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Highly Selective Synthesis of a 1,3,5-Tris-Protected Calix[6]arene-Type Molecular Platform through Coordination and Host–Guest Chemistry

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Abstract: An elegant methodology based on the synergistic combination of coordination and host–guest chemistry led to the highly efficient synthesis of a unique C_{3v}-symmetrical, calix[6]-arene-based molecular platform with three protected amino arms in alternating positions. The key step involves the formation of a stable supramolecular host–guest Zn^{II} complex from a C_{6v}-symmetrical calix[6]hexaamine. Indeed, in the presence of a polar neutral guest and a strong donor that acts as an exogenous ligand, three alternating amino groups of this calix[6]hexaamine are selectively coordinated to the Zn^{II} ion while the three others remain free and are thus much more reactive toward chemical reagents. In addition to this protective role, the metal centre preorganises the C_{3v}-symmetrical complex in such a way that the uncoordinated NH_2 groups are directed toward the outside of the cavity; they are then accessible for a chemical transformation. Hence, reaction of these alternating free amino groups with a protective reagent (i.e., Boc_2O) followed by zinc decoordination quantitatively and selectively yielded the 1,3,5-tris-Boc-protected calixarene derivative on a gram scale. It was shown that the presence of all the partners of the key intermediate Zn complex (i.e., the metal centre, the exogenous ligand and the included guest) is crucial for a high selectivity. Finally, a two step sequence that led to a C_{3v}-symmetrical 1,3,5-tris-acetylated calix[6]hexaamine through the removal of the Boc groups illustrates that the 1,3,5-tris-protected calix[6]hexaamine is a promising molecular platform. Examples of such readily available C_{3v}-symmetrical calixarene-based building blocks are extremely rare in the literature.

Keywords: calixarenes · host–guest systems · molecular platform · regioselectivity · supramolecular chemistry · synthetic methods

Introduction

Efficient selective modifications of concave macrocyclic compounds, such as cyclodextrins,[1] calixarenes[2] or cavitands,[3] are of great interest. Indeed, the controlled introduction of functional groups at well-defined positions is crucial for their use as molecular receptors, machines, sensors, catalysts and new materials.[4] In the calixarene field, many selective functionalisations of calix[4]arenes either on the narrow or the wide rim have been reported.[5] In contrast, examples with the larger and more conformationally flexible calix[6]arenes are rare.[6] This is largely why these oligomers have been less studied despite the fact that their cavity size is much more suitable for host–guest chemistry applications than the tetramers. Nevertheless, direct monomethylation or monobenzylation reactions at one phenolic position have been described in high yields.[7] However, calix[6]arenes displaying a 1,3,5-substitution pattern are more popular as starting materials because they possess an interesting and very useful C_{3v} symmetry. For example, 1,3,5-trimethoxy-p*t*Bu-calix[6]arene has been used for the construction of cryptic *endo* receptors,[8] ligands for metal ions,[9] sensors for anions[10] or ammonium ions,[11] biomimetic metallic complexes,[12] chiral platforms,[13] cage molecules,[14] (pseudo)rotaxanes[15] or for the design of various self-assembled objects.[16] Unfortunately, this compound[17] and the related 1,3,5-tribenzyl derivatives[18] are obtained in only moderate

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yields (ca. 15–35%) and, in most cases, after careful flash chromatography separation. Thus, a readily available 1,3,5-trifunctionalised calix[6]arene would provide an attractive molecular platform suitable for a wide range of applications.

Recently, we described that Zn^{II} coordination by a calix[6]arene bearing three primary amino arms in alternating positions, that is, calix[6]trisamine **1**, provides tetrahedral Zn complexes, [Zn-$\mathbf{1}^{L}_{G}$] (G = guest molecule, L = ligand), with a labile site oriented toward the outside of the cavity for binding to an exogenous ligand (L) (Figure 1).[19] It was shown that the metal ion rigidifies the calixarene core, constraining it into a flattened cone conformation suitable for intracavity binding of polar neutral guests G that are stabilised through charge–dipole and CH–π interactions as well as hydrogen bonding with the calixarene core (for example, see the XRD structure of [Zn-$\mathbf{1}^{Cl}_{EtOH}$] displayed in Figure 1). Interestingly, the host properties of these polarised receptors can be allosterically tuned by the nature of the external ligand L. Indeed, these ligands can be easily exchanged upon the addition of strong coordinating species such as primary amines RNH_2, carboxylates $RCOO^-$ or Cl^-. Another remarkable feature of these supramolecular Zn complexes is their robustness, since no decoordination of the metal ion was observed in presence of an excess of a base such as triethylamine (TEA).

On the basis of these results, we were interested in testing a similar Zn complexation with the readily available corresponding C_{6v}-symmetrical calix[6]hexaamine. Indeed, with such a starting material, it was anticipated that three amino arms in alternating positions could coordinate the metal centre to form a stable tetrahedral Zn complex with an exogenous ligand, while the three other amino arms would be free and well positioned for a chemical reaction. Thus, such a Zn–calixarene complex should be an excellent candidate for a selective 1,3,5-trifunctionalisation.

Here we describe the synthesis of the Zn complex of calix[6]hexaamine **3** and its characterisation in the solid state and in solution. We show that this supramolecular complex can lead quantitatively to a new C_{3v}-symmetrical molecular platform through a direct selective tris-protection of alternating amino arms.

Results and Discussion

Although the synthesis of calix[6]hexaamine **3** was already described in the literature,[20] we prepared it, on a multigram scale, according to a different pathway from the known calix[6]hexaester **2**[21] (Scheme 1). Thus, **2** was first treated with ammonia in MeOH and subsequent reduction of the resulting amide groups by BH_3/THF led to the calix[6]hexaamine **3** in 48% overall yield. The preparation of the corresponding zinc complex was achieved by the addition of one equivalent of $Zn(ClO_4)_2 \cdot 6H_2O$ to a solution of **3** and TEA (3 equiv) in a 4:1 CH_2Cl_2/MeOH solvent mixture. After removal of the CH_2Cl_2 and centrifugation, complex [(Zn-$\mathbf{3}_{MeOH}$)$_2$] was isolated in 84% yield as a white powder (Scheme 1). Its HRMS (ESI-TOF) spectrum in CH_3OH was consistent with a dinuclear dimeric Zn complex, in good accord with the structure observed through XRD analysis (see below).

X-ray quality crystals were obtained by slow evaporation of a cold (4°C) solution of the complex [(Zn-$\mathbf{3}_{MeOH}$)$_2$] in $CHCl_3$/CH_3CN in the presence of a few equivalents of acetamide. The XRD analysis revealed the presence of a dinuclear tetracationic Zn complex that consists of a C_{2h}-symmetrical head-to-head bis-calix[6]arene, namely [(Zn-$\mathbf{3}_{AcNH_2}$)$_2$] (Figure 2, left). The calixarene is in a flattened cone conformation, the aromatic moieties being oriented alternately toward and away from the cavity (Figure 2, right). The dimerisation of the self-complementary Zn–calixarene complex takes place through the coordination of one amino arm of a first subunit to the metal centre of the second subunit. Indeed, the Zn^{II} ion is coordinated by four amino arms in a tetrahedral geometry with classical Zn–N distances (average d(Zn–N) = 2.02 Å). Three of them (N1, N28, N54) belong to the same calixarene subunit and are grafted onto the alternating 1,3,5-aromatic moieties directed toward the outside of the cavity. The fourth amino arm (N59) belongs to the second subunit and is located on an inner aromatic moiety. The two other nitrogen atoms (N58 and N66B) are not coordinated to the metal centre, but one of them is weakly hydrogen bonded to one perchlorate ion (d(O–N) = 3.05 Å, not shown). An acetamide molecule is included in the heart of the calixarene cavity and directs its dipolar

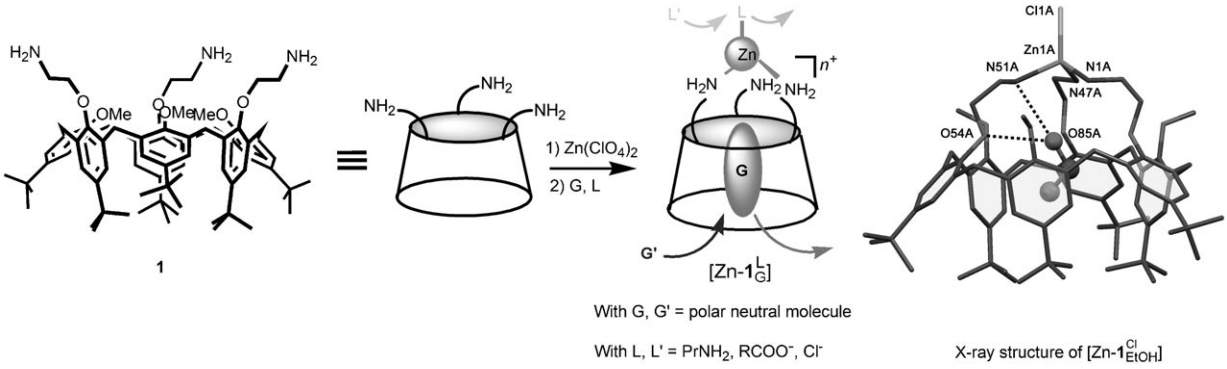
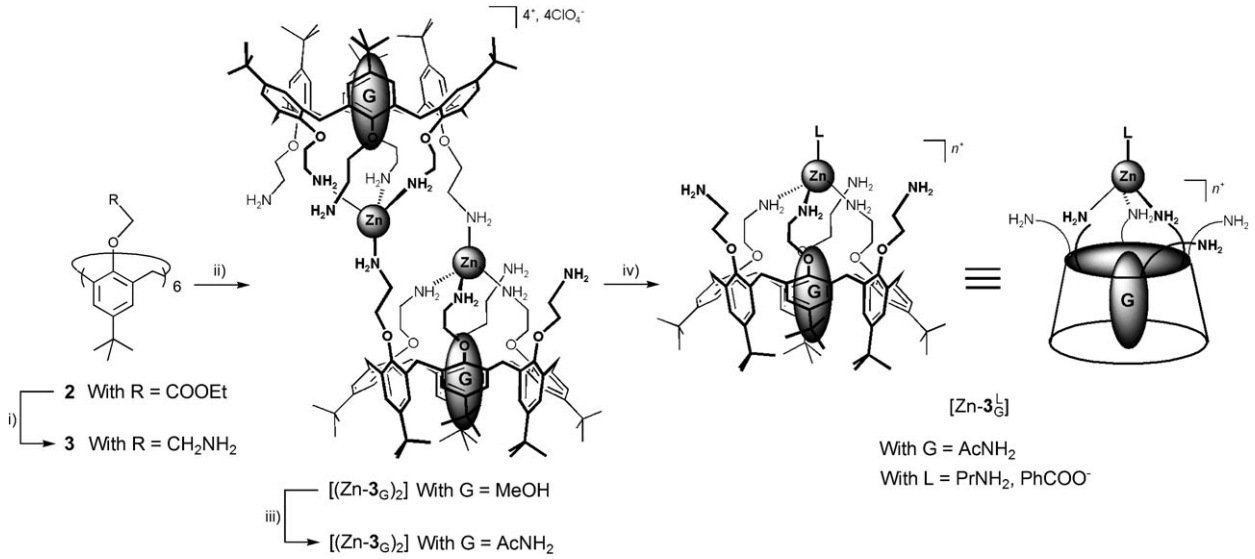


Figure 1. Complexation of Zn^{II} ion by calix[6]trisamine **1** leads to a tunable molecular receptor.[19]



Scheme 1. Synthesis of complexes $[(Zn\text{-}\mathbf{3}_{G})_2]$ and $[Zn\text{-}\mathbf{3}^{L}_{AcNH_2}]$. i) 1) NH_3, MeOH, 2) BH_3/THF, reflux, then EtOH, reflux, 48%; ii) $Zn(ClO_4)_2$, TEA, CH_2Cl_2/MeOH, 84%; iii) $AcNH_2$ (3 equiv per calixarene subunit), $CDCl_3$; iv) $PrNH_2$ or PhCOOH/TEA, $CDCl_3$.

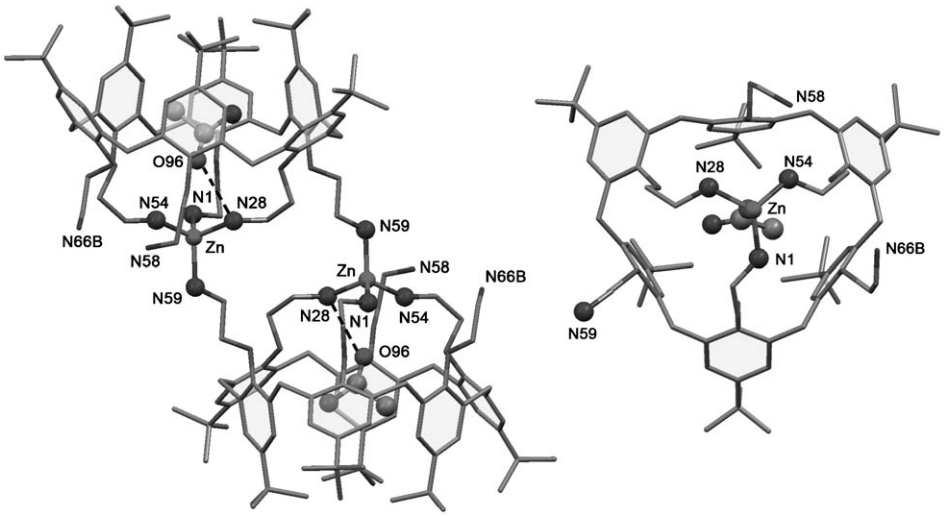


Figure 2. X-ray crystal structure of the complex $[(Zn\text{-}\mathbf{3}_{AcNH_2})_2]$. The calix[6]arenes are depicted as capped-stick models, the zinc ions, the coordinated nitrogen atoms and the included acetamide molecules as ball-and-stick models. The hydrogen bonds are displayed in dark dashed lines. Hydrogen atoms, solvents and counterions have been omitted for clarity. Left: side view of the dinuclear dimeric complex. Right: top view of one Zn–calixarene subunit.

moment toward the Zn^{II} ion, but is not coordinated to the metal centre (d(Zn–O96) = 3.13 Å). The guest is stabilised through an H bond with its host (d(O96–N28) = 2.95 Å), in addition to CH–π (d(C···Ar) ≈ 3.25 Å) and charge–dipole interactions. All these data are very similar to what was observed with the Zn complexes obtained from the parent ligand **1** (see the XRD structure displayed on Figure 1), except that a dimerisation can take place with calixarene **3**, since this hexaamine can give an additional exogenous amino ligand sitting outside of the cavity. This result was very promising, as such a complexation behaviour was expected for the discrimination of three alternating amino arms from the other three.

In a second step, the nature of the complex $[(Zn\text{-}\mathbf{3}_{MeOH})_2]$ in solution was investigated through NMR experiments in $CDCl_3$. While ill-defined ^{1}H NMR spectra were observed over a large temperature range (223–300 K), the displacement of MeOH through addition of a better guest, that is, acetamide (3 equiv per calixarene subunit),[22] led to the complex $[(Zn\text{-}\mathbf{3}_{AcNH_2})_2]$ that displays a slightly sharpened NMR pattern with a high field signal ($\delta = -0.85$ ppm at 300 K) corresponding to the CH_3 group of an acetamide molecule included in the heart of the calixarene cavity (confirmed by a NOESY experiment) and in slow exchange on the NMR timescale (Scheme 1).[23] In addition, a dissymmetrical NMR signature was observed at low temperature (220 K) for this complex (Figure 3 top). All of these results are in good agreement with the persistence of the dimeric C_{2h}-symmetrical supramolecular structure obtained in the solid state.[24]

Interestingly, addition of an excess of $PrNH_2$ or of a PhCOOH/TEA mixture to $[(Zn\text{-}\mathbf{3}_{AcNH_2})_2]$ led to sharpened C_{3v}-symmetrical NMR spectra with one equivalent of $AcNH_2$ still in the calixarene cavity (Figure 3 bottom for L = $PrNH_2$ at 220 K). These new species correspond to the

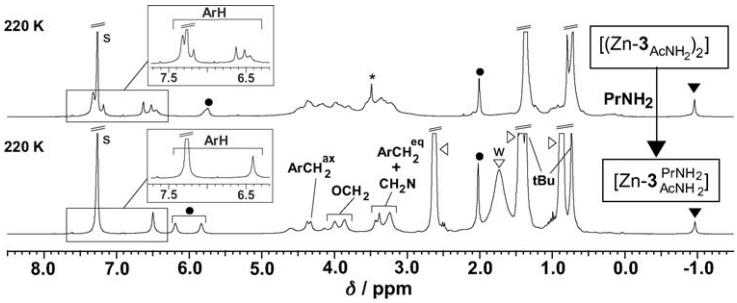


Figure 3. Top: The ^{1}H NMR spectrum ($CDCl_3$, 220 K) of [(Zn-$\mathbf{3}_{AcNH_2}$)$_2$]. Bottom: After the addition of $PrNH_2$ (ca. 37 equiv per calixarene subunit). ●: free $AcNH_2$, ▼: included $AcNH_2$, △: $PrNH_2$. S = solvent, W = water. * = MeOH from the synthesis.

mononuclear complexes [Zn-$\mathbf{3}^{PrNH_2}_{AcNH_2}$] and [Zn-$\mathbf{3}^{PhCOO}_{AcNH_2}$] with an *exo* coordination of either an amino or a benzoato ligand, respectively, to the metal centre, which is similar to what was observed with calix[6]trisamine **1** (Scheme 1, Figure 1).[25] Thus, by addition of a suitable strong external donor ligand, it is clearly possible to produce, in solution, a stable, C_{3v}-symmetrical supramolecular compound [Zn-$\mathbf{3}^{L}_{G}$] with three free alternating amino arms accessible for a subsequent reaction with a protective reagent.

In contrast to the complex [Zn-$\mathbf{3}^{PrNH_2}_{AcNH_2}$] which required the addition of an excess of $PrNH_2$, [Zn-$\mathbf{3}^{PhCOO}_{AcNH_2}$] was an excellent candidate for the selective protection of the uncoordinated amino groups. For this, we tested the classical reaction with highly reactive Boc_2O, since it proceeds under mild conditions and does not produce any byproducts that could modify or disrupt the supramolecular Zn host–guest complex. Moreover, the resulting *t*Bu-carbamate function is one of the most popular amino protecting groups, since it is stable under a large variety of conditions and can be easily removed by trifluoroacetic acid (TFA). Thus, the complex [Zn-$\mathbf{3}^{PhCOO}_{AcNH_2}$] was formed in situ by addition of a mixture of PhCOOH/TEA/$AcNH_2$ (2.5, 5 and 15 equiv per calixarene subunit respectively[26]) to a solution of [(Zn-$\mathbf{3}_{MeOH}$)$_2$] in $CHCl_3$. The further addition of a slight excess of Boc_2O (3.5 equiv per calixarene subunit) led to the desired 1,3,5-tris-protected calix[6]hexaamine **4** in quantitative yield after 7 h at room temperature (RT) and a consecutive decoordination through basic washing (Scheme 2).[27] This highly efficient synthesis does not require any purification by chromatography and was done successfully on a gram scale.[28]

It was shown that the presence of all of the different components of the host–guest Zn complex [Zn-$\mathbf{3}^{PhCOO}_{AcNH_2}$] is crucial for the efficiency of the 1,3,5-tris-Boc protection. Indeed, direct reaction of free calix[6]hexaamine **3** with different amounts of Boc_2O or reaction in the absence of a good guest (i.e., $AcNH_2$) were attempted, but in all cases only complex mixtures of products were obtained. Thus, the role of the metal centre is to rigidify and pre-organise the calixarene in a C_{3v}-symmetrical flattened cone conformation with the free amino arms directed toward the outside of the cavity, as well as to selectively protect the three other alternating amino groups. In addition, the presence of the included acetamide is required for the stabilisation of the whole supramolecular Zn complex as it has been shown previously for related host–guest complexes.[16d–f] Finally, when the reaction was run from [(Zn-$\mathbf{3}_{AcNH_2}$)$_2$], that is without the addition of the exogenous benzoato ligand, a ca. 1:2 mixture of 1,3-di- and 1,3,5-tris-Boc protected calixarenes was obtained.[29,30] This clearly shows that scission of the dimer through the external coordination of the benzoato ligand can liberate the bridging amino arm, leading to an enhancement of its reactivity toward Boc_2O.

Compound **4** was fully characterised and all the signals of its ^{1}H NMR spectrum were assigned by means of 2D NMR experiments (HMQC, HMBC, COSY). The rather simple ^{1}H NMR pattern at RT corresponds to a C_{3v}-symmetrical species in a flattened cone conformation ($\Delta\delta_{ArH} = 0.72$ ppm and $\Delta\delta_{tBu} = 0.62$ ppm) (Figure 4). The aromatic moieties

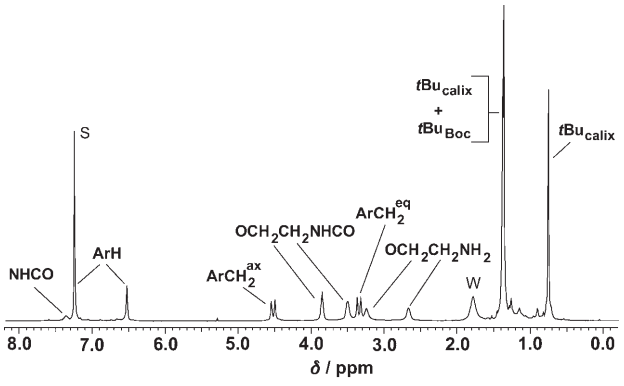
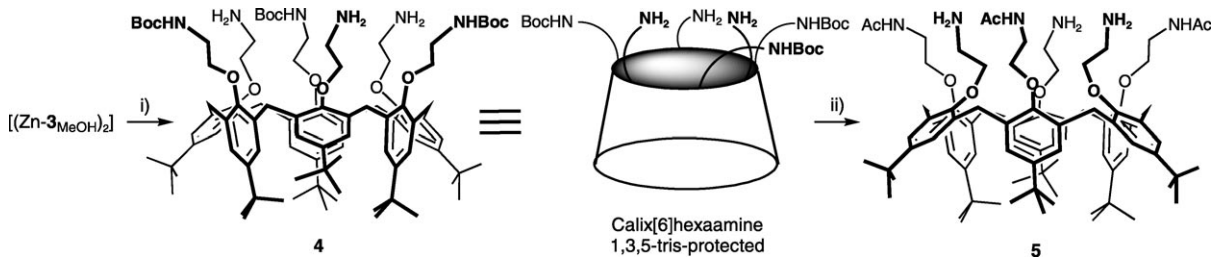


Figure 4. ^{1}H NMR spectrum of **4** ($CDCl_3$, 294 K). S = solvent, W = water.



Scheme 2. Synthesis of 1,3,5-tris-protected calix[6]hexaamine **4** and 1,3,5-tris-acetylated calix[6]hexaamine **5**. i) $AcNH_2$, TEA, PhCOOH, $CHCl_3$, 1 h then Boc_2O, 7 h then NaOH 1 M, 100 %; ii) Ac_2O, pyridine, CH_2Cl_2, then TFA, CH_2Cl_2, then NaOH 1 M, 75 %.

bearing the bulky NBoc groups are oriented toward the inside of the cavity in order to minimise steric interactions. The $ArCH_2$ protons display two sharp doublets as a result of a cone–cone inversion slower than the NMR timescale.

Finally, to illustrate the potential applications of **4** as a building block, its remaining amino groups were easily acylated with Ac_2O and the Boc groups were subsequently removed by TFA. This two-step sequence afforded the 1,3,5-tris-acetylated calix[6]hexaamine **5** in 75% overall yield (Scheme 2).

Conclusion

In conclusion, we developed an elegant and unique strategy for the quantitative 1,3,5-tris protection of a calix[6]hexaamine. This highly selective reaction was achieved thanks to the synergistic combination of coordination and host–guest chemistry. The 1,3,5-tris-Boc protected calixarene **4** can be easily synthesised on a large scale and constitutes a promising molecular platform for the preparation of various sophisticated molecular objects. Current work in our laboratory is directed toward the design of readily available multitopic receptors from this new building block.

Experimental Section

General procedures: CH_2Cl_2 was distilled over CaH_2 under argon. MeOH was distilled over Mg/I_2 under argon. $CHCl_3$ was distilled over P_2O_5 under argon and was quickly filtered through an alumina column before use. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz. Traces of residual solvent or poly(dimethylsiloxane) were used as internal standard. All reactions were performed under an inert atmosphere.

Safety note: Caution! Although we have not encountered any problems, note that perchlorate salts of metal complexes with organic ligands are potentially explosive and should be handled with appropriate precautions.

Calix[6]hexaamine 3:[20] The reaction was performed in a sealed reactor. A fast stream of anhydrous ammonia was bubbled into a solution of compound **2**[21] (10.0 g, 6.7 mmol) in anhydrous methanol (200 mL) over 20 min. The reactor was then sealed and the reaction mixture was stirred at 65°C for 15 h. After cooling to 0°C, the precipitate was isolated by suction filtration and washed with cold methanol then with pentane, yielding the intermediate calix[6]hexaamide as a white solid (8.0 g). Under an inert atmosphere, BH_3/THF (180 mL, 1 M,) was added at 0°C to the isolated calix[6]hexaamide. After the effervescence had stopped, the reaction mixture was heated at reflux for 48 h then cooled to 0°C and ethanol was added dropwise until the effervescence ceased. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethanol (200 mL) and refluxed under an inert atmosphere for 48 h. The ethanol was evaporated under reduced pressure and the residue was heated at 50°C under high vacuum for 7 h. The obtained solid was dissolved in CH_2Cl_2 (200 mL) and washed vigorously with an aqueous solution of NaOH (1 M, 200 mL) for 30 min. The aqueous layer was extracted with CH_2Cl_2 (5×50 mL) and the combined organic layers were washed with water (3×50 mL) then concentrated under reduced pressure. TFA (6 mL) was slowly added to the crude mixture in CH_2Cl_2 (200 mL) at 0°C. The solution was stirred for 45 min at room temperature under an inert atmosphere then concentrated to dryness. The residue was dissolved in the minimum amount of CH_3CN and diethyl ether was added leading to a precipitate, which was isolated by suction filtration and was washed with diethyl ether. The solid was dissolved in CH_2Cl_2 (600 mL) then washed vigorously with an aqueous solution of NaOH (1 M, 450 mL) over a period of 30 min. The aqueous layer was extracted with CH_2Cl_2 (3× 150 mL) and the combined organic layers were washed with water (150 mL) and concentrated under reduced pressure, yielding calix[6]hexaamine **3** as a white solid (4.0 g, 48%). The ^1H NMR spectrum in $CDCl_3$ was more in accordance with the structure of **3** than the NMR data reported in the literature.[20] ^1H NMR (300 MHz, 330 K, $CDCl_3$): $\delta=1.14$ (s, 54H; *t*Bu), 2.82 (brs, 12H; $OCH_2CH_2NH_2$), 3.53 (brs, 6H; $OCH_2CH_2NH_2$), 3.96 (brs, 12H; $ArCH_2$), 6.98 ppm (s, 12H; ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=30.5$, 31.6, 34.3, 42.3, 75.3, 126.0, 133.2, 146.0, 152.6 ppm.

Complex [(Zn-3$_{MeOH}$)$_2$]: Compound **3** (1.00 g, 0.81 mmol) and $Zn(ClO_4)_2\cdot 6H_2O$ (0.30 g, 0.81 mmol) were dissolved in a 4:1 CH_2Cl_2/MeOH solvent mixture (24 mL). TEA (0.35 mL, 2.52 mmol) was then added and the solution was stirred for 1 h at room temperature. After removal of dichloromethane under reduced pressure, the resulting precipitate was isolated by centrifugation and then washed with cold methanol (2×1 mL) yielding complex [(Zn-$\mathbf{3}_{MeOH}$)$_2$] as a white solid (1.04 g, 86%). M.p. 225°C (decomp); the ^1H NMR analysis of the complex was done in presence of acetamide (3 equiv per calixarene subunit) leading to [(Zn-$\mathbf{3}_{AcNH_2}$)$_2$] (see the text): ^1H NMR (300 MHz, 330 K, $CDCl_3$): $\delta=-0.80$ (s, 6H; $CH_3CONH_{2included}$), 0.82 (s, 54H; *t*Bu), 1.41 (s, 54H; *t*Bu), 3.40 (brs, 36H; $OCH_2CH_2NH_2$ + $ArCH_{eq}$), 4.11 (brs, 24H; $OCH_2CH_2NH_2$), 4.45 (brs, 12H; $ArCH_{ax}$), 6.61 (s, 12H; ArH), 7.31 ppm (s, 12H; ArH); complementary ^1H NMR analysis was done through formation of the complex [Zn-$\mathbf{3}^{PrNH_2}_{AcNH_2}$] obtained upon addition of propylamine (17 equiv per calixarene subunit) to a $CDCl_3$ solution of [(Zn-$\mathbf{3}_{AcNH_2}$)$_2$]: ^1H NMR (300 MHz, 294 K, $CDCl_3$): $\delta=-0.86$ (s, 3H; $CH_3CONH_{2included}$), 0.79 (s, 27H; *t*Bu), 1.39 (s, 27H; *t*Bu), 3.40 (brs, 12H; $OCH_2CH_2NH_2$), 3.44 (d, $J=13$ Hz, 6H; $ArCH_{eq}$), 3.96 (brs, 6H; $OCH_2CH_2NH_2$), 4.11 (brs, 6H; $OCH_2CH_2NH_2$), 4.43 (d, $J=15$ Hz, $ArCH_{ax}$), 6.57 (s, 6H; ArH), 7.29 ppm (s, 6H; ArH); IR (KBr): $\tilde{\nu}=3720$–3020, 2956, 1699, 1478, 1457, 1383, 1121 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{156}H_{228}N_{12}O_{24}Cl_3Zn_2$ $[M-2CH_3OH-ClO_4]^+$: 2886.4638; found: 2886.4597.

1,3,5-Tris-protected calix[6]hexaamine 4: Acetamide (0.89 g, 15.07 mmol), triethylamine (0.70 mL, 5.04 mmol) and benzoic acid (0.31 g, 2.54 mmol) were successively added to a solution of complex [(Zn-$\mathbf{3}_{MeOH}$)$_2$] (1.53 g, 0.50 mmol) in $CHCl_3$ (23 mL). The mixture was stirred for 1 h at RT and Boc_2O (0.75 mL, 3.50 mmol) was added. After a further 7 h of stirring,[27] ethylenediamine (1.00 mL, 14.94 mmol) was added to consume the excess Boc_2O and, after 20 min, the reaction mixture was diluted with $CHCl_3$ (75 mL) and washed with an aqueous HCl solution (1 M, 50 mL) for 5 min. The organic layer was washed with water (2×15 mL), with an aqueous solution of NaOH (1 M, 15 mL) for 5 min and again with water (2×10 mL). The organic layer was concentrated under reduced pressure yielding **4** as a white solid (1.53 g, 100%). M.p. 150°C (decomp); ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.76$ (s, 27H; tBu_{calix}), 1.38 (s, 27H; tBu_{calix}), 1.39 (s, 27H; tBu_{Boc}), 2.68 (brs, 6H; $OCH_2CH_2NH_2$), 3.26 (brs, 6H; $OCH_2CH_2NH_2$), 3.36 (d, $J=15$ Hz, 6H; $ArCH_{eq}$), 3.51 (brs, 6H; OCH_2CH_2NHCO), 3.87 (brs, 6H; OCH_2CH_2NHCO), 4.53 (d, $J=15$ Hz, 6H; $ArCH_{ax}$), 6.54 (s, 6H; ArH), 7.26 (s, 6H; ArH), 7.37 ppm (brs, 3H; NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=28.7$, 29.6, 31.3, 31.8, 34.1, 34.4, 41.3, 42.0, 72.1, 76.3, 79.0, 123.2, 128.3, 132.9, 133.1, 145.8, 146.1, 151.1, 153.6, 156.7 ppm; IR (KBr): $\tilde{\nu}=3715$–3100, 2963, 1713, 1482, 1460, 1364, 1176 cm^{-1}; elemental analysis calcd (%) for $C_{93}H_{138}N_6O_{12}\cdot 2H_2O$: C 71.23, H 9.13, N 5.36; found: C 71.41, H 8.94, N 5.28.

1,3,5-Tris-acetylated calix[6]hexaamine 5: Pyridine (0.20 mL, 2.45 mmol) and acetic anhydride (0.10 mL, 1.06 mmol) were successively added to a solution of calixarene **4** (100 mg, 65 μmol) in anhydrous CH_2Cl_2 (3 mL). After 3 h of stirring at RT, the solvents were removed under reduced pressure. The residue was dissolved in ethanol (2 mL) and concentrated again under reduced pressure (this operation was repeated twice). Purification of the crude residue by flash chromatography on silica gel (eluent: CH_2Cl_2/acetone; 7:3) yielded the intermediate 2,4,6-trisacetyl derivative

of **4** as a white solid (89 mg). This was dissolved in CH_2Cl_2 (1 mL) and TFA (0.1 mL) was added. The mixture was stirred for 3 h at RT, concentrated under reduced pressure, then dissolved in CH_2Cl_2 (10 mL) and washed with an aqueous solution of NaOH (1 M, 5 mL). The aqueous layer was extracted with CH_2Cl_2 (2×2 mL) and the combined organic layers were washed with water (2×2 mL) yielding **5** as a white solid (67 mg, 75% overall yield from **4**). M.p. 190°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.76$ (s, 27H; *t*Bu), 1.38 (s, 27H; *t*Bu), 2.06 (s, 9H; CH_3CO), 2.88 (br s, 6H; OCH_2CH_2N), 3.32–3.45 (m, 6H; OCH_2CH_2N), 3.42 (d, $J=15$ Hz, 6H; $ArCH_{eq}$), 3.69 (br s, 6H; OCH_2CH_2NHCO), 3.94 (br s, 6H; OCH_2CH_2NHCO), 4.43 (d, $J=15$ Hz, 6H; $ArCH_{ax}$), 6.51 (s, 6H; ArH), 7.26 (s, 6H; ArH), 8.26 ppm (br s, 3H; NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=23.4$, 30.0, 31.3, 31.7, 34.2, 34.5, 40.3, 40.9, 72.5, 73.6, 123.4, 128.6, 132.8, 133.0, 146.5, 147.1, 150.6, 153.2, 171.5 ppm; IR (KBr): $\tilde{\nu}=3700$–3115, 2956, 1655, 1480, 1383, 1196 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{84}H_{121}N_6O_9$ $[M+H]^+$: 1357.9195; found: 1357.9200.

X-ray structure analysis of complex [(Zn-3$_{AcNH_2}$)$_2$]: X-ray quality crystals were obtained by slow evaporation of a cold (4°C) solution of complex [(Zn-3$_{MeOH}$)$_2$] in $CHCl_3/CH_3CN$ in the presence of acetamide (3 equiv per calixarene subunit). A crystal of dimensions $0.30\times0.15\times0.04$ mm^3 was mounted with Paratone-N oil (Hampton Research) coating and immediately placed in a nitrogen cold stream. X-ray intensity data were collected at 100 K on a Bruker-Nonius X8-APEX2 CCD area-detector diffractometer with $Mo_{K\alpha}$ radiation ($\lambda=0.71073$ Å). Two sets of narrow data frames (240 s per frame) were collected at different values of θ for one initial value of φ and ω, respectively, using 0.5° increments of φ or ω. Data reduction was accomplished with SAINT V7.03.[31] The substantial redundancy in data allowed a semi-empirical absorption correction (SADABS V2.10)[31] to be applied, on the basis of multiple measurements of equivalent reflections. The structure was solved by direct methods, developed by successive difference Fourier syntheses, and refined by full-matrix least-squares methods on all F^2 data by using SHELXTL V6.14.[32] Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms. Crystal structure analysis: monoclinic, space group $P2_1/c$; dimensions: $a=22.7277(11)$, $b=25.0450(13)$, $c=16.7629(6)$ Å, $\beta=93.486(2)$°, $V=9524.0(8)$ Å^3; $Z=2$; total reflections collected: 99337; independent reflections: 16884 (10387 $F_o>4\sigma(F_o)$); data were collected up to a $2\theta_{max}$ value of 50.22° (99.6% coverage). Number of variables: 1048; $R_1=0.1088$, $wR_2=0.2926$, $S=1.051$; highest residual electron density 1.475 e Å^{-3}. CCDC 666859 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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[22] In the case of the parent Zn complexes derived from calix[6]trisamine **1**, $AcNH_2$ was found to be a much better guest than alcohols.
[23] The complexation induced upfield shift (CIS) of this guest is close to the one observed with the Zn complex of calix[6]trisamine **1**, indicating a similar positioning in the cavity and thus a similar way of binding.
[24] See the Supporting Information for details of a complete variable temperature study.
[25] In the case of [Zn-$\mathbf{3}^{PrNH_2}_{AcNH_2}$], we were able to attribute all signals of its ^{1}H NMR spectrum thanks to 2D NMR experiments (HMQC, HMBC, COSY) (see the Experimental Section and the Supporting Information).
[26] This corresponds to the optimised ratio.
[27] It is worth noting that the reaction can be easily monitored by ^{1}H NMR spectroscopy thanks to the formation of calix-polyammonium based host–guest systems closely related to those already reported with calix[6]trisamine **1**.[16d] Thus, an aliquot (30 μL) of the reaction mixture was added to $CDCl_3$ (600 μL) that contained a small amount of TFA (1 μL). Under these conditions, which do not lead to deprotection of the N-Boc groups, zinc decomplexation and protonation of the unprotected amino groups of the calixarene species led to the corresponding poly-NH_3^+ calixarene-type products, which can encapsulate acetamide. In comparison to the intermediate Zn–calixarene species formed during the reaction, these host–guest systems displayed well-defined ^{1}H NMR spectra at RT allowing easier monitoring of the reaction (see the Supporting Information).
[28] As perchlorate salts of metal complexes with organic ligands are potentially explosive, we applied this procedure to the triflate salt of the Zn complex of **3** to produce **4** in quantitative yield. However, we have not encountered any problems when handling the calixarene-derived perchlorate salts.
[29] It was not possible to isolate pure 1,3-di-protected calixarene, but it was clearly shown through careful NMR monitoring of the reaction that it corresponds to a di-protected intermediate of the 1,3,5-tris-protected compound.
[30] This ratio was determined after 8 h of stirring at RT using 3.5 equiv of Boc_2O per calixarene subunit. A prolonged reaction time or the further addition of a large excess of Boc_2O led to the formation of significant amounts of the hexa-protected calixarene. This compound was clearly identified by synthesis of an analytical sample from calix[6]hexaamine **3** (see the Supporting Information).
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