower rim substituents. The ^{1}H NMR spectra of **3g**,**h** evidence, in addition to the resonances relative to the predominant cone conformer, sets of signals of lower intensity consistent with the presence in solution of at least one other noncone conformer.[26] This observation together with the temperature dependence (in the −50 to +135 °C range)[27] detected in the spectra of both compounds indicates that at room temperature a slow (on the NMR time scale) conformational equilibrium is being established. Since the upper rim rotation through the annulus is sterically prevented for *p-tert*-butylcalix[5]arenes,[22] the conformational interconversion observed occurs via the oxygen-through-the-annulus-pathway. For the lower rim intra-annular rotation of **3g** a free energy barrier ($\Delta G^{\ddagger}$) of 16.8 kcal mol^{-1} was calculated from a VT-NMR study.[28]

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(23) The only symmetry element present is a mirror plane bisecting the 'isolated' aryl ring, the one labeled as **a** in the structure **3**,**4** of Scheme 1, and the diametrically opposite methylene bridge.

(24) For calix[5]arene conformation assessments by ^{13}C NMR, see ref 22. For analogous assignment in the calix[4] and calix[6]arene, see Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372. Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R.; Nieto, P. M.; Carramolino, M.; Cuevas, F.; Prados, P.; de Mendoza, J. *Synthesis* **1993**, 380. Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 1542.

(25) Upon heating in $(CDCl_2)_2$ (22−100 °C), the two methoxy resonances of **3b** progressively shifted from 1.94 and 2.82 to 2.54 and 3.01 ppm, respectively.

(26) Conformational assignment of the minor isomer(s) of **3g** was hampered by severe peak broadening. Conversely, a clear and sharp five AB and five singlet pattern, in the aromatic and *tert*-butyl regions, of the less abundant conformer of **3h** restricted the choice among noncone structures to either a partial cone or a 1,3-alternate conformer with C_1 symmetry. However, further attempts to narrow down the options via diastereomeric complex formation, using chiral NMR shift reagents [(*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol or europium(III) tris(*d*,*d*-dicampholylmethanate)], did not produce any doubling of the original peaks.

(27) Low- and high-temperature spectra were recorded in CD_2Cl_2 and $(CDCl_2)_2$, respectively.

(28) The relevant rate constant for conformational interconversion (k_c), coalescence temperature (T_c), and $\Delta\nu_{(ArCH_2Ar)}$ value required for $\Delta G^{\ddagger}$ calculation were determined according to Gutsche's procedure.[22]

The conformational mobility displayed by trimethyl and triethyl esters **3g**,**h** is suppressed in the case of triisopropyl and tri-*tert*-butyl esters **3i** and **3j**, which exist in solution as immobilized and regular cone conformers. The immobile conformation of **3j** is additionally confirmed by the isolation (9%) of the conformer **3k**, locked in a 1,2-alternate arrangement, as a secondary product of the alkylation of **3a** with $BrCH_2CO_2{}^tBu$. The structural assignment of **3k** is based on chemical shift considerations on the $OCH_2CO_2{}^tBu$ resonances. The AB system at δ 3.86 and 3.88 ppm (4 hydrogens) and the signal at δ 36.1 ppm present in the ^1H and ^{13}C NMR spectra indicate the presence of two equivalent bridging methylene groups flanked by two *anti*-oriented aryl residues and would therefore be commensurate with either a C_s symmetric partial cone or 1,2-alternate conformer. By comparing the ^1H NMR spectra of the two isomers **3j** and **3k**, it can be seen that the AB system relative to the diastereotopic hydrogens of the two equivalent $OCH_2CO_2{}^tBu$ groups of the latter is upfield shifted (**3j**: δ 4.56 and 4.67 ppm; **3k**: δ 3.64 and 3.95 ppm). These data are only compatible with a 1,2-alternate conformation in which the resonances of the two adjacent and 'inverted' $OCH_2CO_2{}^tBu$ moieties are shielded by the three remaining up-oriented aryl rings.

In analogy with its *tert*-butylated counterpart **3b**, trimethyl ether **4b** displays in solution a fast equilibrating time-averaged cone-out conformation, and similarly its isolated methoxy group resonates in the ^1H NMR spectrum at higher field (δ 2.46 ppm) than the other two (δ 3.30 ppm). At 300 MHz the 3.0−5.0 ppm region of the ^1H NMR spectra of de-*tert*-butylated derivatives **4c**,**d** is rather complex because of considerable overlapping between the resonances of the oxymethylene hydrogens (polyether chain and lower rim substituents) and those of the bridging methylene groups and consequently does not allow an immediate assessment of the pattern of the latter. Furthermore, although the five distinct ^{13}C NMR resonances (**4c**: δ 29.1, 31.0, 31.2, 34.7, and 38.5 ppm; **4d**: δ 29.3, 31.2, 31.8, 33.0, and 38.0 ppm) for the $ArCH_2$-Ar carbons clearly indicated the presence of inherently chiral structures, the two borderline values at δ 34.7 ppm for **4c** and δ 33.0 ppm for **4d** did not ultimately confirm their conformations as partial cones with C_1 symmetry. Definite structural assignments for **4c**,**d** as partial cone conformers were possible after a combination of COSY and HETCOR NMR experiments which unambiguously established the presence in the ^1H NMR spectra of both derivatives of three AX and two AB systems (see Experimental Section) for the $ArCH_2Ar$ hydrogens.

An overall analysis of the data reported in Table 1 indicates that in solution the conformation of (1,3)-calix[5]arene crown-6 ether derivatives is strongly affected by the steric hindrance of both the lower and upper rim substituents. The cone-out conformation of **3b** suggests that the methoxy groups have a tendency to swing inside the annulus. Replacement of the methyl group with arylalkyl or long chain alkyl groups (Bn, α-Pic, $(CH_2)_3CH(CH_3)_2$, and $(CH_2)_2OCH(CH_3)_2$) generates immobilized structures. Derivatives **3c**−**f** all adopt a distorted cone-in conformation with self-inclusion of the isolated ^{t}Bu moiety inside the calixarene cavity. This tilting motion pushes one of the lower rim pendant groups away from the crown ether bridge and in so doing minimizes the overcrowding generated by the presence of sterically demanding groups. A number of X-ray studies on ether,[11c,22,29] ester,[30] and ketone[21b] derivatives of *p-tert*-butylcalix[5]arene have shown that the cone-in arrangement is a conformational feature commonly encountered also in the solid state. The fluxional behavior of trimethyl and triethyl esters **3g** and **3h** contrasts with the rigid cone and 1,2-alternate conformations of **3i**,**j** and **3k**, respectively. These conformational outcomes corroborate previous findings[31] on the need to introduce groups larger than CH_2CO_2Et at the lower rim to obtain immobile conformational isomers of *p-tert*-butylcalix[5]arenes.

Calix[5]crowns devoid of ^{t}Bu groups at the upper rim are considerably more flexible. Derivative **4b**, bearing three small methyl groups at the lower rim still favors a fast equilibrating time-averaged cone-out conformation, but as soon as the size of the *O*-substituents is increased (e.g., **4c**,**d**) the resulting steric congestion at the lower rim together with the lack of ^{t}Bu groups at the upper rim determine the loss of preorganization of the calix[5]arene cavity in favor of noncone structures in slow (on the NMR time scale) conformational equilibrium, via the phenyl-through-the-annulus-rotation pathway.[21b,31]

Molecular Recognition Properties. The molecular recognition properties of (1,3)-calix[5]arene crown-6 ethers **3** and **4** toward alkylammonium ions were investigated in solution by ^1H NMR spectroscopy, using the four isomeric butylammonium picrates as model substrates of different size and shape. The NMR complexation experiments, carried out at room temperature, involved titration of a $CDCl_3/CD_3OD$ (9:1, v/v) receptor solution with increasing amounts of guest.

(a) Triethers. Initial titration experiments on triethers **3b**−**f** with 1 equiv of the four isomeric picrate salts produced drastic spectral changes only in the case of $^n BuNH_3^+$ ions, indicating selective recognition by the receptors of the linear alkylammonium guest. Inspection of trace b of Figure 3, which refers to an equimolar mixture (5×10^{-3} M) of **3e** and *n*-butylammonium picrate, reveals doubling of the original peaks of the host (trace a) and the guest (trace c), suggesting the presence in solution of a host−guest complex which is slowly exchanging, on the NMR time scale, with the uncomplexed species. The *endo*-cavity nature of this complex is unambiguously supported by the four signals resonating in the δ 0.0 to −2.0 ppm region of the spectrum, which belong to the cavity-included *n*-butyl chain of the guest. ^1H NMR homonuclear decoupling experiments allowed us to assign the different peaks to the respective protons. The deep intrusion of the guest inside the calixcrown cavity is proven by the remarkable upfield complexation induced shifts (CISs) experienced by these resonances (Table 2) which reflect the effectiveness of the shielding caused by the five aryl rings of a cone-arranged calixarene. Furthermore, the generally decreasing magnitude of the CIS values along the α-, β-, γ-CH_2, and CH_3 series indicates a geometry of the complex consistent with the one depicted in Figure 4. That is, the NH_3^+ group pointing toward the lower rim of the calixcrown. The reverse geometry would not justify the trend observed.

Since, on the NMR time scale, the inclusion complex between **3e** and the $^n BuNH_3^+$ ion is in slow exchange with

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(30) Barrett, G.; McKervey, M. A.; Malone, J. F.; Walker, A.; Arnaud-Neu, F.; Guerra, L.; Schwing-Weill, M.-J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1475.
(31) Ferguson, G.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Spek, A. L. *Tetrahedron Lett.* **1998**, *39*, 1965.

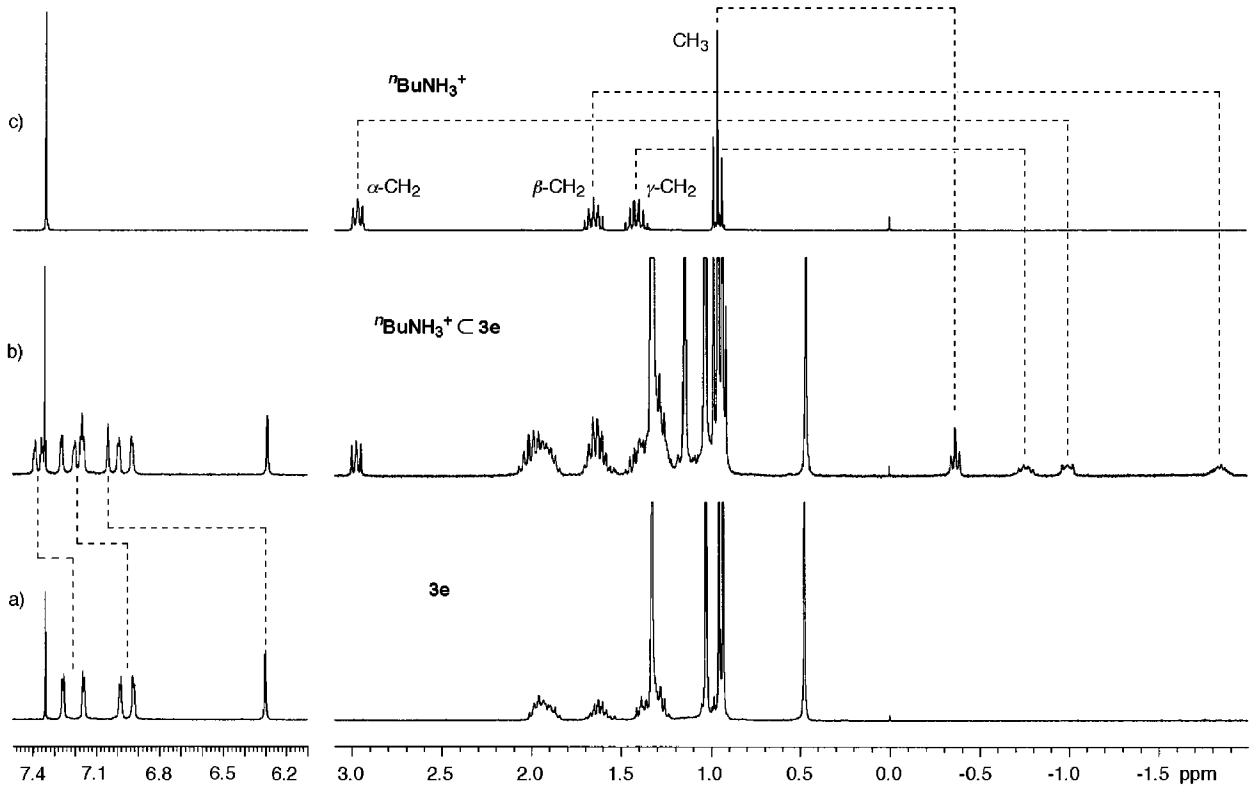

Figure 3. *Endo*-cavity complexation (slow exchanging regime) of the $^{n}BuNH_3^+$ ion by **3e**. Selected regions of the ^1H NMR (300 MHz; $CDCl_3/CD_3OD$, 9:1; 293 K) spectra of (a) free host, (b) the host−guest equimolar mixture, and (c) the free guest.

Table 2. Complexation Induced Shifts (CISs) Experienced by the $^{n}BuNH_3^+$ Ion Resonances upon *Endo*-Cavity Complexation with Hosts 3b−f[a−c]

host	α-CH_2	β-CH_2	γ-CH_2	CH_3
3b	3.86	3.29	1.94	1.19
3c	3.96	3.59	2.24	1.42
3d	3.26	3.54	2.56	1.59
3e	3.97	3.50	2.17	1.33
3f	3.70	3.47	2.14	1.31

[a] In $CDCl_3/CD_3OD$ (9:1, v/v) at 293 K. [b] CIS values (ppm) are calculated as the difference between the resonances of pertinent protons of free and complexed guest. [c] Peak assignments follow from homonuclear decoupling experiments.

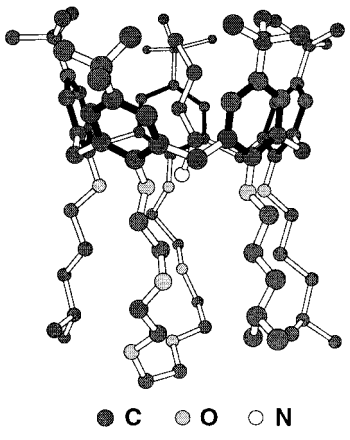

Figure 4. CS Chem3D molecular model of the 1:1 *endo*-cavity complex between calixcrown **3e** and the $^{n}BuNH_3^+$ ion.

the uncomplexed species, its 1:1 stoichiometry and percentage of complexation (or the corresponding association constant (K_a)) were determined by direct ^1H NMR analysis from the peak intensity ratio of an equimolar host−guest solution. Further addition of an excess of $^{n}BuNH_3^+$ ions (up to 5 equiv) to the above-mentioned 1:1 host−guest mixtures caused an increase in the intensity of the set of signals relating to the *endo*-cavity complex with a proportional depletion of the free host. As regards the chemical shifts, some of the free host resonances underwent very minor variations ($\Delta\delta \sim 0.05$ ppm), while those of the *endo*-cavity complex were totally unaffected. Similarly, no appreciable chemical shift change ($\Delta\delta \sim 0.031$ ppm) was observed for the picrate signal on complexation.[32]

The mode of binding discussed above was consistently observed in the complexation experiments between the $^{n}BuNH_3^+$ ion and all the other triether derivatives **3b**−**e** (Table 1). Triether derivative **3d**, because of the enhanced basicity[33] of the isolated picolyl residue, behaves in a peculiar way in the presence of $^{n}BuNH_3^+$ ions. The ^1H NMR spectrum of equimolar amounts of **3d** and *n*-butylammonium picrate showed the presence of additional signals of low intensity, which were assigned to protonated host (∼10%) by comparison with the spectrum obtained after protonation of **3d** with TFA (1 equiv). The easy protonation of the isolated picolyl group is believed to be associated with the juxtaposition of the polyether bridge which stabilizes the pyridinium cation by self-complexation. In so doing **3d** assumes a more regular

(32) A recent study (Talanova, G. G.; Elkarim, N. S. A.; Talanov, V. S.; Hane, R. E., Jr.; Hwang, H.-S.; Bartsch. R. A.; Rogers, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 6019) and some later observations[15b] have shown that a so-called 'picrate effect' (namely a $\pi-\pi$ stabilizing interaction between the picrate counterion of the guest and the aromatic subunit(s) of the host) can be detected by following the upfield shift of the picrate resonance upon complex formation.

(33) An estimate of the acid−base behavior of **3d** (L) in MeOH showed the following log *K* of protonation: log K_1 ($L + H^+ = LH^+$) = 8.6; logK_2 ($LH^+ + H^+ = LH_2^{2+}$) = 4.1; log K_3 ($LH_2^{2+} + H^+ = LH_3^{3+}$) = 3.3.

cone conformation, as suggested by a pronounced downfield induced shift ($\Delta\delta$ 0.95 ppm) observed on the resonance of the isolated ^{t}Bu substituent. This competitive protonation process may therefore account for the lower K_a value (86 M^{-1}) of **3d** with respect to that of the structurally similar tribenzyl ether **3c** (222 M^{-1}).

The formation of *endo*-cavity complexes is limited to the ^{n}BuNH$_3^+$ ion and is not detected with any of the other branched isomers ($^{i-,\ s-,\ t}$BuNH$_3^+$). It should however be mentioned that branched butylammonium ions show a weak interaction with derivatives **3b**−**f**. For instance, the addition of 5 equiv of ^{i}BuNH$_3^+$ ions to **3f** caused minor modifications to its ^{1}H NMR spectrum,[34] the most prominent ones being the chemical shift variations (≅0.17 ppm) induced on the resonances of the ArH and ^{t}Bu hydrogens of the isolated aryl ring. These data, although not compatible with a slow exchanging inclusion complex, suggest a weak interaction of the guest with the crown-6 moiety of the host (see below).

The unique ability of compounds **3b**−**f** to discriminate linear from branched primary alkylammonium ions, via formation of stable *endo*-cavity complexes, can be ascribed to a remarkable steric and electronic complementarity between the preorganized π-rich hydrophobic cavity of the calix[5]arene skeleton and the shape of the guest. In addition to CH−π[35] and cation−π[36] interactions, it seems also reasonable to assume that other noncovalent interactions, such as hydrogen bondings between the cavity-included NH$_3^+$ group and the phenolic oxygen(s) of the host, may contribute to the stabilization of these inclusion complexes. The selectivity observed likely depends on the presence of the ^{t}Bu substituents at the upper rim, which sterically interfere with the branched alkylammonium guests.

Inclusion complexes between organic ammonium ions and calixarene systems in a slow exchanging regime have previously been reported for calix[6]arenes[37] and more recently for biscalix[4]arenes,[38] calix[5]arenes,[31,39] and 1,1′-binaphthyl-derived calix[5]crowns.[40] At the same time, inclusion complexes of calix[5]crowns with quaternary ammonium salts,[15] and water soluble calix[4]arenes[41] with α-amino acids with rapid exchange equilibria have also been described.

(b) Triesters. The remarkable site selectivity displayed by triethers **3b**−**f** for linear alkylammonium ions is somehow lost in the case of triesters **3g**−**j**, which show a dual binding mode with ^{n}BuNH$_3^+$ ions.[19] When exposed to 1 equiv of ^{n}BuNH$_3^+$ under standard titration conditions (5×10^{-3} M; CDCl$_3$/CD$_3$OD, 9:1, v/v; 293 K), compounds **3g**−**j** form *endo*-cavity complexes in the 50−55% range (Table 1), but display a second and competitive binding mode which takes place at the hydrophilic crown ether pocket of the lower rim. This second interaction gives rise to a host−guest complex which has been named *exo*-cavity[19] to distinguish it from the one discussed above. The distinction between the *endo*- and *exo*-cavity binding mode is particularly pronounced in the case of triesters **3i** and **3j**, with a regular and fixed cone conformation, but it is also evident with **3g** and **3h** despite their conformational mobility in solution (see Table 1). The two processes can be differentiated and monitored by ^{1}H NMR spectroscopy. Titration experiments of derivatives **3i**,**j** with ^{n}BuNH$_3^+$ ions (up to 20 equiv) feature two distinct sets of signals, neither of which is compatible with the resonances of the free host. The one whose chemical shifts vary according to the amount of guest added identifies the host−^{n}BuNH$_3^+$ *exo*-cavity complex. In contrast, the second set of signals accounts for the *endo*-cavity complex and, in agreement with a slow exchanging regime, displays chemical shifts that are guest concentration independent. Finally, the intensities of the peaks due to the complexed host correlate with those of the four resonances at very high field (δ −0.4 to −2.0 ppm) which are diagnostic of the cavity-included ^{n}BuNH$_3^+$ guest. Although both binding sites (crown ether moiety and calix[5]arene cavity) actively recognize the ^{n}BuNH$_3^+$ ion, *endo*-complexation is favored, and its percentage increases with increasing amounts of salt, until it levels off to about 80%, after 15 equiv of salt have been added.[19,42]

Table 3. Association Constants (M^{-1}) for the *Exo*-Cavity Complexes between Hosts 3i,j and *i*-, *s*-, and *tert*-Butylammonium Picrate Guests[a,b]

	guest		
host	^{i}BuNH$_3^+$	^{s}BuNH$_3^+$	^{t}BuNH$_3^+$
3i	44	9	< 5
3j	98	15	9

[a] From ^{1}H NMR titrations of the host with the guest in CDCl$_3$/CD$_3$OD (9:1, v/v) at 293 K. [b] Percentage of standard error ≤10%.

For steric reasons, branched alkylammonium ions can only approach the crown ether binding site and therefore form exclusively *exo*-cavity complexes with **3i**,**j**. This binding mode, unlike the *endo*-one, is fast on the NMR time scale and consequently shows a single set of time-averaged signals for both bound and unbound species of host and guest. The association constants for the 1:1 complexes between **3i**,**j** and $^{i-,s-,t}$BuNH$_3^+$ ions were determined by NMR titration experiments as previously described by Schneider.[43] Accordingly, nonlinear curve-fitting of the chemical shift changes (δ_{obs}) measured for the resonances (^{t}Bu and ArH hydrogens of the isolated ring) of the host upon addition of an excess of guest gave the K_a values reported in Table 3.

As an example, the two titration curves of **3j** with isobutylammonium picrate are shown in Figure 5. In this case after addition of 8.8 equiv of salt the singlet relative to the upper rim ^{t}Bu group of the isolated aryl residue moves upfield from δ 0.99 to 0.13 ppm. Concomitantly, the resonance (singlet, 2H) of the isolated aryl residue undergoes an even higher upfield CIS of 1.03 ppm (from δ 6.93 to 5.90 ppm). The signals of the remaining ^{t}Bu

(34) Earlier ^{1}H NMR measurements[18] carried out on **3b** and **3d** after addition of only 2 equiv of branched (C_3 and C_4) RNH$_3^+$ ions had not revealed these spectral changes.

(35) Nishio, M.; Hirota, H.; Umezawa. Y. *The CH/π Interaction. Evidence, Nature, and Consequences*, Wiley-VCH: New York, 1998.

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(40) Caccamese, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Principato, G. *J. Inclusion Phenom. Mol. Recogn.* **2000**, *36*, 67.

(41) Arena, G.; Casnati, A.; Contino, A.; Lombardo, G. G.; Sciotto, D.; Ungaro. R. *Chem. Eur. J.* **1999**, *5*, 738. Arena, G.; Contino, A.; Gulino, F. G.; Magrì, A.; Sansone, F.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **1999**, *40*, 1597.

(42) Notti, A.; Pappalardo, S.; Parisi, M. F. In *Calixarenes 2001*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J. Eds.; Kluwer: Dordrecht, The Netherlands, 2001; chapter 3, pp 54−70.

(43) Schneider, H.-J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442.

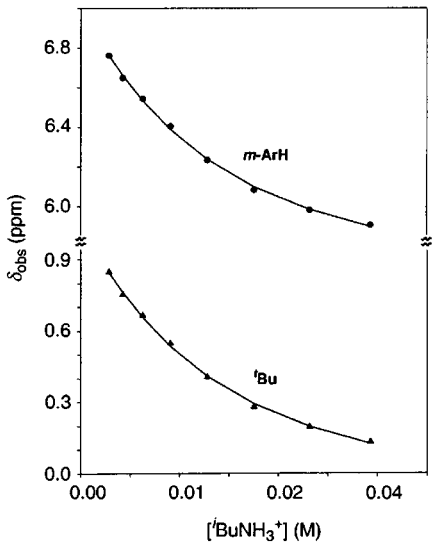

Figure 5. Determination of the association constant (K_a) of the **3j**−^{i}BuNH$_3^+$ *exo*-cavity complex in $CDCl_3/CD_3OD$ (9:1, v/v) at 293 K by nonlinear curve fitting of the experimental data (● and ▲) of a ^{1}H NMR titration (300 MHz; [**3j**] = 6.6−3.3 × 10^{-3} M; [^{i}BuNH$_3^+$] = 2.8 × 10^{-3} − 2.9 × 10^{-2} M). The chemical shifts observed (δ_{obs}) for the ^{t}Bu and ArH hydrogens of the isolated aryl residue of the host are plotted against the total guest concentration.

and aryl groups all drift slightly downfield with respect to those of the free host. The chemical shifts of the guest are less sensitive to complexation. The α-CH_2 resonance of the isobutylammonium moves 0.038 ppm downfield and the picrate[32] one shifts 0.023 ppm upfield. These data are consistent with the formation of an *exo*-cavity complex in which the host rearranges from a regular cone to a cone-in conformation to make room for the incoming guest at the lower rim. The driving force for this second binding process arises from cooperative ion−dipole interactions and hydrogen bonding(s) between the NH_3^+ headgroup of the guest and the oxygen atoms of the polyether chain, with the likely assistance of the carbonyl group(s)[44] of the lower rim substituent(s).

The key role played by a polyether moiety of appropriate length is underlined by a number of previous studies on 1,3-bridged calix[4]crown-6,[10] 1,2-bridged calix[5]-crown-6,[11d,e] and 1,1′-binaphthyl calix[5]crown-6[40] derivatives. Unlike the smaller calixcrown analogues, in all these instances it has been shown that, irrespective of the relative position (1,2- or 1,3-) and the stiffness of the intrabridging chain, the presence of a six-oxygen pattern is essential for complexation of alkyl- and/or arylalkylammonium ions. Host−guest hydrogen bonding formation is supported by the shift of the IR absorption bands (ν_{N-H} 2000→1992 cm^{-1} and δ_{N-H} 1615→1604 cm^{-1}) observed in $CHCl_3$ for a 10/1 ^{i}BuNH$_2$·HCl/**3j** mixture. The same IR spectrum also shows the merging of two carbonyl bands ($\nu_{C=O}$ 1752 and 1718 cm^{-1}) into a single broader absorption centered at 1750 cm^{-1}. Further evidence for carbonyl participation/assistance in hydrogen bonding(s) is provided by a ^{13}C NMR titration experiment. In this experiment, the addition of isobutylammonium picrate (10 equiv) to a $CDCl_3/CD_3OD$ solution of **3j** shifted the carbonyl resonances from δ 169.2 and 169.3 to 168.4 and 169.8 ppm.[45]

The K_a values in Table 3 indicate that the binding of the hosts **3i**,**j** decreases with the increasing size of the alkyl chain of the ammonium guests. In both cases moderate discrimination between ^{i}BuNH$_3^+$ and $^{s-,t}$BuNH$_3^+$ ions is observed, with a selectivity factor for the ^{i}Bu/^{t}Bu pair of ca. 10. This selectivity is ascribed to the rigid and three-dimensional nature of the host. The preferential *exo*-cavity recognition might derive from a lateral interaction between the alkylammonium moiety of the guest and the bulky lower rim substituent(s) of the calixarene backbone.

Qualitative titration experiments on the underivatized calix[5]crown-6 **3a** and **4a**, 1,2-alternate triester **3k**, and de-*tert*-butylated derivatives **4b**−**d** showed no trace of *endo*-cavity complex formation with any of the four alkylammonium ions under investigation. All these compounds behave as monotopic receptors, generally forming weak *exo*-cavity complexes with the four guests without any apparent selectivity. It is interesting to note that although derivative **4b** adopts a cone-out conformation analogous to that of its *tert*-butylated counterpart **3b**, it is not able to form inclusion complexes with ^{n}BuNH$_3^+$ ions. These findings emphasize the central role played by the upper rim ^{t}Bu substituents, not only in the shaping of the cavity and in the control of the conformation upon lower rim derivatization, but also in the guest recognition process. When compared to hydrogen substituents, the ^{t}Bu groups act as sterical sieves toward branched alkylammonium ions and additionally enhance the electron density of the calixarene cavity which in turn facilitates the formation of cation−π and/or CH−π interactions with the linear guest.

Conclusions

The studies described in this paper demonstrate that exhaustive alkylation of 1,3-bridged calix[5]arene crown-6 ethers **3a** and **4a** affords tri-*O*-substituted derivatives in moderate to high yields (45−88%). Providing that sufficiently bulky electrophiles are used, **3a** generally yields rigid conelike conformational isomers (i.e., **3c**−**f** and **3i**,**j**). On the other hand, derivatives with small-sized lower rim substituents (i.e., **3b** and **3g**,**h**) and/or lacking the ^{t}Bu groups at the upper rim (i.e., **4b**−**d**) exist in solution as mixtures of interconverting conformational isomers.

Complexation studies between these host molecules and the four isomeric butylammonium ions have revealed two different binding modes (*endo*- and *exo*-cavity), which can be distinguished and monitored by ^{1}H NMR titration experiments. Triether derivatives display a marked *endo*-cavity selectivity for linear alkylammonium ions, related to the presence of the ^{t}Bu groups at the upper rim. Conversely, conformationally fixed triesters moderately discriminate different branched alkylammonium ions (selectivities for ^{i}BuNH$_3^+$/$^{s-,t}$BuNH$_3^+$ ∼ 10), via a lateral interaction with lower rim pendant group(s), but show a dual binding mode with ^{n}BuNH$_3^+$ ions. Our studies emphasize the versatility of calixarenes as molecular receptors. By an appropriate choice of the upper and lower rim substituents we have been able to confer different recognition properties on the two potential binding sites of calix[5]crowns, by turning them into

(44) Han, S.-Y.; Kang, M.-H.; Jung, Y.-E.; Chang S.-K. *J. Chem. Soc., Perkin Trans. 2* **1994**, 835.

(45) The authors are aware that the chemical shift changes might just arise as a result of the rearrangement of the host from a regular cone to a cone-in conformation.

fairly effective shape-selective receptors of isomeric organic ions. Further tuning of these molecular recognition properties is currently in progress.

Experimental Section[46]

Materials. Compounds **1**,[20] **2**,[16,21] **3a**,[11a] **3b**,[11a,b] and **4a**[11b] were synthesized according to literature procedures. Pentaethylene glycol ditosylate, 4-methylpentanol, and 2-isopropoxyethanol tosylates were prepared by standard methods.[47]

Exhaustive Alkylation of (1,3)-Bridged Calix[5]crown-6 Triols 3a and 4a. General Procedure. Derivatives **3c**, **3e**−**k**, and **4c**,**d** were obtained by treatment of triols **3a** and **4a** (0.5−1 mmol), respectively, with anhydrous K_2CO_3 (10 equiv) and the appropriate electrophile (10 equiv) in dry CH_3CN (20−50 mL), under reflux, for 18−24 h. Progress of the reaction was monitored (TLC) by following the disappearance of the starting triols. The excess of base and KBr formed were filtered off and washed with $CHCl_3$, and the combined organic layers were concentrated to dryness. In the case of triester derivatives the oily residue (containing free calixcrown and calixcrown-K^+ complex) obtained was treated with petroleum ether. The additional inorganic salts precipitated were separated by suction filtration to afford after solvent evaporation the free calixcrown. The reaction residue was then triturated with MeOH and the resulting crude product purified either by direct recrystallization or column chromatography (CC) followed by crystallization from an appropriate solvent. Further details are given for the individual compounds.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,34-tribenzyloxy-33,35-crown-6-calix[5]arene (3c): obtained in 48% yield from **3a** and BnBr after direct recrystallization of the crude product. Mp 113−115 °C (CH_3CN); ^{1}H NMR δ 0.61, 0.98, 1.29 (s × 3, C(CH_3)$_3$, 1:2:2, 45 H), 3.10 and 4.33, 3.10 and 4.48, 3.25 and 4.58 (AX × 3, J = 13.5, 13.9, 14.1 Hz, respectively, ArCH_2Ar, 1:2:2, 10 H), 3.32−3.82 (m, OCH_2CH_2O, 20 H), 4.80 and 4.83 (ABq, J = 11.6 Hz, OCH_2Ph, 4 H), 4.86 (s, OCH_2Ph, 2 H), 6.46 (s, ArH, 2 H), 6.84 and 6.89, 7.14 and 7.17 (ABq × 2, J = 2.5 Hz, ArH, 1:1, 8 H), 7.22−7.57 (m, PhH, 15 H) ppm; ^{13}C NMR δ 28.8, 29.5, 30.0 (ArCH_2Ar), 31.0, 31.3, 31.6 (C(CH_3)$_3$), 33.8, 34.0, 34.1 (*C*(CH_3)$_3$), 70.56, 70.59, 70.7, 71.0, 72.2 (OCH_2), 76.2, 76.3 (*C*H_2Ph), 124.3, 124.9, 125.2, 126.3, 126.7, 127.7, 127.8, 128.2, 128.4, 128.8, 129.1 (*m*-Ar, Ph), 133.3, 133.5, 134.0, 134.1, 134.5, 137.7, 137.9, 144.9, 145.0, 145.1 (*o*-Ar, *p*-Ar, Ph), 151.5, 151.7, 152.8 (*ipso*-Ar) ppm; FAB (+) MS, *m*/*z* 1300 (MNH_4^+). Anal. Calcd for $C_{86}H_{106}O_9$: C, 80.46; H, 8.32. Found: C, 80.62; H, 8.43.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,34-tri-[(2-pyridylmethyl)oxy]-33,35-crown-6-calix[5]arene (3d): obtained in 68% yield from **3a** and 2-(chloromethyl)pyridine hydrochloride (6 equiv) and anhyrous K_2CO_3 (12 equiv) in dry DMF.[11e]

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,34-tri-(4-methylpentyloxy)-33,35-crown-6-calix[5]arene (3e): obtained in 64% yield from **3a** and TsO(CH_2)$_3$CH(CH_3)$_2$ after direct recrystallization of the crude product. Mp 209−214 °C (CH_3CN/CH_2Cl_2); ^{1}H NMR δ 0.48, 1.01, 1.32 (s × 3, C(CH_3)$_3$, 1:2:2, 45 H), 0.94 (d, J = 6.5 Hz, CH(CH_3)$_2$, 18 H), 1.25−1.41 (m, CH_2CH(CH_3)$_2$, 6 H), 1.53−1.69 (m, CH_2CH$_2$CH(CH_3)$_2$, 6 H) 1.84−2.00 (m, C*H*(CH_3)$_2$, 3H), 3.24 and 4.55, 3.26 and 4.51, 3.30 and 4.56 (AX × 3, J = 13.7, 13.2, 14.4 Hz, respectively, ArCH_2Ar, 2:1:2, 10 H), 3.49 (t, J = 5.4 Hz, OCH_2CH_2O, 4 H), 3.73−3.88 (m, OCH_2CH_2O and O$CH_2CH_2CH_2$, 18 H), 3.95 (t, J = 5.5 Hz, OCH_2CH_2O, 4 H), 6.31 (s, ArH, 2 H), 6.90 and 6.96, 7.15 and 7.24 (ABq × 2, J = 2.3, 2.4 Hz, respectively, ArH, 1:1, 8 H) ppm; ^{13}C NMR δ 22.65, 22.70 (CH(*C*H_3)$_2$), 28.00, 28.05 (*C*H(CH_3)$_2$), 28.20, 28.24 (*C*H_2CH(CH_3)$_2$), 28.6, 29.2, 30.4 (Ar*C*H_2Ar), 30.9, 31.4, 31.6 (C(*C*H_3)$_3$), 33.7, 34.0, 34.1 (*C*(CH_3)$_3$), 35.1, 35.3 (*C*H_2CH$_2$CH(CH_3)$_2$), 70.8 (×2), 70.9, 71.1, 72.2, 74.6, 75.2 (OCH_2), 124.0, 124.6, 125.1, 126.5, 126.9 (*m*-Ar), 133.0, 133.4, 133.8, 134.2, 134.7 (*o*-Ar), 144.6 (×2), 144.8 (*p*-Ar), 152.1, 152.4, 153.1 (*ipso*-Ar) ppm; FAB (+) MS *m*/*z* 1282 (MNH_4^+). Anal. Calcd for $C_{83}H_{124}O_9$: C, 78.75; H, 9.87. Found: C, 78.89; H, 9.81.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,34-tri[2-(1-methylethoxy)ethoxy]-33,35-crown-6-calix[5]arene (3f): obtained in 88% yield from **3a** and TsO(CH_2)$_2$OCH(CH_3)$_2$ after direct recrystallization of the crude product. Mp 165−170 °C (CH_3CN); ^{1}H NMR δ 0.74, 0.93, 1.26 (s × 3, C(CH_3)$_3$, 1:2:2, 45 H), 1.17, 1.18 (d × 2, J = 6.1 Hz, CH(CH_3)$_2$, 2:1, 18 H), 3.25 and 4.55, 3.29 and 4.58 (AX × 2, J = 14.1, 14.0 Hz, respectively, ArCH_2Ar, 2:3, 10 H), 3.54 (t, J = 5.3 Hz, OCH_2CH_2O, 4 H), 3.66, 3.67 (sept × 2, J = 6.1 Hz, CH(CH_3)$_2$, 2:1, 3 H), 3.73−4.11 (m, OCH_2CH_2O and OCH_2CH_2O^{i}Pr, 28 H), 6.62 (s, ArH, 2 H), 6.78 and 6.81, 7.13 and 7.15 (ABq × 2, J = 2.5, 2.4 Hz, respectively, ArH, 1:1, 8 H), ppm; ^{13}C NMR δ 22.16, 22.18 (CH(*C*H_3)$_2$), 28.9, 29.9, 30.3 (Ar*C*H_2Ar), 31.1, 31.3, 31.6 (C(*C*H_3)$_3$), 33.8, 33.9, 34.0 (*C*(CH_3)$_3$), 66.9, 67.2, 70.8, 71.0 (OCH_2), 71.7, 71.8 (*C*H(CH_3)$_2$), 72.5, 73.1, 73.3 (OCH_2), 124.3, 124.8, 125.3, 126.2, 126.6 (*m*-Ar), 133.2, 133.3, 133.8, 133.9, 134.6 (*o*-Ar), 144.7, 144.8, 144.9 (*p*-Ar), 151.7, 152.4, 153.0 (*ipso*-Ar) ppm; FAB (+) MS *m*/*z* 1288 (MNH_4^+). Anal. Calcd for $C_{80}H_{118}O_{12}$: C, 75.55; H, 9.35. Found: C, 75.71; H, 9.46.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,34-tri-(methoxycarbonylmethyloxy)-33,35-crown-6-calix[5]-arene (3g):[48] obtained in 57% yield from **3a** and BrCH_2CO_2Me after CC (SiO_2; cyclohexane/AcOEt, 3:1). Mp 184−187 °C (MeOH); ^{1}H NMR δ 0.91, 0.93 1.16 (s × 3, C(CH_3)$_3$, 1:2:2, 45 H), 3.31, 3.36 (d × 2, J = 13.9, 14.5 Hz, respectively, *exo*-ArCH_2Ar, 4:1, 5 H), 3.50−4.01 (m, OCH_2CH_2O, 20 H), 3.79, 3.82 (s × 2, OMe, 1:2, 9 H), 4.60−4.77 (m, *endo*-ArCH_2Ar and OCH_2CO, 11 H), 6.80 (pseudo-s, ArH, 4 H), 6.82 (s, ArH, 2 H), 6.99 and 7.08 (ABq, J = 2.4 Hz, ArH, 4 H) ppm; ^{13}C NMR δ 29.1, 29.7, 30.8 (Ar*C*H_2Ar), 31.2 (×2), 31.5 (C(*C*H_3)$_3$), 33.9, 34.0, 34.1 (*C*(CH_3)$_3$), 51.7, 51.8 (OCH_3), 70.6, 70.78 (×2), 70.83, 71.0, 71.1, 72.7 (OCH_2), 125.0, 125.6, 125.8, 125.9, 126.3 (*m*-Ar), 133.2, 133.3, 133.4, 133.5, 134.2, (*o*-Ar), 145.0, 145.4, 145.6 (*p*-Ar), 151.7, 152.2, 152.7 (*ipso*-Ar), 170.3, 170.5 (C═O) ppm; FAB (+) MS *m*/*z* 1246 (MNH_4^+). Anal. Calcd for $C_{74}H_{100}O_{15}$: C, 72.28; H, 8.20. Found: C, 72.41; H, 8.35.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,34-tri-(ethoxycarbonylmethyloxy)-33,35-crown-6-calix[5]-arene (3h):[48] obtained in 47% yield from **3a** and BrCH_2CO_2Et after CC (SiO_2; cyclohexane/AcOEt, 5:1). Mp 130−134 °C (EtOH); ^{1}H NMR δ 0.89, 0.99, 1.15 (s × 3, C(CH_3)$_3$, 2:1:2, 45 H), 1.30, 1.31 (t × 2, J = 7.1 Hz, OCH_2CH_3, 1:2, 9 H), 3.31 and 4.70, 3.31 and 4.73, 3.37 and 4.79 (AX × 3, J = 13.7, 14.6, 14.2 Hz, respectively, ArCH_2Ar, 2:2:1, 10 H), 3.40−3.86 (m, OCH_2CH_2O, 16 H), 4.01 (t, J = 4.8 Hz, OCH_2CH_2O, 4 H), 4.23, 4.24 (q × 2, J = 7.1 Hz, OCH_2CH_3, 1:2, 6 H), 4.65 (s, OCH_2CO, 2 H), 4.68 and 4.76 (ABq, J = 16.1 Hz, OCH_2CO, 4 H), 6.75 (pseudo-s, ArH, 4 H), 6.94 (s, ArH, 2 H), 6.95 and 7.08 (ABq, J = 2.3 Hz, ArH, 4 H) ppm; ^{13}C NMR δ 14.2 (CH_2CH_3), 29.2, 29.68, 29.71 (Ar*C*H_2Ar), 31.2, 31.3, 31.5 (C(*C*H_3)$_3$), 33.9, 33.99, 34.0 (*C*(CH_3)$_3$), 60.68, 60.72 (O*C*H_2CH$_3$), 70.73, 70.77, 70.84, 70.9, 71.0 71.4, 72.6, (OCH_2), 125.0, 125.7, 125.77, 125.80, 126.3 (*m*-Ar), 133.20, 133.23, 133.47, 133.49, 134.3 (*o*-Ar), 144.9, 145.3, 145.5 (*p*-Ar), 151.9, 152.4, 152.7 (*ipso*-Ar), 169.9, 170.0 (C═O) ppm; FAB (+) MS, *m*/*z* 1288 (MNH_4^+). Anal. Calcd for $C_{77}H_{106}O_{15}$: C, 72.73; H, 8.40. Found: C, 72.91; H, 8.36.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,34-tri-(1-methylethoxycarbonylmethyloxy)-33,35-crown-6-calix-[5]arene (3i): obtained in 70% yield from **3a** and BrCH_2CO_2^{i}Pr

(46) Melting points were determined on a Kofler or electrothermal melting point apparatus and are uncorrected. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, at 300 and 75 MHz, respectively, using TMS as an internal standard. ^{1}H NMR peak assignments follow from COSY and HETCOR experiments. ^{13}C NMR spectra were acquired with the APT technique. FAB (+) mass spectra were recorded using 3-nitrobenzyl alcohol as a matrix. All chemicals were reagent grade and were used without further purification. Anhydrous solvents (MeCN, THF, and DMF) were either obtained commercially or prepared according to standard procedures. All reactions were carried out under anhydrous conditions.

(47) Ouchi, M.; Inoue, Y.; Kanzaki, T.; Hakushi, T. *J. Org. Chem.* **1984**, *49*, 1408.

(48) ^{1}H and ^{13}C NMR data refer to the predominant conformer.

after CC (SiO_2; cyclohexane/AcOEt, 5:1). Mp 101−105 °C (CH_3CN); ^{1}H NMR δ 0.88, 1.02, 1.15 (s × 3, $C(CH_3)_3$, 2:1:2, 45 H), 1.26, 1.27 (d × 2, J = 6.3 Hz, $CH(CH_3)_2$, 1:2, 18 H), 3.31 and 4.71, 3.32 and 4.74, 3.37 and 4.79 (AX × 3, J = 14.5, 14.3, 14.6 Hz, respectively, $ArCH_2Ar$, 2:2:1, 10 H), 3.42−3.98 (m, OCH_2CH_2O, 16 H), 4.00 (t, J = 4.6 Hz, OCH_2CH_2O, 4 H), 4.66 (s, OCH_2CO, 2 H), 4.67 and 4.73 (ABq, J = 16.1 Hz, OCH_2CO, 4 H), 5.08, 5.10 (sept × 2, J = 6.3 Hz, $CH(CH_3)_2$, 1:2, 3 H), 6.72 and 6.74, 6.95 and 7.09 (ABq × 2, J = 2.5, 2.4 Hz, respectively, ArH, 1:1, 8 H), 6.97 (s, ArH, 2 H) ppm; ^{13}C NMR δ 21.86, 21.88 ($CH(CH_3)_2$), 29.3, 29.8 ($ArCH_2Ar$), 31.2, 31.3, 31.5 ($C(CH_3)_3$), 33.9, 34.0 ($C(CH_3)_3$), 68.2, 68.3 ($CH(CH_3)_2$), 70.7, 70.8, 70.9, 71.0, 71.1, 71.5, 72.6 (OCH_2), 125.0, 125.5, 125.7, 125.8, 126.3 (*m*-Ar), 133.2, 133.3, 133.48, 133.50, 134.4 (*o*-Ar), 144.9, 145.2, 145.4 (*p*-Ar), 151.9, 152.5, 152.7 (*ipso*-Ar) 169.5, 169.6 (C=O) ppm. FAB (+) MS, *m*/*z* 1330 (MNH_4^+). Anal. Calcd for $C_{80}H_{112}O_{15}$: C, 73.14; H, 8.59. Found: C, 72.89; H, 8.41.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,34-tri-(1,1-dimethylethoxycarbonylmethyloxy)-33,35-crown-6-calix[5]arene (3j,k): obtained from **3a** and $BrCH_2CO_2{}^tBu$ after CC separation on silica gel using a cyclohexane/AcOEt, 7:1−5:1 gradient.

Cone conformer **3j**: yield 62%, R_f = 0.38 (cyclohexane/AcOEt 3:1); mp 218−222 °C (EtOH); MS, ^{1}H and ^{13}C NMR data have previously been reported.[19] Anal. Calcd for $C_{83}H_{118}O_{15}$: C, 73.53; H, 8.77. Found: C, 73.82; H, 8.89.

1,2-Alternate conformer **3k**: yield 9%, R_f = 0.61, (cyclohexane/AcOEt 3:1); MS, ^{1}H and ^{13}C NMR data have previously been reported.[19] Anal. Calcd for $C_{83}H_{118}O_{15}$: C, 73.53; H, 8.77. Found: C, 73.83; H, 8.94.

31,32,34-Trimethoxy-33,35-crown-6-calix[5]arene (4b): obtained from **4a** and MeI, according to the procedure of Arnaud-Neu et al.,[11b] in 62% yield after CC (CH_2Cl_2/acetone, 6:1), thick oil; ^{1}H NMR δ 2.46, 3.30 (s × 2, OCH_3, 1:2, 9 H), 3.28 and 4.59, 3.43 and 4.39, 3.59 and 4.22 (AX × 3, J = 14.3, 13.9, 15.0 Hz, respectively, $ArCH_2Ar$, 2:2:1, 10 H), 3.57−4.00 (m, OCH_2CH_2O, 20 H), 6.74−7.05 (m, ArH, 15 H) ppm; ^{13}C NMR δ 29.6, 30.2, 30.9 ($ArCH_2Ar$), 60.6, 60.8 (OCH_3), 70.6 (×2), 71.1, 71.6, 73.3 (OCH_2), 122.6, 123.0, 123.3, 128.2, 128.3, 128.7, 129.2, 129.7 (*m*-Ar and *p*-Ar), 134.3, 134.4, 134.7 (×2), 135.0 (*o*-Ar), 154.6, 156.6, 157.8 (*ipso*-Ar) ppm; FAB (+) MS *m*/*z* 792 (MNH_4^+). Anal. Calcd for $C_{48}H_{54}O_9$: C, 74.39; H, 7.02. Found: C, 74.17; H, 7.01.

31$^{\alpha}$,32$^{\beta}$,34$^{\alpha}$-Tribenzyloxy-33,35-crown-6-calix[5]arene (4c):[48,49] obtained in 84% yield from **4a** and BnBr after CC (toluene/AcOEt, 4:1), foam; ^{1}H NMR δ 1.76 (dt, J = 10.5, 3.0 Hz, OCH_2CH_2O, 1 H), 1.90−1.97 (m, OCH_2CH_2O, 1 H), 2.81 (dt, J = 10.5, 3.0 Hz, OCH_2CH_2O, 1 H), 3.19−3.77 (m, OCH_2CH_2O and $ArCH_2Ar$, 22 H), 3.88 and 4.05 (ABq, J = 15.8 Hz, $ArCH_2Ar$, 2 H), 4.25 (d, J = 15.6 Hz, *endo*-$ArCH_2Ar$, 1 H), 4.46 and 4.55 (ABq, J = 11.9 Hz, OCH_2Ph, 2 H), 4.50 (d, J = 11.0 Hz, *endo*-$ArCH_2Ar$, 1 H), 4.51 (d, J = 12.4 Hz, *endo*-$ArCH_2Ar$, 1 H), 4.79 and 4.89 (ABq, J = 11.0 Hz, OCH_2Ph, 2 H), 4.89 (pseudo s, OCH_2Ph, 2 H), 5.36 (dd, J = 7.7, 1.5 Hz, *m*-ArH, 1 H), 6.11 (t, J = 7.7 Hz, *p*-ArH, 1 H), 6.44 (dd, J = 7.7, 1.7 Hz, *m*-ArH, 1 H), 6.57 (dd, J = 7.5, 1.5 Hz, *m*-ArH, 1 H), 6.60 (d, J = 6.6 Hz, *m*-ArH, 1 H), 6.68 (t, J = 7.5 Hz, *p*-ArH, 1 H), 6.74 (t, J = 7.7 Hz, *p*-ArH, 1 H), 6.84−7.55 (m, ArH, PhH, 23 H) ppm; ^{13}C NMR δ 29.1, 31.0, 31.2, 34.7, 38.5 ($ArCH_2Ar$), 68.6, 69.4, 70.1, 70.2, 70.3 (×2), 70.4, 70.6, 71.3, 72.0, 72.1, 73.8, 75.6 (OCH_2), 122.6, 122.8, 122.9, 123.2, 123.8, 126.5, 127.0, 127.5, 127.69, 127.78, 127.81, 127.9, 128.2 (×2), 128.4 (×2), 128.5 (×2), 129.9, 130.3, 130.6, 130.7 (×2), 131.7 (*m*-Ar, *p*-Ar, Ph), 131.8, 132.0, 133.1, 133.6, 133.9, 134.4, 134.6 (×2), 134.9, 136.7, 137.5, 137.7, 137.9 (*o*-Ar, Ph), 153.8, 154.2, 155.9, 156.6, 156.8 (*ipso*-Ar) ppm; FAB (+) MS *m*/*z* 1020 (MNH_4^+). Anal. Calcd for $C_{66}H_{66}O_9$: C, 79.02; H, 6.63. Found: C, 78.68; H, 6.69.

31$^{\alpha}$,32$^{\beta}$,34$^{\alpha}$-(1,1-Dimethylethoxycarbonylmethyloxy)-33,35-crown-6-calix[5]arene (4d):[48,49] obtained in 76% yield from **4a** and $BrCH_2CO_2{}^tBu$ after CC (hexane/AcOEt, 1:1), foam; ^{1}H NMR δ 1.49, 1.52, 1.54 (s, $C(CH_3)_3$, 1:1:1, 27 H), 2.70 and 3.38 (AX, J = 15.9 Hz, $CH_2CO_2{}^tBu$, 2 H), 3.00−4.03 (m, OCH_2CH_2O and $ArCH_2Ar$, 24 H), 3.28 and 4.51 (AX, J = 14.4 Hz, $ArCH_2Ar$, 2 H), 3.30 and 4.34 (AX, J = 14.6 Hz, $ArCH_2Ar$, 2 H), 3.38 and 4.49 (AX, J = 15.9 Hz, $ArCH_2Ar$, 2 H), 4.27 and 4.33 (ABq, J = 15.1 Hz, $CH_2CO_2{}^tBu$, 2 H), 4.29 and 4.43 (ABq, J = 15.0 Hz, $CH_2CO_2{}^tBu$, 2 H), 5.94 (dd, J = 7.6, 1.6 Hz, *m*-ArH, 1 H), 6.08 (dd, J = 7.6, 1.5 Hz, *m*-ArH, 1 H), 6.41 (t, J = 7.6 Hz, *p*-ArH, 1 H), 6.47 (t, J = 7.6 Hz, *p*-ArH, 1 H), 6.51 (br d, J = 7.6 Hz, *m*-ArH, 1 H), 6.97−7.26 (m, *m*-ArH, *p*-ArH, 9 H), 7.89 (dd, J = 7.7, 1.6 Hz, *m*-ArH, 1 H) ppm; ^{13}C NMR δ 28.11, 28.13 (×2) ($OC(CH_3)_3$), 29.3, 31.2, 31.8, 33.0, 38.0 ($ArCH_2Ar$), 69.29, 69.32, 69.9, 70.3, 70.4, 70.6 (×2), 70.7, 70.8, 71.0 (×2), 71.1, 71.2 (OCH_2), 81.0, 81.6, 81.9 ($OC(CH_3)_3$), 122.7, 122.9, 123.3 (×2), 123.9, 126.8, 127.0, 127.8, 128.9, 129.94, 129.97, 130.6, 130.7, 131.3, 132.1 (*m*-Ar, *p*-Ar), 132.2, 132.6, 133.3, 134.0, 134.2, 134.37, 134.46, 134.55, 134.9, 135.1 (*o*-Ar), 153.7, 155.2, 155.5, 156.8, 157.0 (*ipso*-Ar), 167.97, 168.00, 168.7 (C=O) ppm; FAB (+) MS *m*/*z* 1092 (MNH_4^+). Anal. Calcd for $C_{63}H_{78}O_{15}$: C, 70.37; H, 7.31. Found: C, 70.69; H, 7.47.

^{1}H NMR Complexation Experiments. All spectra were recorded at 300 MHz at 293 ± 1 K. Percentages of complexation or the corresponding association constants (K_a) for the *endo*-cavity complex between derivatives **3** and $^nBuNH_3^+$ ions were determined by direct ^{1}H NMR analysis of the peak (host: $ArCH_2Ar$ and/or ArH; guest: α-CH_2 and β-CH_2) intensity ratio of equimolar host−guest solutions. Samples were prepared in the NMR tube by mixing stock solutions of calixcrowns (5.55×10^{-3} M, in $CDCl_3$) and *n*-butylammonium picrate (5×10^{-2} M, in CD_3OD) to a final $CDCl_3/CD_3OD$, (9:1, v/v; 0.8 mL) solvent mixture containing equimolar concentrations (5×10^{-3} M) of host and guest.

K_a values for the *exo*-cavity complexation of **3j,i** with $^{i-,s-,t-}BuNH_3^+$ ions were assessed by nonlinear treatment of the data obtained from ^{1}H NMR titration experiments.[43] Samples were prepared by adding to a 0.5 mL solution of the host (6.6×10^{-3} or 1×10^{-2} M in $CDCl_3/CD_3OD$, 9:1, v/v) successive aliquots of a stock solution of the guest (5.8×10^{-2} or 8.8×10^{-2} M in $CDCl_3/CD_3OD$, 9:1, v/v) to a final volume of 1.0 mL. Eight values of δ_{obs} for the ^{t}Bu and ArH resonances were collected by keeping the [host] to [guest] ratio in the 1/0.45−1/8.8 interval. Nonlinear regression analysis of δ_{obs} vs [guest], using a Jandel Scientific SigmaPlot for Windows software package, provided the K_a values reported in Table 3.

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Supporting Information Available: A table correlating the symmetry and the expected NMR patterns for (1,3)-*p*-*tert*-butylcalix[5]arene crown ether conformers. This material is available free of charge via Internet at http://pubs.acs.org.

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(49) Notations α and β were introduced by Shinkai to define the stereochemistry of calix[4]arene atropisomers having mixed substituents at the lower rim: Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325.