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Synthesis of calix[4]arene–cyclen conjugates

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Abstract—Novel calix[4]arene derivatives constrained in the *cone* or *1,3-alternate* conformations, bearing one or two cyclen (1,4,7,10-tetraazacyclododecane) moieties directly connected to the upper rim, have been synthesized using Buchwald–Hartwig coupling reaction. The complexation ability and hydrolytic activities of selected Zn(II) complexes of these calixarenes were studied. Although the attempts to hydrolyze activated phosphodiester bonds were unsuccessful, the NMR titration experiments revealed binding affinity for chloride, acetate, and benzoate anions in defined stoichiometry.

1. Introduction

1,4,7,10-Tetraazacyclododecane (cyclen) and its metallated analogues have been widely used in molecular recognition[1] and supramolecular catalysis[2] as artificial metalloenzymes. The cyclen moiety is known as a good ligand possessing very high affinity towards transition metals[3] and lanthanide[4] ions. Some metal ions, such as zinc(II), behave as Lewis acids when coordinated with the ligand and offer free binding sites (depending on the nature and properties of their coordination sphere) suitable for reversible coordination of the corresponding binding partners (Lewis bases).[5] As the above metal complexes represent suitable binding sites for a variety of anionic guest molecules, the attachment of cyclen moieties to an appropriate rigid scaffold should lead to highly preorganized artificial receptors with potential applications as metalloenzymes.[6,7] Calix[4]arenes,[8,9] due to their unique three-dimensional structures, easy derivatization, and the tunable shape of the molecules, represent ideal candidates for such a molecular scaffold. While the connection of calix[4]arene and cyclen moieties via a spacer unit has been published very recently,[7] we assumed that using a rigid connection between the two subunits could result in a higher degree of preorganization and enhanced binding properties. In this paper, we report on the synthesis of novel calix[4]arene–cyclen conjugates with the cyclen moiety directly attached to the upper rim of calix[4]arene.

2. Results and discussion

2.1. Synthesis

Based on the previous results on the N-arylation of 1,4,7,10-tetraazacyclododecanes,[10] we used the Buchwald–Hartwig coupling reaction as a synthetic tool for direct *N*-aryl connection. To the best of our knowledge, this method, based on the application of recently developed palladium-catalyzed N-arylation procedures,[11,12] has never been used in calixarene chemistry so far. The synthesis of tris(Boc)cyclenylcalix[4]arenes **8** and **9** in the *cone* conformation, and consequently, the formation of their Lewis-acidic Zn(II) complexes, was accomplished according to Scheme 1. Starting calix[4]arene **3** was selectively monobrominated according to a known procedure[22] using 1 equiv of *N*-bromosuccinimide in butane-2-one at ambient temperature to give monobromocalix[4]arene **6** in 55% yield. On the other hand, dibromocalix[4]arene **7** was obtained in 83% overall yield by regioselective bromination of dipropoxycalix[4]arene **4** using bromine in chloroform at 0 °C (intermediate **5** formed in 95% yield) followed by alkylation with propyl iodide in DMF in the presence of NaH (product **7**, 87% yield) as described by Casnati et al.[23] Both bromocalix[4]arenes **6** and **7** were then subjected to the Buchwald–Hartwig Pd-catalyzed amination reaction with 1,4,7-tris(Boc)cyclen **2**. The cyclen **1** was protected before coupling reaction to avoid the connection of more calixarene molecules on its skeleton. Since the Boc (*tert*-butoxycarbonyl) group has been proven as the most effective protecting group for the synthesis of cyclic polyamines,[13] we subjected cyclen **1** to the reaction with 2.75 equiv of Boc_2O in DCM to form the protected cyclen **2** in 75% yield.[1d] The coupling reaction between bromocalixarene **6** blocked in the *cone* conformation

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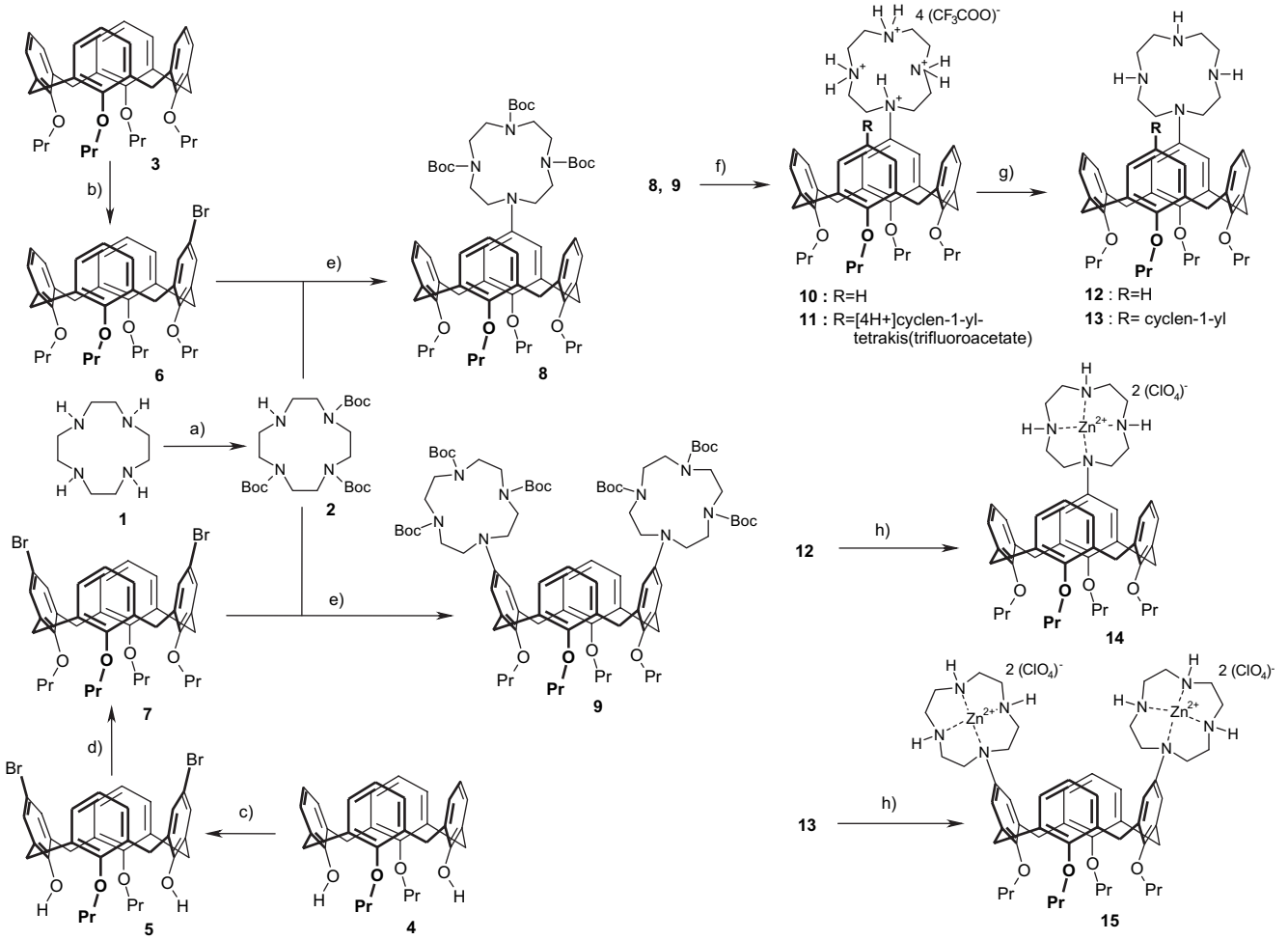


Scheme 1. (a) 2.75 equiv $(Boc)_2O$, CH_2Cl_2, rt (75%); (b) 1 equiv NBS, butane-2-one, rt (55%); (c) Br_2, $CHCl_3$, 0 °C (95%); (d) PrI, NaH, DMF, −10 °C to rt (87%); (e) $Pd(OAc)_2$, P(*t*-Bu)$_3$, *t*-BuONa, toluene, 80–90 °C (66% for **8**, 65% for **9**); (f) CF_3COOH, CH_2Cl_2, rt (quant.); (g) Ion exchanger III; Merck©, CH_3OH–H_2O 10:1 (v/v) (quant.); (h) $Zn(ClO_4)_2 \cdot 6H_2O$, CH_3OH, rt (quant.).

and threefold Boc-protected cyclen **2** was carried out in dry toluene at 80–90 °C in the presence of stoichiometric amount of base (*t*-BuONa), a catalytic amount of palladium acetate, and the corresponding phosphine ligand (see Table 1). Triphenylphosphine was described as the best ligand in the attempts of N-arylation of Boc-protected cyclen using simple aryl halides.[10] However, as shown in Table 1 (run 1), the use of Ph_3P led only to moderate conversion together with a low yield of the required calix–cyclen conjugate **8** in our case. Using a large amount of Pd-source, higher temperature, and a longer reaction time did not improve the yield (run 2). Similar results have been achieved using DPPF as a chelating ligand (Table 1, run 3).

It is known that the reaction rate of the Pd-catalyzed amination reaction is determined by the reductive elimination step in the catalytic cycle,[14] which can be considerably influenced by electronic and steric effects of phosphine ligands used. Indeed, the successful application of more bulky and electron rich phosphine ligands such as PCy_3 and P(*t*-Bu)$_3$ in Pd-catalyzed cross-coupling reactions of aryl halides and secondary amines has precedent in the literature.[15] Consequently, the use of tris(*tert*-butyl)phosphine led immediately to the dramatic improvement of both yield and conversion (run 4). The conversion of the starting bromocalix[4]arene **6** increased to 82% and tris(Boc)cyclenylcalix[4]arene **8** was isolated in 66% after column

Table 1. Yields, stoichiometry, and reaction conditions of Buchwald–Hartwig coupling reactions between calix[4]arenes **6**, **7**, and **16** and protected cyclen **2**

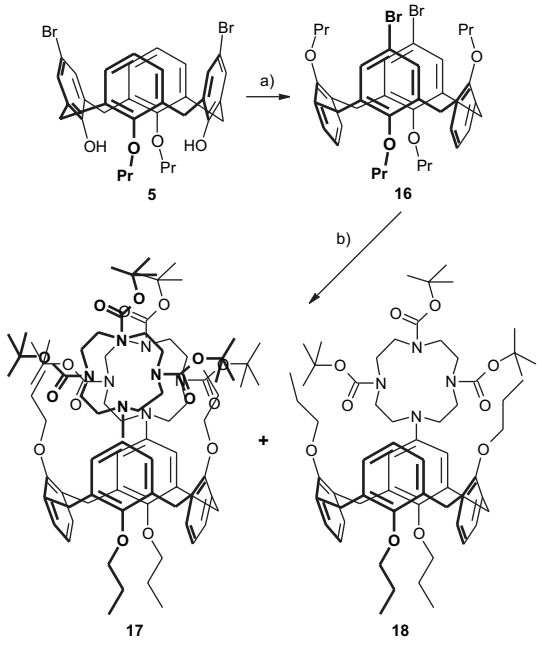
Run	Starting materials	Pd-source (mol %)	Ligand (mol %)	Base (equiv)	*T* (°C)	Time (h)	Product	Yield[a] (%)
1.	**2** (1.1 equiv)+**6**	$Pd(OAc)_2$ (5)	PPh_3 (10)	NaO*t*-Bu (1.3)	80	35	**8**	21 (42)
2.	**2** (1.1 equiv)+**6**	$Pd(OAc)_2$ (15)	PPh_3 (10)	NaO*t*-Bu (1.3)	90	48	**8**	17 (32)
3.	**2** (1.1 equiv)+**6**	$Pd(OAc)_2$ (7)	DPPF (7.5)	NaO*t*-Bu (1.3)	80	70	**8**	19 (31)
4.	**2** (1.05 equiv)+**6**	$Pd(OAc)_2$ (10)	P(*t*-Bu)$_3$ (15)	NaO*t*-Bu (1.3)	80	18	**8**	66 (81)
5.	**2** (2.1 equiv)+**7**	$Pd(OAc)_2$ (10)	P(*t*-Bu)$_3$ (10)	NaO*t*-Bu (2.5)	80	42	**8**	18 (18)
							9	65 (65)
6.	**2** (2.05 equiv)+**16**	$Pd(OAc)_2$ (10)	P(*t*-Bu)$_3$ (15)	NaO*t*-Bu (2.3)	80	2	**17**	55 (57)
							18	24 (25)

[a] Yields in parentheses corrected for recovered starting material.

chromatography. Similarly, the coupling reaction between dibromocalix[4]arene **7** and threefold Boc-protected cyclen **2** was accomplished under identical conditions, using 2.1–2.5 equiv of protected cyclen **2**. Utilization of the already approved P(*t*-Bu)$_3$ led to the required bis[tris(Boc)cyclenyl]-calix[4]arene **9** in high yield, accompanied by a small amount of mono-conjugate **8** (presumably formed by a β-elimination during the coupling of the second cyclen unit). The reaction mixture was easily separated by column chromatography to yield the conjugates **9** and **8** in 65 and 18% yield, respectively, (see Table 1, run 5). The Boc protective groups were removed under acidic conditions (TFA–CH_2Cl_2, rt, overnight) to yield the corresponding *N*-protonated cyclenyl calix[4]arenes **10** and **11** in quantitative yields. These salts were then basified using strongly basic anion exchanger (Ion exchanger III; Merck®) to form quantitatively cyclenyl-calix[4]arene **12** and bis(cyclenyl)calix[4]arene **13**. The corresponding metallated derivatives **14** and **15** were then obtained in quantitative yields (see Scheme 1) by the reaction of free cyclen conjugates with 1 or 2 equiv of $Zn(ClO_4)_2\cdot 6H_2O$ (MeOH, rt, overnight). Structures of all the above mentioned compounds were unambiguously proven by ^{1}H, ^{13}C DEPT NMR, and ESIMS spectra.

To investigate the influence of the calix[4]arene conformation on the Pd-catalyzed N-arylation reaction, the dibromo derivative **16** in the *1,3-alternate* conformation was prepared (Scheme 2). The starting dibromo derivative **5** was alkylated using PrI in anhydrous THF and employing potassium trimethylsilyloxide as a base. Surprisingly, under these conditions the *1,3-alternate* conformer **16** was obtained in higher yield (75%), compared to the commonly used cesium carbonate. Furthermore, under these conditions, derivative **16** can be isolated by simple precipitation without column chromatography.

The Buchwald–Hartwig reaction between the dibromo derivative **16** and protected cyclen **2** gave the best results



Scheme 2. (a) PrI, $(CH_3)_3SiOK$, THF, rt (75%); (b) **2**, $Pd(OAc)_2$, P(*t*-Bu)$_3$, *t*-BuONa, toluene, 80 °C (55% for **17**, 24% for **18**).

in the presence of tris(*tert*-butyl)phosphine and the required bis[tris(Boc)cyclenyl]calix[4]arene (*1,3-alternate*) **17** was obtained in good yield (55%) together with mono-cyclen conjugate **18** (24%) (see Scheme 2). The presence of by-product **18** in the reaction mixture represents the evidence for the β-elimination mechanism as the competitive process accompanying this N-arylation coupling reaction. On the other hand, when we applied this coupling reaction to tetrabromocalix[4]arene in the *1,3-alternate* conformation **19**,[16] we never obtained the required calix[4]arene substituted with four cyclen units. Using either Ph_3P, DPPF or P(*t*-Bu)$_3$

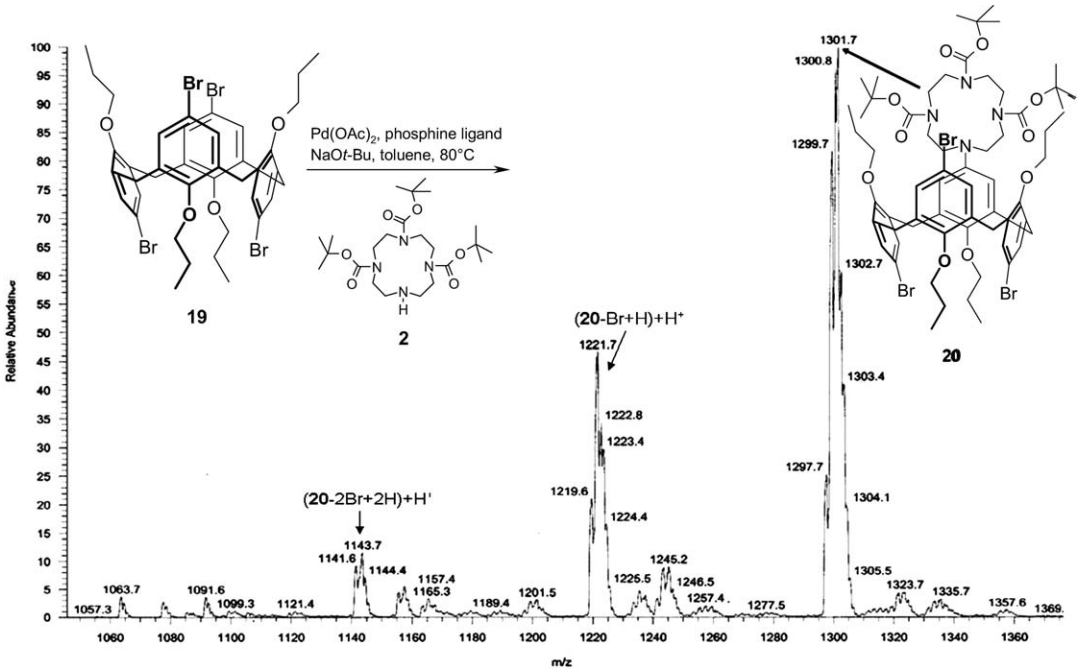


Figure 1. ESIMS (+) of the inseparable reaction mixture after the coupling reaction between tetrabromo-derivative **19** and cyclen **2**.

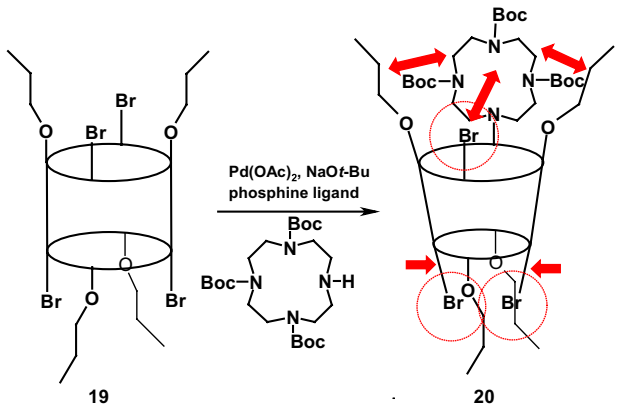


Figure 2. Proposed negative allosteric effect in a *1,3-alternate* derivative.

as phosphine ligands (otherwise under identical conditions as specified above) we have always obtained only very complicated (according to ^{1}H NMR) and inseparable reaction mixtures. As shown by ESIMS analysis of such a mixture, tribromo-tri(Boc)cyclenylcalix[4]arene **20** was obtained together with the β-elimination products (Fig. 1). Surprisingly, not more than one cyclen unit could be appended to the tetrabromocalix[4]arene **19** under the above mentioned conditions. The explanation could lie in the increased steric hindrance in the *1,3-alternate* system. The presence of one bulky tri(Boc)cyclen unit at one side of the calix[4]arene may cause the outstretching of the two proximal propoxy groups, which implies the slight change in the conformation (see Fig. 2). As a consequence, the two bromine atoms on the opposite side of the *1,3-alternate* conformer become closer to each other thus making their substitution impossible. This phenomenon resembles a complexation-induced negative allosteric effect observed in some *1,3-alternate* calixarenes.[17]

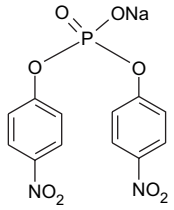
2.2. Complexation study

Having developed the synthetic route leading to the calix[4]-arene–cyclen conjugates in reasonable yields, we have carried out a preliminary study of the hydrolytic activities of the Zn(II) complexes towards the cleavage of phosphodiester bonds. These measurements were done in buffered 0.01 M solution of Tris-base, in a mixture of MeOH–H_2O 9:1 at pH=8 (I=0.1 M). As a model compound containing activated phosphodiester bonds we used sodium bis(*p*-nitrophenyl)phosphate (BNPP). The buffered solution in the UV-cell containing either ligand **14** or **15** ($c=4\times10^{-4}$ mol l^{-1}) and BNPP ($c=1.6\times10^{-5}$ mol l^{-1}) at 30 °C was scanned every 5 min for 9 h in the region between 380 and 420 nm in the UV spectrophotometer. However, the expected absorption signal at 400 nm indicating the presence of free *p*-nitrophenolate anion in the solution was not observed. Thus both Zn-complexes were found to be inactive to cleave the activated phosphodiester bond in BNPP under the conditions used. Neither increasing the pH value to 9, nor increasing the concentration of ligand led to a desired catalytic activity. These results are in agreement with the previous findings of Akkaya and Ozturz.[7] However, the steric hindrance seems to be even more effective here. This could be ascribed to a rigid connection between bulky Zn(II)cyclen and the calix[4]arene moieties. Thus, the entrance to the calixarene cavity seems to be blocked even in the case of the mono Zn(II)cyclenyl derivative **14**, which excludes the efficient binding of the BNPP substrate necessary for the catalytic activity.

Table 2. Complexation constants K_c of conjugate **14** toward selected anions[a] (^{1}H NMR, CD_3CN, 25 °C, 300 MHz)

Anion	Cl^-	AcO^-	BzO^-	$H_2PO_4^-$	HSO_4^-	NO_3^-
K_c [mol^{-1} l]	1120	205	950	[b]	[b]	[c]

[a] Corresponding TBA^+ salts used.
[b] Precipitate formed during the NMR titration.
[c] Small induced chemical shifts (<10 Hz) observed.



Nevertheless, the rigid connection between both subunits was found to be effective in the case of coordination of selected anions. We performed several measurements using ^{1}H NMR titration and Job's plot techniques (acetonitrile-d_3). As follows from Table 2, quite interesting affinity of ligand **14** towards spherical chloride anion and planar acetate/benzoate anions was observed.[18] All these anions formed a complex with ligand **14** with 1:1 stoichiometry (Fig. 3). On the other hand, the presence of the nitrate anion in the solution of **14** didn't cause any changes in the ^{1}H NMR spectrum. Meanwhile, the gradual addition of either $H_2PO_4^-$ or HSO_4^- anions into the CD_3CN solution of **14** led in both cases to the formation of white precipitates (probably the corresponding complexes), which were not further analyzed owing to their total insolubility. Ligand **15** bearing two Zn(II)cyclen units was also subjected to ^{1}H NMR titration experiments with TBA^+chloride$^-$ and TBA^+benzoate$^-$. The addition of these salts to the ligand **15** led in both cases to considerable shifts in ^{1}H NMR spectra, however, the titration curves indicated nontrivial stoichiometry different from 1:1.

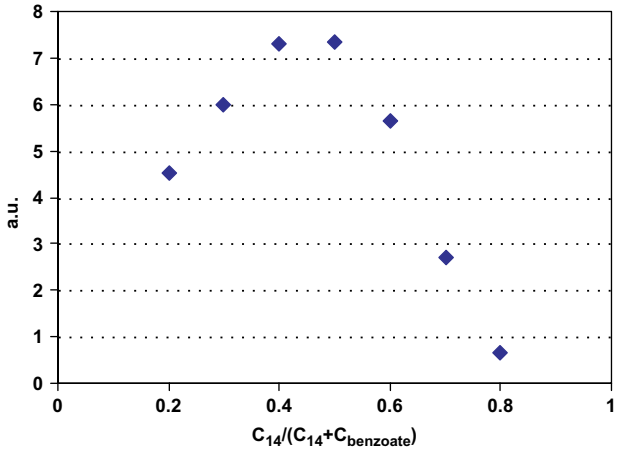


Figure 3. Job's plot for **14**/Bu_4N^+benzoate$^-$ system (300 MHz, CD_3CN, c_{total}=2 mmol l^{-1}).

3. Conclusions

In summary, we have reported the synthesis of calix[4]-arene–cyclen conjugates, with direct *N*-aryl bonds and constrained calixarene conformations. Optimized conditions for the palladium-catalyzed *N*-aryl bond formation to connect protected cyclen with bromocalix[4]arenes were developed. The cyclen ligands were deprotected and converted into the bis-zinc(II) complexes. Attempts to use the complexes to hydrolyze activated phosphodiester bonds were unsuccessful. However, NMR titration experiments revealed binding affinity of the bis complexes in acetonitrile for chloride, acetate, and benzoate anions with defined stoichiometry.

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under nitrogen atmosphere. All dry solvents were prepared according to standard procedures and stored over molecular sieves. Melting points are uncorrected and were determined using a Boetius Block apparatus (Carl Zeiss Jena, Germany). NMR spectra were recorded at 250 and 400 MHz (^{1}H) and at 63 and 100 MHz (^{13}C). The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2, and (C_{quat}) for quaternary carbons. ^{1}H NMR titrations were performed with tetrabutylammonium salts of corresponding anions that were dried and stored in evacuated desiccator over P_2O_5. Elemental analyses were measured on Elementar vario EL (Elementar, Germany) instruments. All samples were dried in the desiccator over P_2O_5 under vacuum (1 Torr) at 80 °C for 8 h. It is known that the elemental analyses of the calixarene derivatives are sometimes ambiguous.[19] Mass spectra were measured using ESI technique on Q-TOF (Micromass) spectrometer or MALDI-TOF technique on HP G2030A (Hewlett Packard) with delayed extraction option. The IR spectra were measured on an FTIR spectrometer, Nicolet 740 or Bruker IFS66 spectrometers equipped with a heatable Golden Gate Diamante ATR-Unit (SPECAC) in $CHCl_3$ and/or in KBr. UV–vis spectra were measured on a JASCO V-530 spectrophotometer. The purity of the substances and the courses of reactions were monitored by TLC using TLC alumina sheets with Silica gel 60 F_{254} (Merck). Preparative TLC chromatography was carried out on 20×20 cm glass plates covered by Silica gel 60 GF_{254} (Merck) or Al_2O_3 type G (Fluka). The column chromatography was performed using Silica gel 60 (Merck).

Compounds **2**,[1d] **3**,[20] **4**,[21] **6**,[22] **7**,[23] and **19**[16] were prepared according to known procedures.

4.2. Synthesis of 5-[4,7,10-tris(Boc)cyclen-1-yl]-25,26,27,28-tetrapropoxycalix[4]arene (*cone*) 8

The protected cyclen **2** (223 mg, 0.47 mmol), 5-bromo-25,26,27,28-tetrapropoxycalix[4]arene (*cone*) **6** (300 mg, 0.447 mmol), and 56 mg of sodium *tert*-butoxide (0.58 mmol) were placed into a Schlenk tube. To this mixture P(*t*-Bu)$_3$ (13.6 mg, 0.067 mmol, 15 mol %) and palladium acetate (10.1 mg, 0.045 mmol, 10 mol %) were added. The solid materials were suspended in absolute toluene (4 ml). The tube was sealed, and the mixture was degassed by three freeze–pump–thaw cycles, then stirred at 80 °C for 18 h. The reaction mixture was cooled to rt, diluted with CH_2Cl_2 (30 ml), filtered through Celite, and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2, PE–EtOAc 10:1–2:1) to give 314 mg (66%) of **8**. Mp: 72 °C (ethyl acetate). R_f=0.66 (SiO_2, PE–EtOAc 2:1). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.04 (m, 12H, –CH_2–CH_3), 1.46 (s, 9H, –C–(CH_3)$_3$), 1.47 (s, 18H, –C–(CH_3)$_3$), 1.94 (m, 8H, –CH_2–CH_3), 3.08 (d, 2H, J=12.7 Hz, Ar–CH_2–Ar, eq.), 3.13 (d, 2H, J=12.7 Hz, Ar–CH_2–Ar, eq.), 3.25 (m, 16H, –N–CH_2–CH_2–N–), 3.76 (m, 8H, –O–CH_2–CH_2–), 4.43 (d, 2H, J=13.1 Hz, Ar–CH_2–Ar, ax.), 4.44 (d, 2H, J=13.2 Hz, Ar–CH_2–Ar, ax.), 6.36 (s, 2H, ArH), 6.39 (m, 6H, ArH), 6.70 (t, 1H, J=7.1 Hz, ArH), 6.88 (d, 2H, J=7.3 Hz, ArH). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 10.1 (+), 10.2 (+), 10.5 (+), 23.0 (−), 23.1 (−), 23.4 (−), 28.5 (+), 28.7 (+), 30.9 (−), 31.3 (−), 49.4 (−), 50.6 (−), 76.7 (−), 76.8 (−), 79.4 (C_{quat}), 79.7 (C_{quat}), 121.9 (+), 127.3 (+), 127.9 (+), 128.5 (+), 134.1 (C_{quat}), 134.5 (C_{quat}), 135.9 (C_{quat}), 136.3 (C_{quat}), 155.8 (C_{quat}), 157.1 (C_{quat}). EA calcd for $C_{63}H_{90}N_4O_{10}$: C, 71.16; H, 8.53; N, 5.27. Found: C, 71.09; H, 8.83; N, 5.18. MS (ESI, 70 eV): *m/z* (rel int.) 1064 $[MH]^+$ (100). IR (KBr) cm^{-1}: 2970, 2927, 1695, 1601, 1462, 1248, 1167 cm^{-1}.

4.3. Synthesis of 5,17-bis[4,7,10-tris(Boc)cyclen-1-yl]-25,26,27,28-tetrapropoxycalix[4]arene (*cone*) 9

The protected cyclen **2** (397 mg, 0.84 mmol), 5,17-dibromo-25,26,27,28-tetrapropoxycalix[4]arene (*cone*) **7** (300 mg, 0.4 mmol), and sodium *tert*-butoxide (96 mg, 1 mmol) were placed into a Schlenk tube. To this mixture P(*t*-Bu)$_3$ (8 mg, 0.04 mmol, 10 mol %) and palladium acetate (9 mg, 0.04 mmol, 10 mol %) were added and the solid materials were suspended in dry toluene (4 ml). The tube was sealed, degassed by three freeze–pump–thaw cycles, and stirred at 80 °C for 42 h. The reaction mixture was then cooled to rt, diluted with CH_2Cl_2 (20 ml), filtered through Celite, and evaporated in vacuum. The crude product was purified by column chromatography (SiO_2, PE–EtOAc 5:1–1:1) to give 77 mg (18%) of mono-conjugate **8** and 399 mg (65%) of compound **9** as white solid. Mp: 114 °C. R_f=0.21 (SiO_2, PE–EtOAc 2:1). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.88 (t, 6H, J=7.3 Hz, –CH_2–CH_3), 1.10 (t, 6H, J=7.3 Hz, –CH_2–CH_3), 1.47 (s, 18H, –C–(CH_3)$_3$), 1.49 (s, 36H, –C–(CH_3)$_3$), 1.80–2.10 (m, 8H, –CH_2–CH_3), 3.02 (d, 4H, J=13.3 Hz, Ar–CH_2–Ar, eq.), 3.45 (br s, 32H, –N–CH_2–CH_2–N–), 3.63 (t, 4H, J=7.7 Hz, –O–CH_2–CH_2–), 3.93 (t, 4H, J=7.1 Hz, –O–CH_2–CH_2–), 4.42 (d, 4H, J=13.1 Hz, Ar–CH_2–Ar, ax.), 6.11 (s, 6H, Ar*H*), 6.53 (s, 4H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 9.9 (+), 10.9 (+), 22.9 (−), 23.6 (−), 28.5 (+), 28.6 (+), 31.5 (−), 50.1 (−), 50.9 (−), 76.4 (−), 77.0 (−), 79.8 (C_{quat}), 117.8 (+), 121.8 (+), 127.0 (+), 133.2 (C_{quat}), 137.5 (C_{quat}), 155.1 (C_{quat}). EA calcd for $C_{86}H_{132}N_8O_{16}$: C, 67.34; H, 8.67; N, 7.30. Found: C, 67.27; H, 8.82; N, 7.19. MS (ESI, 70 eV): *m/z* (rel int.) 1535 $[MH]^+$ (100), 768 $[M+2H^+]^{2+}$ (60). IR (KBr) cm^{-1}: 2974, 2933, 1695, 1466, 1250, 1165 cm^{-1}.

4.4. Synthesis of 5-(1,4,7,10-tetrakis[4H$^+$]cyclen-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene tetrakis-(trifluoroacetate) (*cone*) 10

Compound **8** (202 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (10 ml) and trifluoroacetic acid (0.43 ml, 5.6 mmol) was added. The reaction mixture was stirred for 16 h (until no starting compound was indicated by TLC (SiO_2, EtOAc–MeOH 100:1), evaporated, and dried under vacuum to yield 225 mg of title compound **10** (100%) as a brown viscous solid. Mp: 116–117 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.95 (m, 12H, –CH_2–CH_3), 1.98 (m, 8H, –CH_2–CH_3), 2.71–3.20 (m, 16H, –NCH_2–CH_2–N–), 3.10 (d, 4H, Ar–CH_2–Ar, eq.), 3.70–3.88 (m, 4H, –O–CH_2–CH_2–), 3.93–3.99 (m, 4H, –O–CH_2–CH_2–), 4.43 (d, 4H, Ar–CH_2–Ar, ax.), 6.23–6.31 (m, 3H, Ar*H*), 6.47 (d, 2H, ^3J=7.3 Hz, Ar*H*), 6.74–6.93 (m, 6H, Ar*H*), 8.80–10.4 (br s, 4H, –NH(*H*$^+$)). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 10.0 (+), 10.5 (+), 10.6 (+), 23.0 (−), 23.3 (−), 23.4 (−), 30.9 (−), 43.3 (−), 44.9 (−), 45.5 (−), 51.9 (−), 76.7 (−), 77.3 (−), 77.4 (−), 116.4 (C_{quat}, q, $^1J_{(C,F)}$=287.7 Hz), 121.6 (+), 122.3 (+), 123.4 (+), 127.6 (+), 128.3 (+), 128.9 (+), 134.3 (C_{quat}), 135.7 (C_{quat}), 136.3 (C_{quat}), 140.2 (C_{quat}), 156.2 (C_{quat}), 157.0 (C_{quat}), 161.9 (C_{quat}, q, $^2J_{(C,F)}$=40.2 Hz). MS (ESI, 70 eV) *m*/*z* (rel int.) 763 [MH]$^+$ (50), 382 [M+2H]$^{2+}$ (100). IR (KBr) cm^{-1}: 3630–3310, 2965, 2875, 1685, 1461 cm^{-1}.

4.5. Synthesis of 5,17-bis(1,4,7,10-tetrakis[4H$^+$]-cyclen-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene octakis-(trifluoroacetate) (*cone*) 11

Compound **9** (530 mg, 0.345 mmol) was dissolved in CH_2Cl_2 (10 ml) and trifluoroacetic acid (1.6 ml, 20.7 mmol) was added. Reaction mixture was stirred for 16 h (until no starting compound was indicated by TLC (SiO_2, EtOAc–MeOH 100:1), evaporated, and dried under vacuum. Compound **11** was obtained in quantitative yield as brown viscous solid. Mp: 165–167 °C. ^{1}H NMR ($CDCl_3$–CD_3OD 1:1, 400 MHz) δ (ppm): 0.9 (t, 6H, *J*=7.5 Hz, –CH_2–CH_3), 1.3 (t, 6H, *J*=7.5 Hz, –CH_2–CH_3), 1.87–2.01 (m, 8H, –CH_2–CH_3), 3.05–3.42 (m, 36H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, eq.), 3.66 (t, 4H, *J*=6.7 Hz, –O–CH_2–CH_2–), 4.03 (t, 4H, *J*=8.2 Hz, –O–CH_2–CH_2–), 4.45 (d, 4H, *J*=13.2 Hz, Ar–CH_2–Ar, ax.), 4.98 (br s, 8H, –NH(*H*$^+$)), 6.07 (d, 4H, *J*=7.6 Hz, Ar*H*), 6.18 (t, 2H, *J*=7.5 Hz, Ar*H*), 7.11 (s, 4H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$–CD_3OD 1:1, 100 MHz) δ (ppm): 10.0 (+), 11.1 (+), 23.5 (−), 24.0 (−), 31.4 (−), 43.1 (−), 44.3 (−), 46.0 (−), 51.4 (−), 77.1 (−), 77.6 (−), 117.0 (C_{quat}, q, $^1J_{(C,F)}$=291.0 Hz), 122.6 (+), 124.9 (+), 127.7 (+), 133.3 (C_{quat}), 139.0 (C_{quat}), 142.5 (C_{quat}), 155.8 (C_{quat}), 156.7 (C_{quat}), 162.1 (C_{quat}, q, $^2J_{(C,F)}$=35.7 Hz). MS (ESI, 70 eV) *m*/*z* (rel int.) 933 [MH]$^+$(15), 467 [M+2H]$^{2+}$ (100).

4.6. Synthesis of 5-(cyclen-1-yl)-25,26,27,28-tetra-propoxycalix[4]arene (*cone*) 12

Derivative **10** (225 mg, 0.19 mmol) was dissolved in H_2O–MeOH 1:1 (v/v) mixture (10 ml) and poured onto the column of strongly basic anion exchanger (Ion exchanger III; Merck©). The column was washed with 100 ml of the above solvent mixture and the fractions with basic reaction on pH-paper were combined, evaporated, and dried under vacuum to give 133 mg (95%) of **12** as white solid. Mp: 90–92 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.00 (m, 12H, –CH_2–CH_3), 1.91 (m, 8H, –CH_2–CH_3), 2.63–3.17 (m, 20H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, eq.), 3.83 (m, 8H, –O–CH_2–CH_2–), 4.43 (d, 2H, *J*=13.1 Hz), 4.45 (d, 2H, *J*=13.2 Hz), 6.16 (s, 2H, Ar*H*), 6.59 (m, 9H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 10.3 (+), 10.4 (+), 10.5 (+), 23.2 (−), 23.3 (−), 23.4 (−), 31.0 (−), 31.3 (−), 47.0 (−), 47.4 (−), 49.2 (−), 52.8 (−), 76.7 (−), 76.8 (−), 77.3 (−), 116.7 (+), 121.8 (+), 121.9 (+), 128.0 (+), 135.0 (C_{quat}), 144.0 (C_{quat}), 150.4 (C_{quat}), 156.6 (C_{quat}), 156.8 (C_{quat}). EA calcd for $C_{48}H_{66}N_4O_4$: C, 75.55; H, 8.72; N, 7.34. Found: C, 75.30; H, 8.61; N, 7.19. MS (ESI, 70 eV) *m*/*z* (rel int.) 763 [MH]$^+$ (100), 382 [M+2H$^+$]$^{2+}$ (100). IR (KBr) cm^{-1}: 2962, 2931, 2872, 2362, 1689, 1458, 1199 cm^{-1}.

4.7. Synthesis of 5,17-bis(cyclen-1-yl)-25,26,27,28-tetra-propoxycalix[4]arene (*cone*) 13

Derivative **11** (536 mg, 0.29 mmol) was dissolved in H_2O–MeOH 1:1 (v/v) mixture (20 ml) and poured onto the column of strongly basic anion exchanger (Ion exchanger III; Merck©). The column was then washed with 100 ml of the same solvent mixture and the fractions with basic reaction on pH-paper were combined, evaporated, and dried under vacuum to give 270 mg (99%) of compound **13** as white solid. Mp: 198 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.86 (t, 6H, *J*=7.4 Hz, –CH_2–CH_3), 1.08 (t, 6H, *J*=7.4 Hz, –CH_2–CH_3), 1.80–2.01 (m, 8H, –CH_2–CH_3), 2.68 (s, 8H, –N–CH_2–CH_2–N–), 2.85 (s, 16H, –N–CH_2–CH_2–N–), 3.32 (s, 8H, –N–CH_2–CH_2–N–), 3.06 (d, 4H, *J*=13.3 Hz, Ar–CH_2–Ar, eq.), 3.63 (t, 4H, *J*=6.7 Hz, –O–CH_2–CH_2–), 3.93 (t, 4H, *J*=8.2 Hz, –O–CH_2–CH_2–), 4.38 (d, 4H, *J*=13.2 Hz, Ar–CH_2–Ar, ax.), 6.08 (d, 4H, *J*=7.4 Hz, Ar*H*), 6.21 (t, 2H, *J*=6.9 Hz, Ar*H*), 6.77 (s, 4H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 9.8 (+), 10.9 (+), 22.9 (−), 23.5 (−), 31.2 (−), 46.1 (−), 46.4 (−), 47.6 (−), 52.5 (−), 76.4 (−), 76.8 (−), 119.9 (+), 122.1 (+), 127.1 (+), 133.1 (C_{quat}), 137.1 (C_{quat}), 145.0 (C_{quat}), 152.3 (C_{quat}), 155.1 (C_{quat}). MS (ESI, 70 eV) *m*/*z* (rel int.) 933 [MH]$^+$(10), 476 [M+2H]$^{2+}$ (100). EA calcd for $C_{56}H_{84}N_8O_4$: C, 72.07; H, 9.07; N, 12.01. Found: C, 71.89; H, 9.21; N, 11.91. IR (KBr) cm^{-1}: 3375–3290, 2929, 2873, 1602, 1456, 1222 cm^{-1}.

4.8. Synthesis of 5-([Zn^{2+}]cyclen-1-yl)-25,26,27,28-tetra-propoxycalix[4]arene bis(perchlorate) (*cone*) 14

Conjugate **12** (325 mg, 0.426 mmol) was dissolved in MeOH (10 ml) and $Zn(ClO_4)_2\cdot 6H_2O$ (159 mg, 0.426 mmol) was added. The reaction mixture was stirred at rt for 20 h, and then heated to 50 °C for 1 h. The solvent was evaporated and the residue was dried under vacuum to give 439 mg (quantitative) of **14** as white crystalline solid. Mp: 198 °C (decomp.). ^{1}H NMR ($CDCl_3$–CD_3OD 1:1, 250 MHz) δ (ppm): 0.91–1.06 (m, 12H, –CH_2–CH_3), 1.84–1.97 (m, 8H, –CH_2–CH_3), 2.49–3.05 (m, 16H, –N–CH_2–CH_2–N–), 3.13 (d, 2H, *J*=13.1 Hz, Ar–CH_2–Ar, eq.), 3.15 (d, 2H, *J*=13.2 Hz, Ar–CH_2–Ar, eq.), 3.72 and 3.92 (2m, 8H, –O–

CH_2–CH_2–), 4.42 (d, 2H, J=12.9 Hz, Ar–CH_2–Ar, ax.), 4.43 (d, 2H, J=13.3 Hz, Ar–CH_2–Ar, ax.), 6.38–6.88 (m, 11H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$–CD_3OD 1:1, 63 MHz) δ (ppm): 11.2 (+), 11.6 (+), 11.7 (+), 24.4 (−), 24.6 (−), 24.7 (−), 32.2 (−), 32.3 (−), 44.7 (−), 45.3 (−), 46.8 (−), 55.3 (−), 78.0 (−), 78.6 (−), 78.7 (−), 123.2 (+), 123.8 (+), 124.0 (+), 129.2 (+), 129.8 (+), 130.3 (+), 135.6 (C_{quat}), 136.5 (C_{quat}), 137.3 (C_{quat}), 137.4 (C_{quat}), 142.7 (C_{quat}), 156.2 (C_{quat}), 157.4 (C_{quat}), 158.1 (C_{quat}). MS (ESI, 70 eV, 1% AcOH in MeOH) *m/z* (rel int.) 885 $[M+CH_3COO]^+$ (100), 422 $[M+H_2O]^{2+}$ (40). IR (KBr) cm^{-1}: 3516, 3302, 2960, 2927, 2875, 1460, 1088 cm^{-1}.

4.9. Synthesis of 5,17-bis([Zn^{2+}]cyclen-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene tetrakis(perchlorate) (*cone*) 15

Conjugate **13** (260 mg, 0.28 mmol) was dissolved in MeOH (10 ml) and $Zn(ClO_4)_2\cdot 6H_2O$ (208 mg, 0.56 mmol) was added. The reaction mixture was stirred at rt for 20 h, and then heated to 50 °C for 1 h. The solvent was evaporated and the residue was dried under vacuum to give 407 mg (100%) of **15** as white crystalline solid. Mp: 220 °C (decomp.). ^{1}H NMR (CD_3CN, 250 MHz) δ (ppm): 0.92 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.08 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.81–2.02 (m, 8H, –CH_2–CH_3), 2.77–3.40 (m, 36H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, eq.), 3.66 (t, 4H, J= 6.9 Hz, –O–CH_2–CH_2–), 3.82 (m, 4H, –N–CH_2–CH_2–N–), 4.05 (t, 4H, J=8.2 Hz, –O–CH_2–CH_2–), 4.45 (d, 4H, J=13.0 Hz, Ar–CH_2–Ar, ax.), 6.32 (s, 6H, Ar*H*), 7.17 (s, 4H, Ar*H*). ^{13}C NMR, DEPT (135) (CD_3CN, 63 MHz) δ (ppm): 10.2 (+), 11.2 (+), 24.0 (−), 24.3 (−), 31.5 (−), 44.2 (−), 44.5 (−), 45.9 (−), 54.7 (−), 77.5 (−), 78.2 (−), 123.6 (+), 124.5 (+), 128.7 (+), 133.9 (C_{quat}), 139.0 (C_{quat}), 142.2 (C_{quat}), 156.4 (C_{quat}), 156.9 (C_{quat}). MS (ESI, 70 eV) *m/z* (rel int.) 1361 $[M+3ClO_4]^+$ (10), 631 $(M+2ClO_4)^{2+}$ (80), 415 $[M+ClO_4+2CH_3CN]^{3+}$ (100), 307 $[M+4CH_3CN]^{4+}$ (60). IR (KBr) cm^{-1}: 3700–3300, 3290, 2962, 2875, 1635, 1479 cm^{-1}.

4.10. Synthesis of 5,17-dibromo-25,26,27,28-tetrapropoxycalix[4]arene (*1,3-alternate*) 16

5,17-Dibromo-26,28-dipropoxycalix[4] arene (*cone*) **5** (3 g, 4.5 mmol) and Me_3SiOK (2.89 g, 22.5 mmol) were dissolved in 50 ml dry THF and cooled to −5 °C. Then PrI (2.2 ml, 22.5 mmol) was slowly added. Reaction mixture was then stirred at rt for 120 h. After this time the reaction mixture was quenched with 1 M solution of HCl (100 ml) and extracted three times with $CHCl_3$ (3×30 ml). Combined organic layers were dried over Na_2SO_4 and evaporated to give crude product. Crystallization from $CHCl_3$–MeOH yielded 1.63 g (50%) of pure **16**. Mp: 235–237 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.89 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.03 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.55–1.74 (m, 8H, –CH_2–CH_3), 3.74 (t, 4H, J=7.2 Hz, –O–CH_2–CH_2–), 3.60 (t, 4H, J=7.2 Hz, –O–CH_2–CH_2–), 3.60 (s, 8H, Ar–CH_2–Ar), 6.71 (t, 2H, J=7.5 Hz, Ar*H*), 6.98 (d, 4H, J=7.5 Hz, Ar*H*), 7.19 (s, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 10.4 (+), 10.5 (+), 23.4 (−), 23.5 (−), 36.4 (−), 73.2 (−), 73.5 (−), 114.3 (C_{quat}), 121.7 (+), 130.0 (+), 132.4 (+), 133.1 (C_{quat}), 135.5 (C_{quat}), 155.6 (C_{quat}), 156.5 (C_{quat}). MS (EIMS) *m/z* (rel int.) 750 $[M]^+$ (100). EA calcd for $C_{40}H_{46}O_4Br_2$: C, 64.01; H, 6.18; Br, 21.29. Found: C, 64.05; H, 6.29; Br, 21.18.

4.11. Synthesis of 5,17-bis[4,7,10-tris(Boc)cyclen-1-yl]-25,26,27,28-tetrapropoxycalix[4]arene (*1,3-alternate*) 17

The protected azamacrocycle **2** (388 mg, 0.82 mmol), 5,17-dibromo-25,26,27,28-tetrapropoxycalix[4]arene (*1,3-alternate*) **16** (300 mg, 0.4 mmol), and sodium *tert*-butoxide (88 mg, 0.92 mmol) were placed into a Schlenk tube. To this mixture P(*t*-Bu)$_3$ (14 mg, 0.07 mmol) and palladium acetate (10 mg, 0.044 mmol) were added and the solid materials were suspended in dry toluene (3 ml). The tube was sealed, and degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred at 80 °C for 2 h, cooled to rt, diluted with CH_2Cl_2 (20 ml), filtered through Celite, and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2, PE–EtOAc 10:1–1:1) to give 366 mg (55%) of the title product **17**. Mp: 158–160 °C. R_f=0.22 (SiO_2, PE–EtOAc 2:1). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.67 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.09–1.26 (m, 6H, –CH_2–CH_3), 1.46 (s, 18H, –C–(CH_3)$_3$), 1.47 (s, 36H, –C–(CH_3)$_3$), 1.50–1.60 (br s, 8H, –CH_2–CH_3), 3.22–3.78 (m, 48H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, –O–CH_2–CH_2–), 6.43 (s, 4H, Ar*H*), 6.76 (t, 2H, J=7.4 Hz, Ar*H*), 6.99 (d, 4H, J=7.4 Hz, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 100 MHz) δ (ppm): 10.0 (+), 10.2 (+), 22.2 (−), 23.2 (−), 28.5 (+), 28.6 (+), 38.7 (−), 50.0 (−), 72.1 (−), 72.3 (−), 79.4 (C_{quat}), 79.6 (C_{quat}), 117.7 (+, br), 121.7 (+), 129.4 (+), 133.8 (C_{quat}), 134.4 (C_{quat}), 143.7 (C_{quat}, br), 150.3 (C_{quat}, br), 155.5 (C_{quat}, br), 156.5 (C_{quat}, br), 156.8 (C_{quat}). MS (ESI, 70 eV) *m/z* (rel int.) 1535 $[MH]^+$ (100), 768 $[M+2H]^{2+}$ (15). EA calcd for $C_{86}H_{132}N_8O_{16}$: C, 67.34; H, 8.67; N, 7.30. Found: C, 67.11; H, 8.79; N, 7.22.

The evaporation of first chromatographic fractions yielded 103 mg (24%) of *5-[4,7,10-tris(Boc)cyclen-1-yl]-25,26,27,28-tetrapropoxy-calix[4]arene (1,3-alternate)* ***18*** Mp: 76–78 °C. R_f=0.50 (SiO_2, PE–EtOAc 2:1). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.82–1.00 (m, 12H, –CH_2–CH_3), 1.48 (s, 9H, –C–(CH_3)$_3$), 1.50 (s, 18H, –C–(CH_3)$_3$), 1.58–1.77 (m, 8H, –CH_2–CH_3), 3.33–3.67 (m, 32H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, –O–CH_2–CH_2–), 6.55 (s, 2H, Ar*H*), 6.65 (t, 2H, J=7.4 Hz, Ar*H*), 6.97−7.01 (m, 7H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 10.5 (+), 10.55 (+), 10.6 (+), 23.5 (−), 23.7 (−), 23.8 (−), 28.6 (+), 28.7 (+), 36.2 (−), 36.7 (−), 48.3–49.9 (−, br), 73.9 (−), 74.0 (−), 74.4 (−), 79.4 (C_{quat}), 79.6 (C_{quat}), 120.1 (+, br), 121.3 (+), 121.7 (+), 129.7 (+), 130.0 (+), 130.1 (+), 133.3 (C_{quat}), 133.4 (C_{quat}), 133.7 (C_{quat}), 133.9 (C_{quat}), 143.7 (C_{quat}), 151.0 (C_{quat}), 155.5 (C_{quat}), 156.4 (C_{quat}), 156.7 (C_{quat}), 171.1 (C_{quat}). MS (ESI, 70 eV) *m/z* (rel int.) 1063 $[M]^+$(100). EA calcd for $C_{63}H_{90}N_4O_{10}$: C, 71.16; H, 8.53; N, 5.27. Found: C, 71.07; H, 8.64; N, 5.28.

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