Metal ion complexation in acetonitrile by upper-rim benzyl-substituted, di-ionized calix[4]arenes bearing two dansyl fluorophores

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DOI: http://dx.doi.org/10.3998/ark.5550190.0011.707

Abstract

The influence of Li^+, Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Ag^+, Cd^{2+}, Co^{2+}, Fe^{2+}, Hg^{2+}, Mn^{2+}, Pb^{2+}, Zn^{2+} and Fe^{3+} on the spectroscopic properties of two dansyl (1-dimethylaminonaphthalene-5-sulfonyl) groups linked to the lower rims of a series of three, structurally related, di-ionized calix[4]arenes is investigated by means of emission spectrophotometry. Di(tetramethylammonium) salts of the di-ionized ligands, **L**, **L1** and **L2**, which differ in having no, two and four benzyl groups, respectively, on the upper rim of the calix[4]arene scaffold, are utilized for the spectrofluorimetric titration experiments in MeCN. On complexation by alkaline earth metal cations, the emission spectra undergo marked red shifts. Alkali metal cations cause fluorescence enhancement of benzyl-substituted di-ionized calix[4]arenes **L1** and **L2** with red shifts, except for Li^+ and Cs^+. Transition metal cations and Pb^{2+} interact strongly with the ligands. In particular, Fe^{3+}, Hg^{2+} and Pb^{2+} cause greater than 99 % quenching of the dansyl fluorescence for all three ligands.

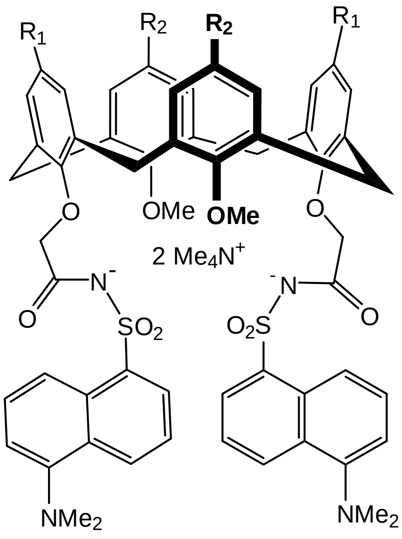
Keywords: Calixarene ligand, fluorescence spectroscopy, stability constant, metal ion complexation

Introduction

Calixarene-based fluorescent sensors utilize calixarene units as molecular scaffolds for the construction of selective ionophores.[1-6] Various chemosensors based on calix[4]arenes bearing fluorescent groups have been synthesized for investigation of their fluorescent responses upon complexation with metal cations.[7-10] Several photoinduced mechanisms have been proposed to explain the changes in fluorescent properties of the fluorophore group upon metal complexation, such as electron transfer (PET), charge transfer (PCT), energy transfer and excimer or exciplex formation or disappearance.

Calix[4]arenes possess a hydrophobic upper rim and a hydrophilic lower rim. They can exist in four different conformations: cone, partial cone, 1,2-alternate and 1,3-alternate.[11] Among these, the cone conformation is used most widely for functionalization. Therefore, studies related to the cone conformation are more frequently encounted than the other conformations.[12-14] The conformation of the calix[4]arene scaffold is important for metal ion complexation.[15] Also, substituents on the upper and/or lower rims may influence the metal ion complexation process. The complex may form due to hydrogen bonding, hydrophobic bonding or electron donor-acceptor interactions.

In an earlier study, we reported the interactions of didansyl-pendent, di-ionized calix[4]arenes with zero, two and four allyl groups on the upper rim (Figure 1) with a variety of metal cation species using spectrophotometric and spectrofluorimetric techniques.[16]

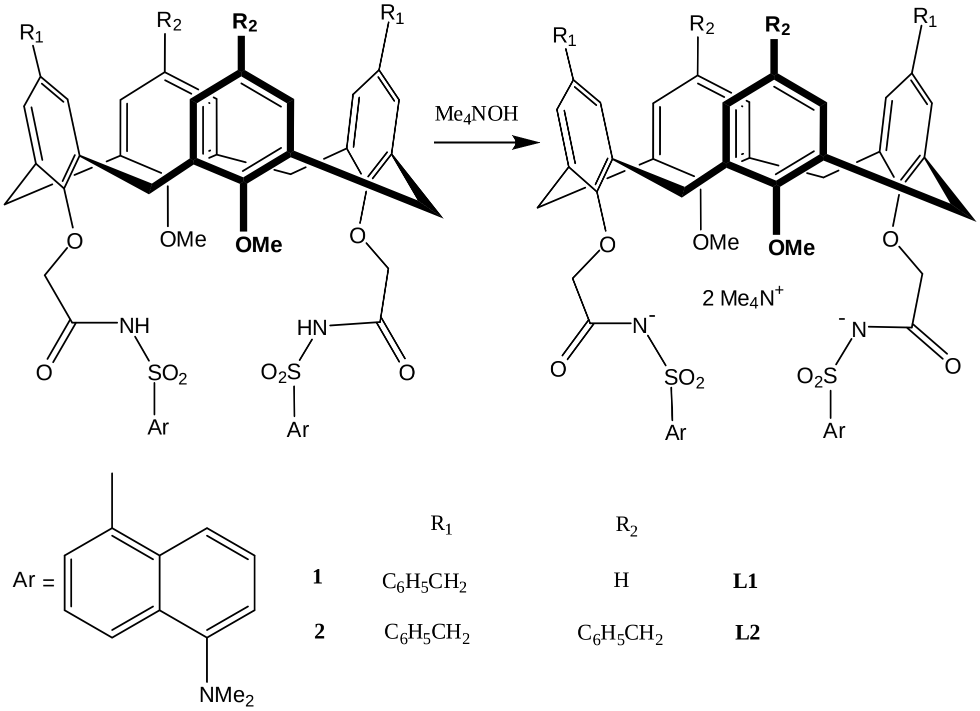


R_1	R_2
H	H
$CH_2CH{=}CH_2$	H
$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$

L

Figure 1. Structures of previously examined di-ionized, didansyl calix[4]arene ligands.

In the present paper, we report the synthesis of two new calix[4]arene ligands **1** and **2** (Figure 2) with two pendent dansyl groups on the lower rim and two and four benzyl groups, respectively, on the upper rim and complexation properties of their di-ionized forms **L1** and **L2** with metal cations. Compared with the earlier investigated upper-rim allyl groups in the ligand series shown in Figure 1, upper-rim benzyl groups are more bulky and provide additional π bonds as potential interaction sites for metal ions. Responses of di(tetramethylammonium) salts of the di-ionized ligands **L1** and **L2** to a variety of metal cations are assessed by spectrofluorometric titration in MeCN. Changes in the fluorescence spectra of **L1** and **L2** in the presence of various metal cations are compared with those reported earlier for **L**, an analog with no benzyl groups on the upper rim. Stability constants and compositions of complexes of Hg^{2+}, Pb^{2+} and Fe^{3+} with **L1** and **L2** are determined. A Stern-Volmer approach is utilized to probe the quenching mechanism.



	R1	R2	
1	$C_6H_5CH_2$	H	**L1**
2	$C_6H_5CH_2$	$C_6H_5CH_2$	**L2**

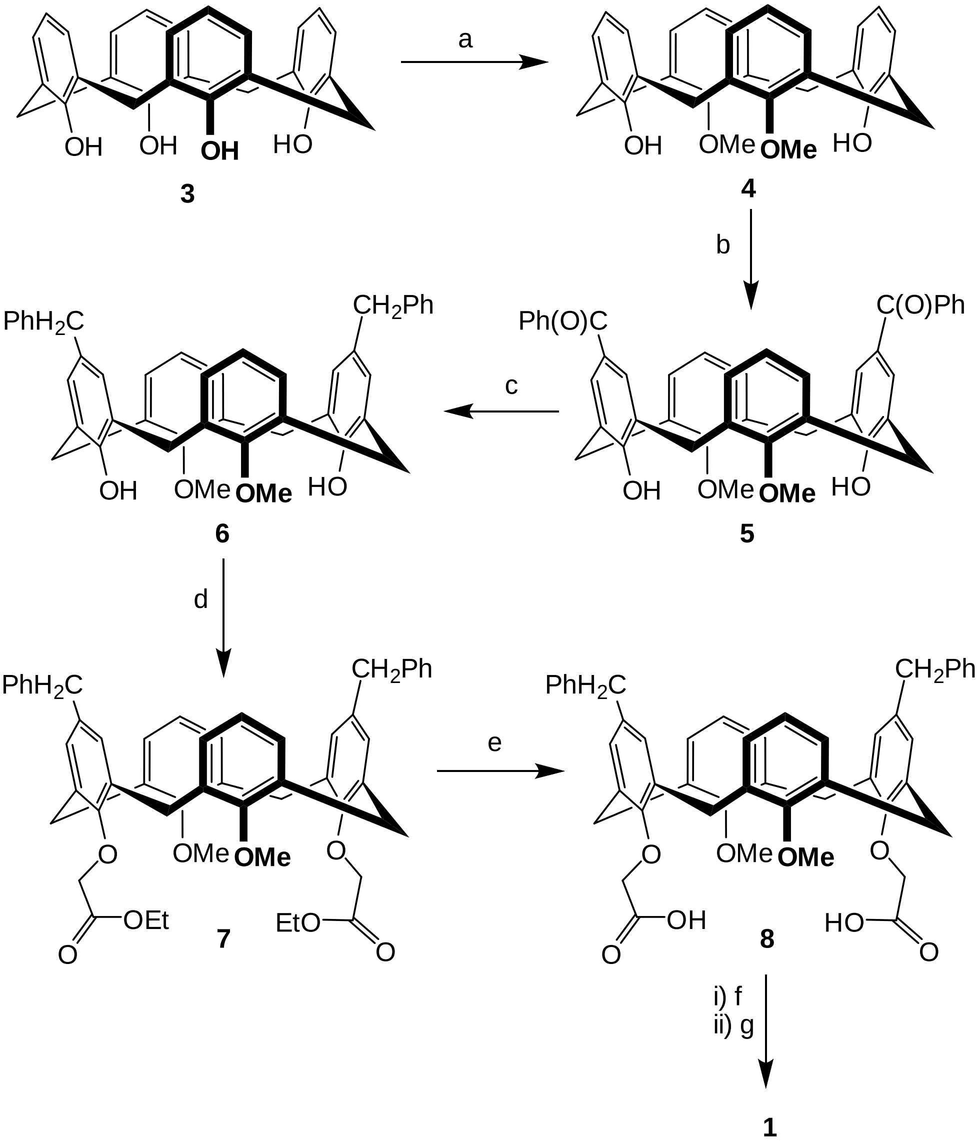
Figure 2. Structures of new didansyl calix[4]arene ionophores **1** and **2** and their di-ionized tetramethylammonium salts **L1** and **L2**, respectively.

Results and Discussion

Ligand synthesis

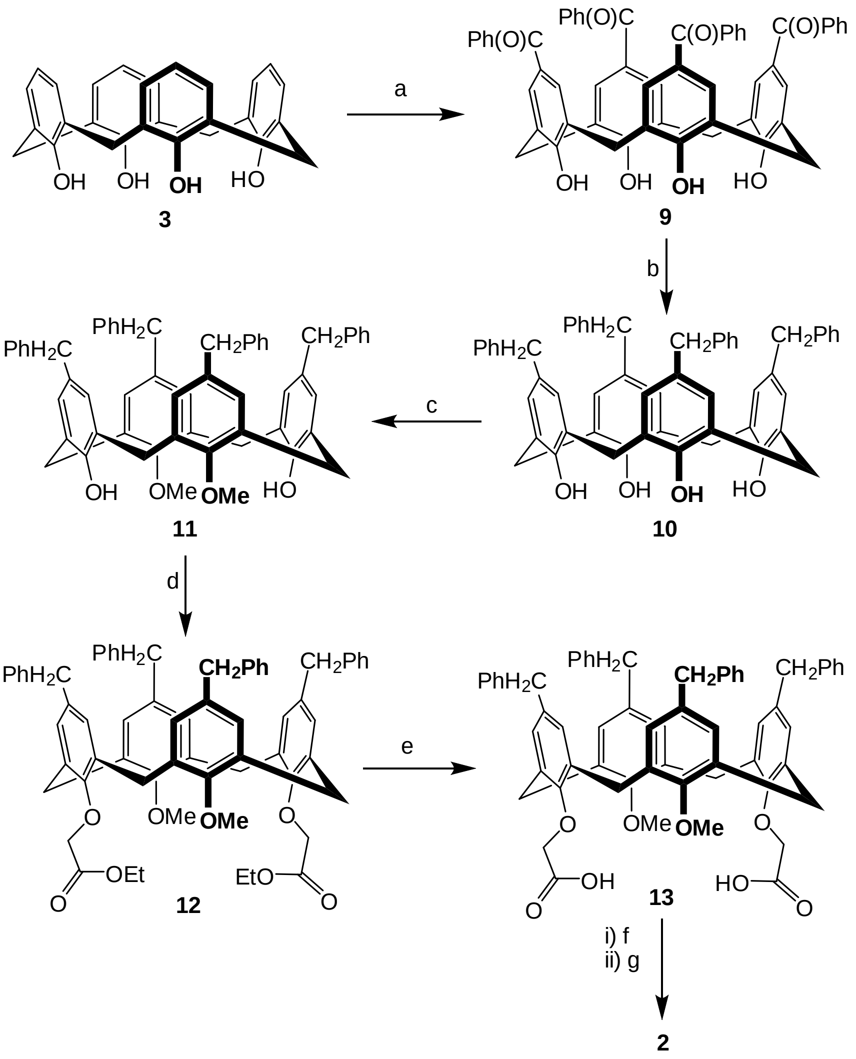
The syntheses of new di-dansylated, di-ionizable calix[4]arene ligands **1** and **2** are summarized in Schemes 1 and 2, respectively.

For the preparation of ligand **1** with two benzyl groups on the upper rim of the calix[4]arene scaffold (Scheme 1), two methyl groups were attached to distal hydroxyl groups of calix[4]arene **3** to give known diether **4**. Friedel-Crafts acylation of **4** with benzoyl chloride and $AlCl_3$ in CH_2Cl_2 gave an 81% yield of the known disubstitution product **5**. Attempted Wolff-Kishner reduction of the two benzoyl groups in **5** was unsuccessful. However, reduction of **5** to the upper-rim dibenzyl compound **6** in 90% yield was achieved with triethylsilane in trifluroacetic acid. Dialkylation of **6** with ethyl bromoacetate and NaH in THF gave a 71% yield of diester **7**, which was hydrolyzed to diacid **8** in 97% yield with Me_4NOH in aqueous THF. Diacid **8** was treated with oxalyl chloride in benzene to produce the corresponding di(acid chloride), which was added to the sodium salt of dansylamide in THF to give the di-dansylated calix[4]arene **1** in 30% yield.



Scheme 1. Synthesis of didansyl di-ionizable calix[4]arene ionophore **1** with two upper-rim benzyl groups: (a) MeOTs, K_2CO_3, MeCN, reflux, 20 h; (b) PhC(O)Cl, $AlCl_3$, CH_2Cl_2, rt, 24 h; (c) Et_3SiH, CF_3CO_2H, rt, 5 h; (d) $BrCH_2CO_2Et$, NaH, THF, rt, 12 h; (e) 10% aq Me_4NOH, THF, reflux, 12 h; (f) $(COCl)_2$, benzene, reflux, 5 h; (g) dansylamide, NaH, THF, rt, 12 h.

For the synthesis of ligand **2** with four benzyl groups attached to the upper rim of the calix[4]arene scaffold (Scheme 2), calix[4]arene **3** was reacted with benzoyl chloride and $AlCl_3$ in CH_2Cl_2 to give the tetrabenzoylated tetrabenzoate ester, which was subjected to basic hydrolysis with NaOH in aqueous MeOH to remove the ester functions.[17] An 89% yield of the tetrabenzoylated calix[4]arene **9** was realized. The benzoyl groups were converted into benzyl groups by reaction with hydrazine hydrate and K_2CO_3 in triethylene glycol to produce a 95% yield of known tetrabenzylated calix[4]arene **10**. Reaction of **10** with K_2CO_3 and MeI in MeCN gave a 91% yield of diether **11**, which was transformed into diester **12** in 90% yield by reaction with ethyl bromoacetate and NaH in THF. Treatment of diester **12** with Me_4NOH in aqueous THF produced diacid **13** in 97% yield. Diacid **13** was treated with oxalyl chloride in benzene to produce the corresponding di(acid chloride), which was added to the sodium salt of dansylamide in THF to give the di-dansylated calix[4]arene **2** in 40% yield.



Scheme 2. Synthesis of didansyl di-ionizable calix[4]arene ionophore **2** with four upper-rim benzyl groups: (a) PhC(O)Cl, $AlCl_3$, CH_2Cl_2, rt, 24 h, then NaOH, aq MeOH, reflux 2 days; (b) $NH_2NH_2{\bullet}H_2O$, K_2CO_3, triethylene glycol; (c) MeI, K_2CO_3, MeCN, reflux, 20 h; (d)

$BrCH_2CO_2Et$, THF, rt, 12 h; (e) Me_4NOH, aq THF, reflux, 12 h; (f) $(COCl)_2$, benzene, reflux, 5 h; (g) dansylamide, NaH, THF, rt, 12 h.

Structures of new compounds **1**, **2**, **6** and **11-13** were verified by their ^{1}H NMR, ^{13}C NMR and IR spectra and by combustion analysis. The ^{1}H NMR spectra of new ionophores **1** and **2** showed broad, poorly defined absorptions revealing conformational mobility in $CDCl_3$ solution.
Ligands **1** and **2** were converted into their di(tetramethylammonium) salts **L1** and **L2**, respectively, by a reported method.[18]

Fluorescence spectra

When excited at 328 nm in MeCN, ligands **L1** and **L2** gave emission bands with maxima at 484 and 482 nm, respectively. Figure 3 shows the effects of 50 equivalents of metal cations on the fluorescence spectra of **L1**. As can be seen from Figure 3a, the emission band intensities increased somewhat in the presence of alkali metal cations with red shifts of the emission band from that of **L1**, except for Li^+. Earlier, we observed quenching with alkali metal cations for analogous allyl-substituted ligands.[16] As can be seen in Figure 3a, the largest red shift was produced by Li^+. Similar results were obtained for alkali metal cations with **L2** (Figure 4a). Thus it was found that increasing the number of benzyl groups on the upper rim from two to four did not change significantly the effect of alkali metal cations on the emission spectra. Previously, we obtained similar results with allyl groups on the upper rim.[16]

The emission band intensity for **L1** was diminished substantially with red shifts for the alkaline earth metal cations (Figure 3b). The effects of $Ba^{2+}$and Sr^{2+} and of Ca^{2+} and Mg^{2+} on the fluorescence spectra are nearly the same for each pair of metal ions. There are larger red shifts and greater quenching for Mg^{2+} and Ca^{2+}. In this case, the responses to Mg^{2+} and Ca^{2+} were similar. For **L2** in the presence of alkaline earth metal cations, the effect was also substantial quenching with red shifts (Figure 4b). The quenching effect of Mg^{2+} was even greater. It is interesting that allyl and benzyl groups on the upper rim caused nearly same effect on the fluorescence spectra for interactions with alkali metal and alkaline earth metal cations.[16]

The effects of transition metal cations and Pb^{2+} on the fluorescence spectra of **L1** and **L2** are presented in Figures 3c and 4c, respectively. Strong quenching of the fluorescence of **L1** and **L2** was observed in the presence of the transition metal cations and Pb^{2+}. However, **L2** caused greater quenching for all transition metal cations and Pb^{2+} (Figure 4c). In particular, Fe^{3+}, Hg^{2+} and Pb^{2+} cause greater than 99 % quenching of the dansyl fluorescence for both ligands **L1** and **L2**.

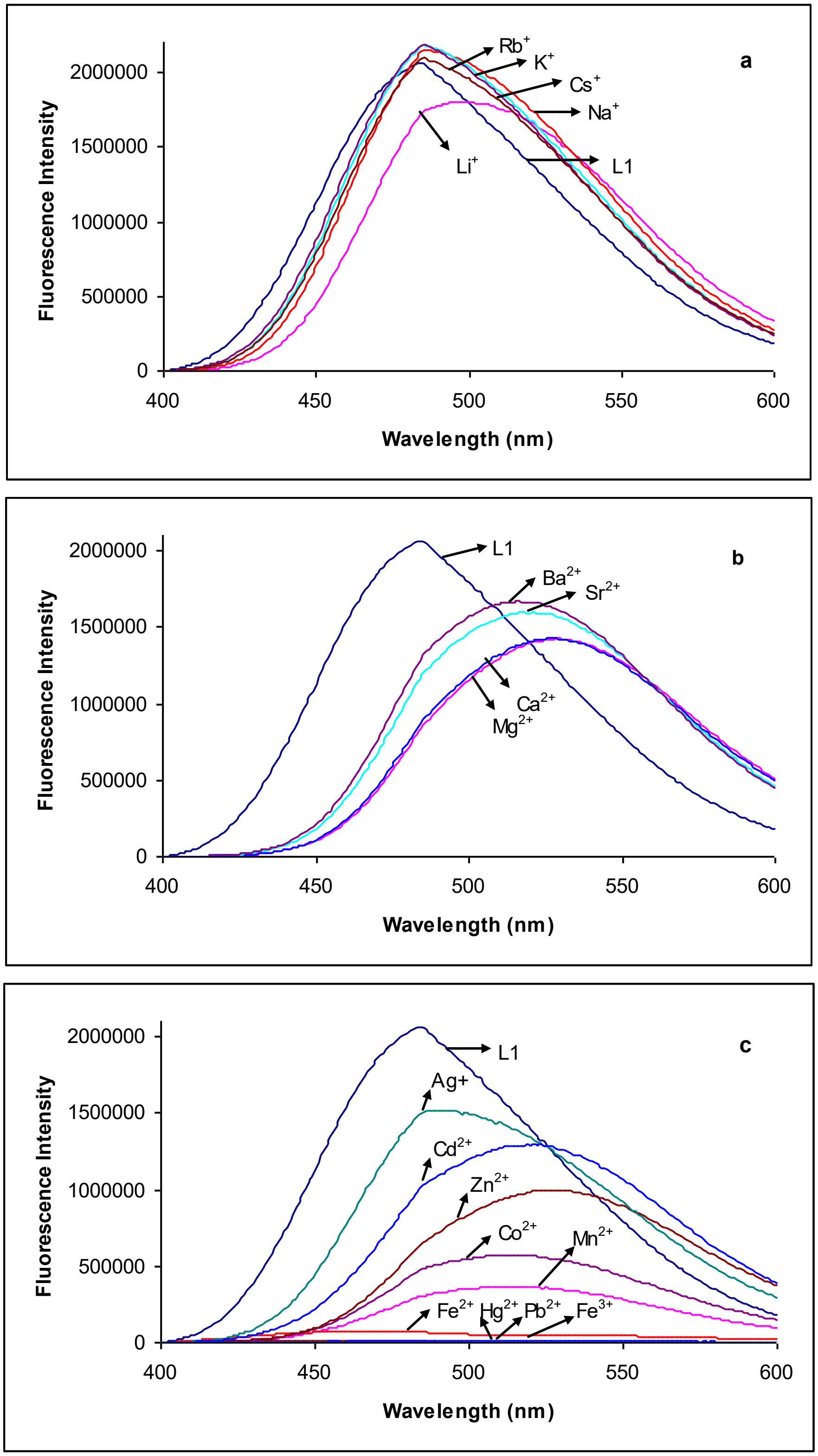


Figure 3. Effect of metal cations on the fluorescence spectra of **L1** in MeCN: (a) for alkali metal cations; (b) for alkaline earth metal cations ; (c) for transition metal cations and Pb^{2+}.

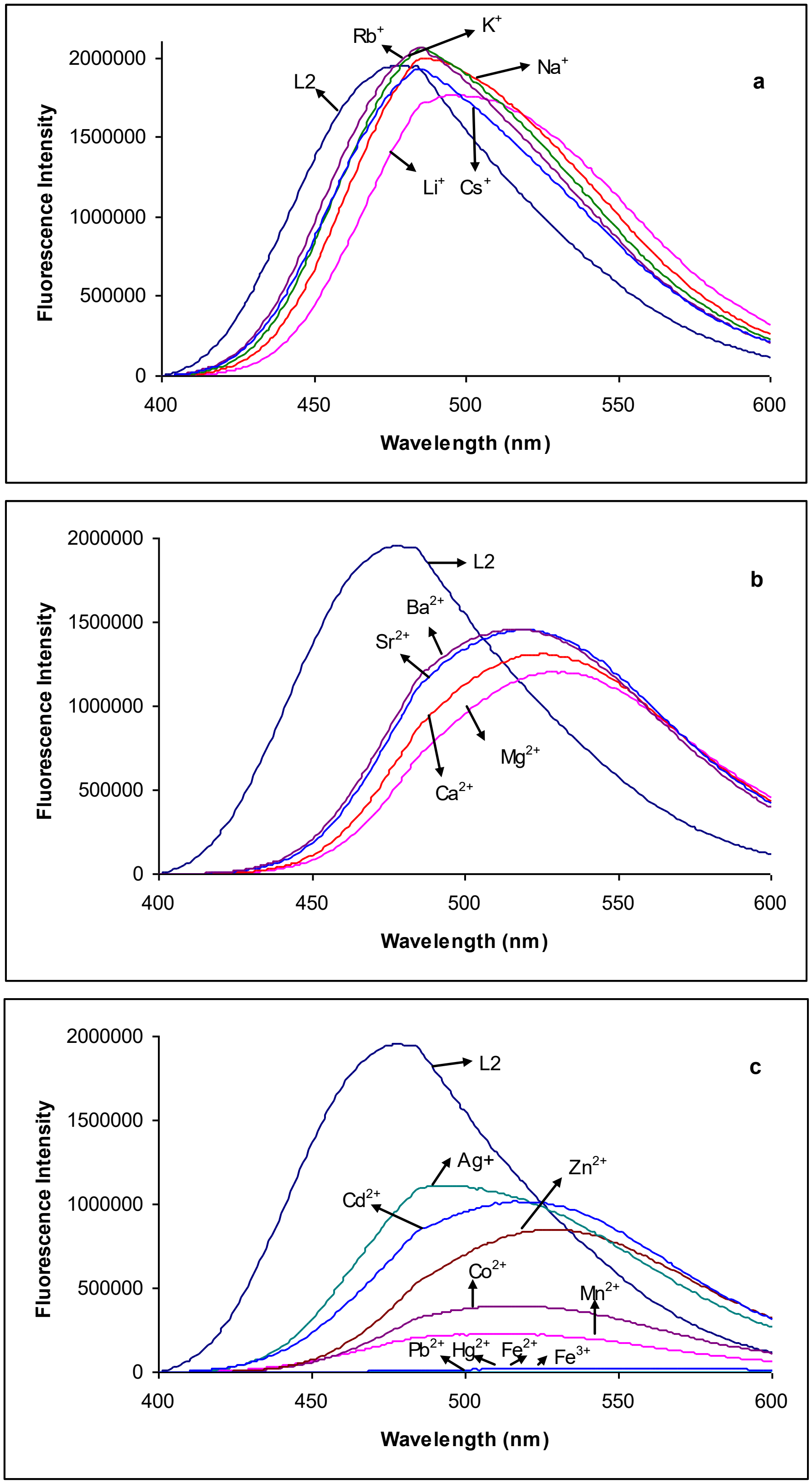


Figure 4. Effect of metal cations on the fluorescence spectra of **L2** in MeCN: (a) for alkali metal cations; (b) for alkaline earth metal cations ; (c) for transition metal cations and Pb^{2+}.

Determination of stability constants

Stability constants and stoichiometries for complexation of Hg^{2+}, Pb^{2+} and Fe^{3+} by ligands **L1** and **L2** in MeCN were determined by spectrofluorimetric titration. The ligand concentration was held constant at 2.58×10^{-5} M. Stoichiometries of the complexes and their stability constants were determined from changes in the fluorescence intensity as a function of the metal ion concentration. Successive decreases of emission with increases of the metal ion concentration were observed in all of the fluorimetric titrations.

Figure 5 shows the fluorescence spectra of **L2** in MeCN with increasing concentrations of Fe^{3+}. The inserts in Figure 5 are a plot of I_o-I *vs.* the ratio of [M]/[L] and a plot of the quantity $I_o/(I_o-I)$ versus 1/[M]. The break in the former at M]/[L] = 1.0 provides strong evidence for formation of a 1:1 complex. Similar plots were found with Pb^{2+} and Hg^{2+} for **L1** and **L2** in MeCN. The stability constant for a complex was obtained from a plot of the quantity $I_o/(I_o-I)$ versus 1/[M]. The ratio of intercept/slope gave the stability constant.[19]

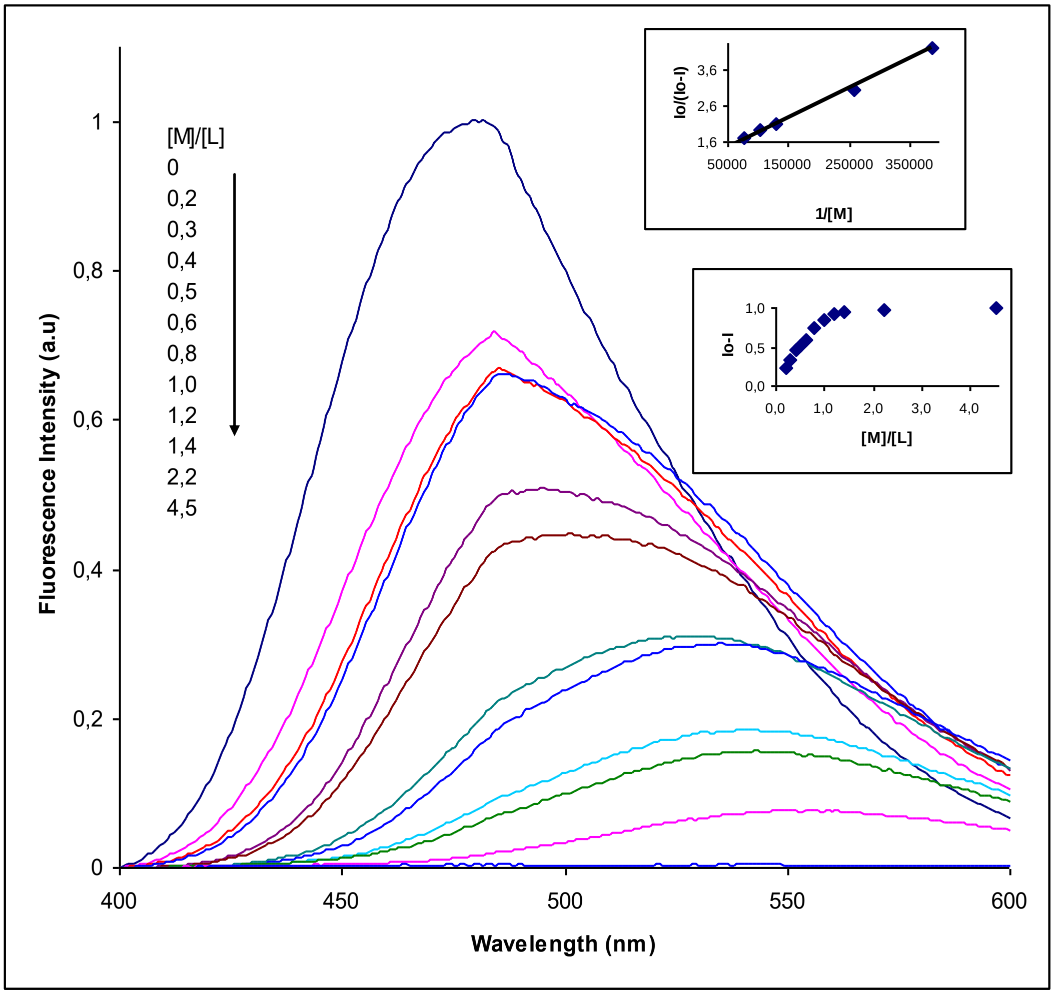


Figure 5. Fluorescence spectra of **L2** in MeCN with increasing amounts of Fe^{3+}. ([**L2**] = 2.58 x10^{-5} M; λ_{exc} = 328 nm; λ_{em} = 482 nm)

Table 1 presents the stability constants and complex stochiometries for complexation of Fe^{3+}, Hg^{2+} and Pb^{2+} by **L**[16], **L1** and **L2**. The log β values vary between 3.94 and 5.12 and show that the ionized ligands interact strongly with these metal ions in MeCN. For 1:1 complexation of Fe^{3+} by the three ligands, the stability constants decrease in the order: **L2** > **L1 > L**. Thus, the attachment of either two or four allyl groups to the upper rim of di-ionized ligand **L** increases the propensity for complexation of Fe^{3+} in MeCN. A similar increase of stability constant for complexation of Fe^{3+} was obtained with the upper-rim allyl-substituted analogues. As seen from the data in Table 1, all three ligands form 1:1 complexes with Fe^{3+}, Hg^{2+} and Pb^{2+}. On the other hand, the upper-rim allyl-substituted analogues formed 1:2 complexes with Fe^{3+}.[16] It is clear that among the ligands **L2** forms the most stable complexes with Fe^{3+}, Hg^{2+} and Pb^{2+}. This result can be explained as arising from the effect of increased π electron density due to the four benzyl groups.

Table 1. Stability constants and stoichiometries for complexation of **L**, **L1** and **L2** with Hg^{2+}, Pb^{2+} and Fe^{3+} in MeCN

	Stability constant (log β) Cation			Complex stochiometry (M:L) Cation		
Ionized ligand	Fe^{3+}	Pb^{2+}	Hg^{2+}	Fe^{3+}	Pb^{2+}	Hg^{2+}
L	3.94±0.02[a]	4.76±0.04[a]	4.53±0.03[a]	1:1[a]	1:1[a]	1:1[a]
L1	4.52±0.01	3.82±0.03	4.04±0.02	1:1	1:1	1:1
L2	5.12±0.03	5.06±0.05	4.96±0.02	1:1	1:1	1:1

[a] Reference 18.

Stern-Volmer analysis

Stern-Volmer analysis was utilized to probe the nature of the quenching process in the complexation of Fe^{3+}, Hg^{2+} and Pb^{2+} by **L1** and **L2**. Stern-Volmer plots are a useful method of presenting data on emission quenching.[22,23] Plotting relative emission intensities (I_o/I) against quencher concentration [Q] yields a linear Stern-Volmer plot for a static quenching process. Expressed as Equation 1, the slope of this line is Ksv, the static quenching constant. I and I_o are fluorescence intensities in the presence and in the absence of added metal cations.

$$I_o/I = 1 + K_{sv}[Q] \qquad (1)$$

Figure 6 shows the steady-state emission Stern-Volmer analysis for complexation of Pb^{2+} by **L2**. For both **L1** and **L2**, linear behavior was observed for complexation of Fe^{3+}, Hg^{2+} and Pb^{2+}. These results are consistent with static quenching.

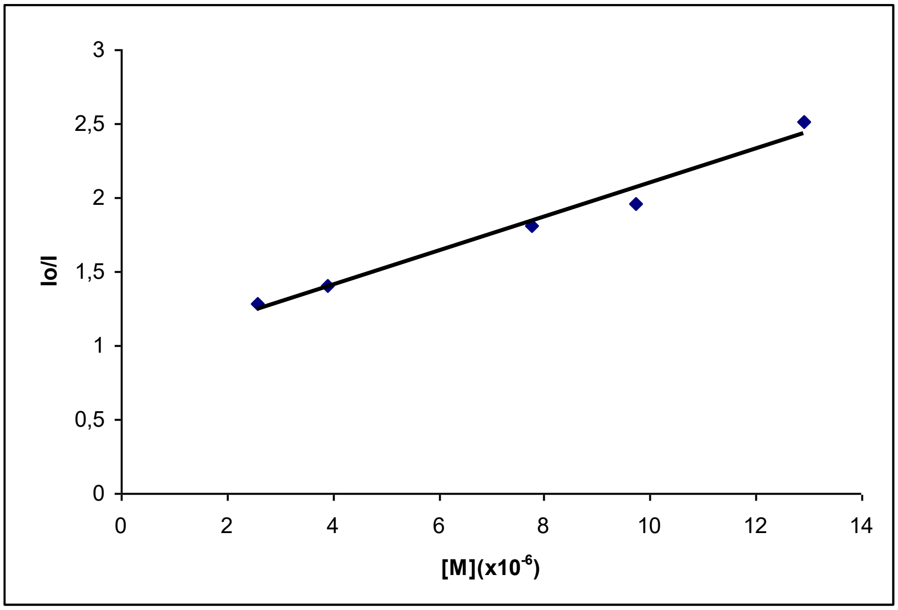


Figure 6. Stern-Volmer plot for the fluorescence quenching of **L2** by Pb^{2+} in MeCN.

Summary

This study investigates the influence of a systematic structural variation within calix[4]arene compounds with two ionized, dansyl group-containing side arms on the lower rim upon their spectroscopic responses to metal ions in MeCN. The upper rim possesses zero, two and four benzyl groups. In the presence of excess metal ions, fluorescence quenching increased in the order: alkali metal cations<alkaline earth metal cations<transition and heavy metal cations. The presence of Fe^{3+}, Hg^{2+} and Pb^{2+} gave greater than 99% quenching of the dansyl fluorescence for the three ligands. For all three of the ionized ligands, only 1:1 (M/L) complexes are formed with these three metal ions. Information gained from this investigation aids in assessing the potential for such di-ionized, dansyl-containing ligands in fluorogenic metal ion sensors.

Experimental Section

General. The ^1H and ^{13}C NMR spectra were recorded with a Varian Unity INOVA 500 MHz FT-NMR spectrometer (^1H at 500 MHz and ^{13}C at 126 MHz) in $CDCl_3$ with Me_4Si as internal standard. Chemical shifts (δ) are given in parts per million downfield from TMS and coupling constant (*J*) values are in hertz. IR spectra were recorded with a Perkin-Elmer model 1600 FT-IR spectrophotometer as deposits from $CDCl_3$ solutions on NaCl plates. Fluorescence spectra were obtained with a SLM Aminco 800C photon counting spectrofluorimeter equipped with a 450-W ozone-free xenon lamp as the light source. Melting points were determined with a Mel-Temp melting point apparatus. Elemental analysis was performed by Desert Analytics Laboratory (now Columbia Analytical Services) of Tucson, Arizona.

All reactions were conducted under nitrogen atmosphere. Reagents were obtained from commercial suppliers and used directly unless otherwise noted. Calix[4]arene **3** was obtained from Eburon Organics International of Lubbock, Texas. Tetrahydrofuran (THF) was dried over sodium with benzophenone as a indicator and distilled just before use. Spectrometric grade acetonitrile (MeCN) from EMD Chemicals was the solvent for the fluorescence measurements. All metal perchlorates purchased from Acros were of the highest available quality and vacuum dried over blue silica gel before use.

The 25,27-dihydroxy-26-28-dimethoxycalix[4]arene **4**[24] was prepared by a reported procedure.

Fluorescence measurements

Fluorescence spectra of the di-ionized ligands (2.58×10^{-5} M) in MeCN solutions containing 50 molar equivalents of the appropriate metal perchlorate salt were measured using a 1-cm quartz cell. The excitation wavelength was 328 nm for all of the ionized ligands. Fluorescence emission spectra were recorded in the range 400-600 nm with a slit width of 1.0 nm.

The stoichiometries of the complexes and their stability constants were determined according to a literature procedure.[19]

Synthesis of 11,23-dibenzoyl-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (5). To a suspension of 26,28-dihydroxy-25,27-dimethoxycalix[4]arene **4** (9.59 g, 21.2 mmol) and $AlCl_3$ (22.60 g, 84.9 mmol) in CH_2Cl_2 (500 mL) was added benzoyl chloride (23.80 g, 169.7 mmol) dropwise over a period of 30 min. The mixture was stirred at room temperature for 24 h and then 5% aq HCl (50 mL) was added. The mixture was poured into ice-water. The mixture was diluted with 1N HCl and extracted with CH_2Cl_2 (2 X 400 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo* to give a yellow solid, which was recrystallized from CH_2Cl_2-MeOH to give an 81% yield of white solid with mp 289-290 ^oC (lit.[20,21] mp >300 ^oC) . IR 3252 (OH), 1649 (C=O) cm^{-1}. ^1H NMR δ 3.47 (d, *J*=13.3 Hz, 4H), 4.02 (s, 6H), 4.30 (d, *J*=13.2 Hz, 4H), 6.79-6.82 (m, 2H), 6.91 (d, *J*=7.6 Hz, 4H), 7.48-7.51 (m, 4H), 7.56-7.60 (m, 2H), 7.65 (s, 4H), 7.74-7.76 (m, 2H), 8.61 (s, 2H). ^{13}C NMR δ 195.7, 157.8, 153.1, 138.7, 132.3, 131.7, 129.7, 129.4, 128.7, 128.1, 127.8, 123.6, 63.9, 31.1. Anal Calcd for $C_{44}H_{36}O_6$•$0.2CH_2Cl_2$: C, 78.33; H, 5.41. Found: C, 78.63; H, 5.60.

Synthesis of 11,23-dibenzyl-25,27-dihydroxy-26,28-dimethoxycalix[5]arene (6). Triethylsilane (8.65 g, 53.0 mmol) was added to a stirred suspension of **5** (5.00 g, 7.58 mmol) in CF_3CO_2H (100 mL) at room temperature and the mixture was stirred for 5 h. Then 20% aq NaOH (500 mL) was added and the mixture was extracted with CH_2Cl_2 (2 X 200 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The red solid residue was washed with THF and the insoluble white solid was collected to give **6** as a white solid with mp 270-272 ^oC in 90% yield. ^1H NMR δ 3.31 (d, *J*=13.6 Hz, 4H), 3.87 (s, 4H), 3.96 (s, 6H), 4.25 (d, *J*=13.1 Hz, 4H), 6.60-7.40 (m, 20H), 7.73 (s, 2H). ^{13}C NMR δ 153.2, 151.3, 141.9, 133.0, 131.3, 129.0, 129.0, 128.8, 128.3, 128.0, 125.8, 125.3, 63.6, 41.0, 31.2. Anal. Calcd for $C_{44}H_{40}O_4$: C, 83.5; H, 6.37. Found: C, 83.37; H, 6.21.

Synthesis of 25,27-bis(ethoxycarboxymethoxy)-11,23-dibenzyl-26,28-dimethoxycalix-[4]arene (7). To a suspension of NaH (1.26 g, 63.2 mmol) in THF (250 mL), **6** (4.00 g, 6.32 mmol) was added and the mixture was stirred at room temperature. When the evolution of hydrogen ceased, a solution of ethyl bromoacetate (4.22 g, 25.28 mmol) in THF (10 mL) was added over a period of 30 min. After the mixture was stirred at room temperature overnight, water was carefully added dropwise to destroy the excess NaH. The mixture was diluted with 1N HCl (200 mL) and extracted with CH_2Cl_2 (2 X 200 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The pale yellow solid residue was chromatographed on silica gel with CH_2Cl_2-EtOAc (40:1) as eluent to give diester **7** as a white solid with mp 154-156 ^oC in 71% yield. IR 1762 (C=O) cm^{-1}. ^1H NMR δ 1.31 (t, *J*=7.2, 6H), 3.00-4.60 (m, 22H), 6.00-74.0 (m, 20H). ^{13}C NMR δ 169.5, 169.4, 158.9, 158.1, 154.4, 153.6, 141.4, 141.2, 136.7, 134.6, 134.3, 132.9, 129.0, 128.7, 128.6, 128.2, 128.1, 125.7, 125.5, 122.6, 72.1, 71.1, 60.9, 60.8, 41.0, 40.7, 30.8. Anal. Calcd for $C_{52}H_{52}O_8$: C, 77.59; H, 6.51. Found: C, 77.66; H, 6.23.

Synthesis of 25,27-bis(carboxymethoxy)-11,23-dibenzyl-26,28-dimethoxycalix[4]arene (8). A mixture of diester **7** (5.00 g, 6.21 mmol), THF (250 mL) and 10% aq Me_4NOH (250 mL) was refluxed overnight. The mixture was acidified to pH ~ 1 with 10% aq HCl. The solvent was removed *in vacuo* and CH_2Cl_2 (2 X 200 mL) was added. The combined organic layers were washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give diacid **8** as a white solid with mp 191-192 ^oC in 97% yield. IR 3760-2505 (O-H), 1757 (C=O) cm^{-1}. ^1H NMR δ 3.27 (d, *J*=13.2, 4H) 3.81 (s, 6H), 1.96 (s, 4H), 4.19 (d, *J*=13.2, 4H), 4.67 (s, 4H), 6.20-7.15 (m, 20H). ^{13}C NMR δ 169.6, 154.1, 141.0, 137.5, 134.9, 132.6, 130.0, 128.9, 128.8, 128.7, 128.5, 126.2, 124.4, 72.1, 63.8, 41.2, 30.7. Anal. Calcd for $C_{48}H_{44}O_8 \cdot CH_2Cl_2$: C, 76.28; H, 5.88. Found: 76.01; H, 6.28.

Synthesis of 25,27-bis[*N*-(5-dimethylaminonaphthalene-1-sulfonyl)carbamoylmethoxy]-11,23-dibenzyl-26,28-dimethoxycalix[4]arene (1). Diacid **8** (0.50 g, 0.67 mmol) was dried by benzene-azeotropic distillation with a Dean-Stark trap. Oxalyl chloride (0.57 mL, 6.7 mmol) was added and the solution was refluxed for 5 h. The solvent was removed *in vacuo* to provide the corresponding di(acid chloride). A solution of the di(acid chloride) in THF (20 mL) was added to a mixture of dansylamide (0.37 g, 1.48 mmol) and NaH (0.16 g, 6.7 mmol) in THF (20 mL). The mixture was stirred overnight at room temperature. Water was added carefully dropwise to decompose the excess NaH. The THF was evaporated *in vacuo* and CH_2Cl_2 (100 mL) was added to the residue. The organic layer was washed with 1N HCl (50 mL) and then water (2 X 50 mL), dried over $MgSO_4$ and evaporated *in vacuo.* The residue was chromatographed on silica gel with CH_2Cl_2-EtOAc (3:1) as eluent. Appropriate fractions were combined and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2. The solution was washed with 10% aq HCl and then water, dried over $MgSO_4$ and evaporated *in vacuo* to give a 30% yield of **1** as a light yellow solid with mp 172-174 ^oC. IR 3453 and 3327 (N-H), 1729 (C=O) cm^{-1}. ^1H NMR δ 2.90-3.90 (m, 34H), 6.20-7.95 (m, 26H), 8.67 (s, 1H), 8.68 (s, 1H), 8.86 (br s, 2H), 9.08 (br s, 2H), 9.68 (br s, 2H). ^{13}C NMR δ 167.2, 151.8, 141.0, 135.6, 133.7, 129.9, 129.8, 128.9, 128.6, 126.0, 46.5, 41.0, 31.9, 29.7, 29.3, 27.2, 26.7, 22.7, 14.1. Anal. Calcd for $C_{72}H_{68}N_4O_{10}S_2$: C, 71.26; H, 5.65; N, 4.62. Found: C, 71.50; H, 5.75; N, 4.50.

Synthesis of 5,11,17,23-tetrabenzoyl-25,26,27,28-tetrahydroxycalix[4]arene (9). To a suspension of calix[4]arene **3** (5.00 g, 11.8 mmol) and $AlCl_3$ (12.60 g, 94.4 mmol) in CH_2Cl_2 (250 mL) was added benzoyl chloride (26.52g, 188.7 mmol) dropwise over a period of 30 min. The mixture was stirred at room temperature for 24 h and then poured into ice-water. The organic layer was separated, washed with 1N HCl and then with 10% aq NaOH (to remove the excess benzoyl chloride) and evaporated *in vacuo*. The yellow solid residue was mixed with MeOH (600 mL) and 10% aq NaOH (200 mL) and the mixture was refluxed for 2 days. The MeOH was evaporated *in vacuo*. The precipitate was filtered to give a yellow solid, which was added to CH_2Cl_2 (1500 mL) and 1N HCl (500 mL). Upon stirring the mixture overnight, the solid dissolved completely. The CH_2Cl_2 layer was separated, washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give a red solid. Chromatography on silica gel with CH_2Cl_2-MeOH (80:1) as eluent gave an 89% yield of **9** as a white solid with mp 326-328 ^{O}C (lit.[25] mp 332-334 ^{o}C, lit.[21] mp 176-178 ^{o}C). Alternatively, recrystallization from CH_2Cl_2-MeOH gave the product in 80% yield. IR 3208 (O-H), 1650 (C=O) cm^{-1}. ^{1}H NMR δ 3.73 (d, *J*=12.4 Hz, 4H), 4.33 (d, *J*=12.0 Hz, 4H) 7.41-7.68 (m, 28H), 10.16 (br s, 4H). ^{13}C NMR δ 194.9, 137.4, 132.4, 131.8, 129.9, 128.4, 96.1, 53.4, 31.4. Anal. Calcd for $C_{56}H_{40}O_8$: C, 79.98; H, 4.79. Found: C,80.03; H, 4.90.

Synthesis of 5,11,17,23-tetrabenzyl-25,26,27,28-tetrahydroxycalix[4]arene (10). To a suspension of **9** (5.00 g, 5.95 mmol) and K_2CO_3 (16.43 g, 119.0 mmol) in triethylene glycol (300 mL) was added hydrazine hydrate (20 mL). The mixture was heated to reflux and water was removed with a Dean-Stark trip. When no additional amount of water was evolved, the Dean-Stark trap was removed and the mixture was refluxed for 20 h and then allowed to cool to room temperature. The mixture was diluted with 1N HCl (200 mL) and extracted with CH_2Cl_2 (2 X 200 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The yellow solid residue was chromatographed on silica gel with hexanes-CH_2Cl_2 (2:1) as eluent to give **10** as a white solid with mp 192-194 ^{o}C (lit.[26] mp 204.5-205.6 ^{o}C) in 95% yield. IR 3172 (O-H) cm^{-1}. ^{1}H NMR δ 3.36 (d, *J*=12.7 Hz, 4H), 3.76 (s, 8H), 4.15 (d, *J*=12.7 Hz, 4H), 6.78 (s, 8H), 7.08-7.32 (m, 20H), 10.13 (s, 4H). ^{13}C NMR δ 147.1, 141.1, 134.5, 129.3, 128.9, 128.4, 128.2, 126.0, 53.4, 41.0, 31.7. Anal. Calcd for $C_{56}H_{48}O_4•0.1CH_2Cl_2$: C, 84.92; H, 6.12. Found: C, 84.58; H, 5.96.

Synthesis of 26,28-dihydroxy-25,27-dimethoxy-5,11,17,23-tetrabenzylcalix[4]arene (11). To a suspension of **10** (3.20 g, 4.08 mmol) in MeCN (200 mL) was added K_2CO_3 (0.62 g, 4.48 mmol) and MeI (1.27 g, 8.98 mmol). The mixture was refluxed for 20 h and then allowed to cool to room temperature. The mixture was evaporated *in vacuo* and the residue was partitioned between CH_2Cl_2 (200 mL) and 1N HCl (200 mL). The organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel with hexanes-EtOAc (30:1) as eluent to give **11** as a white solid with mp 102-104 °C in 91% yield. IR 3353 (O-H) cm^{-1}. ^{1}H NMR δ 3.25 (d, *J*=12.9 Hz, 4H), 3.64 (s, 4H), 3.84 (s, 4H), 3.93 (s, 6H), 4.21 (d, *J*=12.9 Hz, 4H), 6.67 (s, 4H), 6.82 (s, 4H), 6.97-7.01 (m, 4H), 7.10-7.31 (m, 16H), 7.87 (s, 2H). ^{13}C NMR δ 151.7, 151.2, 141.7, 141.2, 133.1, 131.3, 129.5, 129.0, 128.9, 128.7, 128.4, 128.3, 128.2, 125.9, 125.8, 63.5, 41.3, 41.0, 31.3. Anal. Calcd for $C_{58}H_{52}O_4$: C, 85.68; H, 6.45. Found: C, 85.89; H, 6.73.

Synthesis of 25,27-di(ethoxycarboxymethoxy)-26,28-dimethoxy-5,11,17,23-tetrabenzylcalix-[4]arene (12). To a suspension of NaH (0.51 g, 21.4 mmol) in THF (100 mL), **11** (4.35 g, 5.36 mmol) was added and the mixture was stirred at room temperature until the evolution of hydrogen ceased. A solution of ethyl bromoacetate (3.58 g, 21.4 mmol) in THF (10 mL) was added over a period of 30 min and the mixture was stirred overnight at room temperature. Water was carefully added dropwise to destroy the excess NaH. The mixture was diluted with 1N HCl (200 mL) and extracted with CH_2Cl_2 (2 X 200 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel with hexanes-EtOAc (30:1) as eluent to give **12** in 90% yield as an oil. IR 1759 (C=O) cm^{-1}. ^{1}H NMR δ 1.27 (t, 6H), 2.60-4.60 (m, 30H), 6.17-7.41 (m, 28H). ^{13}C NMR δ 169.4, 157.1, 154.7, 153.6, 142.0, 141.3, 136.6, 134.8, 134.6, 134.3, 132.9, 129.5, 129.3, 129.0, 128.8, 128.6, 128.3, 128.2, 128.1, 128.0, 125.9, 125.7, 125.6, 72.1, 70.9, 60.8, 53.4, 41.3, 41.0, 40.9, 30.8. Anal. Calcd for $C_{66}H_{64}O_8$: C, 80.46; H, 6.55. Found: C, 80.11; H, 6.38.

Synthesis of 25,27-di(carboxymethoxy)-26,28-dimethoxy-5,11,17,23-tetrabenzylcalix-[4]arene (13). A mixture of **12** (5.00 g, 5.07 mmol), THF (150 mL) and 10% aq Me_4NOH (100 mL) was refluxed overnight. The mixture was acidified to pH ~ 1 with 10% aq HCl. The solvent was evaporated *in vacuo* to give **13** as a yellowish solid with mp 96-100 °C in 97% yield. IR 3730-2520 (O-H), 1753 (C=O) cm^{-1}. ^{1}H NMR δ 3.22 (d, *J*=13.2 Hz, 4H), 3.46 (s, 4H), 3.79 (s, 4H), 3.88 (s, 4H), 4.16 (d, *J*=13.2 Hz, 4H), 4.65 (s, 4H), 6.22-7.36 (m, 28H). ^{13}C NMR δ 169.6, 153.9, 151,4, 141.2, 140.7, 137.5, 136.3, 135.0, 132.5, 129.9, 129.2, 128.7, 128.5, 128.4, 128.3, 126.2, 125.9, 72.1, 63.8, 41.1, 40.8, 30.62. Anal. Calcd for $C_{67}H_{56}O_8$•$0.3CH_2Cl_2$: C, 78.38; H, 5.98. Found: C, 78.66; H, 6.08.

Synthesis of 25,27-bis[*N*-(5-dimethylaminonaphthalene-1-sulfonyl)carbamoylmethoxy]-5,11,17,23-tetrabenzyl-26,28-dimethoxycalix[4]arene (2). Diacid **13** (0.30 g, 0.32 mmol) was dried by benzene-azeotropic distillation with a Dean-Stark trap. Oxalyl chloride (0.28 mL, 3.3 mmol) was added and the solution was refluxed for 5 h. The solvent was removed *in vacuo* to provide the corresponding di(acid chloride). A solution of the di(acid chloride) in THF (20 mL) was added to a mixture of dansylamide (0.18 g, 0.72 mmol) and NaH (0.080 g, 3.3 mmol) in THF (20 mL). The mixture was stirred overnight at room temperature. Water was added carefully dropwise to decompose the excess NaH. The THF was evaporated *in vacuo* and CH_2Cl_2 (100 mL) was added to the residue. The organic layer was washed with 1N HCl (50 mL) and then water (2 X 50 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel with CH_2Cl_2-EtOAc (2:1) as eluent. Appropriate fractions were combined and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2. The solution was washed with 10% aq HCl and then water, dried over $MgSO_4$ and evaporated *in vacuo* to give a 40% yield of **2** as a light yellow solid with mp 149-151 °C. IR 3355 (N-H), 1731 (C=O) cm^{-1}. ^1H NMR δ 2.78-4.00 (m, 34H), 6.60-8.10 (m, 38H), 8.50-9.20 (m, 6H), 9.94 (br s, 2H). ^{13}C NMR δ 168.1, 156.7, 151.8, 141.8, 141.3, 137.4, 135.5, 135.0, 133.5, 132.3, 131.2, 130.0, 129.8, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 125.9, 125.8, 58.1, 46.0, 41.0, 40.4, 32.3, 29.7, 22.7, 14.1. Anal. Calcd for $C_{86}H_{80}N_4O_{10}S_2$: C, 72.28; H, 5.64; N, 3.92. Found: C, 71.95; H, 5.65; N, 4.10.

Synthesis of the di(tetramethylammonium) salts of the di-ionized ligands L1 and L2. Di(tetramethylammonium) salts of ligands **1** and **2** (**L1** and **L2**, respectively) were prepared according to a published procedure.[18]

Acknowledgements

This work was supported by The Scientific and Technological Research Council of Turkey (TUBITAK). We also thank the Division of Chemical Sciences, Geosciences and Biosciences of the Office of Basic Energy Sciences of the U.S. Department of Energy (Grant DE-FG02-90ER14416) for support of this research. AHG was supported by the Welch Summer Scholar Program of The Welch Foundation.

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