JOC Article

Phenyl-calix[4]arene-Based Fluorescent Sensors: Cooperative Binding for Carboxylates

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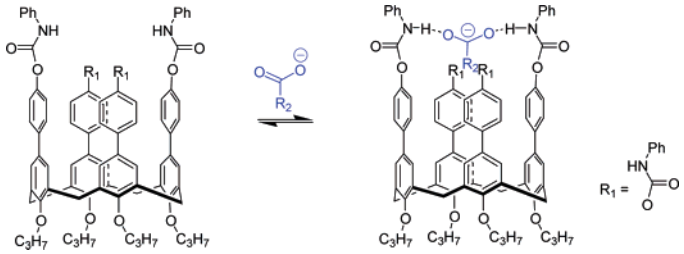

Tetrakis-(4-carbamoylphenyl)-substituted and tetrakis-(4-amidophenyl)-substituted calix[4]arenes as well as the monomeric biphenylcarbamate have been synthesized as fluorescent receptors for anion sensing. Their binding properties with various anions including F^-, CH_3COO^-, Ph-COO^-, and $H_2PO_4^-$ were investigated by fluorescence titrations, Job plot experiments, ^1H NMR spectroscopies, and ESI-MS measurements. Importantly, we have found that calix[4]arene-based sensors exhibit greatly enhanced binding affinity and selectivity toward carboxylates. The binding associations of tetrakis-(4-carbamoylphenyl)-substituted calix[4]arene for carboxylates are 1−2 orders of magnitude greater than those of the monomeric biphenylcarbamate sensor. Such an enhancement in the binding affinity and selectivity is attributed to the cooperative binding of the multiple ligating groups as revealed from the ab inito DFT calculations. Although tetrakis-(4-amidophenyl)-substituted calix[4]arene exhibited relatively weaker binding affinity toward anions, its superior binding selectivity for acetate ion over fluoride ion is evident. Our results also suggest that carbamate functionality is a useful H-bond donor for hydrogen-bonding interactions in molecular recognition and supramolecular chemistry.

Introduction

There are currently considerable efforts on exploring efficient artificial receptors for targeted anion recognition and sensing as anions are ubiquitous and play important roles in biological, medical, environmental, and chemical sciences.[1] Despite the tremendous progress in developing metal ion sensing in recent years,[2] design and synthesis of an artificial receptor/sensor that exhibits high binding affinity and selectivity to a targeted anion still remain a great challenge to the scientific community as anions exhibit a wide range of geometries and selective anionic receptors are difficult to design and synthesize.[1] The design of complementary structural components that show good recognition properties requires building in relatively strong and directional adhesive forces. Among various noncovalent interactions, hydrogen-bonding interactions are particularly useful and

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(1) (a) Haugland, R. P. *The Handbook. A Guide to Fluorescent Probes and Labeling Technologies*, 10th ed.; Molecular Probes Inc.: Eugene, OR, 2005. (b) *Anion sensing*; Stibor, I., Ed.; Springer-Verlag: Berlin 2005. (c) Martinez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103*, 4419−4476. (d) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486−516. (e) Haryley, J. H.; James, T. D.; Ward, C. J. *J. Chem. Soc. Parkin Trans.* **2000**, *1*, 3155−3184. (f) de Silva, A. P.; Nimal Gunaratne, H. Q.; Gunnlaugsson, T.; Huxley, A. J. M.; Mccoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515−1566. (g) *Fluorescent Chemosensors for Ion and Molecule Recognition*; Czarnik, A. W., Ed.; American Chemical Society Books: Washington, DC, 1993. (h) Lhoták, P. *Top. Curr. Chem.* **2005**, *255*, 65−95. (i) Matthews, S. E.; Beer, P. D. *Supramol. Chem.* **2005**, *17*, 411−435.

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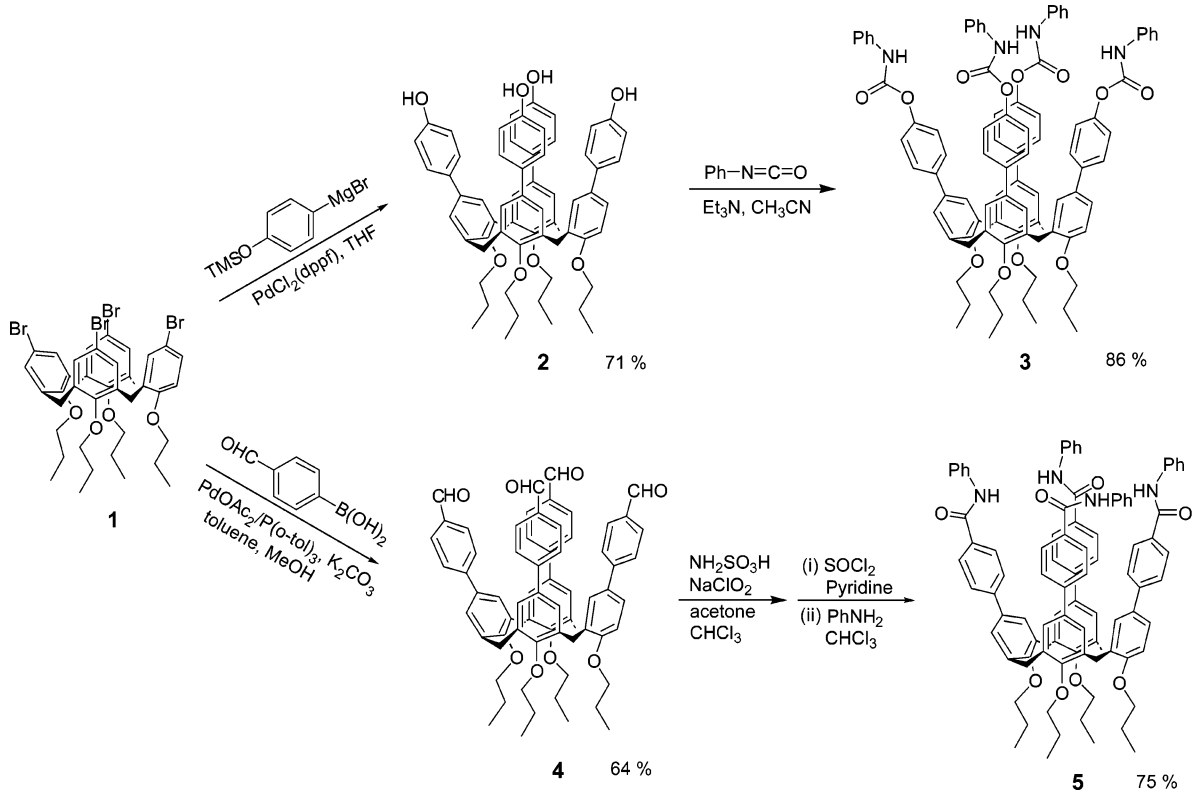
SCHEME 1. Syntheses of Aryl-Substituted Calix[4]arenes 3 and 5



effective in this regard. Receptors bearing functional groups such as amides,[3] ureas,[4] thioureas,[5] and positively charged groups[6] have been widely used to recognize anions via hydrogen-bonding interactions; on the other hand, carbamate functionality is rarely used for this purpose.[7] Strong binding affinity offers potential for high sensitivity at low analyte concentration. To achieve high binding affinity and good selectivity, a rigid and preorganized receptor site that is complementary to the targeted guest is of paramount importance. In addition, receptors/sensors bearing multiple ligating groups have been shown to be useful to promote cooperative binding, which would result in enhanced binding affinity.[8]

Calix[4]arene is greatly used as a molecular scaffold in the design of artificial receptors[9] because of its tunable and unique three-dimensional structure together with the ease of functionalization. On the other hand, there are few examples taking advantage of an extended preorganized rigid platform of calix[4]arene for construction of supramolecular systems.[10] The expanded or extended cavity could be beneficial to the encapsulation and recognition properties. Furthermore, the extended calix[4]arene skeleton with π-conjugated units could act as a chromophore or fluorophore. Upon binding with a guest, the change of the spectral properties would give rise to a sensing mechanism. Anion sensors developed from a change in fluorescence properties upon binding are considered particularly attractive because they offer promise for high sensitivity at low analyte concentration.[1f]

It has been shown that the *cone*-conformed calix[4]arene derivatives bearing four urea functionalities tend to self-assemble into the dimeric capsules via intermolecular hydrogen bonds.[10,11] However, by taking advantage of the structural preorganization of extended cone-conformed phenyl-substituted calix[4]arene

(2) For recent references, see: (a) Desvergne, J. P.; Czarnik, A. W. *Chemosensors of Ion and Molecule Recognition*; Kluwer: Dordrecht, 1997. (b) *Fluorescent Chemosensors for Ion and Molecule Recognition*; Czarnik, A. W., Ed.; American Chemical Society: Washington, DC, 1992. (c) Kim, S. K.; Lee, J. K.; Lee, S. H.; Lim, M. S. Lee, S. W.; Sim, W.; Kim, J. S. *J. Org. Chem.* **2004**, *69*, 2877−2880. (d) Budka, J.; Lhoták, P.; Stibor, I.; Michlová, V.; Sykroa, J.; Cisarová, I. *Tetrahedron Lett.* **2002**, *43*, 2857−2861. (e) Metivier, R.; Leray, I. Valeur, B. *Chem. Eur. J.* **2004**, *10*, 4480−4490. (f) Kim, J. H.; Hwang, A. R.; Chang, S. K. *Tetrahedron Lett.* **2004**, *45*, 7557−7561. (g) Choi, M. J.; Kim, M. Y.; Chang, S. K. *Chem. Commun.* **2001**, 1664−1665. (h) Hanaoka, K.; Kikuchi, K.; Kojima, H.; Urano, Y.; Nagano, T. *J. Am. Chem. Soc.* **2004**, *126*, 12470−12476. (i) Chen, P.; Greenberg, B.; Taghavi, S.; Romano, C.; vander Lelie, D.; He, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2715−2719.

(3) (a) Tomapatanaget, B.; Tuntulani, T.; Chailapakul, O. *Org. Lett.* **2003**, *5*, 1539−1542. (b) Kim, S. K.; Bok, J. H.; Bartsch, R. A.; Lee, J. Y.; Kim, J. S. *Org. Lett.* **2005**, *7*, 4839−4842.

(4) (a) Massimo, B.; Boca, D. L.; Gómez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507−16514. (b) Dudic, M.; Lhoták, P.; Stibor, I.; Lang, K.; Prosková. P. *Org. Lett.* **2003**, *5*, 149−152.

(5) (a) Pfeffer, F. M.; Gunnlaugsson, T.; Jensen, P.; Kruger, P. E. *Org. Lett.* **2005**, *7*, 5357−5360. (b) Liu, S. Y.; Fang, L.; He, Y. B.; Chan, W. H.; Yeung, K. T.; Cheng, Y. K.; Yang, R. H. *Org. Lett.* **2005**, *7*, 5825−5828.

(6) (a) Metzer, A.; Gloe, K. Stephan, H.; Schmidtchen, F. P. *J. Org. Chem.* **1996**, *61*, 2051−2055. (b) Breccia, P.; Van Gool, M.; Pérez-Fernánedz, R.; Martín-Santamaria, S.; Gago, F.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.*, **2003**, *125*, 8270−8284. (c) Amendola, V.; Boiocchi, M.; Fabbarizzi, L.; Palchetti, A. *Chem. Eur. J.* **2005**, *11*, 120−127.

(7) Fang, L.; Chan, W. H.; He, Y. B.; Kwong, D. W. J.; Lee, A. W. M. *J. Org. Chem.* **2005**, *70*, 7640−7646.

(8) (a) Wright, A. T.; Anslyn, E. V. *Org. Lett.* **2004**, *6*, 1341−1344. (b) Wong, M. S.; Xia, P. F.; Zhang, X. L.; Lo, P. K.; Cheng, Y.-K.; Yeung, K.-T.; Guo, X.; Shuang, S. M. *J. Org. Chem.* **2005**, *70*, 2816−2819.

(9) For recent reviews, see: (a) *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001. (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713−1734. (c) Danil de Mamor, A. F.; Cleverley, R. M.; Zapata-Ormachea, M. L. *Chem. Rev.* **1998**, *98*, 2495−2525.

(10) Cho, Y. L.; Rudkevich, D. M.; Rebek, Jr., J. *J. Am. Chem. Soc.* **2000**, *122*, 9868−9869.

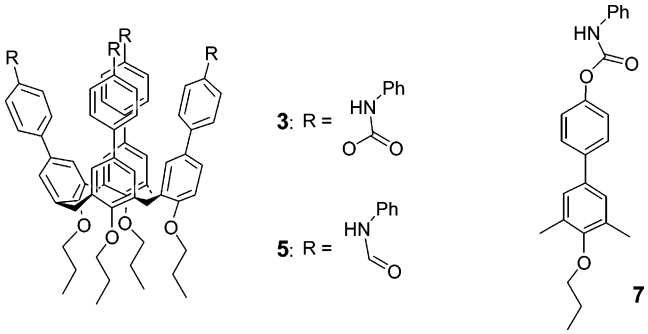
(11) Rebek, J., Jr. *Chem. Commun.* **2000**, 637−643.

TABLE 1. Stoichiometric Ratio (*R*) and Association Constant (*K*) of Tetrakis-(4-carbamoyl-phenyl)-Substituted Calix[4]arene 3, Tetrakis-(4-amidophenyl)-Substituted Calix[4]arene 5, and Monomeric Biphenylcarbamate 7 with Anions

	F^-			CH_3COO^-		$H_2PO_4^-$			$PhCOO^-$	
receptor	R^a	log *K*	*K*	R^a	*K*	R^a	log *K*	*K*	R^a	*K*
3	1:1	3.87[b]				1:1	3.16[b]			
	1:4	21.2[b]		1:1	4.6×10^5[c]	1:4	18.3[b]		1:1	3.9×10^4[c]
5	1:1		8866[c]	1:1	4.4×10^4[c]			–		–
7		3.73[b]					2.57[b]		–	–
	1:1		9582[c]	1:1	4490[c]	1:1		3490[c]	1:1	1000[c]

[a] Determined by the Job plot. [b] Determined from the static quenching equation, $\log(I_o - I)/I = \log K + n \log [A]$. [c] Calculated from nonlinear curve fitting analysis of fluorescent titration data.

together with co-operatively reinforced hydrogen-bonding interactions of appended ligating groups such as carbamate and amide functionalities at the upper (or wide) rim, binding- and selectivity-enhanced phenyl-substituted calixarene-based fluorescent anion sensors have been developed. We herein report the synthesis and investigation of anion binding/sensing studies of novel tetrakis-(4-carbamoylphenyl)-substituted calix[4]arene **3**, tetrakis-(4-amidophenyl)-substituted calix[4]arene **5**, and the



monomeric biphenylcarbamate **7**. We have found that the multiple carbamate-ligated calix[4]arene sensor exhibits superior binding affinity toward carboxylates as compared to the monomeric biphenylcarbamate counterpart.

Results and Discussion

The syntheses of tetrakis-(4-carbamoylphenyl)-substituted calix[4]arene **3** and tetrakis-(4-amidophenyl)-substituted calix-[4]arene **5** are shown in Scheme 1. Palladium-catalyzed Kumada coupling of tetrakisbromocalix[4]arene **1**[12] and (4-(trimethylsilyloxy)-phenyl)magnesium bromide, which was freshly generated by 1-bromo-4-(trimethylsilyloxy)benzene and magnesium turnings, followed by hydrolysis afforded tetrakis(4-hydroxyphenyl)-substituted calix[4]arene **2** in 71% yield. Refluxing of **2** and phenyl isocyanate in the presence of Et_3N in CH_3CN for 24 h afforded tetrakis(4-carbamoylphenyl)-substituted calix[4]-arene **3** in 86% isolated yield. One the other hand, palladium-catalyzed Suzuki coupling of **1** with 4-formylbenzeneboronic acid using $Pd(OAc)_2/P(o\text{-tol})_3$ as a catalyst gave tetrakis(4-formylphenyl)calix[4]arene **4**[13] in a moderate yield. Oxidation of **4** using sodium chlorite in the presence of sulfamic acid[14] yielded the corresponding acid in a quantitative yield. Amidation of carboxyphenylcalix[4]arene via the acid chloride with aniline

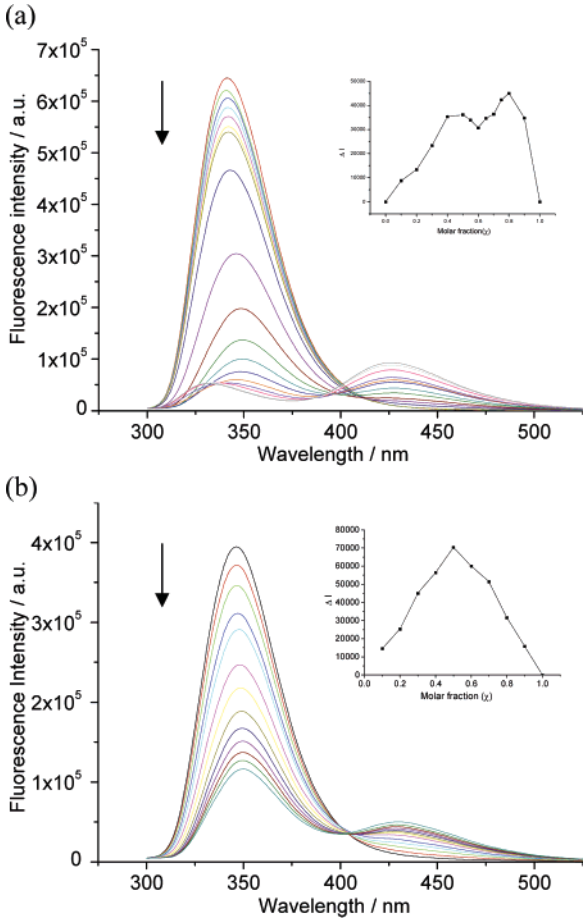


FIGURE 1. (a) Fluorescence spectra of **3** upon addition of various $[F^-]$ in CH_3CN. The inset shows the Job plot of **3** and $[F^-]$. (b) Fluorescence spectra of **3** upon addition of various $[Ph\text{-}COO^-]$ in CH_3CN. The inset shows the Job plot of **3** and $[Ph\text{-}COO^-]$.

afforded the desired tetrakis-(4-amidophenyl)-substituted calix-[4]arene **5** in 75% isolated yield. The monomeric biphenylcarbamate sensor **7** was also prepared accordingly using the same synthetic approach for comparison (see Supporting Information). All the newly synthesized receptors were fully characterized with ^1H NMR, ^{13}C NMR, high-resolution MALDI-TOF, and elemental analyses and found to be in good agreement with the structures.

The binding and sensing properties of **3**, **5**, and **7** with various anions were initially investigated by fluorescence titration. Upon titration of **3** in acetonitrile with various anions ($Bu_4N^+X^-$) including F^-, CH_3COO^-, $H_2PO_4^-$, and $Ph\text{-}COO^-$, the fluorescence intensity of **3** peaked at 350 nm and progressively decreased together with a slight shift of emission maximum (Figure 1). In some cases, there was also a weak emission band

(12) (a) Wong, M. S.; Zhang, X. L.; Chen, D. Z.; Cheung, W. H. *Chem. Commun.* **2003**, 138−139. (b) Wong, M. S.; Xia, P. F.; Lo, P. K.; Sun, X. H.; Wong, W. Y.; Shuang, S. M. *J. Org. Chem.* **2006**, *71*, 940−946. (c) Lo, P. K.; Chen, D. Z.; Meng, Q. W.; Wong, M. S. *Chem. Mater.* **2006**, *18*, 3924−3930.

(13) Wong, M. S.; Nicoud, J.-F. *Tetrahedron Lett.* **1993**, *34*, 8237−8239.

(14) Arduini, A.; Fabbi.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454−1457.

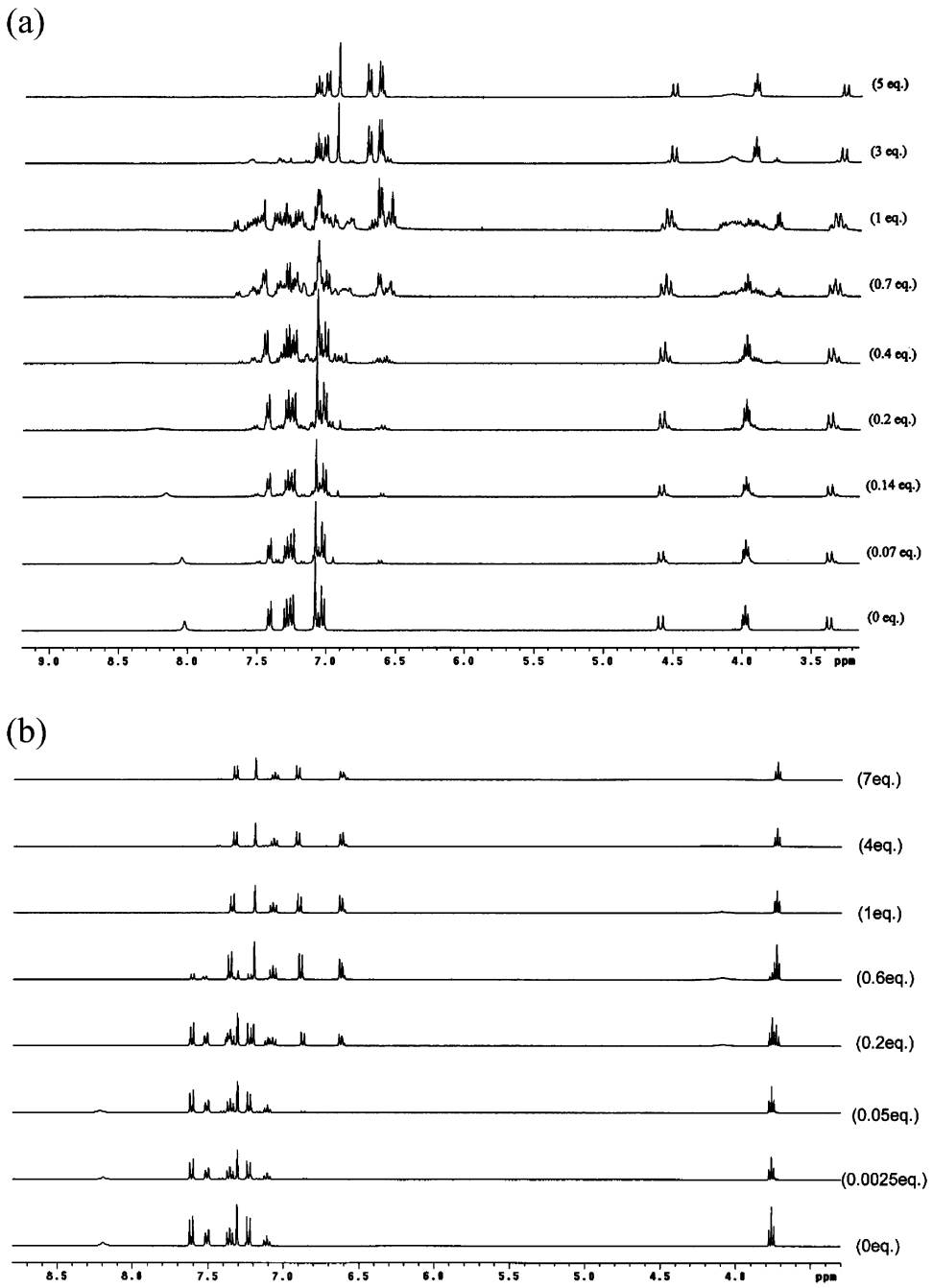


FIGURE 2. Spectra of ^{1}H NMR titration of (a) **3** (1.85 mM) and (b) **7** (10 mM) with *n*-$Bu_4N^+CH_3COO^-$ in CD_3CN.

that slowly emerged at 425−430 nm when an anion was added in a large excess. Interestingly, upon an addition of aqueous acid, the fluorescence intensity was restored and the weak band disappeared. These observations are consistent with the fact that the anion interacts with the N−H protons of the carbamate-appended calix[4]arene through hydrogen bonds. On the other hand, there were no significant spectral changes upon titration of **3** with Cl^-, Br^-, I^-, and HSO_4^- anions, signifying that **3** showed insignificant binding affinity toward these anions. (See Supporting Information.)

In view of the fluorescence titration spectra of **3**, there was a greater extent of intensity quenching after addition of more than 6 equiv of F^- or $H_2PO_4^-$ in contrast to the sequential decrease in fluorescence intensity induced by CH_3COO^- and Ph-COO^- (Figure 1), implying the presence of two binding stages/modes. Job plot analyses showed that **3** first formed 1:1 stoichiometric complexes with F^- and $H_2PO_4^-$ and became 1:4 complexes when F^- and $H_2PO_4^-$ was added in a large excess, respectively. The formation of 1:1 and 1:4 complexes were further confirmed by the ESI-MS measurements showing a base peak or peak at *m/z* 1456.6, 378.3, 1534.6, and 456.2 corresponding to **3**·F^-, **3**·4F^-, **3**·$H_2PO_4^-$, and **3**·4$H_2PO_4^-$, respectively. (See Supporting Information.)

Analyzing the titration data using the static quenching equation[15] consistently supported the existence of two binding

(15) Pang, Y. H.; Yang, L. L.; Shuang, S. M.; Dong, C.; Thompson, M. *J. Photochem. Photobiol., B* **2005**, *80*, 139−144.

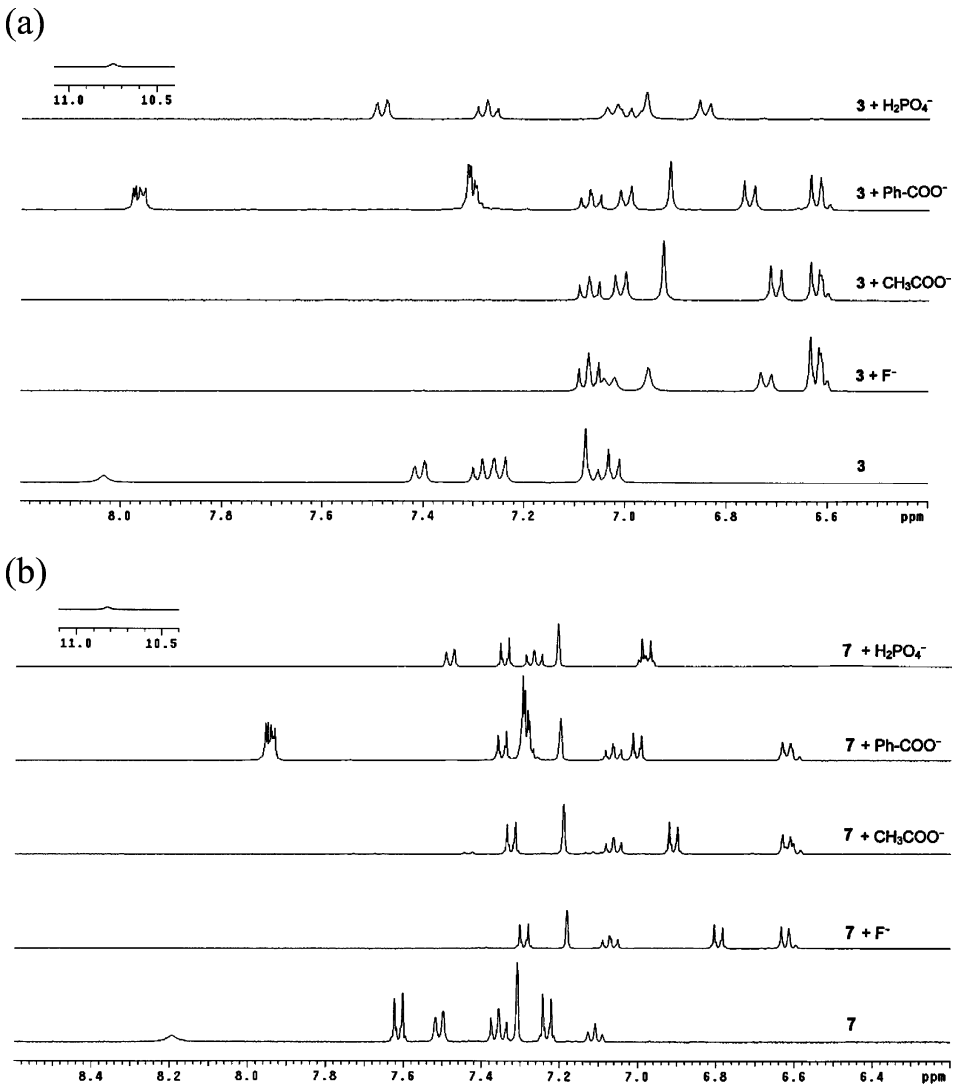


FIGURE 3. ^{1}H NMR spectra of the aromatic region of (a) **3** and (b) **7** and their corresponding hydrogen-bonded complexes upon addition of excess of anions in CD_3CN.

stoichiometries and also provided the estimated binding associations of the two complexes in which the carbamate-appended receptor **3** bound stronger with F^- (log $K_1 = 3.87$, log $K_4 = 21.2$) than $H_2PO_4^-$ (log $K_1 = 3.16$, log $K_4 = 18.3$) in both stoichiometric complexes agreeable to the decreasing basicity of the anions as shown in Table 1. In sharp contrast, the calix[4]arene-based receptor **3** only gave rise to a 1:1 binding with CH_3COO^- and Ph-COO^- according to the Job plot. The binding associations of **3**·CH_3COO^- and **3**·Ph-COO^- as determined by nonlinear curve fitting analysis[16] are 4.6×10^5 M^{-1} and 3.9×10^4 M^{-1}, respectively. The ESI-MS analyses further confirmed a 1:1 stoichiometric complex formation of **3**·CH_3COO^- and **3**·Ph-COO^- with a peak or base peak at *m/z* 1496.8 and 1558.8, respectively. The fluorescent quenching was also observed upon titration of the monomeric biphenylcarbamate sensor **7** with various anions; however, the binding affinities of **7** toward those anions are significantly weaker as compared to those of **3**, particularly for carboxylates. The order of anion affinity of **7** in 1:1 stoichiometries as determined by the Job plot analyses is F^- ($K = 9.6 \times 10^3$ M^{-1}) > CH_3COO^- ($K = 4.5 \times 10^3$ M^{-1}) > $H_2PO_4^-$ ($K = 3.5 \times 10^3$ M^{-1}) > Ph-COO^- ($K = 1.0 \times 10^3$ M^{-1}) which is also consistent to the decreasing basicity of the anions.

On the other hand, upon titration of amidophenyl-substituted calix[4]arene **5** with various anions, only F^- and CH_3COO^- could give rise to significantly progressive fluorescent quenching peaked at 400 nm. The ESI-MS analyses suggested a 1:1 stoichiometric complex formation of **5**·F^- and **5**·CH_3COO^- with a peak at *m/z* 1392.1 and 1432.5, respectively. The binding associations for F^- and CH_3COO^- in a 1:1 binding stoichiometry, which were further confirmed by the Job plot, are 8.9×10^3 M^{-1} and 4.3×10^4 M^{-1}, respectively, as estimated by nonlinear curve fitting analysis of titration data. These results suggested that sensor **5** exhibited higher selectivity for CH_3COO^- than for F^-. The binding associations of **3** and **5** for carboxylates are comparable to those of the best calix[4]arene-based anion receptors; on the other hand, these receptors exhibit much higher selectivity toward acetate over benzoate (for **3**, $K_{acetate/benzoate} \sim 12$; for **5**, $K_{acetate/benzoate} > 10^4$).[1h,1i]

The interactions of the receptor **3**, **5**, and **7** with anions were further investigated by ^{1}H NMR spectroscopy. Complexation of monomeric biphenyl-carbamate receptor **7** with anions was further supported by the growth of a new set of upfield-shifted

(16) Macomber, R. S. *J. Chem. Educ.* **1992**, *69*, 375−378.

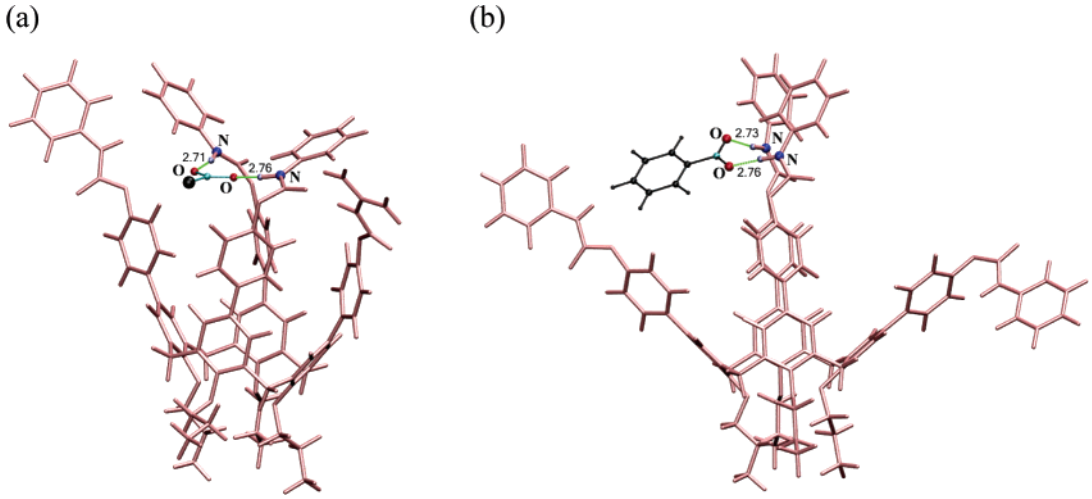


FIGURE 4. Optimized structures of (a) **3**·CH_3COO^- and (b) **3**·Ph-COO^- complexes obtained by B3LYP 6-31G DFT calculations (see the Supporting Information for details). In panel a, the methyl group of acetate is represented as a single black ball for clarity. The pertinent hydrogren bonds are highlighted as green dotted lines delimited by bond lengths (in Å) given by the precursor oxygen (red) and nitrogen (blue) atoms. The calix[4]-arenes are simply rendered as pink sticks.

aromatic protons corresponding to the hydrogen-bonded complex due to a slow exchange in NMR time scale (Figure 2). In particular, large upfield shifts of aromatic protons of **7** upon complexation with F^-, CH_3COO^-, and Ph-COO^- came from N-substituted phenyl ring (i.e., $\Delta\delta$ for *o*-Ar-*H* and *p*-Ar-*H* = 0.89 and 0.50 ppm, respectively, in CD_3CN) (Figure 3). The peak broadening together with diminished intensity of the N−H resonance as well as the upfield shift of aromatic protons of **7** due to the increase in the electron density of the phenyl ring upon an addition of anions consistently supported the formation of the hydrogen bond between the N−H proton of the carbamate moiety and anions. On the other hand, the receptor **7** showed remarkably different in the shifting pattern of proton resonances upon complexation with $H_2PO_4^-$, in which the upfield shifts of the aromatic protons of the carbamate-substituted phenyl ring ($\Delta\delta$ = 0.25−0.27 ppm) are greater than those of N-substituted phenyl ring ($\Delta\delta$ = 0.02−0.12 ppm). There was also a new broad proton resonance growing around 10.5 ppm while the N−H resonance peak decreased progressively (Figure 3). These findings suggest that the hydrogen-bonding interaction formed between the carbonyl of the carbamate moiety and the H−O of $H_2PO_4^-$ is significant.

In view of the spectra of ^{1}H NMR titrations of carbamoylphenyl-substituted calix[4]arene **3** with anions, the evolution of the chemical shifts was very complex due to slow equilibration of mixtures of receptor and receptor−anion complex (Figure 2a). However, the peak broadening and downfield shift of the N−H peaks as well as the overall trend of the upfield shift of the aromatic protons of **3** were evident and were very similar to those of the corresponding monomeric receptor **7**, suggesting that the same binding site/mode is used for the formation of the hydrogen-bonded receptor−anion complex (Figures 2 and 3). The large upfield shifts of aromatic protons of **3** upon complexation with F^-, CH_3COO^-, and Ph-COO^- also originated from N-substituted phenyl rings (i.e., $\Delta\delta$ for *o*-Ar-*H* = 0.78 and *p*-Ar-*H* 0.42 ppm in CD_3CN). Consistent with the monomeric receptor **7**, receptor **3** used a slightly different binding mode with $H_2PO_4^-$ in which the interaction between the carbonyl of the carbamate moiety and H−O of $H_2PO_4^-$ is significantly contributed as shown by the upfield shifts of the aromatic protons of the biphenyl ring ($\Delta\delta$ = 0.18−0.22 ppm) being greater than those of the N-substituted phenyl ring ($\Delta\delta$ for *o*-Ar-*H* = 0.002−0.08 ppm).

^{1}H NMR titrations of **5** with F^- and CH_3COO^- were carried out in CD_3COCD_3 due to insufficient solubility in CD_3CN. In contrast to **3** and **7**, binding of **5** with anions is kinetically fast on the NMR time scale; nevertheless, anion-induced shifts of the proton resonances of **5** were apparent. (See Supporting Information.) The downfield shift and peak broadening of the proton of the N−H moiety as well as the significantly large downfield shift of aromatic protons that are *ortho* to the N-substituent ($\Delta\delta$ = 0.2−0.37 ppm) and to the carbonyl substituent ($\Delta\delta$ = 0.28−0.75 ppm) upon addition of anions suggest the formation of hydrogen-bonded complex.

The very large binding constants obtained for **3**·4F^- and **3**·4$H_2PO_4^-$ hydrogen-bonded complexes are due to the additive effect of the four carbamoyl binding sites of **3** interacting separately with four F^- and four $H_2PO_4^-$ anions, respectively. On the other hand, the greatly enhanced binding of the calix-[4]arene-based receptor **3** toward carboxylates in a 1:1 binding stoichiometry is attributed to the cooperative binding of multiple carbamate ligating groups. As carboxylates are Y-shaped anions, it would be more favorable to have the hydrogen bonds formed between carboxylate and the two opposite −NH groups of carbamoyl moieties flanked from the extended calix[4]arene skeleton. Such a cooperative (or bidentate) binding mode was revealed in both of the optimized structures of **3**·CH_3COO^- and **3**·Ph-COO^- complexes, as shown in Figure 4 according to ab inito B3LYP 6-31G DFT calculations using Gaussian 03.[17] To achieve the bidentate binding mode, the carbamoylphenyl-calix-[4]arene receptor adopts a pinched cone conformation with a diminished cavity for encapsulation which is more pronounced in the benzoate case. This also leads to the methyl group of acetate or the phenyl group of benzoate swayed sideways from the receptor in the complexes. In view of the ^{1}H NMR titration spectra, both of the methyl proton resonances of acetates and aromatic proton resonances of benzoates exhibit no significant upfield shift upon binding with receptor **3** as compared to those of the monomeric receptor **7** (Figures S4 and S8), consistently suggesting that these anions possess no close van der Waal

contact with the receptor. Nevertheless, the binding affinities of carbamoylphenyl-substituted calix[4]arene **3** toward carboxylates are 1−2 orders of magnitudes larger than those of the monomeric biphenylcarbamate sensor **7** (Table 1). Furthermore, such a cooperative binding mode could play a key role in enhancing the binding and selectivity of amidophenyl-substituted calix[4]arene **5** toward CH_3COO^- over F^-.

Conclusions

In conclusion, novel fluorescent anion sensors tetrakis-(4-carbamoylphenyl)-substituted calix[4]arene, tetrakis-(4-amidophenyl)-substituted calix[4]arene, and the monomeric biphenylcarbamate have been designed, synthesized, and investigated by fluorescent titration, ^{1}H NMR spectroscopic, and ESI-MS studies. Importantly, we have demonstrated that tetrakis-(4-carbamoylphenyl)-substituted calix[4]arene sensor shows greatly enhanced binding affinity and selectivity toward these anions as compared to the monomeric biphenylcarbamate counterparts, particularly for carboxylates. Despite a relatively weaker binding affinity toward anions, tetrakis-(4-amidophenyl)-substituted calix[4]arene also exhibits superior binding selectivity for acetate ion over fluoride ion. The binding and selectivity enhancement of phenylcalix[4]arene-based sensors are attributed to the cooperative binding of the multiple carbamoyl ligating groups as revealed from ab inito quantum mechanical calculations. This approach provides an alternative means to design and synthesize binding- and selectivity-enhanced receptors and sensors for carboxylates. Our results also show that carbamate functionality is a useful H-bond donor for hydrogen-bonding interactions in molecular recognition and supramolecular chemistry.

Experimental Section

5,11,17,23-Tetrakis(4-hydroxyphenyl)-25,26,27,28-tetrapropoxycalix[4]arene 2. To a 250 mL two-necked flask containing **1** (0.50 g, 0.55 mmol) in 50 mL of anhydrous THF were added $PdCl_2$(dppf) (24 mg, 5 mol %) and excess freshly prepared 4-trimethylsilyloxyphenylmagnesium bromide.[18] The mixture was heated to reflux in N_2 atmosphere for 3 h. After the solution mixture cooled to room temperature, 20 mL of water was carefully added, and the mixture was then acidified to pH 3−4 using 6 M HCl. After extracting with ethyl acetate (20 × 3 mL), the organic phase was combined and dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by silica gel flash chromatography using gradient elution method with petroleum ether and ethyl acetate as eluent affording a white solid (0.37 g, 71% yield). ^{1}H NMR (270 MHz, CD_3COCD_3, δ) 8.10 (s, 4H), 7.03 (d, J = 8.6 Hz, 8H), 6.96 (s, 8H), 6.62 (d, J = 8.6 Hz, 8H), 4.57 (d, J = 12.7 Hz, 4H), 3.96 (t, J = 7.3 Hz, 8H), 3.32 (d, J = 12.7 Hz, 4H), 2.02−2.10 (m, 8H), 1.07 (t, J = 7.3 Hz, 12H). ^{13}C NMR (67.5 MHz, CD_3COCD_3, δ) 156.8, 156.1, 135.7, 135.5, 133.4, 128.2, 127.1, 115.9, 77.6, 31.8, 24.0, 10.7. IR (KBr) ν_{max} 3426, 3026, 1612, 1517, 1227. MS (FAB) *m/z* 960.8 [M$^+$]. HRMS (MALDI-TOF) Calcd for $C_{64}H_{64}NaO_8$, 983.4498. Found: 983.4465 [M + Na]$^+$.

5,11,17,23-Tetrakis(4-(*N*-phenylcarbamoyl)phenyl)-25,26,27,-28-tetrapropoxycalix[4]arene 3. To a 100 mL flask containing **2** (0.50 g, 0.52 mmol) in 30 mL of CH_3CN were added freshly distilled phenyl isocyanate (0.50 g, 4.2 mmol) and Et_3N (53 mg, 0.52 mmol). The solution mixture was refluxed for 24 h. After the reaction mixture cooled to room temperature, 20 mL of water was added, and the organic phase was extracted with chloroform (20 × 3 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After evaporating the solvents, the residue was washed with MeOH and then purified by silica gel chromatography using gradient elution method with petroleum ether and chloroform affording a white solid (0.64 g, 86% yield). ^{1}H NMR (400 MHz, CD_3COCD_3, δ) 9.00 (b, 4H), 7.54 (d, J = 8.0 Hz, 8H), 7.27 (t, J = 7.6 Hz, 8H), 7.22 (d, J = 8.4 Hz, 8H), 7.11 (s, 8H), 7.02 (t, J = 7.6 Hz, 4H), 6.99 (d, J = 8.8 Hz, 8H), 4.64 (d, J = 13.2 Hz, 4H), 4.02 (t, J = 7.6 Hz, 8H), 3.42 (d, J = 13.2 Hz, 4H), 2.06−2.08 (m, 8H), 1.11 (t, J = 7.2 Hz, 12H). ^{13}C NMR (100 MHz, CD_3COCD_3, δ) 157.2, 152.6, 150.7, 139.8, 139.3, 136.1, 135.2, 129.7, 128.1, 127.9, 123.9, 122.7, 119.4, 77.9, 31.9, 24.2, 10.8. IR (KBr) ν_{max} 3405, 3054, 1745, 1731, 1601, 1506, 1204. HRMS (MALDI-TOF) Calcd for $C_{92}H_{84}N_4NaO_{12}$, 1460.6016. Found: 1460.6064 [M + Na]$^+$. Anal. Calcd for $C_{92}H_{84}N_4O_{12}$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.60; H, 5.93; N, 3.85.

5,11,17,23-Tetrakis(4-formylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene 4. To a 100 mL flask containing **1** (0.23 g, 0.25 mmol) and commercially available 4-formylphenylboronic acid (0.23 g, 1.53 mmol) in 50 mL of toluene were added $Pd(OAc)_2$ (11 mg, 5 mol %), P(*o*-tol)$_3$ (30 mg, 10 mol %), 2 mL of methanol, and 2 mL of 2 M K_2CO_3. The mixture was stirred at 75 °C overnight under N_2. After the mixture was cooled to room temperature, 20 mL of water was added. The reaction mixture was acidified to pH 3−4 using 6 M HCl and then extracted with ethyl acetate (20 × 3 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue obtained was further purified by silica gel flash column chromatography using gradient elution method with petroleum ether and ethyl acetate as eluent affording a white solid (0.18 g, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.85 (s, 4H), 7.56 (d, J = 8 Hz, 8H), 7.22 (d, J = 8 Hz, 8H), 6.98 (s, 8H), 4.60 (d, J = 13.2 Hz, 4H), 3.97 (t, J = 7.2 Hz, 8H), 3.33 (d, J = 13.2 Hz, 4H), 1.96−2.04 (m, 8H), 1.06 (t, J = 7.2 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 191.7, 157.3, 146.7, 135.5, 134.4, 133.5, 129.9, 127.2, 126.7, 77.1, 31.3, 23.3, 10.3. IR (KBr) ν_{max} 3052, 1698, 1603, 1464, 1170. MS (FAB) *m/z* 1008.1 [M$^+$].

5,11,17,23-Tetrakis(4-carboxyphenyl)-25,26,27,28-tetrapropoxycalix[4]arene. To a 100 mL flask containing **4** (0.19 g, 0.19 mmol) in 10 mL of $CHCl_3$ and 30 mL of acetone were added 1 mL aqueous sulfamic acid (0.30 g, 3.1 mmol) and 1 mL aqueous sodium chlorite (0.28 g, 3.1 mmol). The mixture was stirred at room temperature for 1 h and then evaporated to dryness. The solid obtained was washed with water and acetone, affording a quantitative yield of the corresponding acid as a white solid. ^{1}H NMR (270 MHz, DMSO−d_6, δ) 12.4 (b, 4H), 7.65 (d, J = 8.1 Hz, 8H), 7.23 (d, J = 8.1 Hz, 8H), 7.06 (s, 8H), 4.44 (d, J = 13.2 Hz, 4H), 3.90 (t, J = 7.0 Hz, 8H), 3.40 (d, J = 13.2 Hz, 4H), 1.93−1.95 (m, 8H), 1.02 (t, J = 7.3 Hz, 12H). ^{13}C NMR (67.5 MHz, DMSO-d_6, δ) 166.6, 156.3, 144.2, 134.8, 132.8, 129.3, 128.4, 126.6, 125.8, 76.4, 30.4, 22.9, 10.3. IR (KBr) υ_{max} 3434, 3054, 1693, 1608, 1180. MS (FAB) *m/z* 1072.8 [M$^+$]. HRMS (ESI-TOF) Calcd for $C_{68}H_{63}O_{12}$, 1071.4320. Found: 1071.4285 [M − H]$^-$.

5,11,17,23-Tetrakis(4-(*N*-phenylformamido)phenyl)-25,26,27,-28-tetrapropoxycalix[4]arene 5. To a 100 mL two-necked round

(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian, Inc.: Wallingford, CT; 2004.

(18) Xiang, S.; Zhang, Y. L.; Xin, Q.; Li. C. *J. Org. Chem.* **2002**, *67*, 2686.

bottle flask containing 5,11,17,23-tetrakis(4-carboxyphenyl)-25,-26,27,28-tetrapropoxycalix[4]arene (0.15 g, 0.14 mmol) in 30 mL of dry chloroform was added thionyl chloride (0.5 mL, 6.88 mmol) while stirring at room temperature under N_2. The solution mixture was refluxed for 4 h. After removal of the solvent, a white solid was obtained. To the while solid were added 50 mL of dry DCM and 0.2 mL of freshly distilled aniline. The mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was filtered. The residue was first dissolved in 5 mL of DMF and then precipitated by 20 mL of methanol. The precipitate was washed with 10 mL of water, 10 mL of methanol, and 20 mL of diethyl ether affording a white solid **5** (0.147 g, 75% yield). ^{1}H NMR (400 MHz, CD_3COCD_3, δ) 9.39 (s, 4H,), 7.79 (d, J = 8.8 Hz, 8H), 7.76 (d, J = 8.8 Hz, 8H), 7.36 (d, J = 8.0 Hz, 8H), 7.24 (t, J = 7.6 Hz, 8H), 7.20 (s, 8H), 7.05 (t, J = 7.6 Hz, 4H), 4.66 (d, J = 13.2 Hz, 4H), 4.05 (t, J = 7.6 Hz, 8H), 3.47 (d, J = 13.2 Hz, 4H), 2.08−2.13 (m, 8H), 1.12 (t, J = 7.6 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 166.1, 157.8, 144.9, 140.3, 136.4, 134.7, 134.1, 129.4, 128.7, 128.0, 127.1, 124.4, 121.3, 77.9, 30.8, 24.2, 10.8. IR (KBr) ν_{max} 3422, 3055, 1653, 1600, 1532, 1440, 1319. HRMS (MALDI-TOF) Calcd for $C_{92}H_{84}N_4NaO_8$, 1396.6214. Found: 1396.6226 [M + Na]$^+$. Anal. Calcd for $C_{92}H_{84}N_2O_8$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.08; H, 6.32; N, 3.98.

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Supporting Information Available: General experimental details. ^{1}H NMR, ^{13}C NMR, and MS data of **7**. Results of fluorescence titration, ^{1}H NMR titration, Job plots, and ESI-MS for **3**, **5**, and **7** with anions, and ^{1}H NMR and ^{13}C NMR spectra of **3** and **5**. Results of calculations. This information is available free of charge via the Internet at http://pubs.acs.org.

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