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Efficient Synthesis of Calix[6]tmpa: A New Calix[6]azacryptand with Unique Conformational and Host–Guest Properties

Xianshun Zeng,[a] David Coquière,[b] Aurélie Alenda,[b] Eva Garrier,[a] Thierry Prangé,[c] Yun Li,[b] Olivia Reinaud,*[b] and Ivan Jabin*[a]

Abstract: A new C_{3v}-symmetrical calix[6]azacryptand, that is, calix[6]tmpa (**11**), was synthesized by efficient [1+1] macrocyclization reactions. Remarkably, both linear and convergent synthetic strategies that were applied lead to equally good overall yields. Calix[6]tmpa behaves as a single proton sponge and appeared reluctant to undergo polyprotonation, unlike classical tris(2-pyridylmethyl)amine (tmpa) derivatives. It also acts as a good host for ammonium ions. Interestingly, it strongly binds a sodium ion and a neutral guest molecule, such as a urea, an amide, or an alcohol, in a cooperative way. A ^{1}H NMR study indicated that the ligand, as well as its complexes, adopt a major flattened cone conformation that is the opposite of that observed with the previously reported calix[6]cryptands. Characterization of the monoprotonated derivative **11**·H^+ by X-ray diffraction also revealed the presence of a 1,3-alternate conformation, which is the first example of its kind in the calix[6]arene family. This conformer is probably also present in solution as a minor species. The important covalent constraint induced by the polyaromatic tmpa cap on the calixarene skeleton, and conversely from the calix core onto the tmpa moiety, is the likely basis for the unique conformational and chemical properties of this host.

Keywords: calixarenes · cryptands · host–guest systems · supramolecular chemistry

Introduction

Efficient molecular receptors toward either charged or neutral species have been designed from calixarenes.[1] Among the different cyclic oligomers, calix[6]arenes possess a hydrophobic cavity that is well adapted for the inclusion of organic guests. However, they are highly flexible and it is first necessary to constrain them in a cone conformation.[2] For this, a possible strategy consists of grafting a tripodal cap on the narrow rim.[3] In this regard, we have developed an original class of molecular receptors, which consist of a calixarene core rigidified by a tripodal aza cap at the narrow rim.[4] These C_{3v}-symmetrical calix[6]azacryptands (Figure 1) display remarkable host properties toward either ammonium ions, neutral polar molecules, or metal ions, depending on the way they are polarized.[5] These versatile receptors have also been successfully used in chiral recognition processes[6] and in the modeling of active sites of enzymes.[7] In the course of our research, we were interested in introducing a tris(2-pyridylmethyl)amine (tmpa) cap on the calixarene core. Indeed, tmpa has been widely used as an N_4 donor ligand, which mimicks the polyhistidine binding sites in metalloenzymes. Hence, tmpa-based Cu[8] and Fe[9] complexes have been shown to reproduce some aspects of biocatalytic

[a] Dr. X. Zeng, Dr. E. Garrier, Dr. I. Jabin
Unité de Recherche en Chimie Organique et Macromoléculaire (URCOM)
Université du Havre, 25 rue Philippe Lebon, BP 540, 76058 Le Havre cedex (France)
Fax: (+33) 232-744-391
E-mail: ivan.jabin@univ-lehavre.fr

[b] D. Coquière, A. Alenda, Dr. Y. Li, Prof. O. Reinaud
Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques
UMR CNRS 8601, Université René Descartes, 45 rue des Saints Pères
75270 Paris cedex 06 (France)
Fax: (+33) 142-862-183
E-mail: Olivia.Reinaud@univ-paris5.fr

[c] Dr. T. Prangé
Laboratoire de Cristallographie et RMN Biologiques, UMR CNRS 8015
Université René Descartes, 4 avenue de l'Observatoire
75270 Paris Cedex 06 (France)

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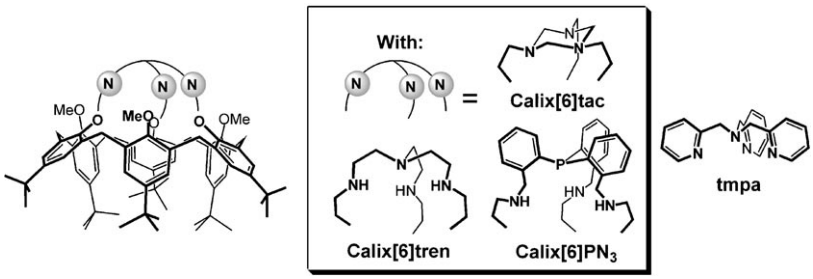


Figure 1. The calix[6]azacryptands[4–7] and tmpa ligand.

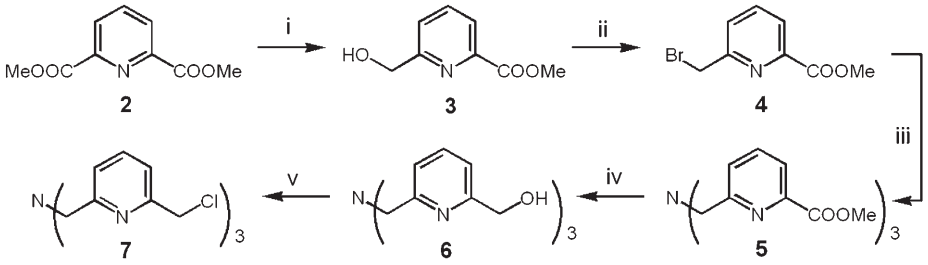
cycles, giving rise to interesting reactive species. The present work describes the synthesis, conformational behaviour, and preliminary host–guest properties of this novel calix[6]azacryptand, namely calix[6]tmpa.

Results and Discussion

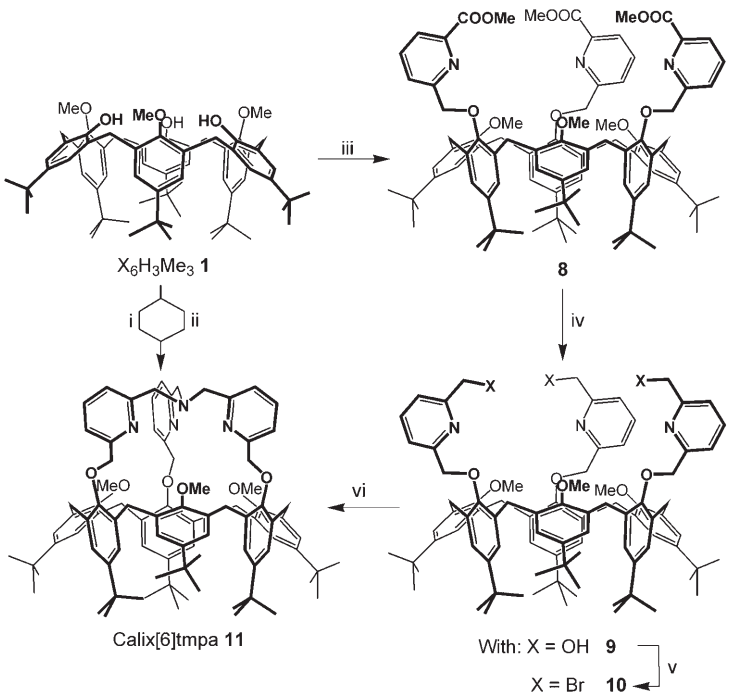
Synthesis of the calix[6]tmpa (11): Different synthetic strategies have been described in the literature for the covalent linkage of a tripodal cap onto the narrow rim of calix[6]arenes.[10] The convergent strategy consists of using a [1+1] macrocyclization reaction between two tripodal partners, that is, the 1,3,5-tris-*O*-methylated calix[6]arene **1** ($X_6H_3Me_3$)[11] or an appropriately 2,4,6-tris-*O*-functionalized derivative and a tripodal cap bearing either nucleophilic or electrophilic groups.[4a,c,12] The linear strategy has been successfully applied with a [3+1] macrocyclization reaction between a calix[6]trisamine and formaldehyde[4b] or through a proton-catalyzed cyclotrimerization of veratryl units.[13] For the synthesis of calix[6]tmpa (**11**), we have investigated both strategies. On the one hand, a tmpa derivative that can be grafted onto **1** through a [1+1] macrocyclization reaction was prepared. On the other hand, we introduced, at the narrow rim of **1**, 6-substituted picolyl arms that can lead to the formation of the tmpa unit through a macrocyclization reaction with ammonia. To our knowledge, only one example of such a direct bi(macrocycle) formation with ammonia has been reported.[14]

For the first strategy, it was necessary to synthesize a tmpa derivative bearing electrophilic groups on the 6-position of the pyridyl residues. The tris-6-hydroxymethyl precursor **6** was described in the literature,[15] but its synthesis was reinvestigated in the course of this work.[16] Our synthetic strategy was based on the recently reported regioselective reduction of the dimethyl pyridine-2,6-dicarboxylate (**2**) into **3** by $NaBH_4$ (87% yield).[17] Treatment of **3** with PBr_3 in chloroform afforded the corresponding 6-bromomethyl derivative **4** in 99% yield. Heating to 50°C in a saturated solution of ammonia in THF containing **4** produced the tmpa derivative **5** in 82% yield. It is remarkable that, under these conditions, the [3+1] product **5** formed instead of the [1+1] adduct or mixtures of compounds. Finally, a classical two-step sequence led to the desired tris[6-(chloromethyl)-2-pyridylmethyl]amine (**7**) in 44% overall yield from **2** (Scheme 1).[18]

The [1+1] macrocyclization reaction between $X_6H_3Me_3$ (**1**) and the tmpa derivative **7** was performed in the presence of a Cs_2CO_3/K_2CO_3 mixture (0.5 and 3 equiv, respectively).[19] Under these basic conditions, calix[6]tmpa (**11**) was isolated in 47% yield. The use of the stronger base NaH led to a lower yield (36%) (Scheme 2). It should be noted that,



Scheme 1. i) $NaBH_4$, $MeOH/CH_2Cl_2$, RT, 87%; ii) PBr_3, $CHCl_3$, RT, 99%; iii) NH_3, K_2CO_3, THF, 50°C, 82%; iv) $NaBH_4$, EtOH, reflux, 82%; v) $SOCl_2$, RT, 76%.



Scheme 2. i) **7**, K_2CO_3, Cs_2CO_3, KI, DMF, 90°C, 47%; ii) **7**, NaH, NaI, THF/DMF, reflux, 36%; iii) **4**, NaH, THF, reflux, 99%; iv) $LiAlH_4$, Et_2O, reflux, 88%; v) PBr_3, $CHCl_3$, RT, 97%; vi) NH_3, Na_2CO_3, THF, 60°C, 62%.

in both cases, no other macrocyclization products could be clearly detected by ^{1}H NMR spectroscopy.

For the second synthetic pathway, $X_6H_3Me_3$ **1** was first alkylated in quantitative yield with an excess of methyl 6-(bromomethyl)picolinate **4** (5 equiv) in the presence of a strong base (NaH). Reduction of the ester groups of **8** by lithium aluminum hydride (LAH) afforded the corresponding tris-hydroxy derivative **9** in 88% yield. Subsequent treatment with PBr_3 led to the tris-bromo derivative **10** in high yield (97%). The ^{1}H NMR spectra of the calix[6]arene derivatives **8**, **9**, and **10** show the presence of a major flattened C_{3v}-symmetrical cone conformation with the anisole *t*Bu substituents in the *out* position ($\delta_{t\mathrm{Bu}}=1.36$–1.38 ppm), their corresponding methoxy group being oriented towards the center of the cavity ($\delta_{\mathrm{OMe}}=2.34$–2.35 ppm) (see the Supporting Information: Figures S15, S17, S19). It is noteworthy however that minor dissymmetrical alternate conformations are detectable, as previously observed for similar calix[6]arenes bearing picolyl residues.[20] Similarly to the preparation of compound **5**, the reaction of calixarene **10** with a saturated solution of ammonia in THF at 60°C led, in the presence of Na_2CO_3, to **11** in 62% yield (Scheme 2). This high yield does not result from a templating effect of the sodium cation since **11** was isolated in a comparable 55% yield when the reaction was conducted in absence of Na_2CO_3.

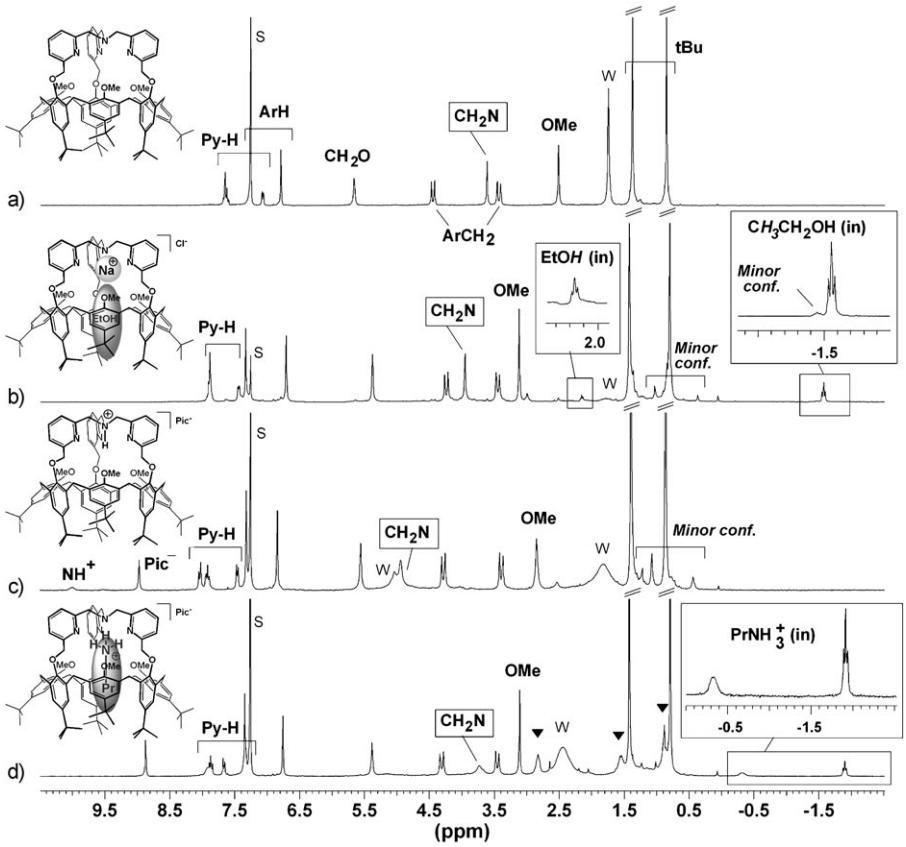


Figure 2. ^{1}H NMR spectra (300 MHz, $CDCl_3$): a) **11** (293 K); b) *endo* complex **11**·Na^+⊃**EtOH** (293 K); c) **11**.H^+,Pic^- (263 K); d) *endo* complex **11**⊃$PrNH_3^+$,Pic^- (263 K); ▼: free $PrNH_2$. Residual solvents, water and the minor conformers (see the text) have been labeled "S", "W" and "*Minor conf.*", respectively.

If we compare the two different pathways for the synthesis of **11**, they appear equally efficient as they lead to similar overall yields from **1** (47% and 52%, respectively), and are both easy to carry out on a large scale.

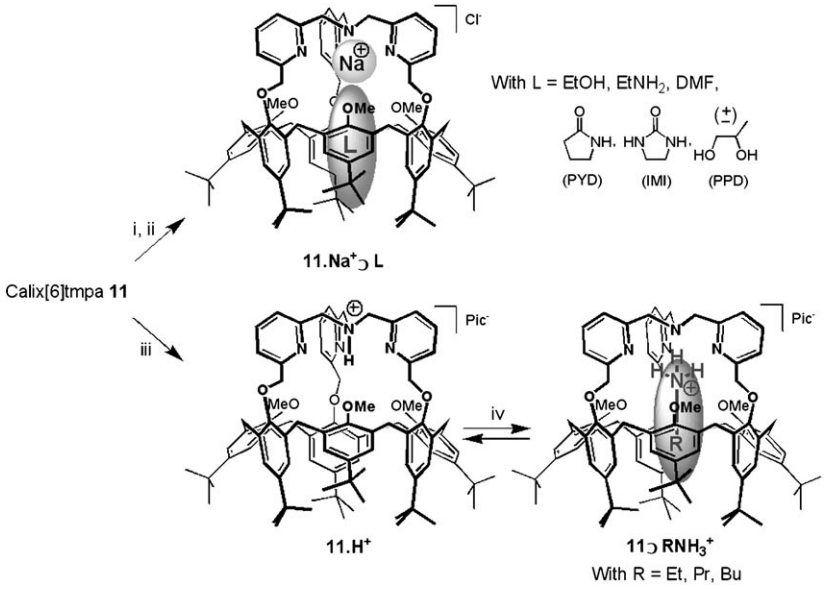
^{1}H NMR conformational study of calix[6]tmpa (11): The conformational properties of **11** have been studied by ^{1}H NMR spectroscopy. The spectrum recorded at 293 K (Figure 2a) is characteristic of a major C_{3v}-symmetrical flattened cone conformation with sharp doublets at $\delta=3.43$ and 4.45 ppm for the $ArCH_2$ methylene protons. The NMR profile barely changed in the 263–330 K temperature range, besides some broadening of the OMe signal at low temperature (see the Supporting Information: Figure S1). An heteronuclear multiple bond correlation (HMBC) experiment allowed the attribution of the *t*BuAr resonances: the aromatic units linked to the tmpa cap present the more high-field shifted resonances ($\delta_{\mathrm{ArH}}=6.80$ ppm, $\delta_{t\mathrm{Bu}}=0.86$ ppm), whereas those belonging to the *t*Bu-anisole units are relatively down-field shifted ($\delta_{\mathrm{ArH}}=7.26$ ppm, $\delta_{t\mathrm{Bu}}=1.37$ ppm) (see the Supporting Information: Figure S23). Hence, the former protons experience the anisotropic ring current from the *t*Bu-anisole aromatic cores. This shows that the *t*BuArO-(tmpa) aromatic units are in an *in*-position, whereas the anisole walls stand away from the C_{3v} axis, thus forming the external shell of the calixarene cavity. Despite the presence of the tmpa cap that precludes the inclusion of all three O-methyl substituents in the calixarene cone conformation due to overcrowding, the corresponding CH_3 protons present a high-field shifted resonance ($\delta_{\mathrm{OMe}}=2.53$ ppm). This can be explained by their relative proximity to the C_{3v} axis and, as a consequence, to the aromatic units of the tmpa and calixarene cores.

Such a conformation differs from those adopted by all other calixazacryptands which we have described so far. Indeed, in the case of calix[6]tac (Figure 1), the capping of the narrow rim produced a calixarene with an inverted flattened cone conformation compared with **11**, that is, the anisole *t*Bu substituents ($\delta_{t\mathrm{Bu}}=0.73$ ppm) being in an *in*-position with their OCH_3 groups far from the C_{3v} axis ($\delta_{\mathrm{OMe}}=3.75$ ppm). For calix[6]tren and PN_3, a straight and regular

cone conformation was observed ($\Delta\delta_{tBu} < 0.09$ ppm and $\delta_{OMe} \approx 3$ ppm). This original conformational behavior of **11** may be related to the more rigid tmpa cap that is constructed from aromatic amines instead of aliphatic amines. Interestingly, such a conformation produces a cavity with a different environment at the narrow rim because the oxygen atoms bearing the tmpa cap are moved away from the C_{3v} axis, directing their lone pair electrons toward the outside of the cavity (Scheme 2 and Figure 2a).

A sodium "funnel complex" based on calix[6]tmpa (11): As in the case of all other calix[6]azacryptands, no inclusion of small neutral molecules by **11** could be evidenced by ^{1}H NMR spectroscopy in $CDCl_3$. Interestingly however, when a chloroform/EtOH solution of **11** was treated with solid NaCl, a new species was produced. After filtration and removal of the solvents, the resulting solid was analyzed by ^{1}H NMR spectroscopy in $CDCl_3$ at 293 K (Figure 2b). It showed new resonances in the high-field region that were unambiguously (COSY and NOESY, see the Supporting Information: Figures S25 and S27) attributed to an ethanol guest molecule. The latter appeared strongly bound to the calix cavity as no free EtOH was observable. The main species is C_{3v}-symmetrical with one equivalent of EtOH in the calixarene cavity ($\delta_{CH_3} = -1.56$, $\delta_{CH_2} = 1.44$, $\delta_{OH} = 2.16$ ppm),[21] possesses a flattened cone conformation similar to that in **11** ($\delta_{tBu} = 1.43$ ppm (for the anisole unit as confirmed by HMBC) and $\Delta\delta_{tBu} = 0.62$ ppm) and up-field shifted CH_2N and Py–H resonances. Therefore, the identity of this new species has been assigned as **11·Na$^+$⊃EtOH**, a *funnel complex* in which the sodium ion allows the efficient hosting of one equivalent of ethanol, as depicted in Scheme 3.[22] The whole NMR spectrum barely changed in the 261–330 K temperature range, and only a slight broadening of the signals belonging to the included EtOH molecule was observed at 330 K. This observation emphasizes the remarkable affinity of the Na$^+$ complex for this neutral guest. Lastly, the co-existence of a minor species was evidenced by the presence of a small triplet at $\delta = -1.45$ ppm (Figure 2b, insert) which was associated to different calixarene resonances, some of which were clearly observable in the 0–2 ppm region. This probably corresponds to a minor alternate conformation, as discussed below.[23] Interestingly, the binding of Na$^+$ and EtOH appeared cooperative. Indeed, when the *endo* complex **11·Na$^+$⊃EtOH** was strongly dried in the solid state under high vacuum, part of the bound EtOH was removed. Redissolving the resulting solid in $CDCl_3$ showed a mixture of **11·Na$^+$⊃EtOH** and free ligand **11.** This shows, in solution and in the absence of EtOH, that the Na$^+$ complex is not stable and the tmpa cap spontaneously releases the cation (probably as NaCl). However, adding approximately three equivelants of ethanol to the solution quantitatively restored the initial complex. This demonstrates that without the EtOH guest, **11** is inefficient at binding Na$^+$. Conversely, without Na$^+$, **11** is inefficient at binding EtOH.

In a chloroform solution, the displacement of the bound EtOH was performed upon the addition of a few molar equivalents of other neutral guests such as (±)-propane-1,2-diol (PPD), pyrrolidin-2-one (PYD), imidazolidin-2-one (IMI), $EtNH_2$ or DMF to the endo-complex **11·Na$^+$⊃EtOH** (Scheme 3). The complexation-induced upfield shifts (CIS) and relative affinities obtained with these guests are reported in Table 1. The relative affinities decrease according to the sequence order IMI ≫ PYD > EtOH > $EtNH_2$. Thus, in contrast to the previously reported Zn^{2+} *funnel complexes*,[5b,24] an alkali metal ion such as Na$^+$ allows the stronger binding of cyclic ureas, amides, and primary alcohols compared with primary amines. This is obviously related to the strong oxophilic character of the harder Na$^+$ ion.



Scheme 3. i) NaCl, $CHCl_3$, EtOH; ii) L (> 1 equiv), $CDCl_3$; iii) PicH (1 equiv), $CDCl_3$; iv) RNH_2 (> 1 equiv), $CDCl_3$.

Characterization by X-ray diffraction and hosting properties of the mono-protonated derivative 11·H$^+$: The host properties of **11** with a protonated aza cap were investigated as well. At 263 K, the addition of approximately 0.5 equivalents of picric acid (PicH) to a solution of **11** in $CDCl_3$ led to the formation of an approximately 1:1 mixture of a new C_{3v}-symmetrical species in slow exchange with **11** when compared with the NMR time scale (see the Supporting Information: Figure S2).[25] When one equivalent of PicH was added, **11** was fully converted into this new species (Figure 2c), which therefore

Table 1. Relative affinities of the neutral guests L towards host **11·Na$^+$** and NMR complexation-induced upfield shifts (CIS) observed upon their *endo* complexation (solvent: $CDCl_3$).

Entry	L	Rel. aff.[a]	CIS [ppm][b]		
			α	β	γ
1	EtOH	1	−2.27	−2.79	-
2	(±)-PPD	0.015	n.d.[c]	n.d.[c]	−2.53[d]
3	$EtNH_2$	0.16	−2.17	−2.72	–
4	DMF	0.33	−1.74	–	−2.61[e]
5	PYD	1.9	–	−2.63	−2.48, −2.86[f]
6	IMI	12.3	–	–	−2.74

[a] Relative affinity calculated at 293 K and defined as $[L_{in}]/[EtOH_{in}]\times[EtOH_T]/[L_T]$, where indexes in = included and T = total amount. Errors estimated ±10%. [b] CIS calculated at 293 K and defined as $\Delta\delta = \delta$(complexed L) − δ(free L). α, β, and γ refer to the relative position of the protons to the oxygen atom or to the nitrogen atom in the case of $PrNH_2$. [c] Not determined due to overlapping of the host and guest signals. [d] γ refers to the relative position of the protons to the oxygen atom of the primary alcohol. [e] Average value of the two inequivalent methyl groups. [f] Values determined for $CH_2CH_2CH_2$ and CH_2N, respectively.

corresponds to the monoprotonated derivative **11·H$^+$** (Scheme 3).[26] It is noteworthy that the addition of a large excess of PicH (ca. 100 equiv) or a stronger acid such as perchloric acid did not affect the NMR spectrum much, beside some broadening of the resonances. This shows that further protonation of the tmpa cap is highly disfavored, in contrast to a simple tmpa unit[27] and to the other calix[6]-azacryptands that easily undergo polyprotonation.[4c,5b,6]

X-ray quality crystals of **11·H$^+$** were grown out of a solution of **11** in $CHCl_3$ that had been treated by a few molar equivalents of $HClO_4$ diluted in EtOH. The crystal unit contains three calixarene cryptands that are monoprotonated as attested by the presence of three perchlorate counterions. Two calixarene cores adopt a flattened cone conformation (see Figure 3, left, for one of these two cone conformations)

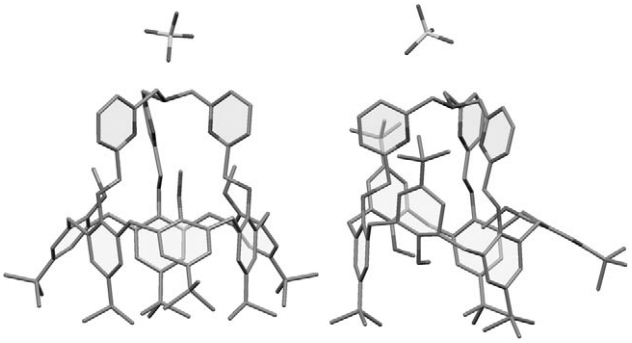


Figure 3. Crystal structure of **11·H$^+$,ClO$_4^-$**. Left: one of the two cone conformations (see the text); Right: 1,3-alternate conformation. Hydrogen atoms and some crystallization solvent molecules have been omitted for clarity.

that fully corresponds to that described for **11** above. It is noteworthy that these flattened cone conformations of **11·H$^+$** present aromatic units that are in alternate *in* and *out* positions compared with the previously reported monoprotonated calix[6] azacryptands (i.e. calix[6]tren·H$^+$ and calix[6]PN_3·H$^+$).[4c,5b] The third calix structure observed in the solid state possesses an unexpected 1,3-alternate conformation (Figure 3, right). One anisole unit presents its *t*Bu substituent in an *out* position with its OMe group pointing towards the center of the calix cavity. The two others are upside down, with their *t*BuAr moieties folded back at the level of the small rim of the calixarene. Interestingly, this 1,3-alternate conformation appears to be stabilized by a series of CH–π interactions: all three methoxy groups are oriented toward the inside of the cavity at relatively short distances from two π bonds belonging to the calix aromatic core, one on each side; the upside down *t*Bu groups are also found next to the pyridine units at distances denoting CH–π interactions (Figure 4). To the best of our knowledge, this is

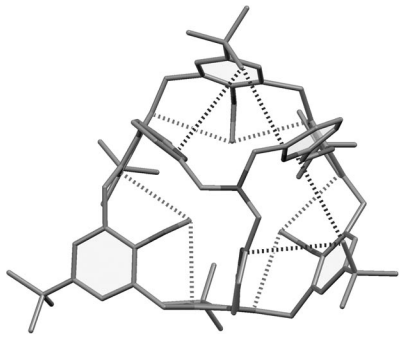


Figure 4. Top view of the 1,3-alternate conformer of **11·H$^+$** displaying the CH–π interactions (dashed lines) between the OMe and the aryl rings on one hand, and between the *t*Bu substituents and the pyridine groups on the other. The C···π distances are between 3.1–3.5 and 3.7–4.1 Å, respectively.

the first example in the solid state of a 1,3-alternate conformation of a calix[6]arene derivative.

The NMR spectrum of **11·H$^+$** (Figure 2c) suggests that in solution too, the protonated calix cryptand adopts two different conformations.[26] The major conformation clearly corresponds to the cone conformation observed in the solid-state structure because it displays a C_{3v}-symmetrical pattern with several data attesting to the monoprotonation of the tmpa cap: 1) a downfield shift of the CH_2N and pyridine (Py–H) signals; 2) the presence of a broad singlet at δ = 10.01 ppm, integrating for one proton and corresponding to the NH$^+$ resonance (D_2O-exchanged). The presence of a minor dissymmetrical conformation is shown by extra resonances clearly observable in the δ = 0–2 ppm region[28] and may well correspond to the 1,3-alternate conformation observed in the solid state. Such a conformation may also be relevant to the minor species detected in the spectrum of complex **11·Na$^+$⊃EtOH** (Figure 2b).

Upon the addition of a large excess of small polar neutral molecules such as DMSO, EtOH, MeOH, and IMI into a solution of **11·H$^+$** in $CDCl_3$, no inclusion was detected even at low temperature (223 K). Indeed, we have previously shown that the recognition of polar neutral molecules

through charge–dipole interactions and hydrogen bonding requires a polycationic cap with multiple NH^+ sites.[5b,29] Yet, the addition of a few equivalents of a primary amine RNH_2 (with R = Et, *n*Pr, or *n*Bu) to **11·H$^+$** led to the formation of C_{3v}-symmetrical *endo* complexes with characteristic high-field-shifted signals for the included alkyl chain (see Figure 2d for R = Pr, and the CIS values reported in Table 2). It is noteworthy that, upon complexation of the amine, the CH_2N signal of the tmpa cap of **11·H$^+$** experienced an impressive high-field shift ($\Delta\delta_{CH_2N} = 1.23$ ppm relative to **11·H$^+$**⊃∅), whereas the Py–H resonances were only slightly affected. This evidences a proton transfer from the tmpa cap to the amine, hence showing that the *endo* complex indeed corresponds to **11**⊃**RNH$_3^+$** rather than to **11·H$^+$**⊃**RNH$_2$** (as schematized in Scheme 3). Although we were unsuccessful in assigning the *t*Bu peaks by HMBC, we can gather from the only moderate changes observed in the ^{1}H NMR spectrum (Figure 2) that the calixarene core of **11**⊃**RNH$_3^+$** likely remains in the flattened cone conformation characteristic of **11**. When the spectrum was recorded at room temperature, the *in* and *out* exchange process of RNH_3^+ remained slower than the NMR time scale, highlighting the strong affinity of the receptor for these ammonium ions. Very interestingly, in the case of the *endo* complex **11**⊃**PrNH$_3^+$**, a splitting of some resonances of the host (i.e. CH_2O and CH_2N of the cap) and of the guest (i.e. CH_3CH_2) was observed at 220 K (see the Supporting Information: Figure S3). This is clearly due to the well-known helical twisting of the three nitrogenous arms of the cap,[20,30] the host providing a chiral C_3 environment sensed by the guest. Finally, competitive binding experiments monitored by ^{1}H NMR spectroscopy at 263 K (see the Experimental Section for the detailed procedure) showed that $PrNH_3^+$ is the best guest, thus corresponding to optimal cavity filling and CH–π interactions (Table 2). Hence, in spite of the conformational differences with calix[6]tren, calix[6]tmpa (**11**) exhibits analogous complexation properties toward ammonium ions, with a comparable positioning of the ions in the heart of the cavity (as indicated by similar CIS values) and an identical guest preference for R = Pr.[5b]

Table 2. Relative affinities of the ammonium ion RNH_3^+ towards host **11** and NMR complexation-induced upfield shifts (CIS) observed upon their endo-complexation in $CDCl_3$.

Entry	Ammonium Ion RNH_3^+	Rel. aff.[a]	CIS [ppm][b]			
			α	β	γ	δ
1	$EtNH_3^+$	0.20	−2.41	−2.38	–	–
2	nPrNH$_3^+$	1	n.d.[c]	−1.87	−2.81	–
3	nBuNH$_3^+$	0.48	n.d.[c]	−1.28	−2.76	−2.63

[a] Relative affinity calculated at 293 K and defined as $[RNH_3^+{}_{in}]/[PrNH_3^+{}_{in}] \times [PrNH_2(H^+)_T]/[RNH_2(H^+)_T]$ where indexes in = included and T = total amount. Errors estimated ±10%. [b] CIS calculated at 263 K and defined as $\Delta\delta = \delta$(complexed ammonium ion) − δ(free ammonium ion). α, β, γ, and δ refer to the relative position of the protons to the charged nitrogen atom of the ammonium ion (i.e. C_δ-C_γ-C_β-C_α-NH_3^+). [c] Not determined due to overlapping of the host and guest signals.

Conclusion

The synthesis of a new C_{3v}-symmetrical calix[6]azacryptand, that is, calix[6]tmpa (**11**), was achieved according to two efficient strategies in remarkably similar overall yields from calixarene **1** (47% and 52%, respectively). Calix[6]tmpa (**11**) and its sodium and protonated derivatives (**11·Na$^+$** and **11·H$^+$**) display conformational properties that differ from the properties previously observed for all the other calix[6]-azacryptands, and are probably due to the high sterical constrains inferred from the tmpa cap. Also, interestingly, the NMR study in $CDCl_3$ showed that whereas **11** readily undergoes monoprotonation in the presence of an acid, it appears reluctant to undergo polyprotonated, unlike the more flexible calix[6]azacryptands presenting alkylamines instead of aromatic amines. The monoprotonated derivative **11·H$^+$** behaves as a good receptor for amines, leading to inclusion complexes **11**⊃**RNH$_3^+$**, but it is not polarized enough to bind small polar neutral molecules in chloroform. Finally, the cooperative complexation of Na^+ in the tmpa cap and neutral guests in the cavity was evidenced, providing the first example of a *funnel complex* binding an alkali-metal cation. This Na^+ complex possesses unique host properties as compared with the related Zn^{2+} funnel complexes[24] since it preferentially includes cyclic ureas, amides, or alcohols rather than primary amines. Hence, **11** provides a new example of synergistic combination of a polyaza site and a calix[6]arene structure. Indeed, on the one hand, a simple tmpa molecule undergoes trisprotonation in the presence of perchloric acid and leads to a bis-tmpa Na^+ complex with $NaClO_4$.[31] Such different behavior shows the importance of geometrical control owing to the calixarene macrocycle. On the other hand, whereas calix[4]arenes functionalized at the small rim with O-donors have been shown to efficiently complex sodium ions,[32] cooperative guest coordination is only possible with a calix[6]arene that provides a wider small rim leaving access for guest binding to Na^+. In conclusion, calix[6]tmpa (**11**) constitutes a new member of the calix[6]azacryptand family with different conformational behavior and promising binding properties toward neutral or charged species.

Experimental Section

General: CH_2Cl_2 was distilled over CaH_2 under argon. $CHCl_3$ was distilled over P_2O_5 under argon. DMF was distilled over silica gel/$MgSO_4$ under argon. Diethyl ether and THF were distilled over sodium/benzophenone under argon. Ethanol was distilled over sodium/diethylphthalate under argon. All reactions were performed under an inert atmosphere. In all cases, NaH was not washed prior to use. Silica gel (230–400 mesh) was used for flash chromatography separations. ^{1}H and ^{13}C NMR spectra were recorded either with a Bruker AC 200, ARX 250, Avance 300 or Avance 500 apparatus. Chemical shifts are expressed in ppm. In most

cases, they were assigned through HMQC and/or HMBC, COSY, NOESY experiments. Traces of residual solvent were used as internal standard. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer using either KBr pellets or the Attenuated Total Reflectance (ATR) method. EIMS analyses were performed with a Finnigan LCQ Advantage apparatus. Elemental analyses were performed at the Service de Microanalyse (I.C.S.N., Gif sur Yvette, France) and at the Laboratoire de Microanalyse Organique (IRCOF, France).

Methyl 6-(hydroxymethyl)picolinate (3): $NaBH_4$ (390 mg, 10.3 mmol) was slowly added, at 0 °C, to a solution of dimethyl pyridine-2,6-dicarboxylate (**2**; 2.00 g, 10.2 mmol) in a dry 7:3 mixture of MeOH/CH_2Cl_2 (100 mL). The reaction mixture was stirred for 3 h at room temperature and then neutralized with an aqueous saturated NH_4Cl solution. After extraction with CH_2Cl_2 (3×50 mL), the combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The resulting crude residue was purified by column chromatography (hexane/EtOAc; 1:1 then 1:2) giving the mono-alcohol **3** (1.49 g, 87 %) as a white solid. The melting point was identical to the one described in the literature:[33] m.p. 88 °C; IR (KBr): $\tilde{\nu}=1742\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.43$ (br s, 1H; OH), 3.98 (s, 3H; OCH_3), 4.86 (s, 2H; CH_2O), 7.54 (d, $J=8$ Hz, 1H; Py–H), 7.85 (t, $J=8$ Hz, 1H; Py–H), 8.02 ppm (d, $J=8$ Hz, 1H; Py–H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=53.0$, 64.7, 123.9, 124.2, 137.8, 147.1; 160.4, 165.7 ppm; EIMS: *m*/*z* (%): 167 ($[M]^+$, 9), 109 (100), 91 (81).

Methyl 6-(bromomethyl)picolinate (4): PBr_3 (1.04 mL, 11.1 mmol) was added, at 0 °C, to mono-alcohol **3** (1.72 g, 10.3 mmol) in anhydrous $CHCl_3$ (150 mL). The reaction mixture was stirred for 4 h at room temperature and then neutralized at 0 °C with an aqueous saturated K_2CO_3 solution. After extraction with CH_2Cl_2 (2×50 mL), the combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure, leading to pure compound **4** as a white solid (2.34 g, 99 %). No further purification of the compound **4** was necessary. The synthesis of compound **4** was previously reported with a different procedure[34] and, to our knowledge, no characterization data has been reported. m.p. 98 °C; IR (ATR): $\tilde{\nu}=1739\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta=4.00$ (s, 3H; OCH_3), 4.65 (s, 2H; CH_2), 7.69 (d, $J=8$ Hz, 1H; Py–H), 7.87 (t, $J=8$ Hz, 1H; Py–H), 8.05 ppm (d, $J=8$ Hz, 1H; Py–H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=33.0$, 53.2, 124.6, 127.4, 138.6, 147.5, 157.5, 165.2 ppm; ESI-MS (CH_3CN): *m*/*z* (%): 230.0 ($[M+H]^+$, 100), 232.0 ($[M+H]^+$, 92); elemental analysis calcd (%) for $C_8H_8BrNO_2$ (230.06): C 41.77, H 3.50, N 6.09; found: C 41.79, H 3.27, N 6.12.

Tris[6-(methoxycarbonyl)-2-pyridylmethyl]amine (5): NH_3 was bubbled into a solution of **4** (2.00 g, 8.69 mmol) in THF (150 mL) at room temperature for 30 min. K_2CO_3 (2.70 g, 19.5 mmol) was then added, the mixture was stirred at 50 °C and the reaction was monitored by ^1H NMR spectroscopy in $CDCl_3$. Once the reaction appeared complete, the solvent was removed under reduced pressure, the resulting residue was dissolved in CH_2Cl_2 (30 mL) and washed with water (20 mL). The aqueous layer was extracted twice with CH_2Cl_2 (2×15 mL) and the combined organic layers were dried with Na_2SO_4. After removal of the solvent under reduced pressure, recrystallization from CH_2Cl_2/Et_2O (1:1) afforded pure product **5** (1.10 g, 82 %) as a white solid. m.p. 94 °C; IR (ATR): $\tilde{\nu}=1738\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$): $\delta=4.02$ (s, 9H; OCH_3), 4.05 (s, 6H; CH_2), 7.80–7.90 (m, 6H; Py–H), 8.01 ppm (d, $J=7$ Hz, 3H; Py–H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=53.3$, 60.3, 124.1, 126.7, 137.8, 147.9, 160.1, 166.2 ppm; ESI-MS (CH_3CN): *m*/*z* (%): 487.3 ($[M+H]^+$, 100); elemental analysis calcd (%) for $C_{24}H_{24}N_4O_6\cdot0.33\,H_2O$ (470.42): C 61.27, H 5.28, N 11.91; found: C 61.29, H 5.05, N 11.86.

Tris[6-(hydroxymethyl)-2-pyridylmethyl]amine (6): $NaBH_4$ (360 mg, 9.52 mmol) was added to a suspension of tris-ester **5** (230 mg, 0.495 mmol) in anhydrous EtOH (8 mL) at 0 °C. The reaction mixture was refluxed for 2 h and the solvent was removed under reduced pressure. The resulting crude residue was dissolved in CH_2Cl_2 (10 mL), washed with brine (2×10 mL), and with an aqueous saturated Na_2CO_3 solution (2 mL). The organic layer was dried with Na_2SO_4 and concentrated. Recrystallization from CH_2Cl_2/Et_2O (1:1) yielded pure **6** (154 mg, 82 %) as a white solid. The characterization data were identical to those described in the literature.[15] ^1H NMR (200 MHz, $CDCl_3$): $\delta=3.70$ (s, 6H; CH_2N), 4.93 (s, 6H; CH_2O), 7.04 (d, $J=8$ Hz, 3H; Py–H), 7.06 (d, $J=8$ Hz, 3H; Py–H), 7.55 ppm (t, $J=8$ Hz, 3H; Py–H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=59.8$, 64.1, 120.5, 121.8, 137.5, 157.9, 160.6 ppm; ESI-MS (CH_3CN): *m*/*z* (%): 381.4 ($[M+H]^+$, 100).

Tris[6-(chloromethyl)-2-pyridylmethyl]amine (7): $SOCl_2$ (22.0 mL, 302 mmol) was added dropwise to compound **6** (3.18 g, 8.36 mmol) at 0 °C. The resulting suspension was stirred for 5.5 h at room temperature and the excess of $SOCl_2$ was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) and an aqueous solution of NaOH (1 M) was added slowly at 0 °C until the mixture became basic (pH > 12). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with water (3×100 mL), dried over Na_2SO_4, and evaporated to dryness. Et_2O (2×150 mL) was added to the resulting brown solid and the solution was stirred for 1 h and filtered. After removal of Et_2O under reduced pressure, compound **7** was obtained as a pure colorless solid (2.77 g, 76 %). This product is not stable at room temperature and decomposes within a few days. However, it is stable at lower temperature (−18 °C) for approximately one month. M.p. 81 °C; IR (KBr): $\tilde{\nu}=1589$, 1574 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.88$ (s, 6H; CH_2N), 4.62 (s, 6H; CH_2Cl), 7.30 (d, $J=8$ Hz, 3H; Py–-H), 7.51 (d, $J=8$ Hz, 3H; Py–H), 7.66 ppm (t, $J=8$ Hz; 3H, Py–H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=$ 46.8, 60.0, 121.1, 122.3, 137.5, 155.9, 159.1 ppm; EIMS (MeOH): *m*/*z* (%): 435 ([*M*
H]$^+$, 100).

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris-[(6-methoxycarbonyl-2-pyridyl)methoxy]calix[6]arene (8): NaH (60 wt % in oil, 1.48 g, 37.0 mmol) was added in small portions into a solution of methyl 6-(bromomethyl)picolinate (**4**; 4.40 g, 19.1 mmol) and $X_6H_3Me_3$ (**1**; 3.89 g, 3.83 mmol) in anhydrous THF (160 mL) at 0 °C. After refluxing for 23 h, the reaction mixture was cooled to 0 °C and water was slowly added until the gas release ceased. The solvent was removed under reduced pressure, the resulting residue was dissolved in CH_2Cl_2 (200 mL) and washed with water (2×25 mL). After solvent evaporation, the residue was triturated with EtOH (10 mL) and the resulting solid was isolated by filtration, yielding compound **8** (5.55 g, 99 %) as a white solid. m.p. 224 °C (decomp); IR (KBr): $\tilde{\nu}=2957$, 1727, 1592, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.82$ (s, 27H; *t*Bu), 1.36 (s, 27H; *t*Bu), 2.34 (s, 9H; OCH_{3calix}), 3.42 (d, $J=15$ Hz, 6H; $ArCH_2$), 3.98 (s, 9H; OCH_{3pyr}), 4.57 (d, $J=15$ Hz, 6H; $ArCH_2$), 5.20 (s, 6H; OCH_2), 6.70 (s, 6H; ArH_{calix}), 7.26 (s, 6H; ArH_{calix}), 7.96 (t, $J=7$ Hz, 3H; Py–H), 8.07 (d, $J=7$ Hz, 3H; Py–H), 8.19 ppm (d, $J=7$ Hz, 3H; Py–H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=29.7$, 31.2, 31.7, 34.1, 34.3, 53.0, 60.4, 74.7, 123.9, 124.1, 124.7, 128.1, 133.0, 133.6, 138.1, 146.1, 146.4, 147.2, 151.4, 154.4, 158.9, 165.8 ppm; elemental analysis calcd (%) for $C_{93}H_{111}N_3O_{12}\cdot2.5\,H_2O$ (1507.94): C 74.07, H 7.75, N 2.79; found: C 73.87, H 7.66, N 2.59.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris-[(6-hydroxymethyl-2-pyridyl)methoxy]calix[6]arene (9): $LiAlH_4$ (50 mg, 1.3 mmol) was added into a solution of calix[6]arene **8** (200 mg, 0.14 mmol) in anhydrous Et_2O (14 mL). After refluxing for 16 h, the reaction mixture was cooled to 0 °C and HCl (4 N) was slowly added until pH < 3. The solvent was removed under reduced pressure and the resulting residue was dissolved in CH_2Cl_2 (50 mL), washed with an aqueous solution of NaOH (1 M, 15 mL) and then twice with water (2×10 mL). After solvent evaporation, EtOH (2 mL) was added to the residue and the resulting solid was isolated by filtration, yielding compound **9** (167 mg, 88 %) as a white solid. m.p. 225 °C (decomp); IR (KBr): $\nu=$ 2961, 1597, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.84$ (s, 27H; *t*Bu), 1.38 (s, 27H; *t*Bu), 2.35 (s, 9H; OCH_3), 3.43 (d, $J=15$ Hz, 6H; $ArCH_2$), 4.61 (d, $J=15$ Hz, 6H; $ArCH_2$), 4.76 (s, 6H; CH_2OH), 5.11 (s, 6H; $PyrCH_2O$), 6.72 (s, 6H; ArH_{calix}), 7.18 (t, $J=4$ Hz, 3H; Py–H), 7.28 (s, 6H; ArH_{calix}), 7.75–7.86 ppm (m, 6H; Py–H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=29.8$, 31.3, 31.8, 34.2, 34.4, 60.4, 64.0, 75.0, 119.4, 120.2, 123.9, 128.1, 133.2, 133.8, 137.8, 146.0, 146.3, 151.6, 154.5, 157.0, 158.2 ppm; elemental analysis calcd (%) for $C_{90}H_{111}N_3O_9\cdot2\,H_2O$ (1414.90): C 76.40, H 8.19, N 2.97; found: C 76.66, H 8.03, N 2.65.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris-[(6-bromomethyl-2-pyridyl)methoxy]calix[6]arene (10): PBr_3 (0.300 mL,

3.19 mmol) was added to a solution of calix[6]arene **9** (600 mg, 0.435 mmol) in $CHCl_3$ (50 mL) and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured into an aqueous K_2CO_3 (sat.) solution (150 mL) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (2×30 mL) and the combined organic layers were dried with Na_2SO_4. After filtration and removal of the solvent under vacuum, pure compound **10** (661 mg, 97 %) was obtained as a white solid. m.p. 151 °C (decomp); IR (KBr): $\tilde{\nu}$ = 2961, 1593, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83 (s, 27H; *t*Bu), 1.38 (s, 27H; *t*Bu), 2.34 (s, 9H; OCH_3), 3.42 (d, J = 15 Hz, 6H; $ArCH_2$), 4.57 (s, 6H; CH_2Br), 4.58 (d, J = 15 Hz, 6H; $ArCH_2$), 5.11 (s, 6H; CH_2O), 6.71 (s, 6H; ArH_{calix}), 7.27 (s, 6H; ArH_{calix}), 7.41 (d, J = 7 Hz, 3H; Py–H), 7.80–7.89 ppm (m, 6H; Py–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 31.3, 31.8, 34.0, 34.2, 34.4, 60.4, 75.0, 120.9, 122.4, 123.9, 128.1, 133.2, 133.7, 138.1, 146.0, 146.3, 151.5, 154.5, 156.1, 158.2 ppm; elemental analysis calcd (%) for $C_{90}H_{108}Br_3N_3O_6{\cdot}2H_2O$ (1603.59): C 67.41, H 7.04, N 2.62; found: C 67.18, H 6.69, N 2.55.

Calix[6]tmpa (11):

Method A: $X_6Me_3H_3$ (**1**; 508 mg, 0.500 mmol) was added to a mixture of NaH (60 wt % in oil, 90 mg, 2.3 mmol) and NaI (50 mg, 0.33 mmol) in anhydrous THF (80 mL) and anhydrous DMF (80 mL). The solution was stirred for 30 min and compound **7** (327 mg, 0.750 mmol) was added in one portion. The reaction mixture was refluxed for 48 h and then the solvent was removed under reduced pressure. The resulting residue was dissolved in dichloromethane (100 mL) and washed with water (3×50 mL). The organic layer was separated and concentrated to dryness. The resulting residue was triturated with ethanol (10 mL) and pure calix[6]tmpa (**11**) was isolated by centrifugation as a white solid (240 mg, 36 %).

Method B: A suspension of $X_6Me_3H_3$ (**1**; 300 mg, 0.295 mmol), compound **7** (142 mg, 0.326 mmol), K_2CO_3 (124 mg, 0.897 mmol), Cs_2CO_3 (48 mg, 0.15 mmol), and KI (25 mg, 0.15 mmol) in anhydrous DMF (20 mL) was stirred vigorously at room temperature for 2 h and then at 90 °C for 64 h. After the mixture was allowed to cool back to room temperature, DMF was removed under vacuum to dryness. CH_2Cl_2 (100 mL) and HCl (2 M, 1.5 mL) were added to the residue and the solution was stirred for 1 h at room temperature. The organic layer was separated, washed with H_2O (2×50 mL), then stirred with an aqueous NaOH solution (5 M, 4.5 mL) for 1 h at room temperature. The organic layer was again separated and washed three times with H_2O (first with 2×50 mL for a few minutes, then with 100 mL for 1 h) to remove any trace of sodium cation. After evaporation of CH_2Cl_2 under reduced pressure, the aqueous suspension was filtered over celite. The solid phase was washed successively with H_2O (3×50 mL), EtOH (3×50 mL), CH_2Cl_2 (3×20 mL), and finally extracted with $CHCl_3$ (4×20 mL). Evaporation of the $CHCl_3$ fractions yielded the desired pure product **11** (187 mg, 47 %).

Method C: NH_3 was bubbled for 1 h into a solution of calix[6]arene **10** (170 mg, 0.108 mmol) in THF (100 mL) at room temperature. Na_2CO_3 (20 mg, 0.19 mmol) was added and the reaction mixture was heated at 60 °C for 16 h. The solvent was removed under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL), washed with an aqueous solution of NaOH (1 M, 5 mL) and with water (2×100 mL). After evaporation of CH_2Cl_2, the suspension was filtered over celite. The solid phase was washed successively with H_2O (2×10 mL), CH_2Cl_2 (2×5 mL), and finally extracted with $CHCl_3$ (4×10 mL) to yield pure **11** (90 mg, 62 %). m.p. > 260 °C; IR (KBr): $\tilde{\nu}$ = 2951, 1591 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.86 (s, 27H; *t*Bu), 1.37 (s, 27H; *t*Bu), 2.53 (s, 9H; OCH_3), 3.43 (d, J = 15 Hz, 6H; $ArCH_2$), 3.63 (s, 6H; CH_2N), 4.45 (d, J = 15 Hz, 6H; $ArCH_2$), 5.65 (s, 6H; CH_2O), 6.80 (s, 6H; ArH_{calix}), 7.08 (d, J = 7 Hz, 3H; Py–H), 7.26 (s, 6H; ArH_{calix}), 7.61–7.66 ppm (m, 6H; Py–H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 31.0, 31.2, 31.9, 34.2, 34.4, 60.1, 61.4, 74.9, 117.8, 121.9, 124.3, 128.6, 133.5, 134.0, 136.6, 145.8, 146.0, 151.7, 155.9, 157.5, 160.0 ppm; elemental analysis calcd (%) for $C_{90}H_{108}N_4O_6{\cdot}CH_2Cl_2{\cdot}3H_2O$ (1480.82): C 73.81, H 7.90, N 3.78; found: C 74.12, H 7.69, N 3.59.

11·H$^+$,Pic$^-$ and *endo* complexes 11⊃RNH$_3^+$,Pic$^-$: PicH (1 equiv) was added to a solution of **11** (3 mg, 2 μmol) in $CDCl_3$ (0.6 mL). The corresponding ^1H NMR spectrum showed the formation of the monoprotonated species **11·H$^+$,Pic$^-$**: ^1H NMR ($CDCl_3$, 300 MHz, 263 K): δ = 0.87 (s, 27H; *t*Bu), 1.40 (s, 27H; *t*Bu), 2.85 (s, 9H; OCH_3), 3.40 (d, J = 15 Hz, 6H; $ArCH_2$), 4.29 (d, J = 15 Hz, 6H; $ArCH_2$), 4.95 (s_b, 6H; CH_2N), 5.56 (s, 6H; CH_2O), 6.85 (s, 6H; ArH_{calix}), 7.32 (s, 6H; ArH_{calix}), 7.46 (d, J = 8 Hz, 3H; Py–H), 7.92 (t, J = 8 Hz, 3H; Py–H), 8.04 (d, J = 8 Hz, 3H; Py–H), 8.97 (s, 2H; Pic^-), 10.09 ppm (br s, 1H; NH^+).

RNH_2 (> 1 equiv) was then added to the NMR tube leading to the quantitative formation of complex **11⊃RNH$_3^+$,Pic$^-$** as shown by ^1H NMR spectroscopy.

For R = Et: ^1H NMR ($CDCl_3$, 500 MHz, 263 K) δ = −1.28 (t, J = 7 Hz, 3H; CH_{3guest}), 0.33 (m, 2H; CH_3CH_{2guest}), 0.79 (s, 27H; *t*Bu), 1.40 (s, 27H; *t*Bu), 3.32 (s, 9H; OCH_3), 3.48 (d, J = 15 Hz, 6H; $ArCH_2$), 3.63 (s_b, 6H; CH_2N), 4.25 (d, J = 15 Hz, 6H; $ArCH_2$), 5.31 (s, 6H; CH_2O), 6.69 (s, 6H; ArH_{calix}), 7.31–7.34 (m, 9H; 6 ArH_{calix} + 3Py–H), 7.75 (d, J = 7 Hz, 3H; Py–H), 7.81 (t, J = 7 Hz, 3H; Py–H), 8.85 ppm (s, 2H; Pic^-).

For R = Pr: ^1H NMR ($CDCl_3$, 300 MHz, 263 K): δ = −1.91 (t, J = 7 Hz, 3H; CH_{3guest}), −0.33 (s_b, 2H; CH_3CH_{2guest}), 0.78 (s, 27H; *t*Bu), 1.41 (s, 27H; *t*Bu), 3.10 (s, 9H; OCH_3), 3.44 (d, J = 15 Hz, 6H; $ArCH_2$), 3.72 (s_b, 6H; CH_2N), 4.30 (d, J = 15 Hz, 6H; $ArCH_2$), 5.38 (s, 6H; CH_2O), 6.75 (s, 6H; ArH_{calix}), 7.30–7.35 (m, 9H; 6 ArH_{calix} + 3Py–H), 7.66 (d, J = 7 Hz, 3H; Py–H), 7.87 (t, J = 7 Hz, 3H; Py–H), 7.89 (br s, 3H; $NH_3^+{}_{guest}$), 8.87 ppm (s, 2H; Pic^-).

***endo* complex 11·Na$^+$,Cl$^-$⊃EtOH**: A mixture of **11** (5 mg, 3.7 μmol) and NaCl (9.5 mg, 0.16 mmol) in $CHCl_3$ (0.8 mL) and EtOH (0.3 mL) was stirred at room temperature for 1 h and then filtered. After evaporation of the solvents, $CDCl_3$ (0.6 mL) was added and the quantitative formation of complex **11·Na$^+$,Cl$^-$⊃EtOH** was shown by ^1H NMR spectroscopy. ^1H NMR ($CDCl_3$, 300 MHz, 293 K): δ = −1.56 (t, J = 7 Hz, 3H; CH_{3guest}), 0.81 (s, 27H; *t*Bu), 1.35–1.50 (m, 29H; *t*Bu + CH_{2guest}; determined by the COSY experiment), 2,16 (t, J = 6 Hz, 1H; OH_{guest}), 3.13 (s, 9H; OCH_3), 3.45 (d, J = 15 Hz, 6H; $ArCH_2$), 3.96 (br s, 6H; CH_2N), 4.25 (d, J = 15 Hz, 6H; $ArCH_2$), 5.38 (s, 6H; CH_2O), 6.71 (s, 6H; ArH_{calix}), 7.34 (s, 6H; ArH_{calix}), 7.44 (d, J = 6 Hz, 3H; Py–H), 7.82–7.96 ppm (m, 6H; Py–H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.7 ($CH_3CH_2OH_{in}$), 29.5, 31.3, 31.8, 34.3, 34.5, 57.6 ($CH_3CH_2OH_{in}$), 58.7, 61.4, 75.6, 118.4, 123.7, 124.1, 129.6, 131.8, 132.7, 139.7, 146.6, 147.0, 150.8, 153.6, 158.2, 159.3 ppm.

Determination of the relative affinities of the ammonium ions RNH$_3^+$ (with R=Et, Pr or *n*Bu) toward host 11 through ^{1}H NMR competitive binding studies: For a typical procedure: $EtNH_2$ (ca. 8 equiv) and $PrNH_2$ (ca. 5 equiv) were successively added into a $CDCl_3$ solution (0.60 mL) containing **11·H$^+$,Pic$^-$** (prepared as above) at room temperature. A ^1H NMR spectrum recorded at 293 K showed the guest resonances of both *endo* complexes **11⊃EtNH$_3^+$,Pic$^-$** and **11⊃PrNH$_3^+$,Pic$^-$** besides the signals corresponding to the free amines. The integrations of the methyl group of the free amines and of the included ammonium guests were used to calculate the relative affinity defined as $[EtNH_3^+{}_{in}]/[PrNH_3^+{}_{in}]\times[PrNH_2(H^+)_T]/[EtNH_2(H^+)_T]$, where indexes "in" and "T" stand for "included" and "total amount", respectively (errors estimated ±10 %). Given the large excess of free amines versus **11·H$^+$**, the relative affinities were calculated considering that the slight difference of pK_a between the different free amines was negligible.

Determination of the relative affinities of the neutral guests L (with L = (±)-PPD, PYD, EtOH, DMF, IMI, EtNH$_2$) toward host 11·Na$^+$ through ^{1}H NMR competitive binding studies: For a typical procedure: $EtNH_2$ (ca. 7 equiv) was added into a $CDCl_3$ solution (0.60 mL) containing **11·Na$^+$⊃EtOH** (prepared as above) at room temperature. A ^1H NMR spectrum recorded at 293 K showed the guest resonances of both *endo* complexes **11·Na$^+$⊃EtNH$_2$** and **11·Na$^+$⊃EtOH** besides the signals corresponding to the free EtOH and $EtNH_2$. The integrations of the free and included EtOH and $EtNH_2$ allowed us to calculate the relative affinity defined as $[EtNH_{2in}]/[EtOH_{in}]\times[EtOH_T]/[EtNH_{2T}]$, where indexes "in" and "T" stand for "included" and "total amount", respectively (errors estimated ±10 %).

XRD structure determination of 11·H$^+$,ClO$_4^-$: A prismatic colorless crystal was rapidly fished out of the mother liquor with a cryoloop and frozen under a cold nitrogen stream (100 K). Diffraction data were recorded at the BM-14 beamline (ESRF Synchrotron, Grenoble) and consist of 100 three-degree rotation frames. Distance was set as to get the highest possible resolution (1.01 Å) compatible with the wavelength in

use (0.964 Å). Data reductions and averages were done with the HKL package of programs.[35] The structure was solved with the SHELXD program, part of the SHELX package.[36] Refinements with anisotropic thermal factors were conducted with the SHELXH program. Final statistics are as following: space group $P\bar{1}$ (triclinic) with three independent molecules ($Z=6$); parameters: $a=17.806(1)$, $b=28.698(1)$, $c=31.229(1)$ Å; $\alpha=67.175(5)$, $\beta=79.256(4)$, $\gamma=83.793(5)°$; final R factor = 0.0975 for 21031 observed F_o (criterion 4σ(Fo)) and 0.1003 for all data (25549 F_o). Associated to the three ligands are eight $CHCl_3$ and three ClO_4^- ions. Two additional individual peaks were refined as water molecules. Mw = 5318.01. Total chemical formula: $[C_{90}H_{109}N_4O_6^+,\ ClO_4^-]_3$, $8{\cdot}CHCl_3$, $2{\cdot}H_2O$. CCDC-298120 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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[18] It is noteworthy that **7** decomposed within a few days at room temperature and thus should be kept at low temperature.

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[22] A similar NMR pattern was obtained when a solution of EtONa (21%) in EtOH was added to a $CDCl_3$ solution of **11** (see the Supporting Information: Figure S4). Similarly, the addition of a solution of EtOK in EtOH to a $CDCl_3$ solution of **11** led to the formation of the *endo* complex **11·K⁺⊃EtOH**. However, a total conversion was not obtained even in presence of an excess of EtOK, showing a weaker binding of K^+.

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[26] Similar NMR spectra of **11·H⁺** were obtained upon the addition of either EtCOOH or trifluoroacetic acid or perchloric acid to a $CDCl_3$ solution of **11** (see the Supporting Information for **11·H⁺,ClO₄⁻**: Figure S22).

[27] For a simple tmpa ligand, three successive protonation constants have been reported: $K=2.7$, 4.5 and 6.3. Hence, if the calix-tmpa ligand were to present the same basic properties, it should easily undergo polyprotonation in a strong acidic medium. See: J. C. Mareque-Rivas, R. Prabaharan, R. Torres Martin de Rosales, *Chem. Commun.* **2004**, 76–77.

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