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Synthesis and host–guest properties of a calix[6]arene based receptor closed by an internal ion-paired cap

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Abstract

The straightforward synthesis of a C_s symmetrical calix[6]arene possessing carboxylic acid groups as well as an ammonium arm is described. This calixarene can encapsulate ammonium ions through a highly selective recognition process thanks to the presence of an internal ion-paired cap that preorganizes the cavity and constitutes an efficient binding site.

Keywords: Calixarenes; Host–guest chemistry; Supramolecular chemistry; Molecular recognition; Ammonium ion

There is a growing interest in the design of artificial hosts useful for catalysis or for the sensing of either charged or neutral species.[1] These receptors can also contribute to a better understanding of the recognition processes occurring in biological systems.[2] Since bioactive molecules like neurotransmitters (i.e., dopamine, serotonin, γ-aminobutyric acid (GABA) or acetylcholine) are ammonium ions, the synthesis of efficient receptors for such cationic species is particularly interesting.[3] In this context, the use of calix[4]arenes has been largely studied.[4,5] However, their cavity is not large enough to accommodate organic molecules and these have been mostly used as a molecular platform for the preorganization of an external binding site.[6] The size of the cavity of calix[6]arenes[7] is well adapted for the encapsulation of ammonium ions[8] but these flexible oligomers are scarcely studied since these usually need to be rigidified in the cone conformation in order to display such host–guest properties. For this, the introduction of covalent bridges[9] and, especially tripodal aza-units on the narrow rim, has shown to constitute a valuable strategy. These calix[6]aza-cryptands[10] can bind either ammonium ions or contact ion-pairs depending on the nature of their aza-cap (i.e., polyamino or polyamido).[11] Recently, we have also developed an alternative strategy that consists in using electrostatic interactions between ammonium and carboxylate groups for the building of self-assembled receptors.[12] In particular, C_{3v} symmetrical calix[6]arenes bearing three carboxylic acid groups have shown to exhibit remarkable host–guest properties toward ammonium ions even in polar and protic solvents (Fig. 1).[13] Indeed, upon deprotonation with amines (I or II), these calix[6]arenes can be shaped in a well-defined cone conformation thanks to the formation of an ion-paired cap between their carboxylate groups and the bridging ammonium counter-ions. The resulting self-assembled receptors can recognize large polycyclic or bioactive ammonium ions through a combination of hydrogen bonding, electrostatic, and CH–π interactions. However, these systems are quite complicated since these required the addition of external ammonium ions for the building of the ion-paired cap. Thus, we were interested in the design of a calix[6]arene based receptor possessing both carboxylate and ammonium groups, an internal ion-paired cap being expected with such a receptor.

Herein, we report the synthesis of a calix[6]arene dissymmetrically substituted by two carboxylic acid groups and

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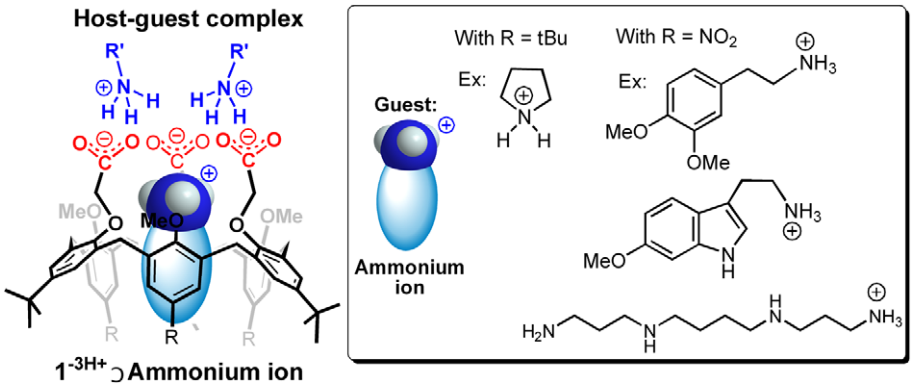
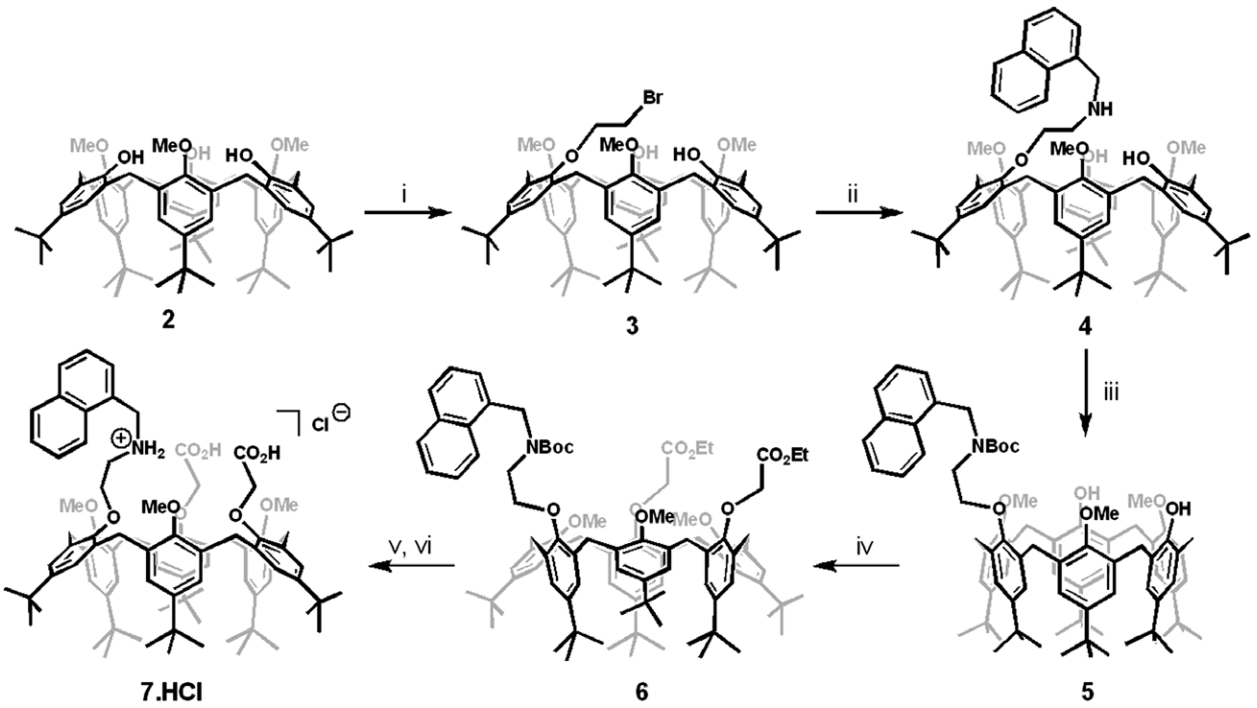


Fig. 1. Self-assembled ion-paired receptors for the binding of ammonium ions.

one ammonium arm and preliminary results concerning its host–guest properties toward ammonium ions.

In order to prevent any competing self-inclusion processes of the ammonium arm, we chose to introduce a bulky 1-naphthalenemethylamine residue on the narrow rim. Hence, the desired dissymmetrically substituted compound **7** was obtained through a straightforward synthesis from the known C_{3v} symmetrical 1,3,5-trismethoxycalix[6]arene **2**[14] (Scheme 1). First, a selective alkylation with 1,2-dibromoethane according to a reported procedure led to the mono-alkylated derivative **3**.[15] A further reaction with an excess of 1-naphthalenemethylamine in the presence of DIPEA gave the mono-amino calix[6]arene **4** which was used in the next step without any purification.[16] Protection of the amino group with $(Boc)_2O$ led to the pure compound **5**[17] in 66% yield over two steps after flash chromatography purification. The remaining phenolic units were then alkylated with ethyl bromoacetate in the presence of an excess of NaH, affording **6**[18] in high yield. Finally, the removal of the Boc group with TFA[19] and a subsequent saponification of the ester functions with NMe_4OH produced the desired dissymmetrically substituted calixarene **7** which was isolated through its hydrochloride salt **7·HCl**[20] in 62% yield.

The conformational properties of the new calix[6]arene derivatives **4–7·HCl** were investigated through ^1H NMR spectroscopy in $CDCl_3$, all the signals being attributed through 2D NMR analyses (COSY, HMQC, HMBC). The NMR patterns of compounds **3–7·HCl** are characteristic of C_s symmetrical structures that adopt either a major



Scheme 1. Synthesis of receptor **7**. Reagents and conditions: (i) see Ref.15; (ii) 1-Naphthalenemethylamine, DIPEA, DMF, 100 °C, 16 h; (iii) Boc_2O, TEA, THF, rt, 16 h, 66% over 2 steps; (iv) $BrCH_2COOEt$, NaH, THF, reflux, 16 h, 94%; (v) TFA, $CHCl_3$, rt, 4 h; (vi) NMe_4OH (10%), THF, reflux, 16 h, then HCl, 62% overall yield from **6**.

flattened cone conformation (in the case of **3**, **4**, **6**, and **7·HCl**: ΔtBu >0.54 ppm) or a straight conformation (in the case of **5**: ΔtBu = 0.17 ppm) (see the structures displayed in Scheme 1). The grafting of the bulky methylamino-naphthalene unit leads to a rigidification of the calixarene core since sharp doublets are observed for the ArCH_2 signals of **4**–**7·HCl**, indicating that their cone-cone interconversion is slow on the NMR spectral timescale. Similarly to the monobromo-calix[6]arene **3**,[21] compound **4** displays unusual high-field shifted resonances for the alkyl linker between the amino group and the calixarene core (δ_{OCH_2} = 2.54 ppm, δ_{NCH_2} = 1.88 ppm), while the methoxy groups are directed toward the outside of the cavity (δ_{OMe} >3.24 ppm). This is compatible with a partial inclusion of the protic amino arm inside the aromatic cavity which is likely due to hydrogen bonding interactions with the phenolic moieties. In contrast, calixarenes **5** and **6** adopt the opposite cone conformation with the bulky Boc groups and the ester arms ejected from the cavity and the methoxy groups pointing inside the cavity (δ_{OMe} <2.45 ppm for **6**).[22] As expected, in the case of the final compound **7·HCl**, the ammonium and carboxylic acid groups are in close proximity,[23] the OMe groups being expelled from the cavity (δ_{OMe} >3.46 ppm). This clearly shows the formation of an intramolecular hydrogen bonded cap that closes the hydrophobic cavity and preorganizes the calixarene in a well-defined conformation ideal for the *endo*-complexation of organic guests.

The host–guest properties of receptor **7** toward ethyl and propylammonium ions were explored by ^{1}H NMR spectroscopy in $CDCl_3$ at 260 K. These ammonium ions were chosen for the study since their size and shape fit very well to the hydrophobic cavity of a calix[6]arene substituted by *pt*Bu groups on the wide rim.[11] Thus, the addition of $PrNH_2$ (≥2 equiv) to **7·HCl** led to the in situ formation of $PrNH_3^+$ through deprotonation of the COOH groups of the host and a unique NMR pattern corresponding to the *endo*-complex $\mathbf{7}^{-H+} \supset \mathbf{PrNH_3^+}$ was obtained (Fig. 2). Indeed, associated to a calixarene signature characteristic of the conformation displayed in Figure 2 (δ_{OMe} >3.4 ppm), high field signals corresponding to the inclusion of 1 equiv of $PrNH_3^+$ were observed ($\delta_{CH_2CH_3}$ = −0.85 ppm, δ_{CH_3} = −1.91 ppm) (see inset, Fig. 2).[24] Similarly, the inclusion of $EtNH_3^+$ was evidenced through the addition of $EtNH_2$ (≥2 equiv) to a $CDCl_3$ solution of **7·HCl** (signals of the included $EtNH_3^+$: δ_{CH_2} = 0.30 ppm, δ_{CH_3} = −1.51 ppm). These results show a highly selective process that results from the establishment of intramolecular ionic interactions and hydrogen bonding interactions between the carboxylate groups and the ammonium arm of the host. This internal ion-paired cap can act as an efficient binding site for a second ammonium ion encapsulated in the calixarene cavity, the recognition of this cationic guest taking place probably through ionic and hydrogen bonding interactions. In addition, CH–π interactions between the alkyl chain of the ammonium ion and the aromatic moieties of the calixarene core should contribute to the stabilization of the whole edifice.[25]

In summary, we have developed the efficient synthesis of a new C_s symmetrical calix[6]arene **7** bearing on the narrow rim two carboxylic acid groups as well as a 1-naphthalenemethylamino arm. Upon deprotonation of the COOH

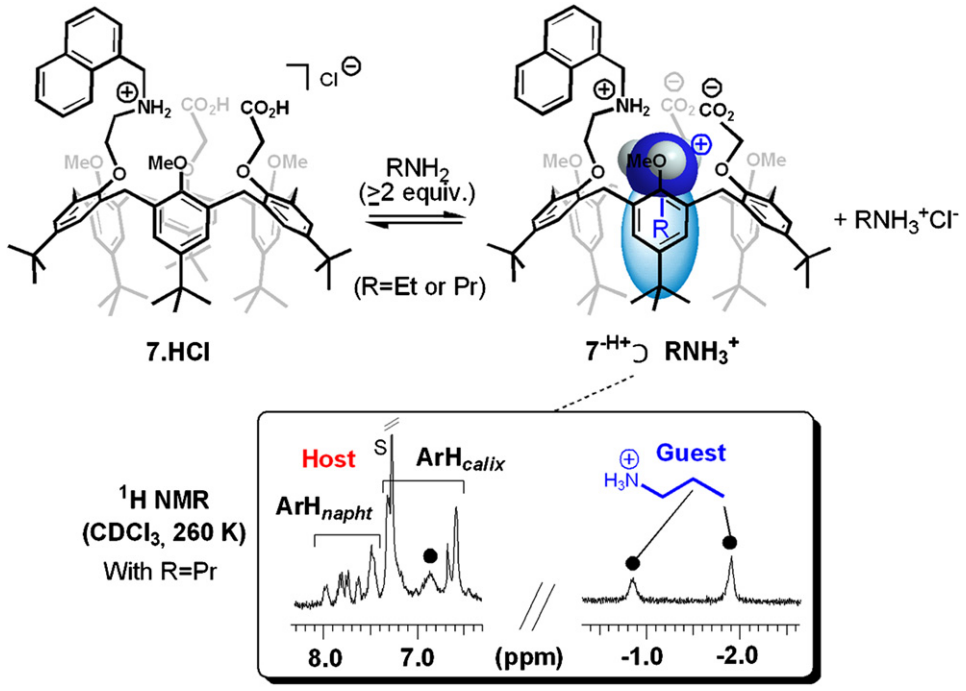


Fig. 2. *endo*-Complexation of RNH_3^+ (R = Et or Pr) by molecular receptor $\mathbf{7}^{-H+}$. Inset: selected regions of the ^{1}H NMR spectrum of $\mathbf{7}^{-H+} \supset \mathbf{PrNH_3^+}$ that are characteristic of the host and guest. ●: Signals of the guest ammonium.

groups, this calixarene behaves as an efficient molecular *endo*-receptor for ammonium ions thanks to the presence of an internal ion-paired cap that polarizes the receptor, preorganizes the cavity and provides multiple hydrogen bonding acceptor groups. Current work is directed toward the design of related fluorescent and water-soluble molecular receptors devoted to the sensing of bioactive ammonium ions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.085.

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16. Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 9H, *t*Bu), 0.98 (s, 18H, *t*Bu), 1.27 (s, 18H, *t*Bu), 1.40 (s, 9H, *t*Bu), 1.88 (s_b, 2H, CH_2N), 2.54 (s_b, 2H, OCH_2), 3.24–3.78 (m, 15H, $ArCH_2 + OCH_3$), 3.80–4.00 (m, 4H, $ArCH_2 + NHCH_{2Napht}$), 4.16 (d, $J = 15$ Hz, 2H, $ArCH_2$), 4.44 (d, $J = 15$ Hz, 2H, $ArCH_2$), 6.55 (s, 2H, ArH_{Calix}), 6.80 (s, 2H, ArH_{Calix}), 6.90 (s, 2H, ArH_{Calix}), 7.04 (s, 2H, ArH_{Calix}), 7.12 (s, 2H, ArH_{Calix}), 7.26 (s, 2H, ArH_{Calix}), 7.34–7.49 (m, 4H, ArH_{Napht}), 7.70 (d, $J = 8$ Hz, 1H, ArH_{Napht}), 7.78–7.87 (m, 1H, ArH_{Napht}), 8.04–8.15 (m, 1H, ArH_{Napht}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 30.0, 30.5, 31.2, 31.5, 31.6, 31.9, 32.0, 34.1(8), 34.2, 34.4, 34.5, 48.8 (CH_2N), 50.7 ($NHCH_2Ar$), 60.3 (OCH_3), 61.2 (OCH_3), 72.3, (OCH_2), 124.4, 124.6, 124.7, 125.5, 125.8, 126.1, 126.1(6), 126.8, 127.0, 127.2, 127.4, 128.0, 128.6, 132.3, 132.7, 132.8, 133.4, 133.7, 134.0, 142.0, 145.8, 146.0, 146.9, 151.0, 152.2, 153.7, 154.4.
17. Compound **5**: Mp 147–148 °C; IR (KBr): ν 3510, 3368, 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 330 K) δ 1.02 (s, 18H, *t*Bu), 1.14 (s, 9H, *t*Bu), 1.19 (s, 27H, *t*Bu), 1.51 (s_b, 9H, Boc), 2.72 (s, 3H, OCH_3), 3.52 (s, 6H, OCH_3), 3.63–3.91 (m, 12H, $OCH_2CH_2N + ArCH_2$), 4.01 (d, $J = 15$ Hz, 2H, $ArCH_2$), 4.24 (d, $J = 15$ Hz, 2H, $ArCH_2$), 5.15 (s, 2H, $NBocCH_{2Napht}$), 6.88 (d, $J = 2$ Hz, 2H, ArH_{Calix}), 6.91 (s, 2H, ArH_{Calix}), 6.93 (s, 2H, ArH_{Calix}), 6.97 (s, 2H, ArH_{Calix}), 6.99 (s, 2H, ArH_{Calix}), 7.03 (d, $J = 2$ Hz, 2H, ArH_{Calix}), 7.46 (m, 4H, ArH_{Napht}), 7.74 (m, 1H, ArH_{Napht}), 7.83 (m, 1H, ArH_{Napht}), 8.09 (m, 1H, ArH_{Napht}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 28.8, 30.7, 30.9, 31.6, 31.7, 31.9, 32.1, 34.2, 34.3(8), 34.4, 34.4(5), 46.8, 47.4, 49.7, 50.7, 60.6(8), 60.7, 61.8, 71.4, 80.3 ($OC(CH_3)_3$), 123.7, 124.2, 125.5, 125.6, 125.9, 126.0, 126.3, 126.4, 127.0, 127.3, 128.4, 128.8, 128.9, 132.0, 132.7, 133.2, 133.5, 134.0, 134.1, 142.2, 146.6, 146.8, 146.9, 150.1, 152.8, 153.4, 155.8, 156.1; ESI-MS calcd for $C_{87}H_{111}NO_8$ ($M+Na^+$) 1320.82; found 1320.67; Anal. Calcd for $C_{87}H_{111}NO_8$,$4H_2O$: C, 76.22; H, 8.75; N, 1.02. Found: C, 76.13; H, 8.78; N, 1.02.
18. Compound **6**: Mp 119–120 °C; IR (KBr): 1762, 1738, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 330 K) δ 0.84 (s, 27H, *t*Bu), 1.29 (t, $J = 7$ Hz, 6H, OCH_2CH_3), 1.38 (s, 9H, *t*Bu), 1.40 (s, 18H, *t*Bu), 1.48 (s, 9H, Boc), 2.26 (s, 6H, OCH_3), 2.45 (s, 3H, OCH_3), 3.05–3.90 (m, 10H, $OCH_2CH_2N + ArCH_2$), 4.26 (q, $J = 7$ Hz, 4H, OCH_2CH_3), 4.57 (m, 10H, $ArCH_2 + OCH_2COOEt$), 5.19 (s_b, 2H, $NBocCH_2Napht$), 6.70 (s, 6H, ArH_{Calix}), 7.23 (s, 2H, ArH_{Calix}), 7.27 (s, 4H, ArH_{Calix}), 7.40–7.67 (m, 4H, ArH_{Napht}), 7.74 (d, $J = 5$ Hz, 1H, ArH_{Napht}), 7.85 (d, $J = 8$ Hz, 1H, ArH_{Napht}), 8.20 (d, $J = 8$ Hz, 1H, ArH_{Napht}); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 14.6, 28.1, 28.8, 29.7, 30.1, 30.5, 31.5, 32.0, 34.3, 34.6, 60.3, 60.5, 61.4, 70.2, 80.4 ($OC(CH_3)_3$), 123.7, 125.7, 126.2, 126.8, 128.5, 133.3, 133.8, 146.1, 146.2, 146.6, 151.8, 154.9, 169.6 (*C*OOEt). ESI-MS calcd for $C_{95}H_{123}NO_{12}$ ($M+Na^+$) 1493.90; found 1493.73.

19. *For analytical purpose the resulting free amino calix[6]arene bearing two ester arms was isolated. Selected data:* Mp 117–119 °C; IR (KBr): 1762, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 330 K) δ 0.86 (s_b, 27H, *tBu*), 1.31 (t, $J = 7$ Hz, 6H, OCH_2CH_3), 1.38 (s, 27H, *t*Bu), 2.28 (s, 6H, OCH_3), 2.43 (s, 3H, OCH_3), 3.16 (s_b, 2H, CH_2N), 3.43 (d, $J = 15$ Hz, 2H, $ArCH_2$), 3.49–3.79 (m, 4H, $ArCH_2$), 4.05 (s_b, 2H, OCH_2), 4.27 (q, $J = 7$ Hz, 4H, OCH_2CH_3), 4.39 (s, 2H, $NHCH_{2Napht}$), 4.42–4.62 (m, 10H, $ArCH_2 + OCH_2COOEt$), 6.70 (s, 4H, ArH_{Calix}), 6.74 (s, 2H, ArH_{Calix}), 7.25 (s, 6H, ArH_{Calix}), 7.35–7.58 (m, 4H, ArH_{Napht}), 7.75 (d, $J = 8$ Hz, 1H, ArH_{Napht}), 7.83 (d, $J = 8$ Hz, 1H, ArH_{Napht}), 8.21 (d, $J = 8$ Hz, 1H, ArH_{Napht}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 28.1, 30.5, 31.5, 31.9, 34.3, 34.5, 49.8, 53.8, 60.4, 60.4(9), 61.4, 70.0, 124.0, 125.7, 126.0, 126.6, 128.5, 129.0, 132.2, 132.6, 133.3, 133.9, 134.2, 146.2, 146.6, 151.9, 154.8, 169.6 (*C*OOEt); ESI-MS calcd for $C_{90}H_{115}NO_{10}$ ($M+H^+$) 1370.86; found 1371.13; Anal. Calcd for $C_{90}H_{115}NO_{10},H_2O$: C, 77.83; H, 8.49; N, 1.01. Found: C, 78.18; H, 8.73; N, 1.05.

20. Compound **7·HCl**: Mp 190 °C; IR (KBr): 1685 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 18H, *t*Bu), 0.88 (s, 9H, *t*Bu), 1.33 (s, 9H, *t*Bu), 1.36 (s, 18H, *t*Bu), 3.44-3.68 (m, 18H, $CH_2N + 2\ OCH_3 + ArCH_2 + 2\ OCH_2$), 3.81 (s, 3H, OCH_3), 3.97 (s_b, 2H, OCH_2), 4.31 (d, $J = 15$ Hz, 2H, $ArCH_2$), 4.36–4.57 (m, 4H, $ArCH_2$), 4.92 (s_b, 2H, $NHCH_{2Napht}$), 6.49–6.61 (m, 4H, ArH_{Calix}), 7.21 (s, 4H, ArH_{Calix}), 7.23 (s, 4H, ArH_{Calix}), 7.51 (m, 2H, ArH_{Napht}), 7.64 (m, 1H, ArH_{Napht}), 7.87 (d, $J = 8$ Hz, 2H, ArH_{Napht}), 7.97 (m, 1H, ArH_{Napht}), 8.28 (m, 1H, ArH_{Napht}), 9.31 (s_b, 2H, NH_2^+). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.2, 29.0, 31.2, 31.5, 31.6, 31.9, 34.2(8), 34.3, 34.6, 48.8 (CH_2N), 49.1 ($NHCH_{2Napht}$), 60.5 (OCH_3), 60.9 (OCH_3), 69.4 (OCH_2), 70.2 (OCH_2), 123.7, 123.9, 124.2, 125.6, 126.5, 127.3, 127.4, 127.7, 128.4, 129.1, 130.6, 131.0, 132.3, 132.7, 132.8, 133.0, 133.1, 134.1, 134.2, 146.1, 146.2, 147.0, 153.0, 153.5, 172.8 (*C*OOH). HRMS (ESI-TOF) calcd for $C_{86}H_{108}NO_{10}^+$ (M^+) 1314.7973; found 1314.7970.

21. *Resonances of the bromoethyl arm of* **3**: $\delta_{OCH_2} = 2.87$ ppm, $\delta_{CH_2Br} = 2.34$ ppm.

22. In the case of **5**, one of the OMe groups was included inside of the cavity, that is, $\delta_{OMe} = 2.72$ ppm.

23. *Indeed, in comparison to* **6**, *the* OCH_2CO *resonance of* **7·HCl** *is strongly high-field shifted:* $\delta_{OCH_2CO} = 4.57$ and 3.60 ppm *for* **6** and **7·HCl**, respectively, (determined by HMQC analysis).

24. In contrast, when a large excess of the corresponding ammonium salt (i.e., $PrNH_3^+Pic^-$) was added to **7·HCl**, only a trace of the *endo*-complex $\mathbf{7 \cdot HCl \supset PrNH_3^+}$ was observed (signals of the included $PrNH_3^+$: $\delta_{CH_2CH_3} = -0.99$ ppm, $\delta_{CH3} = -1.56$ ppm). This result confirms that the deprotonation of the COOH groups of the host is required, highlighting the importance of ion-pair interactions in the recognition process.

25. Such CH–π interactions have been observed in closely related host–guest complexes, see Ref. 11.