Selective N-Protection of a Tetraamino Calix[4]arene Tetraether

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Introduction

Calixarenes are [1$_n$] metacyclophanes consisting of phenolic units.[1] Especially calix[4]arenes have been successfully used as building blocks for the construction of highly sophisticated molecules in fields such as molecular recognition,[2] self-assembly,[3] or crystal engineering.[4] Various methods have been developed for the complete and partial substitution of calix[4]arenes both at the wide[5] (upper) and at the narrow (lower) rim[6] in order to introduce the desired functional groups in appropriate arrangements.

Tetraamino calix[4]arenes such as **1** are easily synthesized by ipso-nitration of *tert*-butyl calix[4]arene tetraethers[7] and subsequent reduction of the resulting tetranitro compounds.[8] Their *complete* N-acylation led to various derivatives forming for instance self-assembling molecular capsules[9] or stable complexes with cations[10] or anions.[11] It is evident that a partial acylation or protection of the amino groups and consequently the possibility of introducing different acyl groups would enormously increase the synthetic potential of compounds such as **1**.

We have found now conditions to acylate one, two adjacent, or three amino groups of **1** by BOC-anhydride.[12] The *partially* protected compounds **2**, **5**, and **9** provide an easy access to various mono-, 1,2-di- and tri-N-acylated calix[4]arenes and to the corresponding "mixed" tetra-*N*-acyl derivatives containing two different *N*-acyl residues.

Results and Discussion

Tetraamine **1** was reacted with various amounts of BOC-anhydride in CH_2Cl_2 at room temperature. With 3 equiv of BOC-anhydride, a mixture of acylated products was obtained from which the tri-BOC-monoamine **2** and the tetra-BOC derivative **3c** were isolated by column chromatography in 54 and 20% yields, respectively (Scheme 1). Trace amounts of the 1,2-di-BOC-derivative **5** were also found under these conditions. When the acylation of **1** was carried out with 2 equiv of BOC-anhydride, **5** was formed in 48% isolated yield.[13] In this case traces of compound **2** could be chromatographically detected. With 1 equiv of BOC-anhydride, triamine **9** was formed in 36% yield along with a very small amount of diamine **5**. It is important to note that under all these conditions the 1,3-di-BOC-protected derivative could not be detected. Thus, the partially protected calixarenes **2**, **5**, and **9** can be easily obtained in gram quantities, although their simpliest purification is achieved by column chromatography.

The statistical amounts of mono-, di-, and triacylated compound expected under the respective stoichiometric conditions would be 42.2%, 37.5% (1,2- plus 1,3-isomer), and 42.2%, respectively.[14] The pronounced preference of 1,2- over 1,3-diacylation cannot be explained by statistical reasons which require a 2:1 ratio of the 1,2- and 1,3-isomers. Hydrogen bonding, steric, and conformational factors may be assumed to explain this surprising selectivity.

The structures of monoamine **2,** diamine **5**, and triamine **9** were unambiguously proved by ^{1}H NMR and mass spectrometry while the frequently overlapping ^{13}C NMR spectra were less useful. The ^{1}H NMR spectrum of compound **2** contains two singlets and two meta-coupled doublets[15] for the aromatic protons, two pairs of doublets for the methylene protons of the bridges (Figure 1), and two singlets (2:1 ratio) for the protons of the *tert*-butyl groups in accordance with the expected pattern for a

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(14) The yields to be expected under statistical conditions follow from the combination of probabilities. For example, if 3 mol of BOC-anhydride are used per mole of tetraamine (= stoichiometric conditions for a triacylated product) the probability to find a certain amino group acylated is 3/4, to find it nonacylated 1/4 (complete conversion of BOC-anhydride assumed). The probability of getting a certain triacylated derivative is 3/4·3/4·3/4·1/4. This has to be multiplied with the respective binomial coefficient 4 (4 possibilities exist for a triacylated compound, since each of the 4 amino groups may be reacted) leading to an overall probability of $(3/4)^3 \cdot 1/4 \cdot 4 = 0.421875$ for the triacylated product. Thus, 42.2% should be found, if the reaction is purely statistical.

(15) The coupling was detected by a COSY spectrum.

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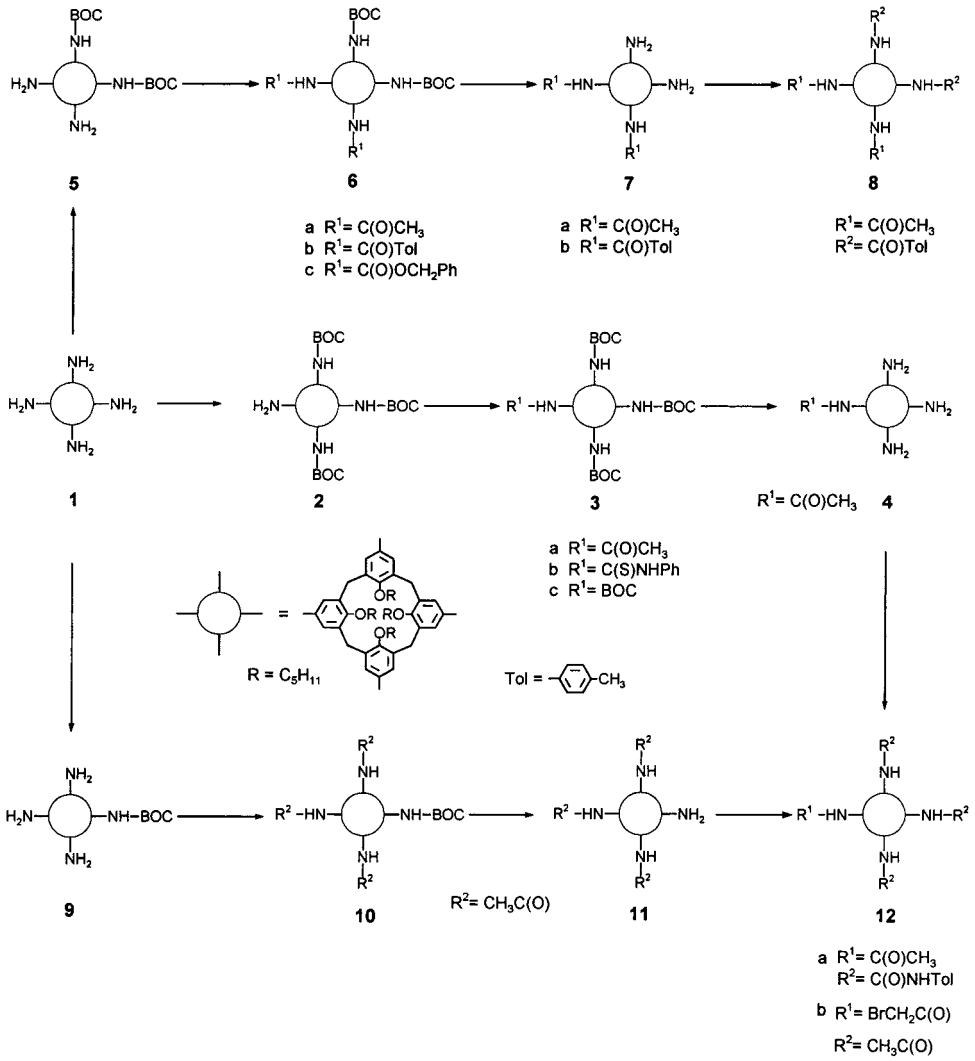
Scheme 1



trisubstituted calix[4]arene. A principally analogous spectrum for a compound with C_s symmetry was also observed for the triamine **9**.

In contrast, the ^{1}H NMR spectrum of **5** exhibits *three pairs* of doublets (ratio 1:2:1) for the methylene protons of the bridges (Figure 1) and four broad singlets (or in the case of **6b** four meta-coupled doublets) for the aromatic protons as expected for calix[4]arenes with different p-substituents in the 1,2- and 3,4-position. The corresponding 1,3-disubstituted derivative would show *two* singlets for the aromatic protons and *one pair* of doublets for the methylene protons of the bridges.

Reaction of the remaining amino group in **2** with AcOAc (Et_3N, rt) or phenyl isothiocyanate (THF, rt) led to the acetamide **3a** and the phenylthiourea **3b**. The selective cleavage of the BOC groups (TFA, CH_2Cl_2, rt) in **3a** gave quantitatively the *monosubstituted* calix[4]-arenetriamine **4** (isolated in form of its trifluoroacetate) which upon further acylation by *p*-tolyl isocyanate (THF, Et_3N, rt) was transformed into the triureacalix[4]arene **12a** (70% yield). Alternatively the C_s calixarene derivatives **10**, **11,** and **12b** could be prepared starting from monoprotected compound **9**.

Similar reaction sequences performed with diamine **5** resulted in a series of 1,2-disubstituted calix[4]arene derivatives. Namely, the reaction of **5** with AcOAc (Et_3N, rt) or the Schotten−Baumann acylation with *p*-methylbenzoyl chloride and benzyl chloroformate (EtOAc/H_2O, K_2CO_3) gave tetraamides **6a**−**c**. Subsequent deprotection with TFA resulted in diamines **7a**,**b**. The following acylation of **7b** (AcOAc, Et_3N, rt) afforded the "mixed" tetraamide **8** that is also available by acylation of **7a**.

These examples demonstrate that the partially BOC-protected aminocalix[4]arenes can be used for the *rational* synthesis of various derivatives mono-, 1,2-di-, and trisubstituted by amino or *N*-acyl groups at the wide rim of the macrocycle. It is important to mention that attempts of the direct partial acylations of tetraamine **1** with AcOAc, 4-methylbenzoyl chloride, and 4-methylphenyl isocyanate led to mixtures difficult to separate. Partially protected compounds analogous to **2**, **5**, and **9** should be available in a similar way from tetraamino calix[4]arenes fixed in the cone conformation by ether residues different to pentyl. They are apparently promising starting materials for the synthesis of various functional molecules including larger self-assembling structures.

Experimental Section

Tri-BOC-calix[4]arene 2. To a vigorously stirred solution of the tetraaminocalixarene **1**[8] (1.0 g, 1.30 mmol) in dry CH_2Cl_2 (100 mL) was added a solution of BOC-anhydride (0.856 g, 3.92 mmol) in CH_2Cl_2 (10 mL) dropwise. After 24 h of stirring at room temperature, the reaction mixture was evaporated in vacuo. The

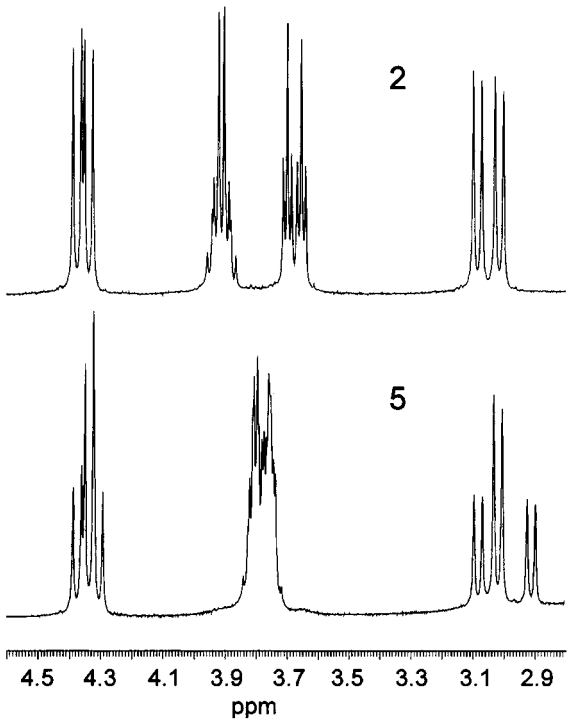


Figure 1. Section of the ^{1}H NMR spectra (500 MHz, $CDCl_3$, rt) of monoamine **2** and diamine **5**.

pure product was isolated by flash column chromatography (EtOAc/hexane 6/4) where it was eluted after a small fraction of tetra-BOC-calix[4]arene **3c**. **2**: yield 0.75 g (54%); yellowish powder: mp 130−131 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (s, 1H), 7.08, 6.83, 6.34, 6.10, 5.71 (five s, each 2H), 4.37, 4.33 (two d, J = 13.4 Hz, each 2H), 3.95−3.86 (m, 4H), 3.69, 3.65 (two t, J = 6.6 Hz, each 2H), 3.08, 3.01 (two d, J = 13.7 Hz, each 2H), 1.91−1.76 (m, 8 H), 1,54 (s, 18 H), 1.51−1.45 (m, 4H), 1,43 (s, 9H), 1.41−1.31 (m, 8H), 1.28−1.18 (m, 4H), 0.96−089 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.64, 153.50, 153.08, 136.80, 134.28, 134.15, 131.81, 124.01, 119.38, 119.36, 115.23, 80.01, 79.10, 75.06, 74.83, 71.06, 70.73, 29.94, 29.89, 29.58, 29.47, 28.54, 28.49, 28.36, 28.04, 22.71, 22.58, 14.06, 13.93; FD-MS, *m/z* 1065.4 (20, M), 965.0 (100, M-BOC). Anal. Calcd for $C_{63}H_{92}N_4O_{10}\cdot H_2O$: C, 69.84; H, 8.74; N, 5.17. Found: C, 69.93, H, 8.57, N, 5.04.

Tetra-BOC-calix[4]arene 3c: yield 20 %; white solid: mp 199−200 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.59 (s, 8H), 6.15 (s, 4H), 4.34 (d, J = 13.4 Hz, 4H), 3.68 (t, J = 6.4 Hz, 8H), 3.06 (d, J = 13.2 Hz, 4H), 1.91−1.72 (m, 8H), 1,48 (s, 36H), 1.38−1.25 (m, 16 H), 0.96−0.83 (m, 12H); FD-MS, *m/z* 1165.4 (100, M). Anal. Calcd for $C_{68}H_{100}N_4O_{12}$: C, 70.06, H, 8.65, N, 4.81; Found: C, 70.03; H, 8.60; N, 4.83.

1,2-Di-BOC-calix[4]arene 5. Compound **5** was prepared in the same way as **2** from the tetraamino calixarene **1** (2.0 g, 2.60 mmol) and BOC-anhydride (1.13 g, 5.20 mmol). Isolation and purification by flash column chromatography (EtOAc/hexane 1/1): yield 1.2 g (48%); yellowish powder; mp 133−134 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.01, 6.62, 6.42 (three s, each 2H), 6.04 (d, J = 3.6 Hz, 4 H), 4.36 (d, J = 13.7 Hz, 1H), 4.33 (d, J = 13.4 Hz, 2H), 4.30 (d, J = 13.1 Hz, 1H), 3.81−3.61 (m, 8 H), 3.08 (d, J = 13.7 Hz, 1H), 3.01 (d, J = 13.4 Hz, 2H), 2.91 (d, J = 13.1 Hz, 1H), 1.89−1.69 (m, 8 H), 1,48 (s, 18H), 1.42−1.30 (m, 16H), 0.95−0.83 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.03, 153.72, 150.15, 139.69, 135.69, 135.63, 135.50, 131.68, 122.09, 115.59, 115.50, 79.42, 74.93, 74.75, 31.08, 29.71, 28.38, 28.32, 28.29, 22.26, 14.02; MALDI-TOF-MS, *m/z* 965.0 (100, M). Anal. Calcd for $C_{58}H_{84}O_8N_4\cdot H_2O$: C, 70.84; H, 8.82; N, 5.70. Found: C, 70.77; H, 8.77; N, 5.70.

Mono-BOC-calix[4]arene 9. Compound **9** was prepared in the same way as **2** from the tetraamino calixarene **1** (1.0 g, 1.30 mmol) and BOC-anhydride (0.282 g, 1.30 mmol). Isolation and purification by flash column chromatography (EtOAc/hexane 1/1, followed by EtOAc): yield 0.4 g (36%); yellowish powder; mp 135−136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 6.28 (s, 4 H), 6.18, 5.77 (two s, each 2H), 4.30 (d, J = 12.8 Hz, 2H), 4.26 (d, J = 12.3 Hz, 2H), 3.86−3.75 (m, 4 H), 3.68−3.60 (m, 4H), 3.21 (br s, 6H), 2.98 (d, J = 13.5 Hz, 2H), 2.87 (d, J = 13.2 Hz, 2H), 1.85−1.74 (m, 8 H), 1.42 (s, 9 H), 1.41−1.17 (m 16 H), 0.92−0.87 (m, 12 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.66, 150.61, 149.70, 136.66, 136.51, 134.83, 134.71, 131.53, 123.60, 79.06, 74.97, 74.84, 74.73, 31.08, 29.85, 29.56, 28.45, 28.39, 28.19, 22.74, 22.63, 14.08, 13.96; FD-MS, *m/z* 864.6 (100, M). Anal. Calcd for $C_{53}H_{76}N_4O_6$: C, 73.58; H, 8.85; N, 6.48. Found: C, 73.37; H, 8.76; N, 6.31.

Tetraamidocalix[4]arene 3a. To a solution of the monoamine **2** (0.3 g, 0.28 mmol) in Ac_2O (20 mL) was added Et_3N (0.5 mL) in one portion, and the reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was dissolved in EtOH (20 mL) and reprecipitated with water. The precipitate was filtered off and dried in vacuo. **3a**: yield 0.23 g (74%); white solid; mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.95, 6.91, 6.36, 6.33, 6.16 (five s, each 2H), 6.10 (s, 1H), 4.34 (d, J = 13.2 Hz, 4H), 3.95−3.85 (m, 4H), 3.70−3.59 (m, 4H), 3.05 (d, J = 13.1 Hz, 4 H), 2.00 (s, 3H), 1.82−1.77 (m, 8H), 1.50 (s, 18H), 1.47−1.42 (m, 4H), 1.40 (s, 9H), 1.37−1.29 (m, 8 H), 1.25−1.14 (m, 4H), 0.95−0.84 (m, 12H); FD-MS, *m/z* 1106.9 (100, M). Anal. Calcd for $C_{65}H_{94}N_4O_{11}\cdot H_2O$: C, 69.35; H, 8.60; N, 4.98. Found: C, 69.19; H, 8.48; N, 4.76.

Tetraamidocalix[4]arene 3b. To a stirred solution of the amine **2** (0.2 g, 0.18 mmol) in dry THF (10 mL) was added phenyl isothiocyanate (0.03 mL, 0.37 mmol) under nitrogen in one portion, and the reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and hexane was added. The precipitate was filtered off and dried in vacuo. **3b**: yield 0.2 g (92%); white solid; mp 135−136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36−7.18 (m, 8H), 7.09 (s, 1H), 6.95, 6.37, 6.28, 6.22 (four s, each 2H), 5.75 (s, 1H), 4.39 (d, J = 13.2 Hz, 2H), 4.32 (d, J = 12.6 Hz, 2H), 3.96−3.91 (m, 4 H), 3.74−3.67 (m, 2H), 3.63−3.57 (m, 2H), 3.11−3.03 (m, 4H), 1.87−1.76 (m, 8H), 1.60−1.23 (m, 43 H), 0.90 (t, J = 6.4 Hz, 12 H); FD-MS, *m/z* 1107.4 (9, M − OC_4H_9), 1065.3 (100, M − C_7H_6NS). Anal. Calcd for $C_{70}H_{97}N_5O_{10}S\cdot H_2O$: C, 68.99; H, 8.19; N, 5.74. Found: C, 68.98; H, 8.09; N, 5.60.

Triaminocalix[4]arene 4. To a stirred solution of **3a** (0.2 g, 0.18 mmol) in CH_2Cl_2 (20 mL) was added TFA (20 mL) in one portion. The reaction mixture was stirred at room temperature for 2 h and then diluted with toluene (50 mL). The solvent was evaporated in vacuo to dryness, and the powder obtained was dried in vacuo at 100 °C for 3 h. **4**: yield 0.2 g (97%); yellow solid; mp 251−252 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1 H), 7.19, 6.86, 6.20, 6.16 (four s, each 2H), 4.29 (d, J = 13.0 Hz, 4H), 3.95−3.80 (m, 4H), 3.77−3.65 (br m, 4H), 3.22 (d, J = 13.1 Hz, 2H), 3.12 (d, J = 13.0 Hz, 2H), 1.98 (s, 3H), 1.90−1.74 (m, 8H), 1.50−1.19 (m, 16H), 0.95−085 (m, 12H); FD-MS, *m/z* 806.9 (100, M). Anal. Calcd for $C_{56}H_{73}N_4O_{11}F_9$: C, 58.51; H, 6.41; N, 4.88. Found: C, 58.47; H, 6.21; N, 4.78.

Tetraamidocalix[4]arene 6a. Compound **6a** was prepared in the same way as **3a** from diamine **5** (0.3 g, 0.31 mmol), Ac_2O (20 mL), and Et_3N (0.5 mL). **6a**: yield 0.3 g (94%); white solid; mp 165−166 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36 (br s, 2H), 6.70−6.69 (br m, 4H), 6.54 (s, 4H), 6.30 (s, 2H), 4.35 (d, J = 13.0 Hz, 4H), 3.82−3.72 (m, 8H), 3.05 (d, J = 13.1 Hz, 4H), 2.05 (s, 6H), 1.92−1.70 (m, 8H), 1.45 (s, 18H), 1.35−1.32 (m, 16H), 0.90 (t, J = 6.6 Hz, 12H); FD-MS, *m/z* 974.8 (36, M − Ac), 874.6 (100, M − Ac − BOC) 1048.9 (24, M). Anal. Calcd for $C_{62}H_{88}N_4O_{10}$: C, 70.96; H, 8.45; N, 5.34. Found: C, 70.70; H, 8.14; N, 5.23.

Tetraamidocalix[4]arene 6b. To a vigorously stirred suspension of diamine **5** (0.3 g, 0.31 mmol) in EtOAc (30 mL) and Na_2CO_3 (1 N, 50 mL) was added *p*-methylbenzoyl chloride (3−5 mL) in two portions. The mixture was intensively stirred at room temperature for 20−30 min. The organic layer was separated washed with Na_2CO_3 (1N, 50 mL) and water (2 × 50 mL). Solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 and reprecipitated with hexane. The white precipitate was filtered off, washed with hexane, and dried in vacuo. **6b**: yield 0.28 g (83%); white solid; mp 161−162 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.73 (d, J = 8.3 Hz, 4H), 7.19 (m, 6H), 6.95, 6.87, 6.62, 6.57 (four d, J = 2.5 Hz, each 2 H), 6.30 (br s, 2H), 4.41 (d,

J = 12.5 Hz, 1H), 4.39 (d, J = 12.0 Hz, 2H), 4.36 (d, J = 12.0 Hz, 1H), 3.87−3.77 (m, 8H), 3.14 (d, J = 12.0 Hz, 1H), 3.11 (d, J = 12.0 Hz, 2H), 3.07 (d, J = 12.1 Hz, 1H), 2.37 (s, 6H), 1.87 (m, 8H), 1.35 (s, 34H), 0.91 (t, J = 6.2 Hz, 12H); FD-MS, m/z 1201.4 (100, M). Anal. Calcd for $C_{74}H_{96}N_4O_{10}\cdot 0.5H_2O$: C, 73.42; H, 8.08; N, 4.63. Found: C, 73.11; H, 8.10; N, 4.99.

Tetraamidocalix[4]arene 6c. Compound **6c** was prepared in the same way as **6b** from diamine **5** (0.3 g, 0.31 mmol), benzyl chloroformate (5−7 mL), EtOAc (30 mL), and Na_2CO_3 (1 N, 50 mL). **6c**: yield 87%; white solid; mp 106−107 °C;^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38−7.30 (m, 10 H), 6.59 (s, 4 H), 6.55 (s, 4H), 6.38, 6.17 (two s, each 2H), 4.34 (d, J = 13.0 Hz, 4H), 3.80−3.74 (m, 8H), 3.05 (d, J = 13.1 Hz, 4H), 1.82 (m, 8H), 1.63 (s, 4H), 1.41 (s, 18H), 1.38−1.32 (m, 16H), 0.90 (t, J = 6.2 Hz, 12 H); FD-MS, m/z 1233.2 (100, M). Anal. Calcd for $C_{74}H_{96}N_4O_{12}$: C, 72.05; H, 7.84; N, 4.54. Found: C, 71.96; H, 7.83; N, 4.42.

Diaminocalix[4]arene 7a. Compound **7a** was prepared in the same way as **4** from **6a** (0.2 g, 0.19 mmol), CH_2Cl_2 (20 mL), and TFA (20 mL). **7a**: yield 0.2 g (98%); yellow solid; mp 215−216 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.45 (s, 2H), 6.93, 6.79 (two d, J = 1.5 Hz, each 2H), 6.63 (s, 4H), 4.31 (d, J = 12.7 Hz, 4H), 3.83−3.78 (m, 8H), 3.27 (d, J = 13.2 Hz, 1H), 3.17 (d, J = 13.0 Hz, 2H), 3.06 (d, J = 13.1 Hz, 1H), 1.91 (s, 6H), 1.84 (br m, 8H), 1.34 (br m, 16H), 0.89 (br m, 12H); FD-MS, m/z 848.8 (100, M). Anal. Calcd for $C_{56}H_{74}N_4O_{10}F_6\cdot H_2O$: C, 61.41; H, 6.99; N, 5.12; Found: C, 61.50; H, 6.65; N, 5.12.

Diaminocalix[4]arene 7b. Compound **7b** was prepared in the same way as **4** from **6b** (0.2 g, 0.18 mmol), CH_2Cl_2 (20 mL), and TFA (20 mL). **7b**: yield 0.2 g (90%); yellow solid; mp 230−231 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.82 (s, 2H), 9.50 (br s, 6H), 7.77 (d, J = 8.3 Hz, 4H), 7.25 (d, J = 8.3 Hz, 4H), 7.23, 7.09, 6.72, 6.69 (four s, each 2H), 4.36 (d, J = 12.5 Hz, 4H), 3.84−3.85 (m, 8H), 3.36−3.11 (m, 4H), 2.33 (s, 6H), 1.88 (br m, 8H), 1.36 (br m, 16 H), 0.90 (br m, 12H); FD-MS, m/z 1000.7 (100, M).

Tetraamidocalix[4]arene 8. Compound **8** was prepared in the same way as **3a** from **7b** (0.2 g, 0.16 mmol), Ac_2O (20 mL), and Et_3N (0.5 mL). **8**: yield 72%; white powder; mp 187−188 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.04 (s, 2H), 7.76−7.69 (m, 6H), 7.22−7.17 (m, 4H), 6.96−6.94 (m, 4H), 6.74, 6.70 (two s, each 2H), 4.41−4.35 (m, 4H), 3.82−3.80 (m, 8H), 3.10−3.04 (m, 4H), 2.35 (s, 6H), 2.04 (s, 6H), 1.85 (br m, 8H), 1.34 (br m, 16H), 0.91 (br m, 12H); FD-MS, m/z 1084.6 (100, M).

Tetraamidocalix[4]arene 10. Compound **10** was prepared in the same way as **3a** from **9** (0.2 g, 0.23 mmol), Ac_2O (20 mL), and Et_3N (0.5 mL). **10**: yield 0.2 g (88%), white solid; mp 175−176 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.79 (br s, 1H), 7.63 (br s, 2H), 6.78−6.47 (m, 9H), 4.33 (d, J = 13.1 Hz, 4 H), 3.81−3.73 (m, 8H), 3.03 (d, J = 13.6 Hz, 4H), 2.11−1.61 (m, 17H), 1.45 (s, 9H), 1.33 (br m, 16H), 0.89 (br m, 12H). FD-MS, m/z 916.7 (100, M − OC_4H_9), 991.0 (90, M). Anal. Calcd for $C_{59}H_{82}N_4O_9\cdot 0.5H_2O$: C, 70.83; H, 8.37; N, 5.60. Found: C, 70.84; H, 8.18; N, 5.23.

Aminocalix[4]arene 11. Compound **11** was prepared in the same way as **4** from **10** (0.2 g, 0.20 mmol), CH_2Cl_2 (20 mL), and TFA (20 mL). **11**: yield 0.2 g (99%); white solid; mp 210−212 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.69 (s, 2H), 9.39 (br s, 3H), 9.14 (s, 1H), 7.30, 7.07, 6.51, 6.37 (four s, each 2H), 4.30 (br m, 4H), 3.88 (br m, 4H), 3.72−3.67 (m, 4H), 3.17−3.04 (m, 4H), 1.98 (s, 9H), 1.84 (br m, 8H), 1.44−1.27 (m, 16H), 0.90−0.89 (m, 12H); FD-MS, m/z 890.5 (100, M).

Tetraamidocalix[4]arene 12a. Compound **12a** was prepared in the same way as **3b** from **4** (0.2 g, 0.24 mmol), p-tolyl isocyanate (0.1 mL, 0.96 mmol), THF (5 mL), and Et_3N (1 mL). **12a**: yield 70%; white solid; mp 220−221 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.27−8.01 (m, 6H), 7.40−6.65 (m, 20H), 4.30 (br d, 4H), 3.82−3.73 (br m, 8H), 3.09−3.04 (m, 4H), 2.19 (s, 9H), 1.98−1.76 (br m, 11H), 1.48−1.25 (br m, 16H), 0.91 (br m, 12H); FD-MS, m/z 1205.8 (100, M).

Tetraamidocalix[4]arene 12b. Compound **12b** was prepared in the same way as **6b** from **11** (0.1 g, 0.09 mmol), EtOAc (10 mL), Na_2CO_3 (1 N, 50 mL), and bromoacetyl chloride (1 mL). **12b**: yield 0.06 g (66%); white solid; mp 280−281 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.22 (s, 1H), 8.65 (s, 1H), 8.59, 6.60, 6.56, 6.44, 6.39 (five s, each 2H), 4.10 (d, J = 12.3 Hz, 2H), 4.09 (d, J = 13.1 Hz, 2H), 3.58 (s, 2 H), 3.56−3.49 (m, 8H), 2.80 (d, J = 13.2 Hz, 4H), 1.72 (s, 3H), 1.69 (s, 6H), 1.59−1.55 (m, 8H), 1.10−1.06 (m, 16H), 0.64 (t, J = 6.2 Hz, 12H); FD-MS, m/z 1011.9 (100, M).

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