JOC Article

Synthesis and Structure of Lower Rim C-Linked *N*-Tosyl Peptidocalix[4]arenes

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Received March 3, 2003

Chiral p-*tert*-butylcalix[4]arenes functionalized at the lower rim with amino acid residues have been prepared. The ^{1}H and ^{13}C NMR spectra indicate that the macrocycles preferably adopt a cone conformation. Calix[4]arenes bearing amino acid moieties were prepared as a class of receptors selective for anions that are bound through hydrogen bonding with the NH group. The association constants are dependent on the nature of the substituents at the lower rim. Derivative **9** shows the strongest complexation and the largest selectivity for *N*-tosyl-(L)-alaninate. Finally, a preliminary X-ray crystal study of the difunctionalized receptor **6f** shows the "*flattened cone*" conformation in the solid state.

Introduction

Calixarenes and their derivatives have been extensively used in the past few years as receptors to recognize a wide variety of ions or inorganic and organic guest molecules, forming host−guest or supramolecular complexes.[1]

Many calixarene chemists focus their interest on the syntheses of chiral analogues, which are expected to act as synthetic enzymes. Their syntheses have so far been carried out by simply attaching chiral residues to the upper or lower rim of the calixarene skeleton and using the inherent chirality of their structures.[2]

It would be interesting to incorporate amino acid or peptide moieties into calixarenes to achieve the chirally modified macrocyclic ligands.[3,4] These chiral macrocyclic derivatives may serve as good candidates in future studies of chiral recognition, chiral catalysis, and asymmetric induction properties. Many approaches have been developed with amino acids, especially the recent results presented by Lazzarotto et al. which represent a novel class of chiral receptors in that the amino acid units are linked to the calix[4]arene platform through their carboxy groups. The synthesis of calix[4]arenes bridged at the upper rim with small peptides is described. They show interesting in vitro antimicrobial activity[5] toward Gram-positive bacteria. Meanwhile M. Ziniæ and co-workers gave clear evidence for the intra- and intermolecular hydrogen-bonded organization of the calix[4]arene amino acid derivatives.[6] Very limited data are available in the literature for the upper[7] or lower rim[8] C-linked peptidocalixarene 1,3-disubstituted (amino acid or dipeptide) derivatives that describe the possibility of formation of dimers through intermolecular hydrogen bonds. Amide groups introduced into the upper[9−14] or lower rim[11] of calixarenes, which are able to form intramolecular hydrogen bonding, give strong conformational stability of the calixarene substructure.[15]

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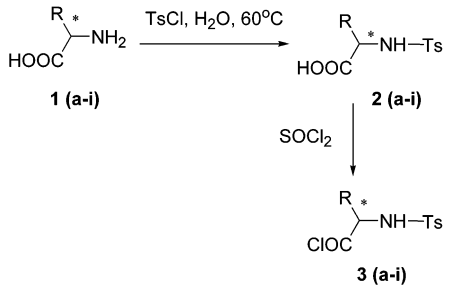
10.1021/jo034275j CCC: $25.00
Published on Web 07/18/2003

SCHEME 1. Preparation of the *N*-Tosyl-amino Acid Chloride Derivatives 3



Meanwhile, other groups have reported the synthesis and properties of chiral calixarenes functionalized with aminophosphonates,[16] esteracetamides,[17] cyclopeptides,[18] ureas,[19,20] sugars,[21,22] amino acids,[8,23−27] and peptides.[28−33]

In this paper, we describe the syntheses of various 1,3-chiral cone *p-tert*-butyl calix[4]arenes functionalized with D or L amino acid units. Their structures were determined by NMR spectroscopy (^{1}H, ^{13}C), mass spectrometry, specific rotations, elemental analysis, IR, melting points, and X-ray crystal structure for one of them. The amino acids were D- and L-alanine, isoleucine, leucine, phenylalanine, and valine and were introduced on the lower rim of *p-tert*-butylcalix[4]arene. The host−guest complexation of various anions was studied by H^1 NMR spectroscopy.

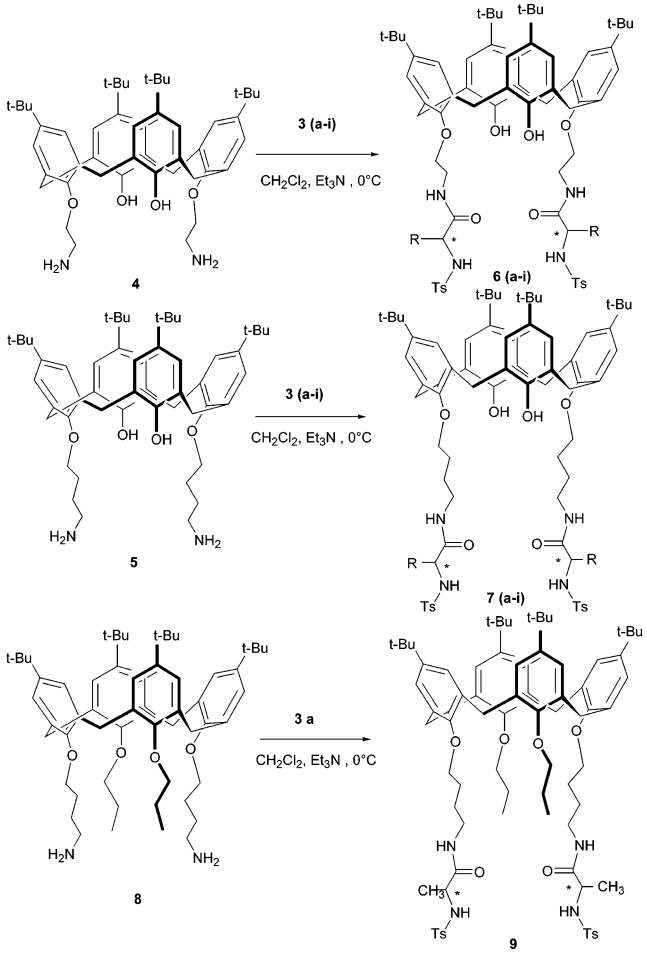
Results and Discussion

The amino acid chloride derivatives **3a**−**i** were prepared from the corresponding amino acid in two steps as shown in Scheme 1. After protection of the amino group with a tosyl group to give the *N*-tosyl-amino acid derivatives **2a**−**i** (Table 1),[34] a chlorination reaction with thionyl chloride gives the amino acid chlorides **3a**−**i**.

TABLE 1. Synthesis of *N*-Tosyl-2-amino Acid Derivatives 2

2	R	yield (%)	mp (°C)
a, D-alanine	Me	86	130−131
b, L-alanine	Me	83	
c, D-valine	*i*-Pr	62	144−146
d, L-valine	*i*-Pr	61	
e, D-phenylalanine	CH_2Ph	42	156−157
f, L-phenylalanine	CH_2Ph	40	
g, D-leucine	*i*-Bu	64	122−124
h, L-leucine	*i*-Bu	67	
i, L-isoleucine	$CH(CH_3)CH_2CH_3$	58	134−136

SCHEME 2. Synthesis of Calixarene Derivatives 6, 7, and 9



The syntheses of all the amides **6**, **7**, and **9** were accomplished by using a condensation reaction of amino acid chlorides **3a**−**i** with the diamino (ethoxy or butoxy) calix[4]arene derivatives **4** and **5** in dry CH_2Cl_2 with Et_3N as catalyst (Scheme 2). The calix[4]arene derivatives substituted by chiral amino acid were obtained in high yields. Their constitution was established by ^{1}H NMR, ^{13}C NMR, ESI data, and elemental analysis, and also confirmed by the amide group absorption in the FT-IR spectra.

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TABLE 2. Selected ^{1}H NMR Data of 6a and 7g in Different Solvents[a]

	solvent	N*H*-CO	N*H*-Ts	Ar*H*	ArCH_2Ar	ArCH_2Ar
6a	DMSO-d_6	8.23	7.93	7.15	4.1−4.3 (2 doublets)	3.4−3.5 (1 multiplet)
	$CDCl_3$	8.06	5.53	6.81, 7.03	4.16 and 4.24 (2 doublets)	3.22 and 3.31 (2 doublets)
7g	DMSO-d_6	7.91	7.80	7.10	4.17 (1 doublet)	3.40 (1 doublet)
	$CDCl_3$	7.26	5.95	6.80, 7.10	4.25 and 4.26 (2 doublets)	3.3−3.4 (2 doublets)

[a] Chemical shift are given in ppm

While the structures of derivatives **4** and **5** show the typical splitting pattern for a disubstituted calixarene, the ^{1}H NMR spectra of compounds **6a**−**i** and **7a**−**i** ($CDCl_3$) are more complex, reflecting the chirality imposed by the amino acid moieties. The ^{1}H NMR spectra at ambient temperature were identical for each pair of enantiomers. The signals of CH_2O and CH_2N*H* are broad and poorly resolved, indicating a dynamic effect typical for high molecular mass compounds with strong dipolar interactions of nuclei and steric hindrance of rotation.[35]

The 1,3-*N*-tosyl peptidocalix[4]arenes **6a**−**i** and **7a**−**i** show significant changes on going from nonpolar ($CDCl_3$) to polar solvent (acetone-d_6 or DMSO-d_6). In $CDCl_3$, the structure of alanine and leucine derivatives **6a** and **7g** not only indicates that they possess the cone conformation, but also provides evidence for asymmetric structural features. All of them have two pairs of doublets around 3.40 and 4.20 ppm (Table 2) that are due to the nonequivalency of the protons of the methylene bridge (Ar-CH_2-Ar). As previously reported in the literature,[7] this can be explained by the presence of chiral substituents and indicates a significant degree of structural rigidity.

In DMSO-d_6, one singlet for the aromatic protons (7.15 and 7.10 ppm for **6a** and **7g**, respectively) is found (Figures 1 and 2, Table 2), while in $CDCl_3$ one singlet and one doublet are observed for **6a** (6.81 and 7.03 ppm, respectively) and two singlets for **7g** (6.80 and 7.10 ppm). This is in accordance with C_4 symmetry and suggests the formation of a C_2 *flattened cone* conformation.[36]

While the NH-CO signal appears at similar chemical shifts in $CDCl_3$ and in DMSO-d_6 (Table 2), the signal of NH-Ts is strongly shifted upfield in $CDCl_3$ indicating intramolecular hydrogen bond formation in apolar solvent. A J_{CH-NH} coupling constant of greater than 8 Hz (8.46 and 8.28 Hz for **6a** and **7g**, respectively, in $CDCl_3$) was measured, indicating that the amino acid moieties adopt an extended conformation.[37] This allows us to point out a possible dimerization of peptidocalix[4]arenes which have been revealed by ESI mass studies.

ESI (positive-ion) mass spectra of **6g**−**i** show the peak of a dimer in addition to the peak of a monomer. However, the peak intensities of the dimer are weaker than that for the monomer ([dimer]$^+$/[monomer]$^+$) (8−16%). For **7a**−**i**, no peak corresponding to dimeric structure is visible.

Compound **6f** gave crystals (from CH_2Cl_2/EtOH) suitable for a preliminary X-ray analysis. It confirmed that these peptidocalix[4]arene derivatives **6a**−**i** and **7a**−**i** adopt a *flattened cone* conformation. These results in the solid state are in accordance with those in the liquid state. In $CDCl_3$, intramolecular hydrogen bonding between the amino acids units for **6**−**7** is observed, which confirms that the calixarene derivatives adopt a *flattened cone* conformation. In DMSO-d_6, the intramolecular hydrogen bonds are broken and the compounds adopt a 1,3-disubstituted *cone* conformation. The presence of intramolecular hydrogen bonds in the solid state is confirmed by the IR spectra in the solid state for all of the calixarene derivatives **6** and **7**. In the IR spectra of **6** and **7**, the NH stretching bands at 3260−3360 cm^{-1} corresponding to hydrogen-bonded NH are much stronger than those of free NH at 3420 cm^{-1}.[6]

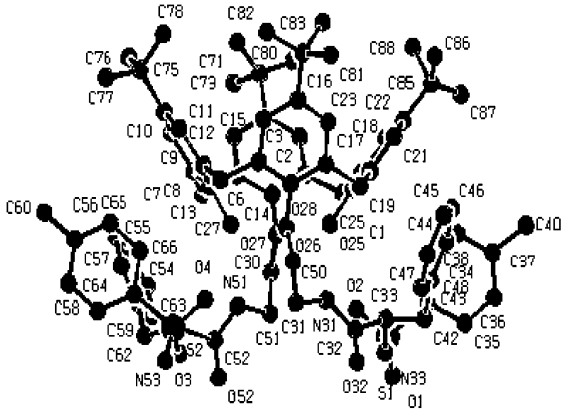

FIGURE 1. Numbering scheme of compound **6f**.

From X-ray analysis of **6f**, it is shown that the asymmetric unit contains two macrocycles and three ethanol molecules. Figure 1 gives the numbering scheme of **6f**. Each macrocycle is noted A or B. The two macrocycles adopt the *cone* conformation. Due to the low quality of the crystal, a well-refined high-resolution structure could not be obtained. However, to describe the conformation an isotropic refinement was made that permits the description as follows.

The δ angles giving the orientations of the phenolic units with respect to the reference plane of the methylene groups[38] have values of 117.3(4)°, 126.1(4)°, 115.9(5)°, and 129.0(5)° for A and 115.1(4)°, 129.6(4)°, 113.8(4)°, and 127.0(3)° for B. The representation of the molecular conformation as described by Ugozzoli et al.[39] is C_1 − +, − +, − +, − + for both molecules A and B. Concerning the substituents at the OH groups, dihedral angles between planes of the phenyl rings have been calculated. For macrocycle A the I−II angle is 81.9(7)° and the III−IV angle is 79.8(6)°. For macrocycle B the I−II angle is 79.7(6)° and the III−IV angle is 74.9(5)° (plane I: C34 → C39, plane II: C43 → C48, plane III: C54 → C59, plane

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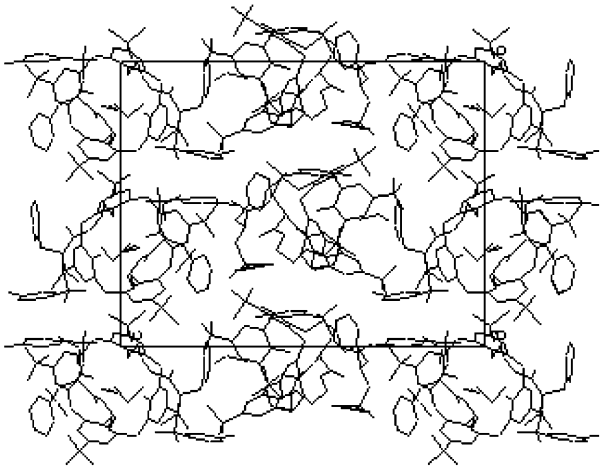

FIGURE 2. Packing view down "*a*" of compound **6f**.

IV: C63 → C68). On the other hand we have calculated the following angles: C28−C51−C54 is 93.7° for A and 94.9° for B and C26−C31−C34 is 95.0° for A and 94.1° for B. These values near the perpendicularity show how the substituants go outside the macrocycles. All the values obtained show that the two independent macrocycles have the same conformation. Concerning hydrogen bonds in the calixarene, we find only an intramolecular bond between O25−O28 and O26−O27:

D - H - - - A	D-H	H- -A	D- -A	DH- -A
A : O25 - H25 - - - O28	0.82	1.984	2.673 Å	141.2°
O27 - H27 - - - O26	0.82	2.058	2.727 Å	138.5°
B : O25 - H25 - - - O28	0.82	1.951	2.646 Å	142.0°
O27 - H27 - - - O26	0.82	1.991	2.709 Å	146.0°

The title compound crystallizes with three ethanol molecules. However, one of them is in a disordered position with occupation 0.42 and 0.58. Due to the disorder these two molecules were refined isotropically. There are hydrogen bonds between two of them: O502- - -O602 = 2.857 Å. There are no hydrogen bonds between ethanol and calixarene. Figure 2 shows the packing down "*a*".

Complexation Study

The introduction of hydrogen bonding donor and acceptor groups at the *lower rim* of calixarenes might have affected their host−guest properties and gave rise to new possibilities for anion complexation. We report a preliminary study of the complexation properties of various anions such as tetrabutylammonium chloride, bromide, dihydrogen phosphate, hydrogen sulfate, and *N*-tosyl-(L)-alaninate. The recognition properties of compounds **6a**, **7a**, and **9** were investigated by ^{1}H NMR experiments in $CDCl_3$. A large downfield shift of the NH proton of the amide function was observed upon addition of *n*-tetrabutylammonium salts of anions to host derivatives. The ^{1}H NMR titration curve of complexation with Cl^-, Br^-, HSO_4^-, $H_2PO_4^-$, and *N*-tosyl-(L)-alaninate to host **9** is depicted in Figure 3.

In all cases the stoichiometry is 1:1 as was confirmed by Job plots (see for an example Figure 4). The association constants of the three anion receptors were determined by the Benesi−Hildebrand method[40] and are summarized in Table 3.

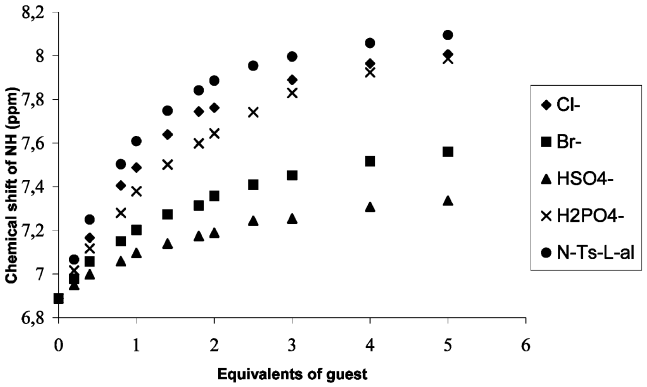

FIGURE 3. Titration curve of calix[4]arene **9** with Bu_4NCl, Bu_4NBr, Bu_4NHSO_4, $Bu_4NH_2PO_4$, and Bu4N-N-Ts-L-alaninate in $CDCl_3$. Concentration of the host is 10^{-2} M.

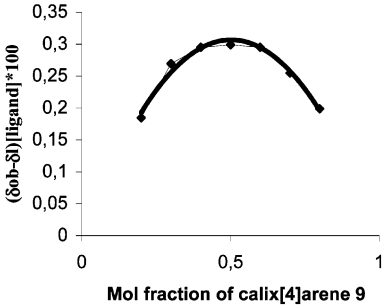

FIGURE 4. Job plot of the titration of 0.01 M Bu_4NCl with 10^{-2} M calix[4]arene **9** in $CDCl_3$.

TABLE 3. K_{ass} **Values (M^{-1}) of 6a, 7a, and 9**

compd	Cl^-	Br^-	HSO_4^-	H_2PO_4-	*N*-tosyl-(L)-alaninate
7a	988				1626
6a	5137	4212			4836
9	4906	3885	3856	2309	6924

The data in Table 3 show that the association constant for anion binding of the various calix[4]arene derivatives is strongly dependent on the nature of the substituent at the *lower rim* and confirm previously described results.[41] Thus, we observed that the complexation is higher for derivative **7a** than for **6a** according to the length of the spacer. In an attempt to further increase the strength of the anion complexation, we prepared the more lipophilic derivative **9**. As shown in Table 3, this compound gave the better binding constants. A good selectivity for Cl^- and Br^- (compared to previously described results[42]) is present and no complexation or only weak complexation is observed for HSO_4^- and $H_2PO_4^-$. It is well-known that the size-fit relationship between host and guest plays a crucial role in molecular recognition. The size of the calix[6]arene seems to be more suitable for these anions.[43] According to the litera-

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ture,[44] a better selectivity of carboxylate over inorganic anions was observed.

The ligands **6a**, **7a**, and **9** strongly bind anions (the K_{as} values vary from 1000 to 6900 M^{-1}). These results are better compared with previously described *upper-rim* C-linked peptidocalixarenes.[7] Our results are in accordance with those obtained with peptidocalixarenes in which the conformational flexibility has been reduced at the *upper-rim*.[44] The authors show that these ligands form strong complexes in acetone-d_6 with carboxylate anions such as *N*-acetyl-(L)-alaninate (K_{as} = 4900 M^{-1}). Ungaro et al.[45] reported that aromatic α-amino acids are more strongly bounded than aliphatic ones. H-bonding interactions between the carboxylate anions and the amide NH groups, together with Π−Π stacking, are mentioned to explain the selectivity of such anion receptors. In our case, the *N*-tosyl protecting group may play a cooperative role in the binding and could explain the enhancement in the host−guest complexation of alaninate. The enantioselective recognition of chiral carboxylates is an important goal. The anion receptors **6**, **7**, and **9** show promising ability for chiral discrimination.

Conclusion

New chiral calix[4]arene-amino acid conjugates have been prepared by using the reaction of the *N*-tosylated acid chlorides of five (D or L) amino acids with calix[4]arene derivatives. We have verified that these hosts adopt a rigid *flattened cone* conformation. The perpendicular geometry of the phenyl rings participates in the general chirality of the macro-ring. The introduction of amino acid moieties into the lower rim of calix[4]arene places the chiral groups distant from the internal aromatic cavity of calix[4]arene, which allows secondary interactions of the amino acid functional groups with homochiral guests. TREN-derived sulfonamides[46] and sulfonated[47] and amino acid[7] calix[4]arene derivatives form complexes with anions. The *N*-tosylated calix[4]arene derivatives **6**, **7**, and **9** might be suitable for the synthesis of hydrophobic neutral anion receptors which are able to bind anions in a 1:1 stoichiometry through hydrogen bonding. High binding constants are observed and the better selectivity is obtained for *N*-tosyl-(L)-alaninate as expected. This class of receptors opens new horizons for chiral discrimination of carboxylate derivatives.

Experimental Section

General Methods. Solvents were purified and dried by standard methods prior to use. All reactions were carried out under nitrogen. Column chromatography was performed with silica gel 60 (0.040−0.063 nm). Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained at 300.13 and 75 MHz ($CDCl_3$, TMS as internal standard). Mass spectra were obtained by electrospray technique (positive mode). The elemental analyses were performed at the Service Central d'Analyse, CNRS, Solaize, France.

General Procedure for the Preparation of the *N*-Tosyl-2-amino Acid 2. To a stirred suspension of amino acid **1** (22 mmol) in 50 mL of water at room temperature was added 2.64 g (66 mmol) of NaOH and 5 g (26.4 mmol) of *p*-toluene sulfonyl chloride. The mixture was stirred at 60 °C for 6 h. The combined basic layers were cooled to −5 °C and acidified (pH 1) by the addition of concentrated HCl. The precipitate was collected by filtration, washed with cold H_2O and EtOH, and air-dried to give the tosylamino acid **2** as a white solid.[29]

General Procedure for the Preparation of the Amino Acid Chlorides 3. Thionyl chloride (0.1 mL, 1.46 mmol) was added dropwise to a solution of the *N*-tosyl-2-amino acid **2** (0.977 mmol) in 20 mL of benzene and the mixture was stirred at 60 °C for 3 h. The unreacted $SOCl_2$ and solvent were removed by distillation. Compounds **3** were used for the next reaction without further purification.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(aminoethoxy)-26,28-dihydroxycalix[4]arene (4). Compound **4** was prepared according to known procedures, reported previously in the literature[42,48,49] (for reduction we imposed the procedure using BH_3·THF instead of $LiAlH_4$).

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(aminobutoxy)-26,28-dihydroxycalix[4]arene (5). Compound **5** is obtained by using the same procedure as for compound **4**.[42] The product was purified by recrystallization ($CH_3OH/CHCl_3$) to give a white powder (82%): mp 162−164 °C. ^{1}H NMR δ 0.96 (s, 18H), 1.27 (s, 18H), 1.88−2.00 (br, 8H), 2.90−3.00 (br, 4H), 3.26 (d, 4H, J = 12.2 Hz), 3.90−4.00 (br, 4H), 4.21 (d, 4H, J = 12.2 Hz), 6.79 (s, 4H), 7.03 (s, 4H). ^{13}C NMR δ 25.5, 27.6, 31.4, 32.0, 32.1, 34.2, 41.5, 76.6, 122.8, 125.5, 128.24, 129.3, 133.4, 142.7, 149.9, 153.4. IR 3352.68 (NH_2). ES-MS (*m*/*z*) 813.6 $[M + Na]^+$ (calcd 813.55), 791.5 $[M + H]^+$ (calcd 791.56). Anal. Calcd for $C_{52}H_{74}N_2O_4$: C, 78.94; H, 9.43; N, 3.54. Found: C, 78.71; H, 9.40; N, 3.49.

General Procedure for the Preparation of the Amino Acid Calixarene Derivatives 6 and 7. The solution of amino acid chloride **3** prepared above in dry CH_2Cl_2 (15 mL) was added dropwise to a solution of *p-tert*-butylcalix[4]arene diamine **4** or **5** (0.4 mmol) and triethylamine (52 mg, 0.88 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C. The mixture was stirred at room temperature for 12 h, washed with 1 N HCl (2 × 50 mL) and water (50 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the solid residue was purified by column chromatography to give **6** and **7**.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-D-alanylaminoethoxy)-26,28-dihydroxycalix[4]arene (6a) and 5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-alanylaminoethoxy)-26,28-dihydroxycalix[4]arene (6b). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 6/4 to obtain **6a** or **6b** as a white powder (**6a**: 141 mg, 61%; **6b**: 132 mg, 56%): mp 241−243 °C. **6a**: $[\alpha]^{20}_D$ +15.3 (*c* 0.15, $CHCl_3$). **6b**: $[\alpha]^{20}_D$ +5.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR δ 0.95 (s, 18H), 1.06 (d, 6H, J = 6.9 Hz), 1.23 (s, 18H), 2.31 (s, 6H), 3.22 (AB, 2H), 3.31 (AB, 2H, J = 13.4 Hz), 3.21−3.85 (m, 10H), 4.16 (AB, 2H, J = 13.0 Hz), 4.24 (AB, 2H, J = 13.4 Hz), 5.53 (d, 2H, J = 8.46 Hz), 6.81 (s, 4H), 7.03 (d, 4H), 7.11 (d, 4H, J = 8.1 Hz), 7.49 (d, 4H, J = 8.28 Hz), 8.01 (s, 2H), 8.06 (br s, 2H). ^{13}C NMR δ 19.7, 21.9, 31.4, 32.0, 32.3, 34.4, 40.0, 53.2, 75.8, 126.1, 127.5, 128.12, 130.1, 133.1, 137.5, 143.4, 148.3, 149.2, 171.9. IR 3289 (NH, OH), 1653 (CO). ES MS (*m*/*z*) 1207.5 $[M + Na]^+$ (calcd 1207.59), 1185.5 (calcd 1185.61). Anal. Calcd for $C_{68}H_{88}N_4O_{10}S_2$: C, 68.89; H, 7.48; N, 4.72. Found: C, 68.69; H, 7.41; N, 4.77.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-D-valylaminoethoxy)-26,28-dihydroxycalix[4]arene (6c) and 5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-valylami-

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noethoxy)-26,28-dihydroxycalix[4]arene (6d). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 5/5 to give **6c** or **6d** as white crystals (**6c**: 192.5 mg, 78%; **6d**: 168 mg, 68%): mp 140−142 °C. **6c**: $[\alpha]^{20}_D$ −15.7 (*c* 0.3, $CHCl_3$). **6d**: $[\alpha]^{20}_D$ +26.0 (*c* 0.3, $CHCl_3$). ^{1}H NMR: δ 0.76−0.78 (dd, 12H, J = 6.78 Hz, J = 6.78 Hz), 1.06 (s, 18H), 1.31 (s, 18H), 2.08−2.14 (m, 2H), 2.37 (s, 6H), 3.36 (AB, 2H, J = 13.2 Hz), 3.42 (dd, 4H, J = 13.2 Hz), 3.61−3.66 (m, 6H), 3.96 (m, 4H), 4.26 (AB, 2H, J = 13.2 Hz), 4.29 (AB, 2H, J = 13.0 Hz), 5.41 (d, 2H, J = 8.67 Hz), 6.91 (s, 4H), 7.11 (s, 4H), 7.23 (d, 4H, J = 8.1 Hz), 7.70 (d, 4H, J = 8.28 Hz), 7.85 (s, 2H), 8.08 (br s, 2H). ^{13}C NMR δ 17.4, 19.6, 21.9, 32,4, 31.5, 31.97, 32.4, 34.4, 39.6, 62.4, 75.7, 126.1, 126.4, 127.8, 128.4, 128.5, 130.0, 133.14, 137.3, 143.4, 148.3, 149.3, 149.7, 171.0. IR 3315 (NH, OH), 1669 (CO). ES-MS (*m*/*z*) 1263.6 $[M + Na]^+$ (calcd 1263.65), 1241.6 $[M + H]^+$ (calcd 1241.67). Anal. Calcd for $C_{72}H_{96}N_4O_{10}S_2 \cdot H_2O$: C, 68.64; H, 7.86; N, 4.45. Found: C, 68.98; H, 7.90; N, 4.49.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-D-phenylalanylaminoethoxy)-26,28-dihydroxycalix[4]arene (6e) and 5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-phenylalanylaminoethoxy)-26,28-dihydroxycalix[4]arene (6f). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 5/5 to give **6e** or **6f** as a white powder (**6e**:144 mg, 54%; **6f**: 155 mg, 58%): mp 117−119 °C. **6e**: $[\alpha]^{20}_D$ +113.5 (*c* 0.4, $CHCl_3$). **6f**: $[\alpha]^{20}_D$ −29.5 (*c* 0.4, $CHCl_3$). ^{1}H NMR δ 1.11 (s, 18H), 1.35 (s, 18H), 2.41 (s, 6H), 2.51 (d, 1H, J = 13.5 Hz), 2.55 (d, 1H, J = 13.6 Hz), 3.09 (d, 1H, J = 14.1 Hz), 3.13 (d, 1H, J = 14 Hz), 3.33 (AB, 2H, J = 13.2 Hz), 3.37 (AB, 2H, J = 13.4 Hz), 3.92−4.25 (m, 10H), 4.36 (d, 2H, J = 12.6 Hz), 4.42 (d, 2H, J = 13.4 Hz), 5.00 (d, 2H, J = 6.27 Hz), 6.53 (d, 4H, J = 7.17 Hz), 6.96−7.11 (m, 4H), 7.16 (s, 4H), 7.26 (d, 4H, J = 8.1 Hz), 8.61 (s, 2H), 8.72 (br s, 2H). ^{13}C NMR δ 21.9, 31.5, 32.6, 32.6, 39.2, 40.0, 59.0, 76.3, 126.3, 126.6, 127.0, 128.1, 128.3, 126.2, 126.4, 129.9, 131.3, 133.3, 137.2, 136.3, 143.5, 143.5, 148.2, 149.3, 150.0, 171.0. IR 3316 (NH, OH), 1671 (CO). ES-MS (*m*/*z*) 1359.6 $[M + Na]^+$ (calcd 1359.65), 1337.4 $[M + H]^+$ (calcd 1337.67). Anal. Calcd for $C_{80}H_{96}N_4O_{10}S_2$: C, 71.83; H, 7.23; N, 4.19. Found: C, 71.68; H, 7.19; N, 4.00.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-D-leucylaminoethoxy)-26,28-dihydroxycalix[4]arene (6g) and 5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-leucylaminoethoxy)-26,28-dihydroxycalix[4]arene (6h). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 3/7 to give **6g** or **6h** as white crystals (**6g**: 170 mg, 67%; **6h**: 157 mg, 62%): mp 144−146 °C. **6g**: $[\alpha]^{20}_D$ +5.2 (*c* 0.5, $CHCl_3$). **6h**: $[\alpha]^{20}_D$ −33.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR δ 0.48 (d, 6H, J = 5.67 Hz), 0.65 (d, 6H, J = 5.82 Hz), 1.20 (s, 18H), 1.29 (s,18H), 1.42−1.46 (m, 4H), 1.83 (br, 2H), 2.39 (s, 6H), 3.41 (dd, 4H, J = 12.8 Hz, J = 13.2 Hz), 3.74−3.87 (m, 6H), 3.99−4.05 (m, 4H), 4.30 (d, 2H, J = 13.0 Hz), 4.34 (d, 2H, J = 13.2 Hz), 5.32 (d, 2H, J = 9.03 Hz), 6.91 (s, 4H), 7.11 (s, 4H), 7.22 (d, 4H, J = 8.07 Hz), 7.68 (d, 4H, J = 8.31 Hz), 8.17 (s, 2H), 8.34 (br s, 2H). ^{13}C NMR δ 21.0, 21.0, 21.9, 23.4, 31.5, 32.0, 32.5, 34.3, 39.7, 42.9, 55.9, 76.0, 126.2, 126.5, 127.8, 128.2, 128.3, 128.6, 130.0, 133.1, 137.3, 143.6, 148.4, 149.2, 149.9, 172.1. IR 3319 (NH, OH), 1659 (CO). ES-MS (*m*/*z*) 1291.6 $[M + Na]^+$ (calcd 1291.68), 1269.6 $[M + H]^+$ (calcd 1269.70) 2561.30 $[2M + Na]^+$ (calcd 2561.38), 2539.30 $[2M + H]^+$ (calcd 2539.40). Anal. Calcd for $C_{74}H_{100}N_4O_{10}S_2$: C, 70.00; H, 6.94; N, 4.41. Found: C, 69.71; H, 7.95; N, 4.33.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-isoleucylaminoethoxy)-26,28-dihydroxycalix[4]arene (6i). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 3/7 to give **6i** as a white powder (186 mg, 74%): mp 143−145 °C. **6i**: $[\alpha]^{20}_D$ −6.0 (*c* 0.15, $CHCl_3$). ^{1}H NMR δ 0.68−0.77 (m, 12H), 0.6−1.04 (s + m, 20H), 1.32−1.40 (s + m, 20H), 1.72−1.74 (m, 2H), 2.37 (s, 6H), 3.35 (dd, 4H, J = 13.2 Hz), 3.64−4.05 (m, 10H), 4.30 (dd, 4H, J = 13.2 Hz, J = 13.2 Hz), 5.43 (d, 2H, J = 9.03 Hz), 6.90 (s, 4H), 7.12 (s, 4H), 7.24 (d, 4H, J = 8.28 Hz), 7.72−7.75 (s + d, 6H, J = 9.6 Hz), 8.04 (br s, 2H). ^{13}C NMR δ 11.7, 15.8, 21.9, 24.4, 31.4, 32.4, 34.3, 38.5, 39.6, 62.0, 75.7, 126.0, 126.4, 126.8, 128.5, 128.6, 130.1, 133.0, 137.3, 143.4, 143.9, 148.2, 149.4, 149.7, 171.0. IR 3297 (OH, NH), 1668 (CO). ES-MS (*m*/*z*) 1291.6 $[M + Na]^+$ (calcd 1292.68), 1269.6 $[M + H]^+$ (calcd 1269.70), 2561.3 $[2M + Na]^+$ (calcd 2561.38), 2539.4 $[2M + H]^+$ (calcd 2539.40). Anal. Calcd for $C_{74}H_{100}N_4O_{10}S_2$: C, 70.00; H, 7.94; N, 4.41. Found: C, 69.34; H, 7.98; N, 4.40.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-D-alanylaminobutoxy)-26,28-dihydroxycalix[4]arene (7a) and 5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-alanylaminobutoxy)-26,28-dihydroxycalix[4]arene (7b). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 6/4 to give **7a** or **7b** as a white powder (**7a**: 147.5 mg, 58%; **7b**: 152 mg, 60%): mp 135−137 °C. **7a**: $[\alpha]^{20}_D$ +30.5 (*c* 0.2, $CHCl_3$). **7b**: $[\alpha]^{20}_D$ −102.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR δ 0.93 (s, 18H), 1.19 (d, 6H, J = 6.96 Hz), 1.34 (s, 18H), 1.85−2.00 (br m, 8H), 2.41 (s, 6H), 3.35−3.57 (m, 10H), 3.92−4.10 (m, 6H), 4.22 (d, 2H, J = 13.2 Hz), 4.28 (d, 2H, J = 13.0 Hz), 6.14 (d, 2H, J = 8.64 Hz), 6.77 (s, 4H), 7.13 (s, 4H), 7.22 (s, 2H), 7.25 (d, 4H, J = 8.10 Hz), 7.40 (br, 2H), 7.70 (d, 4H, J = 8.28 Hz). ^{13}C NMR δ 19.6, 21.9, 26.5, 27.50, 31.4, 32.0, 32.1, 34.3, 39.7, 53.0, 77.1, 125.6, 126.0, 127.5, 128.3, 128.49, 130.2, 132.5, 136.2, 137.7, 142.6, 143.9, 150.3, 172.7. IR 3298 (NH, OH), 1658 (CO). ES-MS (*m*/*z*) 1263.7 $[M + Na]^+$ (calcd 1263.65), 1241.7 $[M + H]^+$ (calcd 1241.67). Anal. Calcd for $C_{72}H_{96}N_4O_{10}S_2 \cdot H_2O$: C, 68.63; H, 7.86; N, 4.44. Found: C, 68.70; H, 7.89; N, 4.59.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-D-valylaminobutoxy)-26,28-dihydroxycalix[4]arene (7c) and 5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-valylaminobutoxy)-26,28-dihydroxycalix[4]arene (7d). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 5/5 to give **7c** or **7d** as a white powder (**7c**: 138 mg, 61%; **7d**: 126 mg, 56%): mp 134−136 °C. **7c**: $[\alpha]^{20}_D$ +126.5 (*c* 0.2, $CHCl_3$). **7d**: $[\alpha]^{20}_D$ +11.0 (*c* 0.2, $CHCl_3$). ^{1}H NMR δ 0.72 (d, 6H, J = 6.78 Hz), 0.83 (d, 6H, J = 6.78 Hz), 0.96 (s, 18H), 1.32 (s, 18H), 1.85−2.00 (m, 8H), 2.40 (s, 6H), 3.31−3.40 (m, 8H), 3.67 (dd, 2H, J = 5.10 Hz, J = 5.07 Hz), 3.91−4.06 (m, 4H), 4.22 (d, 2H, J = 13.2 Hz), 4.28 (d, 2H, J = 13.0 Hz), 5.79 (d, 2H, J = 8.67 Hz), 6.80 (s, 4H), 7.07−7.10 (m + d, 6H, J = 2.64 Hz, ArH), 7.25 (d, 4H, J = 8.49 Hz), 7.40 (s, 2H), 7.75 (d, 4H, J = 8.28 Hz). ^{13}C NMR δ 17.6, 19.6, 21.9, 26.4, 27.7, 30.1, 31.4, 32.1, 34.3, 39.8, 62.6, 76.7, 125.6, 126.0, 126.8, 128.2, 128.3, 130.0, 132.7, 137.4, 142.4, 143.8, 146.4, 150.2, 150.7, 171.6. IR 3296 (NH, OH), 1650 (CO). ES-MS (*m*/*z*) 1319.8 $[M + Na]^+$ (calcd 1319.71), 1297.6 $[M + H]^+$ (calcd 1297.73). Anal. Calcd for $C_{68}H_{88}N_4O_{10}S_2$: C, 68.89; H, 7.48; N, 4.72; O, 13.49. Found: C, 68.69; H, 7.41; N, 4.77.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-D-phenylalanylaminobutoxy)-26,28-dihydroxycalix[4]arene (7e) and 5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-phenylalanylaminobutoxy)-26,28-dihydroxycalix[4]arene (7f). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 6/4 to give **7e** or **7f** as a white powder (**7e**: 195 mg, 74%; **7f**: 174 mg, 64%): mp 111−113 °C. **7e**: $[\alpha]^{20}_D$ +5 (*c* 0.5, $CHCl_3$). **7f**: $[\alpha]^{20}_D$ −23.3 (*c* 0.15, $CHCl_3$). ^{1}H NMR δ 0.97 (s, 18H), 1.34 (s, 18H), 1.91−2.10 (br m, 8H), 2.38 (s, 6H), 3.31 (dd, 2H, J = 8.50 Hz), 3.02 (d, 2H, J = 13.0 Hz), 3.06 (d, 1H, J = 5.60 Hz), 3.33−3.46 (br m), 3.98−4.06 (br m, 6H), 4.29 (t, 4H, J = 12.6 Hz, J = 12.0 Hz), 5.78 (d, 2H, J = 7.92 Hz), 6.81 (s, 4H), 6.90−6.93 (m, 4H), 6.93−7.26 (m, 16H), 7.48 (s, 2H), 7.49 (d, 4H, J = 8.28 Hz). ^{13}C NMR δ 21.9, 26.3, 27.5, 31.4, 32.1, 32.6, 39.3, 39.9, 58.8, 76.9, 125.6, 126.0, 127.1, 127.5, 128.3, 128.9, 129.7, 130.0, 132.7, 136.3, 136.8, 142.4, 143.6, 147.4, 150.3, 150.7, 171.5. IR 3305 (OH, NH), 1656 (CO). ES-MS (*m*/*z*) 1415.5 $[M + Na]^+$ (calcd 1415.71), 1394.6 $[M + H]^+$ (calcd 1393.73). Anal. Calcd for $C_{84}H_{104}N_4O_{10}S_2 \cdot H_2O$: C, 71.14; H, 7.58; N, 3.96. Found: C, 71.52; H, 7.56; N, 3.99.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-D-leucylaminobutoxy)-26,28-dihydroxycalix[4]arene (7g) and 5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-leucylaminobutoxy)-26,28-dihydroxycalix[4]arene (7h). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 3/7 to give **7g** or **7h** as a white powder (**7g**: 161 mg, 64%; **7h**: 151 mg, 60%): mp 179−181 °C. **7g**: $[\alpha]^{20}_D$ +179.0 (*c* 0.1, $CHCl_3$). **7h**: $[\alpha]^{20}_D$ −20.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR δ 0.57 (d, 4H, J = 5.67 Hz), 0.81 (d, 4H, J = 5.46 Hz), 0.96 (s, 18H), 1.33 (s, 18H), 1.51−1.53 (br m, 6H), 1.79−1.98 (br m, 8H), 2.40 (s, 6H), 3.33−3.39 (m, 8H), 3.86−4.01 (m, 6H), 4.25 (d, 2H, J = 13.2 Hz), 4.26 (d, 2H, J = 13.0 Hz), 5.25 (d, 2H, J = 8.28 Hz), 6.80 (s, 4H), 7.10 (s, 4H), 7.26 (br, 2H), 7.26 (d, 4H, J = 7.92 Hz), 7.42 (s, 2H), 7.76 (d, 4H, J = 8.28 Hz). ^{13}C NMR δ 21.3, 21.9, 23.4, 24.7, 26.4, 27.5, 31.4, 32.1, 32.2, 39.8, 42.8, 56.1, 77.0, 125.6, 126.0, 127.8, 128.3, 130.0, 132.7, 137.4, 142.4, 143.9, 147.4, 150.3, 151.4, 172.9. IR 3361 (NH), 3113 (OH), 1665 (CO). ES-MS (*m*/*z*) 1347.7 [M + Na]$^+$ (calcd 1347.74), 1325.7 [M + H]$^+$ (calcd 1325.76). Anal. Calcd for $C_{78}H_{108}N_4O_{10}S_2$: C, 70.66; H, 8.21; N, 4.23. Found: C, 70.64; H, 8.61; N, 3.93.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-isoleucylaminobutoxy)-26,28-dihydroxycalix[4]arene (7i). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 3/7 to give **7i** as white crystals (130 mg, 55%): mp 162−164 °C. **7i**: $[\alpha]^{20}_D$ −25.7 (*c* 0.3, $CHCl_3$). ^{1}H NMR δ 0.71 (d, 6H, J = 6.78 Hz), 0.70−0.85 (m, 6H), 0.97 (s, 18H), 0.95−1.10 (m, 2H), 1.32 (s, 18H), 1.40−1.50 (m, 2H), 1.69−1.95 (m, 10H), 2.40 (s, 6H), 3.32−3.38 (m, 8H), 3.70−3.74 (dd, 2H, J = 5.50 Hz), 3.97−4.03 (m, 4H), 4.26 (dd, 4H, J = 13.0 Hz), 5.75 (d, 2H, J = 8.67 Hz), 6.80 (s, 4H), 7.08−7.09 (br m, 6H), 7.25 (d, 4H, J = 6.78 Hz), 7.40 (s, 2H), 7.75 (d, 4H, J = 8.28 Hz). ^{13}C NMR δ 11.7, 15.9, 21.9, 24.6, 26.4, 27.7, 31.4, 32.1, 32.2, 34.3, 38.5, 39.8, 62.1, 76.7, 11.9, 125.6, 126.0, 127.8, 128.3, 130.0, 132.8, 137.4, 142.3, 143.9, 147.4, 150.2, 150.7, 171.5. IR 3358 (OH, NH), 1665 (CO). ES-MS (*m*/*z*) 1347.8 [M + Na]$^+$ (calcd 1347.74), 1325.4 [M + H]$^+$ (calcd 1325.76). Anal. Calcd for $C_{78}H_{108}N_4O_{10}S_2 \cdot 2H_2O$: C, 68.77; H, 8.31; N, 4.11. Found: C, 68.40; H, 8.38; N, 3.84.

5,11,17,23-Tetra-4-*tert*-butyl-25,27-di(*N*-tosyl-L-alanylaminobutoxy)-26,28-dipropoxycalix[4]arene (9). The product was purified by column chromatography on silica gel eluting with EtOAc/hexane 5/5 to give **9** as a white powder (80 mg, 45%): mp 126−128 °C. **9**: $[\alpha]^{20}_D$ −22.8 (*c* 0.75, $CHCl_3$). ^{1}H NMR δ 0.89 (s, 18H), 1.06 (t, J = 7.35 Hz, 6H), 1.26−1.31 (s + d, 24 H), 1.50−1.57 (m, 4H), 1.91−1.96 (q, J = 7.35 Hz), 2.12−2.18 (m, 4H), 2.45 (s, 6H), 3.14 (AB, J_{AB} = 12.42 Hz), 3.70 (t, J = 7.35 Hz), 3.89 (q, J = 7.35 Hz, 2H), 4.01 (t, J = 8.10 Hz), 4.38 (AB, J_{AB} = 12.42 Hz), 6.03 (d, J = 7.89 Hz), 6.52 (s, 4H), 6.93 (s t large, 2H), 7.06 (s, 4H), 7.32 (d, J = 8.10 Hz, 4H), 7.81 (d, J = 8.31 Hz, 4H). ^{13}C NMR δ 11.20, 19,53, 21.97, 23.97, 26.44, 28.23, 31.50, 31.62, 32.09, 34.02, 34.43, 40.79, 53.19, 74.83, 77.64, 124.91, 125.82, 127.56, 130.25, 132.57, 135.57, 137.29, 144.22, 144.42, 145.12, 153.09, 154.85, 172.12. IR 1656.52 (CONH), 3284.26 (NH). ES-MS (*m*/*z*) [M + Na]$^+$ 1347.8 (calcd 1347.74), [M + H]$^+$ 1325.8 (calcd 1325.76), [M + K]$^+$ 1363.8 (calcd 1363.71). Anal. Calcd for $C_{78}H_{108}N_4O_{10}S_2$: C, 70.66; H, 8.21; N, 4.23. Found: C, 70.22; H, 8.07; N, 3.98.

Single-Crystal X-ray Diffraction. Single crystals were obtained from CH_2Cl_2/EtOH and mounted on a glass fiber. X-ray data were collected at 173 K on a Kappa CCD diffractometer at the Centre de Diffractometrie Henri Longchambon (UCB LYON 1). All calculations were performed with DENZO,[50] SHELXS97,[51] SHELXL97,[51] and PLUTON.[52] Non-H atoms were refined anisotropically; H atoms were included at calculated positions and refined riding on C, N, or O.

Crystal data for $C_{74}H_{100}N_4O_{10}S_2$ (6f): a = 16.440(3) Å, b = 19.767(4) Å, c = 25.584(5) Å, β = 98.27(3)°, V = 8228(3) Å, monoclinic, space group $P2_1$, Z = 4, D_x = 1.151 g·cm^{-3}, μ = 1.25 cm^{-1}. Full-matrix least-squares isotropic refinement was based on 9768 reflections for 843 parameters; R = 0.108 [$I > 2\sigma(I)$], Rw = 0.340, GOF = 1.249, largest difference peak = 1.16 e Å^{-3}.

^{1}HNMR Titrations. A 10 mM solution of the host in $CDCl_3$ was prepared. To 0.5 mL of this solution was added 0−5 equiv of tetrabutylammonium salts in the ^{1}H NMR tube and the spectra were recorded. The chemical shifts of the NH proton were followed and plotted against the equivalents of guest added.

Job Plot. Stick solutions for the host (10 mM) and for the tetrabutylammonium salts (10 mM) in $CDCl_3$ were prepared. The ^{1}H NMR tubes were filled with 500-μL solutions of the host and guest in the following volume ratios: 50:450, 100:400, 150:350, 200:300, 250:250, 300:200, 400:100, and 450:50.

Acknowledgment. The authors thank the CMCU and EZUS-LYON I, ANVAR for their financial support.

Supporting Information Available: ^{1}H NMR (300 MHz) spectra of **6a** and **7g** in DMSO-d_6 and in $CDCl_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034275J

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