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Narrow-Rim Functionalization of Calix[4]arene through Ugi-4CR: Synthesis of a Series of Calix[4]arene Peptoids

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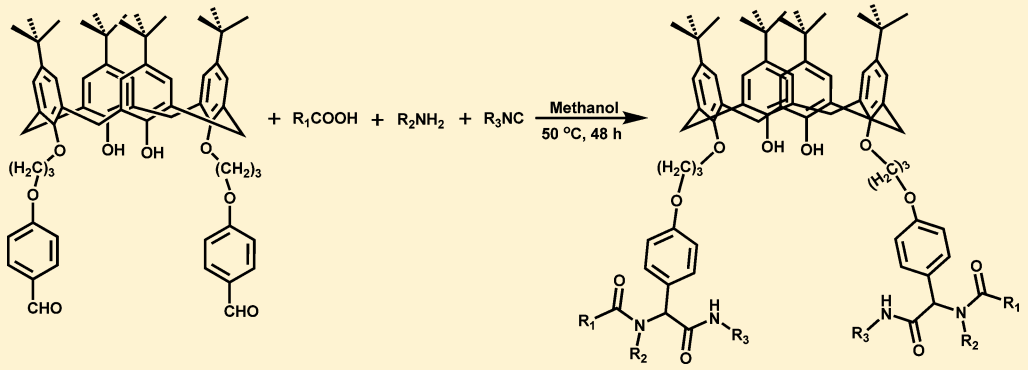
Supporting Information



ABSTRACT: Adaptation of Ugi-4CR for the narrow-rim modification of calix[4]arene toward the synthesis of a series of tripeptoid and tetrapeptoid calix[4]arenes is described. The metal ion/organic cation binding properties of the newly synthesized peptoid calix[4]arenes were also investigated.

INTRODUCTION

Calixarenes, which are probably the most readily available synthetic molecular baskets, enjoy a considerable reputation for being applied in diverse areas.[1] The incredible development of calix[4]arenes as molecular receptors is related to the many possible structural and functional modifications of their core molecular architecture,[2] which constitutes a hollow cavity flanked by a hydrophobic upper rim and a hydrophilic lower rim. The introduction of suitable donor groups at the lower rim and upper rim of calixarenes produces powerful and selective ionophores, particularly for spherical metal ions.

Among the various calix[4]arene derivatives, those adorned with multivalent groups such as peptides or peptide-like motifs are attractive in host−guest chemistry, since they provide a variety of functional groups—hydrophobic, polar, and charged groups—that can interact with other molecules through hydrogen-bonding, electrostatic, and van der Waals interactions. In addition, amino acid units introduce chirality and afford the potential for stereoselective recognition.[3,4] The most widely investigated peptidocalixarenes are those bearing amino acids at the lower rim,[5] particularly due to their ability to bind small molecules and metals. The synthesis of such calixarenes involves selective protection of the lower rim followed by multiple steps using established techniques for the formation of peptide bonds.

Among narrow-rim functionalizations of calix[4]arenes, 1,3-disubstitution at the lower rim has become more attractive due to the presence of two phenolic OH groups (which provide extra coordination sites) and its ability to maintain a cone conformation by retaining two hydrogen bonds at the lower rim. A number of 1,3-diconjugates of calix[4]arene are known in the literature for their ion and molecular recognition.[6]

As part of our general interest in calixarene chemistry, we have been involved in working out the potential for functionalizing calix[4]arene with multivalent groups using a multicomponent strategy. We have successfully demonstrated the synthetic utility of the multicomponent methodology toward the synthesis of a series of upper-rim-substituted peptoid derivatives of calix[4]-arene through the Ugi-4-component reaction (Ugi-4CR) of diisocyano and diamino calix[4]arenes.[7] The Ugi-4CR[8a] occupies a leading position among isocyanide-based multicomponent reactions (IMCR),[8b] since it represents a valuable method to access a peptide-like moiety, such as α-acylaminocarboxamide, in a straightforward manner by coupling isocyanides with carbonyl compounds, primary amines, and carboxylic acids. The conjugation of multivalent groups at the lower rim of calixarenes involves many steps. Since the lower-rim-functionalized calix[4]arene can provide preorganized binding cores suitable for various ions and molecular species, we were interested in implementing a multicomponent strategy at the lower rim of calix[4]arenes, as it enables the rapid functionalization with promising complexity and diversity by a simple one-pot reaction with great efficiency.

Here, we demonstrate a versatile synthesis of the lower-rim-substituted calix[4]arene peptoids based on the Ugi-4CR

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of calix[4]arene diametrically substituted with benzaldehyde groups.

RESULTS AND DISCUSSION

We commenced our investigation on the feasibility of the Ugi reaction at the narrow rim with a 1,3-disubstituted aldehyde functionalized calix[4]arene in the hope that this method would enrich the chemical repertoire of calix[4]arene, because the method provides easy access to tripeptoids.[8c] The required starting material **1** was synthesized in good yields using previously reported synthetic procedures.[9,10]

The dialdehyde **1** was then reacted with benzoic acid (**2a**), toluidine (**3a**) and cyclohexyl isocyanide (**4a**) by simply combining the four components in 2,2,2-trifluoroethanol (TFE). Stirring the mixture at room temperature after 48 h gave the highly functionalized α-acylaminocarboxamide derivative **5aaa** in 52% yield. When we replaced TFE with a more benign and common solvent such as methanol at room temperature, the product was obtained in 58% yield. However, the same reaction at 50 °C furnished the product **5aaa** in 83% yield (Scheme 1).

In order to study the scope of the method, we applied the same procedure to different acids and amines. In all cases, the expected products were obtained in good yields (Table 1). When the reaction was repeated with naphthyl isocyanide as one of the components under optimal conditions, it failed to give the desired product. However, a moderate yield of the corresponding product was obtained when the reaction was conducted in TFE at room temperature, affording the tripeptoid **5aab** (Table 1, entry 10) in 52% yield.

To increase the scope and utility of this route, we then incorporated some biologically relevant amino acids such as N-BOC-gly, N-BOC-L-ala, and N-BOC-L-trp (Table 1, entries 7–9), which would further introduce one more peptoid bond equivalent at the narrow rim. The synthesis of tetrapeptoid derivatives of calix[4]arene is otherwise very difficult and involves multiple steps. We also incorporated the biologically important pyramidine unit as well (Table 1, entry 6). The reaction was shown to be tolerant to a wide range of substituents on the different components. That several useful functionalities such as halo-group-containing substrates capable of undergoing further manipulation were readily incorporated into the final products was particularly pleasing. The products have been characterized by the usual spectroscopic techniques, and their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic data are in agreement with the proposed structures.

To understand the conformational preferences and rigidity of these new compounds, as a representative example, compound **5baa** was subjected to a variable-temperature ^{1}H NMR study, and it presented a few significant changes (Figure 1). As the temperature was lowered from 298 to 223 K, the OH protons, which were discernible as a multiplet, underwent a profound downfield shift of about 0.88 ppm and appeared as a broad singlet. This suggested that a dramatic increase in the intramolecular hydrogen bonding occurred. Considerable changes in the chemical shift values of aromatic protons were also observed. Moreover, a marginal upfield shift of NH and downfield shift of CH (at the spiro center) protons occurred with shift values of 0.22 and 0.30 ppm, respectively, which suggested that some sort of rearrangement in the spatial orientation of compound **5baa** is occurring at lower temperatures (Figure 1).

To get some insights into the intramolecular hydrogen bonding occurring in compound **5baa**, the ^{1}H NMR spectrum in a polar solvent (acetone-d_6) was also obtained (Figure 2). The proton which appeared at around δ 7.10 ppm was assigned to the −NH proton on the basis of its correlation with the −CH proton of the cyclohexyl group in the COSY spectrum (Figure S5, Supporting Information). Downfield shifts of OH protons (∼0.81 ppm) and NH protons (∼1.4 ppm) were noticed, indicating that both the OH and NH groups participate in significant hydrogen-bonding interactions in nonpolar solvent. Furthermore, the ^{1}H NMR spectrum of **5baa** was recorded in DMSO-d_6 as well, a solvent which is even more competitive for hydrogen bonds. A more significant downfield shift was found to occur in this case for −NH protons (∼2.2 ppm) (Figure S6, Supporting Information). To further prove the occurrence of intramolecular hydrogen-bonding interactions in **5baa**, we also carried out a ^{1}H NMR titration experiment by adding small aliquots of acetone (10–50 μL) to a solution of **5baa** in $CDCl_3$ (Figure 3). When acetone was added gradually and the spectrum recorded in each case, it was observed that the chemical shift values of the −OH and −NH protons underwent gradual downfield shifts. This indicates the possible rupture of intramolecular hydrogen bonds involving NH (probably with the carbonyl groups in the peptoid framework) and OH protons and formation of new hydrogen bonds with the acceptor acetone. We could rule out intermolecular hydrogen bonding of **5baa** in

Scheme 1. Ugi Reaction of Compound 1

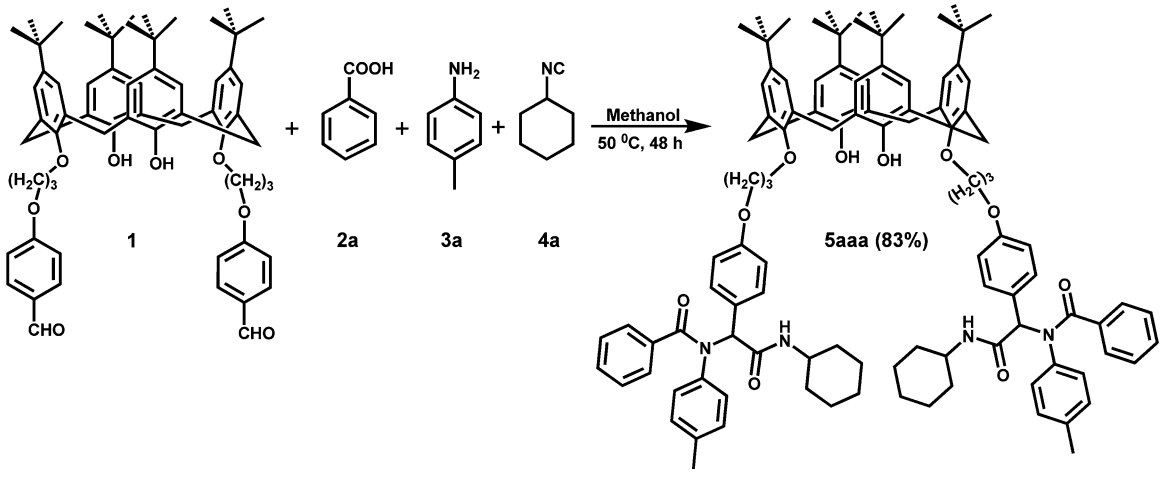

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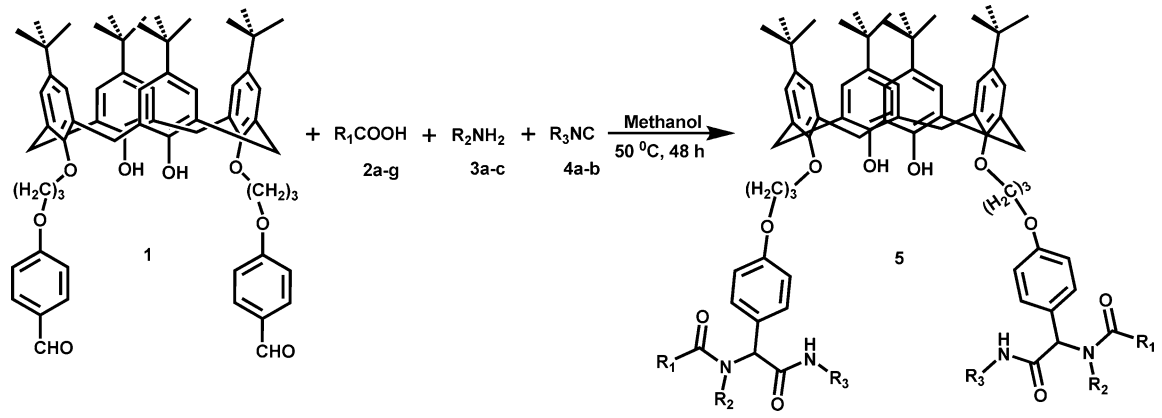
Table 1. Ugi-4CR of Compound 1



Entry	R_1	R_2	R_3	Yield (%)
1	2a	3a	4a	**5aaa**, 83
2	2a	3b	4a	**5aba**, 79
3	2b	3a	4a	**5baa**, 77
4	2a	3c	4a	**5aca**, 80
5	2c	3a	4a	**5caa**, 74
6	2d	3a	4a	**5daa**, 75
7	2e	3c	4a	**5eca**, 76
8	2f	3c	4a	**5fca**, 74
9	2g	3a	4a	**5gaa**, 72
10[a]	2a	3a	4b	**5aab**, 52

[a]The reaction was carried out in TFE at room temperature.

$CDCl_3$, since its ^1H NMR spectra recorded at different concentrations did not show any significant changes.

We further investigated the ionic binding ability of these new tripeptoids. Compounds **5caa**, **5daa**, and **5gaa** were examined. However, preliminary binding studies toward anions (fluoride, chloride, bromide, iodide, benzoate, acetate, perchlorate, and bisulfate) and organic cations (benzylammonium ion) using UV−vis and ^1H NMR spectroscopy indicated no significant

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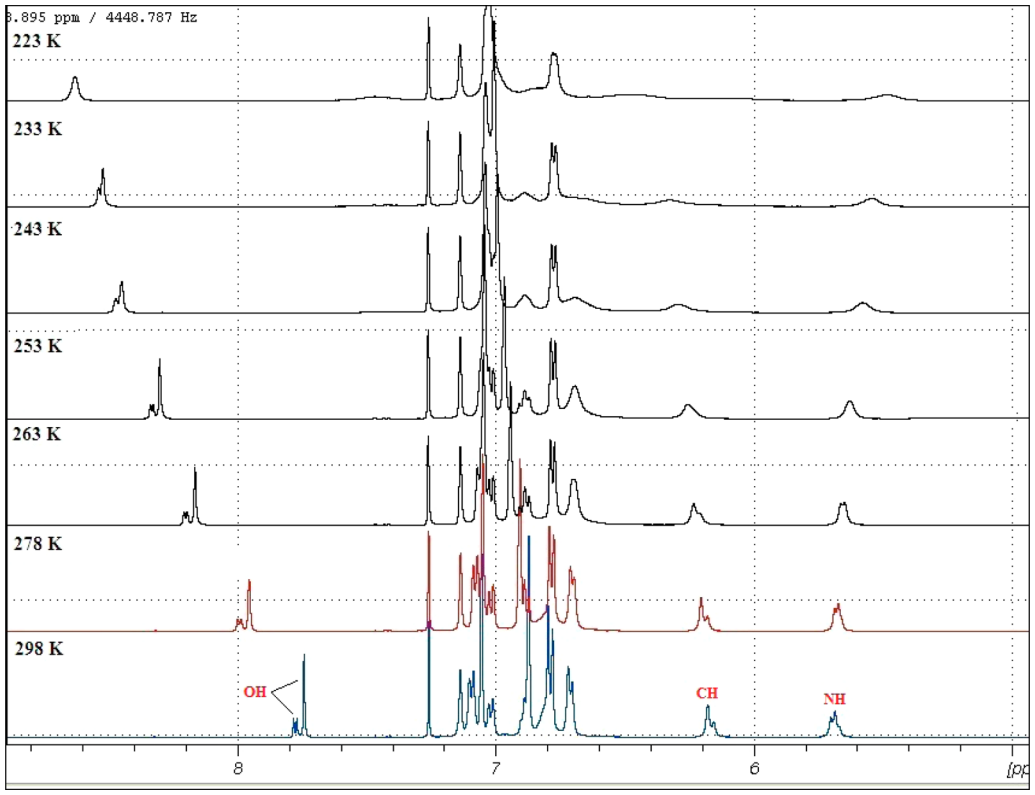

Figure 1. Variable-temperature 500 MHz ^{1}H NMR spectra of **5baa** in $CDCl_3$. Full spectra are available in the Supporting Information (Figure S3).

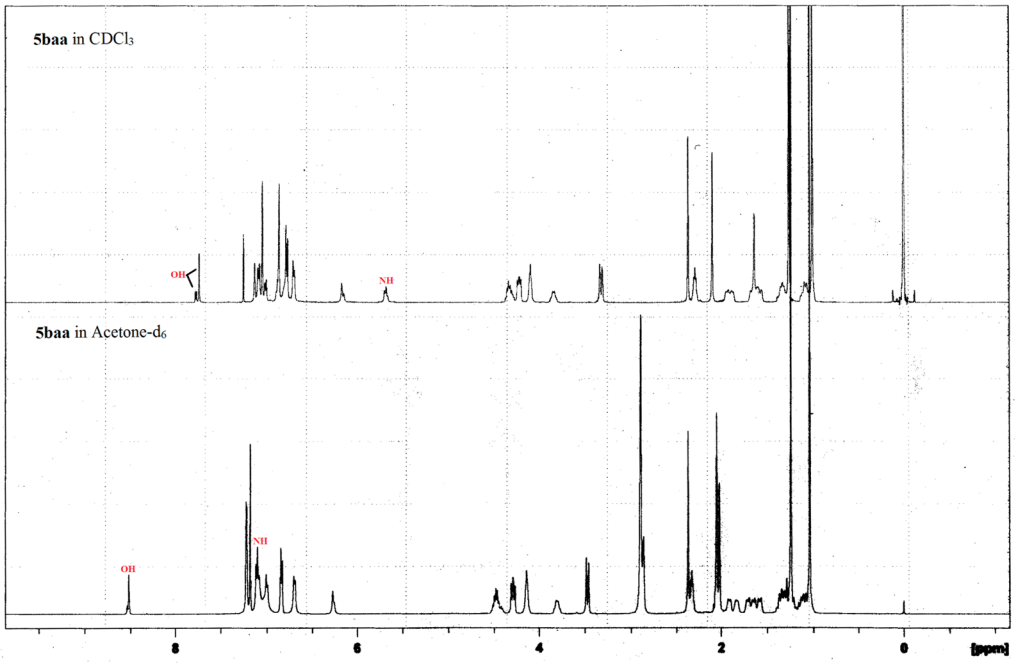

Figure 2. Comparison of ^{1}H NMR spectra of compound **5baa** in $CDCl_3$ and acetone-d_6.

activity. In a cation binding study with cations as metal perchlorates (Cr^{3+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Hg^{2+}, Ag^{+}, Pb^{2+}, Cd^{2+}, Na^{+}, K^{+}, Ca^{2+}, Al^{3+}) compound **5gaa** showed selective binding affinity toward Cu^{2+}. The core **5gaa** showed no fluorescence, and this may be because the peptide bond quenches tryptophan fluorescence by excited-state electron transfer (peptide is an efficient intramolecular quencher).[11,12] Moreover, Cu^{2+} is a known quencher due to its paramagnetic nature.[13] Hence, the binding studies were carried out by UV−vis spectrophotometric techniques.

Figure 4 shows the result of the absorption titration of **5gaa** with Cu^{2+} in CH_3CN. Without cations, **5gaa** showed an intense absorption band centered at 282 nm (ε = 33052 M^{-1} cm^{-1}). Upon gradual addition of Cu^{2+}, the 282 nm band decreased and a new band appeared at 472 nm which reached a maximum intensity (ε = 17263 M^{-1} cm^{-1}) on addition of 30 equiv of Cu^{2+}.

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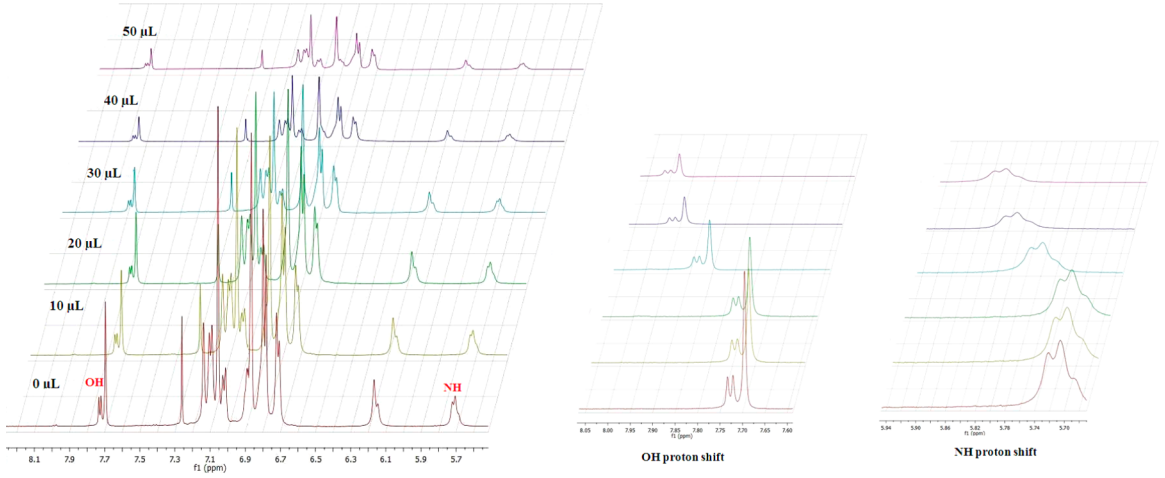

Figure 3. ^{1}H NMR spectra of **5baa** in $CDCl_3$ upon gradual addition of acetone (10−50 μL). Full spectra are available in the Supporting Information (Figure S4).

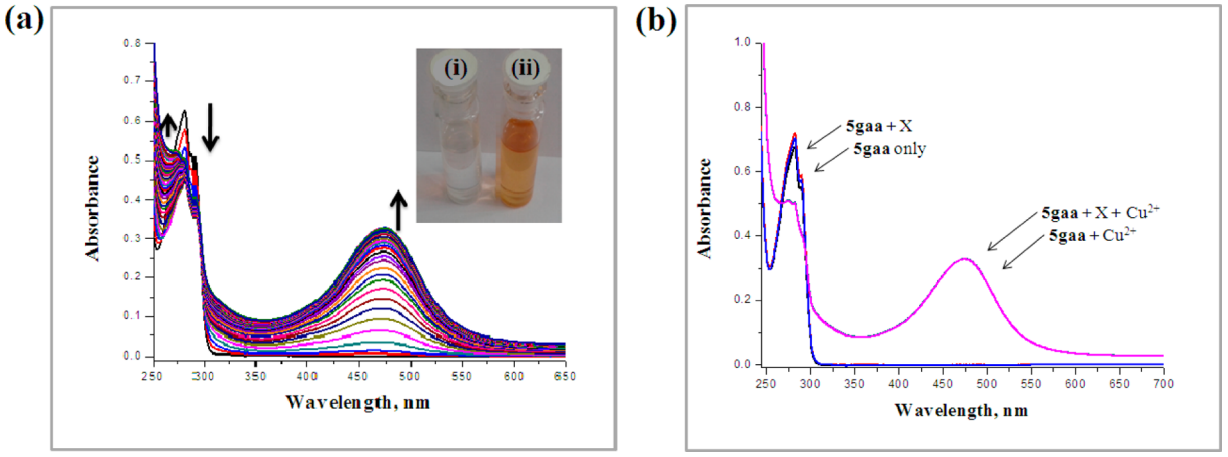

Figure 4. (a) Change in absorption spectra of **5gaa** (50 μM) in CH_3CN upon addition of 0−30 equiv of Cu^{2+}. The inset shows the color change of the solution upon Cu^{2+} addition: (i) **5gaa** alone; (ii) **5gaa** + Cu^{2+}. (b) UV−vis spectra of **5gaa** (50 μM) in CH_3CN in the presence of Cu^{2+} ion and miscellaneous cations including Cr^{3+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Hg^{2+}, Zn^{2+}, Ag^{+}, Pb^{2+}, Cd^{2+}, Na^{+}, K^{+}, Ca^{2+}, and Al^{3+} (40 equiv) in CH_3CN.

As shown in the inset picture (Figure 4a), the solution color changed gradually from colorless to orange upon incremental addition of Cu^{2+}.

A detailed investigation of the titration results revealed that an isosbestic point existed at 296 nm in the range of 0−4 equiv of Cu^{2+} (Figure S1, Supporting Information). On further addition of Cu^{2+} (4−30 equiv) (Figure S2, Supporting Information), a new peak began to appear at 274 nm. The complex band at 474 nm continuously increased, and the orange color became more intense. Addition of Cu^{2+} beyond this concentration did not lead to any further spectral changes. These changes suggest some sequential binding of Cu^{2+} with the ligand **5gaa**.[14] ESI-MS analysis of a CH_3CN solution containing ligand and Cu^{2+} did not show any clear mass assigned to the complex, and a clear stoichiometry also could not be assigned, as a Job plot was not obtained. These may be due to the low stability of the complex formed.[14]

UV−vis spectral changes (Figure 4b) of **5gaa** in competitive metal ion complexation were also observed in the presence of Cr^{3+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Hg^{2+}, Zn^{2+}, Ag^{+}, Pb^{2+}, Cd^{2+}, Na^{+}, K^{+}, Ca^{2+}, and Al^{3+} in CH_3CN (perchlorate counteranion). It may be mentioned that these cations as such did not lead to any significant changes in the visible region. In the presence of these miscellaneous competitive cations, compound **5gaa** still showed a UV band shift as well as a color change from colorless to orange, indicating that the wavelength shift of absorbance resulting from the addition of the Cu^{2+} ion is not influenced by any subsequent addition of miscellaneous cations. All of these experiments imply that the selectivity of **5gaa** for the Cu^{2+} ion over other competitive cations is remarkably high.

The distinctive color change of a ligand on complexation with certain metal ions has an important role in a possible sensing system. Therefore, it is worth mentioning that the colorimetric detection of Cu^{2+} by **5gaa** is unaffected even in the presence of 40 equiv of many other cations. Thus, the ligand **5gaa** enables selective detection of Cu^{2+}.

■ CONCLUSION

In conclusion, we have successfully introduced an operationally simple multicomponent synthetic route at the lower rim of calix[4]arene toward a new series of peptoid derivatives of calix[4]arene which accommodate rich multivalent groups that could find potential applications in supramolecular chemistry. We incorporated biologically relevant amino acids such as N-BOC-gly, N-BOC-L-ala, and N-BOC-L-trp and the pyramidine unit as well. Several useful functionalities such as halo-group-containing

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substrates capable of undergoing further manipulation also were readily incorporated into the final products. We observed that, among the new calix[4]arene derivatives synthesized, compound **5gaa** showed a selective change in UV absorption and color toward the Cu^{2+}cation in CH_3CN. Competition experiments and the visual changes in **5gaa** give a solid foundation for the design of an optimal host molecule for Cu(II) ion which can be applied to industrial and environmental fields.

EXPERIMENTAL SECTION

All the chemicals were of the best grade commercially available and were used without further purification. All of the solvents were purified according to standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate binder. Gravity column chromatography was performed using neutral alumina, and hexane−ethyl acetate mixtures were used for elution. The perchlorate salts of Cr(II), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Hg(II), Ag(I), Pb(II), Cd(II), Na(I), K(I), and Ca(II) used in this study were purchased from Aldrich.

Melting points were determined on a melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) and ^{1}H−^{1}H correlation spectra (COSY) were recorded on a 500 MHz NMR spectrophotometer ($CDCl_3$ as solvent unless otherwise stated). Chemical shifts for ^{1}H NMR spectra are reported as δ units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.25, singlet). Multiplicities are given as follows: s (singlet); d (doublet); dd (doublet of doublets); t (triplet); bs (broad singlet). Coupling constants are reported as *J* values in Hz.

Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03, triplet).

Mass spectra were recorded under ESI/HRMS at 60000 resolution using a mass spectrometer (analyzer type: orbitrap). IR spectra were recorded on FT-IR spectrometer.

General Procedure for the Synthesis of α-Acyloxycarboxamidocalixarene (5) by the U-4CR (except 5aab). Compound **1** (0.0257 mmol), amine **2** (0.1027 mmol), carboxylic acid **3** (0.1284 mmol), and isocyanide **4** (0.1027 mmol) were taken up in 1 mL of methanol, and the reaction mixture was heated at 50 °C for 48 h. The solvent was removed in vacuo. The product was purified by column chromatography on neutral alumina (hexane/EtOAc).

Procedure for the Synthesis of Derivative 5aab. Compound **1** (0.0257 mmol) and amine **2a** (0.1027 mmol) were stirred in 1 mL of TFE for 2 h. Then, carboxylic acid **3a** (0.1284 mmol) and naphthyl isocyanide **4b** (0.1027 mmol) were added and the reaction mixture was stirred for 48 h at room temperature. The solvent was removed in vacuo. The product was purified by column chromatography on neutral alumina (hexane/EtOAc).

Compound ***5aaa:*** 0.034 g, 83% yield; R_f = 0.36 (35/75 EtOAc/hexane); white solid; mp 103−105 °C; IR (KBr) ν_{max} 3327, 2955, 2928, 2857, 1679, 1636, 1511, 1484, 1246 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (m, OH, 2H), 7.29 (d, *J* = 8.0 Hz, ArH, 4H), 7.17 (m, ArH, 6H), 7.11 (m, ArH, 4H), 7.05 (s, ArH, 4H), 6.87 (m, ArH, 4H), 6.80 (m, ArH, 8H), 6.75 (m, ArH, 4H), 6.10 (s, CH, 2H), 5.88 (m, NH, 2H), 4.29 (m, OCH_2, $ArCH_2Ar$, 4H), 4.11 (m, OCH_2, 4H), 3.85 (m, CH, 2H), 3.32 (d, *J* = 12.5 Hz, $ArCH_2Ar$, 4H), 2.30 (m, CH_2, 4H), 2.12 (s, CH_3, 6H), 1.91 (m, CH_2, 4H), 1.60 (m, CH_2, 4H), 1.33 (m, CH_2, 4H), 1.27 (m, CH_2, *t*-Bu, 22H), 1.11 (m, CH_2, 4H), 1.01 (m, *t*-Bu, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C═O), 168.8 (C═O), 158.8, 150.6, 149.4, 141.7, 138.6, 136.7, 136.4, 132.7, 131.6, 130.0, 129.9, 129.2, 128.9, 128.5, 127.7, 127.5, 127.0, 125.6, 125.1, 114.4, 72.8, 65.9, 64.6, 48.7, 34.0, 33.8, 32.9, 32.8, 31.7, 31.0, 29.9, 25.5, 24.9, 24.8, 20.9; HRMS (ESI-MS) calcd for $C_{106}H_{124}N_4O_{10}$ $[M + H]^+$ 1613.9395, found 1613.9361.

Compound ***5aba:*** 0.037 g, 79% yield; R_f = 0.38 (35/75 EtOAc/hexane); white solid; mp 110−112 °C; IR (KBr) ν_{max} 3329, 2956, 2929, 2857, 1678, 1648, 1512, 1481, 1247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (m, OH, 2H), 7.34 (bs, ArH, 2H), 7.29 (d, *J* = 7.5 Hz, ArH, 4H), 7.24 (m, ArH, 2H), 7.20 (m, ArH, 2H), 7.13 (m, ArH, 8H), 7.05 (s, ArH, 4H), 6.90 (m, ArH, 2H), 6.85 (m, ArH, 8H), 6.61 (t, *J* = 8.0 Hz, ArH, 2H), 6.12 (m, CH, 2H), 5.78 (m, NH, 2H), 4.34 (m, OCH_2, 4H), 4.23 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 4.10 (m, OCH_2, 4H), 3.84 (m, CH, 2H), 3.33 (d. *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 2.32 (m, CH_2, 4H), 1.93 (m, CH_2, 4H), 1.61 (m, CH_2, 4H), 1.34 (m, CH_2, 4H), 1.24 (m, *t*-Bu, CH_2, 20H), 1.08 (m, CH_2, 6H), 1.00 (m, *t*-Bu, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C═O), 168.6 (C═O), 159.0, 150.6, 149.4, 147.2, 142.1, 141.7, 139.2, 135.9, 135.8, 132.7, 131.7, 131.6, 130.2, 129.5, 128.5, 128.4, 127.7, 126.5, 125.6, 125.1, 114.6, 92.7, 72.7, 64.6, 48.9, 48.8, 34.0, 33.8, 32.8, 31.7, 31.0, 29.9, 25.5, 24.9, 24.8, 21.0; HRMS (ESI-MS) calcd for $C_{104}H_{118}I_2N_4O_{10}$ $[M + H]^+$ 1837.7015, found 1837.6958.

Compound ***5baa:*** 0.035 g, 77% yield; R_f = 0.56 (35/65 EtOAc/hexane); white solid; mp 133−135 °C; IR (KBr) ν_{max} 3338, 2929, 2857, 1682, 1640, 1511, 1483, 1246 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (m, OH, 2H), 7.11 (m, ArH, 6H), 7.06 (s, ArH, 4H), 7.02 (m, ArH, 2H), 6.87 (m, ArH, 6H), 6.79 (m, ArH, 8H), 6.71 (m, ArH, 4H), 6.16 (m, CH, 2H), 5.70 (m, NH, 2H), 4.32 (m, OCH_2, 4H), 4.21 (m, $ArCH_2Ar$, 4H), 4.10 (m, OCH_2, 4H), 3.84 (m, CH, 2H), 3.33 (m, $ArCH_2Ar$, 4H), 2.34 (s, CH_3, 6H), 2.29 (m, CH_2, 4H), 2.10 (s, CH_3, 6H), 1.92 (m, CH_2, 4H), 1.61 (m, CH_2, 4H), 1.34 (m, *t*-Bu, CH_2, 24H), 1.10 (m, CH_2, 6H), 1.00 (s, *t*-Bu, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9 (C═O), 168.6 (C═O), 158.9, 150.6, 149.4, 147.3, 141.7, 137.3, 137.1, 135.8, 132.8, 132.7, 132.6, 131.7, 129.8, 128.9, 128.7, 127.9, 127.7, 126.7, 125.7, 125.2, 122.1, 114.5, 72.7, 64.9, 64.6, 48.8, 34.0. 33.8, 32.9, 32.8, 31.7, 31.0, 29.9, 25.5, 24.9, 24.8, 20.9, 19.4; HRMS (ESI-MS) calcd for $C_{108}H_{126}Br_2N_4O_{10}$ $[M + H]^+$ 1797.7919, found 1797.7896.

Compound ***5aca:*** 0.034 g, 80% yield; R_f = 0.23 (35/65 EtOAc/hexane); white solid; mp 179−181 °C; IR (KBr) ν_{max} 3329, 2955, 2928, 2856, 1678, 1632, 1510, 1484 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (m, OH, 2H), 7.29 (m, ArH, 6H), 7.17 (m, ArH, 10H), 7.05 (s, ArH, 4H), 6.86 (m, ArH, 6H), 6.80 (m, ArH, 4H), 6.47 (m, ArH, 4H), 6.16 (s, CH, 2H), 5.86 (m, NH, 2H), 4.34 (m, OCH_2, 4H), 4.25 (m, $ArCH_2Ar$, 4H), 4.11 (m, OCH_2, 4H), 3.84 (m, CH, 2H), 3.61 (s, OCH_3, 6H), 3.35 (m, $ArCH_2Ar$, 4H), 2.30 (m, CH_2, 4H), 1.94 (m, CH_2, 4H), 1.62 (m, CH_2, 4H), 1.33 (m, CH_2, 4H), 1.27 (s, *t*-Bu, 18H), 1.09 (m, CH_2, 6H), 1.01 (s, *t*-Bu, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (C═O), 168.9 (C═O), 158.8, 158.1, 150.6, 149.4, 147.2, 141.7, 136.4, 132.7, 131.7, 129.7, 129.1, 128.4, 127.7, 127.6, 126.9, 125.6, 125.1, 114.6, 114.4, 113.3, 72.8, 64.6, 60.4, 55.1, 48.7, 34.0, 33.8, 32.8, 31.7, 31.0, 29.9, 25.5, 24.9, 24.8; HRMS (ESI-MS) calcd for $C_{106}H_{124}N_4O_{12}$, $[M + H]^+$ 1645.9294, found 1645.9249.

Compound ***5caa:*** 0.035 g, 74% yield; R_f = 0.46 (35/65 EtOAc/hexane); light yellow solid; mp 73−75 °C; IR (KBr) ν_{max} 3326, 2955, 2924, 2854, 1655, 1607, 1534, 1512, 1483, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (m, ArH, 2H), 7.75 (m, OH, 2H), 7.55 (d, *J* = 8.0 Hz, ArH, 2H), 7.32 (d, *J* = 8.0 Hz, ArH, 2H), 7.14 (m, ArH, 6H), 7.05 (s, ArH, 4H), 6.87 (m, ArH, 6H), 6.80 (m, ArH, 4H), 6.71 (m, ArH, 4H), 6.19 (m, CH, 2H), 5.86 (m, NH, 2H), 4.33 (m, OCH_2, 4H), 4.23 (m, $ArCH_2Ar$, 4H), 4.10 (m, OCH_2, 4H), 3.86 (m, CH, 2H), 3.33 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 2.30 (m, CH_2, 4H), 2.08 (s, CH_3, 6H), 1.95 (m, CH_2, 4H), 1.65 (m, CH_2, 4H), 1.30 (m, CH_2, *t*-Bu, 24H), 1.09 (m, CH_2, 6H), 1.00 (m, *t*-Bu, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3 (C═O), 166.9 (C═O), 159.0, 150.6, 149.4, 147.2, 145.4, 138.1, 136.5, 132.7, 132.3, 131.9, 130.9, 129.7, 129.5, 129.4, 129.0, 128.2, 127.7, 127.1, 125.6, 125.2, 122.4, 115.3, 114.5, 72.8, 65.0, 64.6, 60.4, 34.0, 33.8, 32.8, 31.7, 31.0, 29.9, 25.5, 24.9, 21.0, 20.1; HRMS (ESI-MS) calcd for $C_{106}H_{120}Br_2N_6O_{14}$ $[M + H]^+$ 1859.7307, found 1859.7253.

Compound ***5daa:*** 0.036 g, 75% yield; R_f = 0.46 (35/65 EtOAc/hexane); white solid; mp 106−108 °C; IR (KBr) ν_{max} 3331, 2926, 2854, 1655, 1609, 1541, 1511, 1248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (m, ArH, 2H), 7.71 (m, OH, 2H), 7.11 (m, ArH, 4H), 7.05 (s, ArH, 6H), 6.86 (s, ArH, 6H), 6.79 (d, *J* = 7.0 Hz, ArH, 4H), 6.75 (m, ArH, 4H), 6.18 (d, *J* = 15 Hz, CH, 2H), 5.87 (dd, J_1 = 18.5 Hz, J_2 = 8 Hz, NH, 2H), 4.30 (m, OCH_2, 4H), 4.23 (m, $ArCH_2Ar$, 4H), 4.10 (m, OCH_2, 4H), 3.87 (m, CH, 2H), 3.33 (d, *J* = 12.5 Hz, $ArCH_2Ar$, 4H), 2.43 (s, CH_3, 6H), 2.30 (m, CH_2, 4H), 2.13 (s, CH_3, 6H), 1.97 (m, CH_2, 2H), 1.89 (m, CH_2, 4H), 1.61 (m, CH_2, 4H), 1.36 (m, CH_2, 4H), 1.27 (s, *t*-Bu, 18H), 1.14 (m, CH_2, 6H), 1.00 (s, *t*-Bu, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C═O), 167.7 (C═O), 165.3, 161.3, 159.1, 158.9, 150.6, 149.4, 147.2, 138.6, 134.7, 132.7, 131.8, 130.3, 128.9, 127.7, 125.7,

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125.6, 125.2, 114.4, 110.9, 72.8, 64.6, 63.9, 48.8, 34.0, 33.8, 33.2, 32.8, 31.8, 31.0, 29.9, 25.5, 24.9, 24.8, 21.1, 14.3; HRMS (ESI-MS) calcd for $C_{104}H_{122}Br_2N_8O_{10}S_2$, $[M + H]^+$ 1865.7170, found 1865.7154.

Compound ***5eca****:* 0.034 g, 76% yield; R_f = 0.35 (40/60 EtOAc/hexane); white solid; mp 230−232 °C; IR (KBr) ν_{max} 3291, 2956, 2928, 2856, 1715, 1652, 1610, 1510, 1245 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, OH, 2H), 7.59 (bs, ArH, 2H), 7.05 (s, ArH, 4H), 6.96 (d, J = 8.5 Hz, ArH, 4H), 6.86 (s, ArH, 4H), 6.76 (m, ArH, 6H), 6.51 (bs, ArH, 2H), 6.37 (bs, ArH, 2H), 5.98 (s, CH, 2H), 5.59 (d, J = 8.0 Hz, NH, 2H), 5.43 (bs, NH, 2H), 4.30 (m, OCH_2, 4H), 4.21 (m, $ArCH_2Ar$, 4H), 4.09 (m, OCH_2, 4H), 3.78 (m, CH, 2H), 3.70 (s, OCH_3, 6H), 3.57 (m, CH_2, 4H), 3.32 (d, J = 13.0 Hz, $ArCH_2Ar$, 4H), 2.29 (m, CH_2, 4H), 1.92 (m, CH_2, 2H), 1.79 (m, CH_2, 2H), 1.61 (m, CH_2, 8H), 1.40 (s, t-Bu, 18H), 1.31 (m, CH_2, 4H), 1.27 (s, t-Bu, 18H), 1.09 (m, CH_2, 4H), 1.00 (s, t-Bu, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (C═O), 168.6 (C═O), 159.4 (C═O), 158.9, 155.7, 150.6, 149.4, 147.2, 141.7, 132.7, 131.8, 131.5, 130.5, 127.7, 126.2, 125.6, 125.1, 114.4, 114.3, 79.4, 72.8, 64.6, 64.5, 55.3, 48.8, 43.7, 34.0, 33.8, 32.8, 31.7, 31.0, 29.9, 28.3, 25.5, 24.9, 24.8; HRMS (ESI-MS) calcd for $C_{106}H_{138}N_6O_{16}$ $[M + H]^+$ 1752.0247, found 1752.0186.

Compound ***5fca****:* 0.034 g, 74% yield; R_f = 0.41 (40/60 EtOAc/hexane); white solid; mp 124−126 °C; IR (KBr) ν_{max} 3327, 2953, 2932, 2856, 1716, 1654, 1610, 1510, 1487, 1247 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (m, OH, 2H), 7.59 (m, ArH, 2H), 7.04 (s, ArH, 4H), 6.96 (m, ArH, 4H), 6.87 (s, ArH, 4H), 6.74 (m, ArH, 6H), 6.58 (m, ArH, 4H), 6.09 (m, CH, 2H), 5.63 (m, NH, 2H), 5.28 (m, NH, 2H), 4.25 (m, OCH_2, $ArCH_2Ar$, 8H), 4.11 (m, OCH_2, 4H), 3.82 (m, CH, 2H), 3.71 (m, OCH_3, 6H), 3.32 (m, $ArCH_2Ar$, 4H), 2.29 (m, CH_2, 4H), 1.88 (m, CH_2, 4H), 1.63 (m, CH_2, CH, 6H), 1.43 (m, t-Bu, 18H), 1.35 (m, CH_2, 6H), 1.26 (m, t-Bu, CH_2, 20H), 1.18 (m, CH_2, 4H), 1.09 (m, CH_3, 6H), 1.01 (s, t-Bu, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9 (C═O), 168.8 (C═O), 168.3 (C═O), 160.3, 159.2, 158.8, 150.6, 149.4, 147.2, 141.6, 132.7, 131.9, 131.8, 131.4, 131.0, 127.7, 126.2, 125.6, 125.1, 79.3, 72.8, 64.6, 55.3, 48.8, 47.6, 34.0, 33.8, 33.1, 32.9, 32.8, 31.7, 31.0, 29.9, 28.3, 25.5, 24.9, 19.1, 18.6; HRMS (ESI-MS) calcd for $C_{108}H_{142}N_6O_{16}$ $[M + H]^+$ 1780.0560, found 1780.0488.

Compound ***5gaa****:* 0.036 g, 72% yield; R_f = 0.29 (40/60 EtOAc/hexane); white solid; mp 78−80 °C; IR (KBr) ν_{max} 3333, 2924, 2855, 1654, 1609, 1511, 1364, 1246, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (m, NH, 2H), 7.79 (m, OH, 2H), 7.38 (m, ArH, 4H), 7.22 (m, ArH, 6H), 7.05 (m, ArH, 10H), 6.88 (m, ArH, 8H), 6.75 (m, ArH, 4H), 6.60 (m, ArH, 2H), 6.49 (bs, ArH, 2H), 5.91 (m, CH, 2H), 5.13 (m, NH, 2H), 4.54 (m, CH, 2H), 4.29 (m, OCH_2, $ArCH_2Ar$, 8H), 4.10 (m, OCH_2, 4H), 3.80 (m, CH, 2H), 3.31 (m, $ArCH_2Ar$, 4H), 3.12 (m, indolyl-CH, 2H), 2.88 (m, indolyl-CH, 2H), 2.25 (m, CH_2, CH_3, 10H), 1.88 (m, CH_2, 4H), 1.63 (m, CH_2, 6H), 1.34 (m, t-Bu, CH_2, 40H), 1.05 (m, t-Bu, CH_2, 24H); ^{13}C NMR (125 MHz, $CDCl_3$): 172.8 (C═O), 168.8 (C═O), 168.4 (C═O), 158.7, 158.5, 155.0, 150.6, 149.4, 147.2, 141.8, 137.9, 136.1, 132.6, 131.8, 130.3, 129.6, 128.2, 127.7, 125.7, 125.2, 123.5, 121.6, 118.9, 114.2, 113.9, 111.3, 110.9, 79.4, 72.7, 64.7, 52.1, 48.8, 48.7, 34.0, 33.9, 33.8, 32.8, 31.7, 31.0, 29.9, 29.7, 28.3, 25.5, 24.9, 21.1, 21.0; HRMS (ESI-MS) calcd for $C_{124}H_{152}N_8O_{14}$ $[M + H]^+$ 1978.1506, found 1978.1467.

Compound ***5aab****:* 0.023 g, 52% yield; R_f = 0.42 (35/65 EtOAc/hexane); red solid; mp 100−102 °C; IR (KBr) ν_{max} 3313, 3054, 2957, 2925, 2857, 1699, 1628, 1555, 1510, 1485, 1390, 1283, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (m, OH, 2H), 7.68 (m, ArH, 8H), 7.36 (s, ArH, 10H), 7.24 (m, ArH, 8H), 7.18 (d, J = 21 Hz, CH, 2H), 7.12 (m, ArH, 2H), 7.04 (m, ArH, 4H), 6.84 (m, ArH, 12H), 6.78 (m, ArH, 4H), 6.27 (m, NH, 2H), 4.36 (m, OCH_2, 4H), 4.23 (m, $ArCH_2Ar$, 4H), 4.08 (m, OCH_2, 4H), 3.30 (m, $ArCH_2Ar$, 4H), 2.31 (m, CH_2, 4H), 2.13 (s, $ArCH_3$, 6H), 1.26 (m, t-Bu, 18H), 0.99 (m, t-Bu, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6 (C═O), 168.5 (C═O), 159.0, 150.6, 149.4, 147.2, 141.6, 138.3, 137.0, 135.9, 135.3, 133.8, 131.7, 131.6, 130.6, 130.1, 129.5, 129.1, 128.7,128.6, 128.5, 127.7, 127.6, 127.4, 126.4, 126.2, 125.6, 125.1, 124.8, 120.2, 116.8, 114.6, 72.7, 65.2, 64.7, 34.0, 33.8, 31.9, 31.7, 31.0, 29.7, 24.9, 22.7; HRMS (ESI-MS) calcd for $C_{114}H_{116}N_4O_{10}$ $[M + H]^+$ 1700.8769, found 1700.8645.

Titration with Analytes. Because of the poor solubility of metal perchlorates in chloroform, all of the UV−visible experiments reported in this work were carried out in acetonitrile. The UV−visible spectra of the receptors in the presence of analytes were recorded as increasing amounts of analytes were added to the acetonitrile. Titration plots were generated by using Origin 6.0 (Microcal software).

■ ASSOCIATED CONTENT

Supporting Information

Figures giving spectroscopic characterization data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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