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Conformation-Selective Synthesis and Binding Properties of *N*-Benzylhexahomotriaza-*p*-chlorocalix[3]trinaphthylamide

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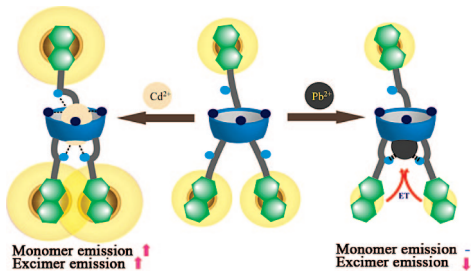

N-Benzylhexahomotriaza-*p*-chlorocalix[3]trinaphthylamide in partial cone conformation was selectively synthesized by appropriately controlling the steric effect during the amidation reactions of *N*-benzylhexahomotriaza-*p*-chlorocalix[3]tri-(ethyl acetate) in cone or partial cone conformations with use of 1-aminomethylnaphthalene. The conformation was confirmed by ^{1}H, ^{13}C, and 2D NMR and X-ray single-crystal analysis. Analyses of the complexes revealed that recognition is strongly affected by Cd^{2+}, Pb^{2+}, and F^{-} ions.

On the basis of the concepts provided by host−guest chemistry, cation and anion sensing has recently risen to a dominant position in research devoted to the detection of designated species.[1] This rapid growth is derived from the realization of the diverse roles played by cations and anions in biological and environmental systems.[2,3]

Calixarenes and the related macrocycles have received a lot of recent attention due to their molecular recognition properties.[3,4] In recent years, the homocalixarenes, hexahomotrioxacalixarenes (or oxacalix[3]arenes),[5] hexahomotrithiacalixarenes (or thiacalix[3]arenes),[6] and hexahomotriazacalixarenes (or azacalix[3]arenes), have been synthesized as parts of a class of compounds called expanded calixarenes.[7] From a structural point of view, they are of a similar size to 18-crown-6. However, their topology provides 3-D cavities which can better envelop the substrates. It is well-known that the more coordinating sites that are present then, generally, the higher the complex stability.[8] Therefore, to optimize the number of such binding sites, oxygen and sulfur atoms on oxa- and thiacalix[3]arenes are typically replaced with nitrogen in the azacalixarenes. Nevertheless, the azacalixarenes have received relatively little attention, mainly because they can only be synthesized in relatively low overall yields. Thus, there are only a limited number of studies of the solution conformations, solid-state structures, and complex formation properties of these molecules and, unlike calixarenes, the conditions for functionalization to provide a specific conformation have rarely been reported. Previously, Hampton and co-workers[9] showed that the conformations of azacalix[3]arenes were cone and partial cone, based on NMR and X-ray single-crystal studies, but most research has focused on studying only the cone conformations.[7–9] Metal complexes of the cone conformation with an extraction method, such as UO_2^{2+} in the presence of a high concentration of NaCl,[7a] lanthanide ions,[7b] and alkali metals,[7c] have been reported. Moreover, Thuéry et al.[10] prepared UO_2^{2+}, Nd^{3+}, and Yb^{3+} complexes of azacalixarenes without using any bases and obtained crystals of the complexes suitable for crystallographic analyses.

Recently, we reported that the cone conformation of N_7-hexahomotriazacalix[3]cryptand (**3**) can serve as a highly selective receptor for chloride ions.[11] Its selectivity can be altered to preferentially bind bromide ions over other halide ions by complexing with zinc ions, presumably due to allosteric and ion-pair effects as illustrated in Scheme 1. However, partial cone conformation was not reported in this study. To further

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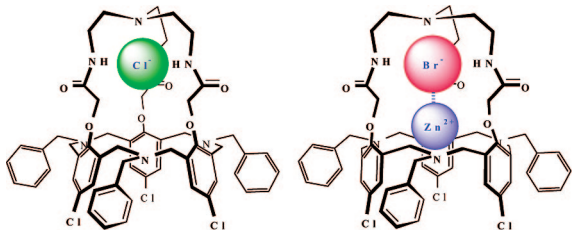
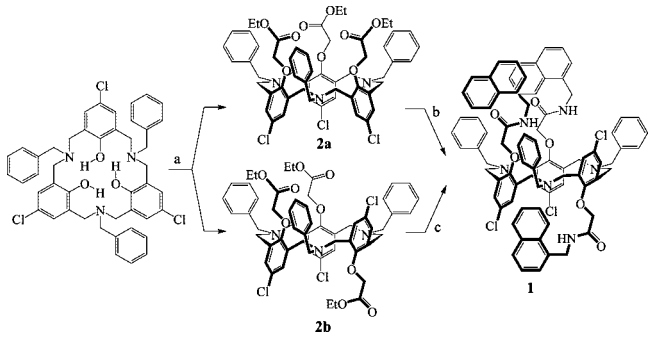
SCHEME 1. Cone Conformation of N_7-Hexahomotriazacalix[3]cryptand (3) Can Serve As a Highly Selective Receptor for Chloride Ions or Be Adapted to Preferentially Bind Bromide Ions in the Present Zinc Ions



SCHEME 2. Synthesis of 1[a]



[a] Reagents and conditions: (a) ethyl bromoacetate, NaH, THF, DMF, reflux, 72 h, **2a** (21%) and **2b** (31%); (b) 1-aminomethylnaphthalene, toluene:MeOH (1:1), rt, 3 d, **1** (41%); (c) 1-aminomethylnaphthalene, toluene:MeOH (1:1), rt, 7 d, **1** (42%).

understand the properties of azacalix[3]arenes, this work reports a conformational selective synthesis, the X-ray crystal structures, and the binding properties of *N*-benzylhexahomotriaza-*p*-chlorocalix[3]trinaphthylamide (**1** in Scheme 2). To the best of our knowledge, this is the first example showing the complex formation ability of a partial cone azacalix[3]arene.

The synthesis of *N*-benzylhexahomotriaza-*p*-chlorocalix[3]-trinaphthylamide (**1**) was carried out as schematically shown in Scheme 2. Alkylation of *N*-benzylhexahomotriaza-*p*-chlorocalix[3]arene with ethyl bromoacetate in the presence of NaH in THF/DMF produced compound **2a** (*cone conformation*, 21% yield) and compound **2b** (*partial cone conformation*, 31% yield). The reactions between **2a** and **2b** with 1-aminomethylnaphthalene afforded only the partial cone conformer of *N*-benzylhexahomotriaza-*p*-chlorocalix[3]trinaphylamide (**1**) with 41% and 42% yields, respectively. More interestingly, during the preparation of **1** by starting with **2a**, the conformation changed from cone to partial cone. This may be due to the small energetic barrier of aromatic flipping by passing the para position through the cavity for cone-to-partial cone inversion of azacalix[3]arene, which provides a more stable partial cone conformer as a result of the steric effect and solvent polarity.[12] The structure of compound **2a** was confirmed by X-ray single-crystal analysis, as shown in Figure 1a.

The proposed partial cone conformation of *N*-benzylhexahomotriaza-*p*-chlorocalix[3]trinaphylamide (**1**) was confirmed by ^{1}H, ^{13}C, 2D NMR and X-ray single crystal studies (Supporting Information). In the ^{1}H NMR spectrum of **1**, the methylene protons of the $Ar_{calix}CH_2N$ bridges are presented as two AB doublets at 3.91 (J_{H-H} = 15.0 Hz), 3.58 (J_{H-H} = 15.0 Hz), 2.57 (J_{H-H} = 13.4 Hz), and 2.28 (J_{H-H} = 13.4 Hz) ppm and as a signal in a multiplet at 2.99−2.71 ppm. The other doublets for the methylene protons of $Ar_{nap}CH_2NH$ appear at 5.11, 5.04,

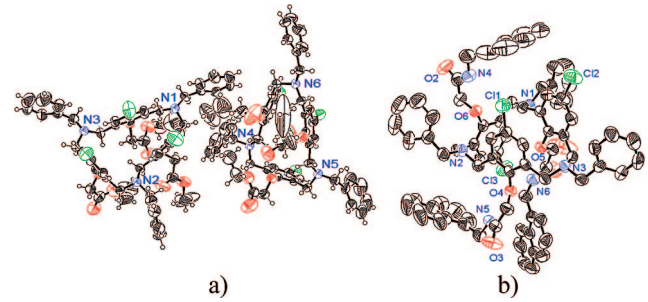


FIGURE 1. ORTEP drawing of (a) *N*-benzylhexahomotriaza-*p*-chlorocalix[3]tri(ethyl acetate) (**2a**) and (b) *N*-benzylhexahomotriaza-*p*-chlorocalix[3]trinaphthylamide (**1**). The displacement ellipsoids are drawn at the 50% probability level.

5.00, 4.93, and 4.89 ppm with germinal coupling constants of 4.8, 5.6, 4.8, 4.8, and 5.2 Hz, respectively. In the parent hexahomotriazacalix[3]arene, which adopts a regular C_{3v} cone conformation, the six protons of $Ar_{calix}H$ exists as a singlet at δ 7.01 ppm.[10] In this case, the three singlets of $Ar_{calix}H$ are observed at 6.51, 6.44, and 6.36 ppm. The ^{13}C NMR spectrum also confirms the partial cone conformation of the azacalix[3]arene macroring of **1**. $Ar_{nap}CH_2NH$ appears as two peaks (41.6, 41.2 ppm) and $Ar_{calix}CH_2N$ splits into four peaks (72.8, 52.7, 52.5, and 52.0 ppm). ^{13}C signals of Ar_{calix} connected with hydrogen also have three peaks, at 130.2, 130.1, and 129.5 ppm. These findings suggest that the three O-substituents have different environments, which implies that **1** is in a stable partial cone conformation. The X-ray single-crystal structure of **1**[13] also strongly supports the partial cone conformation, as shown in Figure 1b. The results show the cavity of azacalix[3]arene macroring (7.92 × 4.92 Å^2) for cation and free N−H for anion binding sites of **1**.

It is well-known that hexahomotriazacalix[3]arene is a strong metal ion complexing agent[7,10] and an amide derivative that can complex anions.[11] Generally, a naphthylene-based fluorophore can form a monomer and excimer[13] that can be observed in a fluorescent spectrum at wavelengths of 336 and 423 nm, respectively. However, the excimer formation of fluorophores that contain more than one fluorogenic unit can be either inter- or intramolecular, in which the former depends on the concentration and solvent polarity. The ratio of excimer to monomer can be observed by the ratio of intensities of excimer to monomer ($I_{excimer}/I_{monomer}$ or I_e/I_m). From the fluorescent spectrum, it was observed that ligand **1** exhibits a strong monomer emission at 336 nm and an excimer emission at 423 nm, suggesting that the two naphthalene units are in a face-to-face π-stack so as to form a dynamic excimer.[14] The ratio of I_e/I_m increases when the concentration of fluorophore **1** decreases (Figure S1, Supporting Information). This may be because, at low concentra-

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(13) X-ray data were collected on a Bruker SMART CCD area detector. The crystal structure was solved by direct methods and refined by full-matrix least-squares. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined by using the riding model. All calculations were performed with a crystallographic software package, WinGX v1.64.05. Crystal data for **1**: $C_{84}H_{75}Cl_3N_6O_6 \cdot 3H_2O$, M_r = 1424.90, monoclinic, space group $P\bar{1}$, a = 16.1795(3) Å, b = 16.5809(3) Å, c = 16.6482(2) Å, α = 92.624(1)°, β = 105.880(1)°, γ = 112.174(1)°, V = 3921.97(11) Å^3, Z = 2, ρ_{calc} = 1.207 g cm^{-3}, $2\theta_{max}$ = 30.54°, Mo Kα (λ = 0.71075 Å), μ = 0.176 mm^{-1}, $\theta-\omega$ scans, T = 293(2) K, 28143 independent reflections, 20620 unique reflections ($I > 2.0\sigma(I)$), 924 refined parameters, R_1 = 0.1276, Rw = 0.3142, $\Delta\rho_{max}$ = 1.204 e Å^{-3}, $\Delta\rho_{min}$ = −0.395 e Å^{-3}; CCDC 673516. See the Supporting Information for crystallographic data in CIF format.

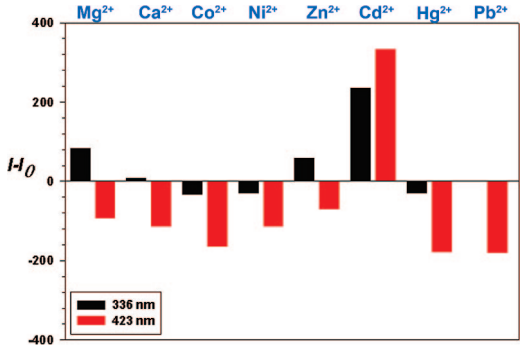

FIGURE 2. Fluorescence changes ($I - I_o$) of **1** upon addition of various metal ions. Conditions: **1** (1 μM) in DMSO, excitation at 285 nm, metal nitrate and chloride (300 equiv) in DMSO. I is the fluorescence emission intensity of complexes **1**. I_o is the fluorescence emission intensity of free **1**.

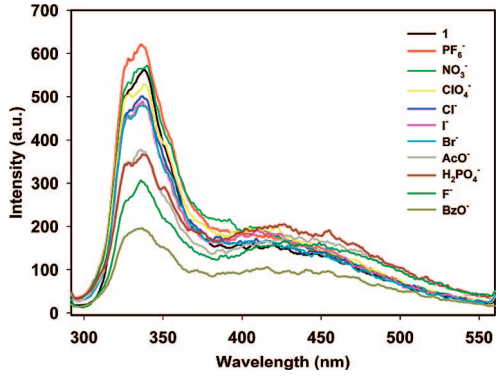

FIGURE 3. Fluorescence emission spectra of **1** upon addition of various anions. Conditions: **1** (0.1 μM) in DMSO, excitation at 285 nm, TBAX (300 equiv) in DMSO.

tions where there is a low percentage of intermolecular interaction, the two naphthyl groups which are on the same side of the azacalix[3]arene platform form an intramolecular excimer and give an excimer emission at 423 nm.

The other naphthyl moiety, where no intermolecular interaction occurs, remains a monomer, but its monomer emission at 336 nm is quenched because the nitrogen atoms are sharing electrons with PET. At higher concentrations, the intermolecular interaction increases, leading to the formation of a hydrogen bond between the amide groups from a side containing a single residue. This hydrogen bond formation prevents the face-to-face stacking of naphthyl moieties and the PET process, leading to increased monomer emission.

The fluorescence intensity changes of **1** were investigated to determine the cation (Figure 2) and anion (Figure 3) binding abilities. In the case of cations, it was found that **1** exhibits Pb^{2+}, Hg^{2+} and Co^{2+} (strong quenching), and Cd^{2+} (strong enhancing) selectivity over the other metal cations studied, as shown in Figure 2. These data imply that **1** binds metal ions with different modes. In the case of Pb^{2+}, only excimer fluorescence is strongly quenched, which is likely to be due not only to the reverse PET from the naphthyl groups to the electron-deficient carbonyl oxygen atoms but also to a heavy-metal ion effect.[15] This may then suggest that Pb^{2+} is strongly bound in a cavity on the side containing two naphthylamide units.

In the case of Cd^{2+}, both monomer and excimer emissions increased with its presence, strongly suggesting that the Cd^{2+} ion preferentially binds by nitrogen atoms of the azacalix[3]arene macroring and is weakly chelated by the carbonyl groups from both sides of azacalix[3]arene, and that consequently the PET and heavy metal effects are excluded. The azacalix[3]arene template, which has a similar structure to that of azacrown ether,[16] exhibits excellent binding with Cd^{2+} and shows, for the first time, the advantage of the azacalixarene framework over the parent calixarene.[7] UV−vis spectroscopy was employed to determine the stoichiometry and stability constants for the complexes with use of the SIRKO program.[17] According to the extent of the observed absorption spectra changes, the association constants of **1** were obtained, and are summarized in Table 1. The data indicate that ligand **1** binds strongly with Pb^{2+} (log β = 4.68 M^{-1}) and Cd^{2+} (log β = 4.53 M^{-1}). The titration profiles of absorption changes of **1** with Cd^{2+} and Pb^{2+} are shown in Figures S3 and S4 (Supporting Information) which show the different patterns. The absorptions of the azacalix[3]arene unit in receptor **1** at wavelengths of 285 and 296 nm strongly decrease upon an addition of Cd^{2+}. In case of Pb^{2+}, the decreases of absorption of these two wavelengths are less pronounced, while the absorption at a wavelength around 265 nm strongly increases. This result confirms that both cations were bound with different modes.

TABLE 1. Stability Constants (log β)[a] of 1:1 Complexes of 1 with Cations and Anions in DMSO by the UV−Vis Titration Method (T = 25 °C, I = 0.01 M Bu_4NPF_6)

cation	log β (M^{-1})	anion	log β (M^{-1})
Mg^{2+}	2.13 (0.01)[b]	F^-	4.21 (0.09),[b] 9.71 (0.01)[c]
Ca^{2+}	2.01 (0.04)[b]	Cl^-	2.37 (0.05)[b]
Co^{2+}	4.08 (0.09)[b]	Br^-	not determined
Ni^{2+}	1.83 (0.04)[b]	I^-	not determined
Cu^{2+}	2.06 (0.08)[b]	NO_3^-	2.03 (0.01)[b]
Zn^{2+}	3.23 (0.09)[b]	ClO_4^-	2.20 (0.01)[b]
Cd^{2+}	4.53 (0.04)[b]	$H_2PO_4^-$	not determined
Hg^{2+}	2.12 (0.01)[b]	AcO^-	2.43 (0.02),[b] 9.29 (0.03)[c]
Pb^{2+}	4.68 (0.04)[b]	BzO^-	2.83 (0.01),[b] 9.43 (0.03)[c]

[a] Mean values of $n \geq 3$ (for cations) and $n \geq 2$ (for anions) of independent determinations with standard deviation σ_{n-1} on the mean in parentheses. [b] 1:1 complex (AL). [c] 2:1 complex (A_2L).

For the anion sensor study, the fluorescence reveals a quenching effect from a PET mechanism on the monomer peak. The excimer peak, however, has a much lower effect, indicating that allosteric effect-induced conformation changes do not favor the binding of anions. The ^1H MNR spectra of **1** anions also strongly support this notion revealing that only the signals of amide protons shift (Figure S2, Supporting Information), and thus that anions were likely bound by hydrogen bonds with the amide groups.

To obtain an insight into the selectivity of anion binding, UV−vis spectroscopy was employed to study the interaction

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of compounds **1** with anionic guests. Upon the addition of anions, the absorption spectra of **1** changed (see Table S1, Supporting Information). From the derived stability constants (Table 1) of compound **1** complexes with anions, it can be concluded that **1** prefers to complex F^- over the other anions tested by forming 1:1 complexes.

In summary, the partial-cone conformation of *N*-benzylhexahomotriaza-*p*-chlorocalix[3]trinaphthylamide (**1**) was selectively synthesized from both cone and partial-cone triester intermediates coupling with 1-aminomethylnaphthalene. The crystal structures of **1** and **2a** were confirmed by X-ray crystallography. On the basis of fluorescent, UV−vis, and ^{1}H NMR spectra changes upon cation and anion complex formation, it has been noted that **1** displays strong binding with Cd^{2+} (by using nitrogen at the azacalix[3]arene framework), Pb^{2+} and Co^{2+} (by using the carbonyl of amide groups from the side of azacaliz[3]arene containing two naphthyl groups), and F^- (by using hydrogen bonds between the NH part of the amide with anions).

Experimental Section

Synthesis of *N*-Benzylhexahomotriaza-*p*-chlorocalix[3]tri(ethyl acetate) (2). The synthetic procedures of **2a** and **2b** have been modified from our previous work[11] by replacing the methyl bromoacetate with ethyl bromoacetate. Column chromatography on silica gel (hexane/EtOAc = 9:1, v/v) of crude product afforded a 21% yield of **2a** (X-ray data demonstrated in the Supporting Information) (0.135 g, 0.130 mmol) as a deep yellow oil. **2a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.26 (m, 12H, Ar*H*), 7.18 (t, 3H, J_{H-H} = 7.2 Hz, Ar*H*), 6.90 (s, 6H, Ar*H*), 4.28 (s, 6H, OCH_2CO), 4.22 (q, 6H, J_{H-H} = 7.6 Hz, OCH_2CH$_3$), 3.61 (s, 6H, NCH_2Ar), 3.44 (dd, 12H, J_{H-H} = 14.4, 7.6 Hz, NCH_2Ar), 1.28 (t, 9H, J_{H-H} = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MH$_Z$, $CDCl_3$) δ 169.1, 152.3, 139.2, 133.9, 130.1, 129.0, 128.9, 128.9, 128.6, 127.3, 71.0, 62.4, 52.5, 52.1, 14.4; IR (KBr) ν 3063, 3028, 2981, 2929, 2803, 1757, 1448, 1372, 1292, 1188, 1118, 1065, 1030, 879, 743, 701 cm^{-1}; MS (MALDI-TOF) calcd for $[C_{57}H_{60}Cl_3N_3O_9]^+$ *m*/*z* 1035.34, found 1036.92 $[M + H]^+$. Anal. Calcd for $C_{57}H_{60}Cl_3N_3O_9$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.95; H, 5.71; N, 4.00. **2b** (pale yellow solid, 31%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 2H, Ar*H*), 7.31 (t, J = 7.6 Hz, 3H, Ar*H*), 7.38−7.30 (m, 10H, Ar*H*), 7.02 (s, 4H, Ar*H*), 6.98 (s, 2H, Ar*H*), 4.31 (br d, 2H, OCH_2CO), 4.15 (s, 4H, OCH_2CH$_3$), 4.13 (s, 2H, OCH_2CH$_3$), 4.11 (br d, 2H, OCH$_2$CO), 3.79−3.22 (m, 20H, OCH$_2$CO and NCH$_2$Ar), 1.24 (m, 9H, OCH$_2$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 169.0, 155.8, 154.1, 139.4, 138.6, 134.8, 133.4, 132.9, 131.6, 130.4, 129.6, 129.3, 129.2, 128.8, 128.5, 128.4, 128.1, 127.4, 127.3, 70.8, 70.3, 63.0, 60.9, 59.4, 53.0, 52.7, 52.4, 14.4, 14.3; IR (KBr) ν 3063, 3028, 2981, 2922, 2852, 2804, 1756, 1446, 1376, 1291, 1187, 1121, 1063, 1030, 891, 743, 700 cm^{-1}; MS (MALDI-TOF) calcd for $[C_{54}H_{54}Cl_3N_3O_9]^+$ *m*/*z* 1035.34, found 1036.92 $[M + H]^+$. Anal. Calcd for for $C_{57}H_{60}Cl_3N_3O_9$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.82; H, 5.92; N, 3.93.

Synthesis of *N*-Benzylhexahomotriaza-*p*-chlorocalix[3]trinaphthylamide (1). A solution of **2a** (0.135 g, 0.130 mmol) was charged with a solution of 1-napthymethylamine (0.072 g, 0.456 mmol) in 1:1 methanol:toluene mixture (10 mL). The solution was refluxed for 3 days. After removing the solvents, the crude mixture was purified by column chromatography of the precipitate on silica gel (hexane/EtOAc = 3:2, v/v), which gave **1** (0.073 g, 0.053 mmol, 41%) as a white solid. A solution of **2b** (0.207 g, 0.200 mmol) was charged with a solution of 1-napthymethylamine (0.207 g, 0.700 mmol) in 1:1 methanol:toluene mixture (10 mL). The solution was refluxed for 7 days. After removing the solvents, the crude mixture was purified by column chromatography of the precipitate on silica gel (hexane/EtOAc = 3:2, v/v), which gave **1** (0.114 g, 0.087 mmol, 42%) as a white solid: ^{1}H NMR (400 MHz, CDCl3) δ 8.10−8.08 (m, 3H, ArH_{nap}), 8.01−7.97 (m, 4H, ArH_{nap}), 7.91 (d, J_{H-H} = 7.2 Hz, 2H, ArH_{nap}), 7.64−7.57 (m, 8H, ArH_{nap}), 7.64−7.57 (m, 4H, ArH_{nap}), 7.32−7.21 (m, 9H, ArH_{calix}), 7.14 (d, J_{H-H} = 6.8 Hz, 2H, ArH_{calix}), 7.09 (d, J_{H-H} = 7.6 Hz, 4H, ArH_{calix}), 7.02 (s, 1H, CH$_2$N*H*CO), 6.86 (s, 2H, CH$_2$NHCO), 6.51 (s, 2H, ArH_{calix}), 6.44 (s, 2H, ArH_{calix}), 6.36 (s, 2H, ArH_{calix}), 5.11 (d, J_{H-H} = 4.8 Hz, 2H, ArCH_2NH), 5.04 (d, J_{H-H} = 5.6 Hz, 1H, ArCH_2NH), 5.00 (d, J_{H-H} = 4.8 Hz, 1H, ArCH_2NH), 4.93 (d, J_{H-H} = 4.8 Hz, 1H, ArCH_2NH), 4.89 (d, J_{H-H} = 5.2 Hz, 1H, ArCH_2NH), 3.91 (d, J_{H-H} = 15.2 Hz, 2H, ArCH_2N), 3.80 (s, 2H, OCH_2CO), 3.58 (d, J_{H-H} = 14.8 Hz, 2H, ArCH_2N), 3.09 (s, 2H, OCH_2CO), 2.99−2.71 (m, 12H, ArCH_2N and OCH_2CO), 2.57 (d, J_{H-H} = 12.8 Hz, 2H, ArCH_2N), 2.28 (d, J_{H-H} = 14.0 Hz, 2H, ArCH_2N); ^{13}C NMR (100 MH$_Z$, $CDCl_3$) δ 167.3, 167.2, 153.1, 152.0, 138.6, 137.8, 134.2, 134.1, 133.5, 133.3, 133.1, 132.5, 131.7, 131.5, 130.2, 130.1, 129.7, 129.5, 129.3, 129.2, 129.1, 129.0, 128.8, 128.7, 128.5, 128.4, 128.3, 127.7, 127.5, 127.1, 127.0, 126.4, 126.3, 126.0, 125.5, 123.9, 123.6, 72.8, 71.4, 63.0, 60.0, 52.7, 52.5, 52.0, 41.6, 41.2; IR (KBr) ν 3419, 3059, 2921, 2837, 2810, 1679, 1594, 1524, 1436, 1364, 1251, 1193, 1124, 1041, 884, 797, 789, 745, 701 cm^{-1}; MS (MALDI-TOF) calcd for $[C_{84}H_{75}Cl_3N_6O_6]^+$ *m*/*z* 1368.48, found 1369.67 $[M + H]^+$. Anal. Calcd for $C_{84}H_{75}Cl_3N_6O_6$: C, 73.59; H, 5.51; N, 6.31. Found: C, 73.56; H, 5.53; N, 6.14.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds including NMR spectra and crystal structures of *N*-benzylhexahomotriaza-*p*-chlorocalix[3]trinaphthylamide (**1**) (CIF) and *N*-benzylhexahomotriaza-*p*-chlorocalix[3]tri(ethyl acetate) (**2a**) (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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