Bis-8-hydroxyquinoline-Armed Diazatrithia-15-crown-5 and Diazatrithia-16-crown-5 Ligands: Possible Fluorophoric Metal Ion Sensors

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The synthesis and preliminary photophysical properties of a series of diazatrithia-15-crown-5 and diazatrithia-16-crown-5 ligands containing two 8-hydroxyquinoline sidearms are reported. The ligands were prepared by a two-step process. First, diazatrithiacrown ethers **11** and **12** were prepared by treating bis(α-chloroamide) **5** with various dimercaptans followed by reduction using a boron−THF complex. Hydroxymethyl-substituted macrocycle **12** was rearranged to hydroxy-substituted diazatrithia-16-crown-5 in refluxing aqueous HCl. Macrocyclic diamines **11**−**13** were converted to either 5-chloro-8-hydroxyquinolin-7-ylmethyl-substituted diazatrithiacrown ethers **14**−**16** by a Mannich aminomethylation reaction or to 8-hydroxyquinolin-2-ylmethyl-substituted diazatrithiacrown ethers **17**−**19** by reductive amination using 8-hydroxyquinoline-2-carboxaldehyde. Preliminary photophysical studies show that ligands **16** and **19** exhibit increased fluorescence in the presence of Zn^{2+}, indicating that these ligands could be chemical sensors for Zn^{2+}.

Introduction

There is much interest in the development of compounds that selectively respond to specific metal ions for use as ion sensors.[1] Emphasis has been placed on the development of compounds that selectively respond to the presence of specific metal ions through changes in redox potentials,[2] UV absorption,[3] or fluorescence spectra.[1,4]

We have studied several series of macrocyclic ligands with appended chromophores and fluorophores for use as selective metal-ion chemosensors.[5] 8-Hydroxyquinoline is an analytical ligating reagent wherein its fluorescence is changed upon complexation with certain metal ions.[6] 8-Hydroxy- and 8-methoxyquinoline appended diaza-18-crown-6 ligands **1**−**4** (Figure 1) prepared in our laboratory have important ligating and luminescent properties when treated with certain metal ions.[4,5] Ligand **1** with the two 5-chloro-8-hydroxyquinoline (CHQ) substituents attached through CHQ positions 7 has a high affinity for Mg^{2+} (log K = 6.82 in MeOH) and lower affinity for the other alkaline earth and alkali metal ions (log K = 2.89−5.31 in MeOH).[5d] Ligand **4**, on the other hand, exhibits very strong affinities in MeOH for Ba^{2+} and K^+ (log K = 12.2 and 6.7, respectively) and no affinity for Mg^{2+}.[5d]

Ligands **1** and **2** have proven to be effective chemosensors for Mg^{2+} and Hg^{2+}, respectively.[4] Uncomplexed **1** and **2** exhibit very weak luminescence bands at 540 nm in MeOH/H_2O (1:1 v/v), which are consistent with the luminesence behavior of 8-hydroxyquinoline in protic solvents. Addition of Mg^{2+} to **1** and Hg^{2+} to **2** in neutral 1:1 MeOH/H_2O solutions results in strong enhancements of the luminesence bands at 520 nm (**1**)[4a] and 476 nm (**2**).[4b] These increases in luminsence occurred even in the presence of other metal ions. Ligand **3** has an 8-methoxyquinoline attached through its position 2 rather than position 7 as in **1** and **2**. As a chemosensor, **3** selectively binds and selectively responds to Cd^{2+}.[7] A large increase in the fluorescence of **3** occurs in the presence of Cd^{2+} and Zn^{2+}; however, the log K value for the association of Cd^{2+} with **3** is 2 orders of magnitude greater than that of Zn^{2+} (6.1 vs 3.98 in MeOH). Addition of K^+, Ca^{2+}, Sr^{2+},

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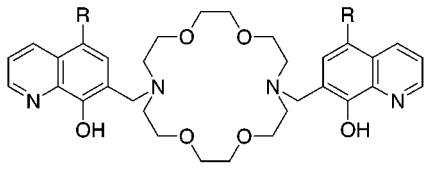
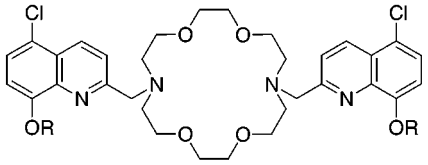


1 R = Cl
2 R = NO_2



3 R = OCH_3
4 R = OH

Figure 1. Compounds mentioned in the Introduction.

Ba^{2+}, Cu^{2+}, and Ni^{2+} ions increases the luminescence of **3** by varying amounts, but they form weaker complexes with **3.** These findings show that **3** is a promising candidate as a chemosensor in a sensory device for Cd^{2+}.[7]

This paper reports the synthesis and preliminary photophysical properties of a series of diazatrithia-15-crown-5 and diazatrithia-16-crown-5 ligands containing two 8-hydroxyquinoline sidearms. The introduction of sulfur atoms in the crown ether ring was expected to enhance selectivity toward various transition and post-transition metal ions, leaving more or less unaffected the luminescence properties of the 8-hydroxyquinoline units, which have proven to be suitable for metal ion sensing.

Results and Discussion

Synthesis of Diazatrithia Crown Ethers. Secondary ring nitrogen atoms in crown ethers offer a convenient site for attachment of alkyl substituents. The crablike synthesis of diazacrown ethers using the bis(α-chloroacetamide)s provides a relatively high yield method to form macrocycles containing two secondary amine functions.[5b,8] In this regard, bis(α-chloroamide) **5** was treated with various dimercaptans in MeCN using a carbonate base to form macrocylic diazatrithiadiamides **6**−**8** in good yields (Scheme 1). As expected, the larger 2:2 cycloaddition products, macrocyclic tetraamides **9** and **10,** were also isolated in two cases in small yields. The NMR spectra of **9** and **10** were similar to those of **6** and **8**, respectively. High dilution techniques helped minimize the production of these undesired byproducts. Macrocyclic diazatrithia ligands **11** and **12** were prepared by reducing macrocyclic diamides **6** and **8**, respectively, using a borane-THF complex. Initially, work up of the borane reduction products was done in refluxing 6 M HCl, but this process caused the formation of unexpected rearrangement and ring-opened products as discussed below. Exposure to 6 M HCl at room temperature for a period of 10 min, along with extraction, was adequate for freeing the desired product from boron giving diazatrithia-18-crown-6 (**11**) and hydroxymethyl-substituted diazatrithia-15-crown-5 (**12**) in good yields.

The rearrangement product of **12** proved to be a new hydroxy-substituted diazatrithia-16-crown-5 (**13**) (Scheme 2). Ligand **13** is also of value in our research program. In an acid environment with heating, the protonated primary hydroxyl group from **12** becomes a leaving group when attacked by the neighboring ring sulfur atom. This leads to a charged epithio intermediate that is in turn attacked by water at the carbon atom most able to support a positive charge, forming **13**. A minor product from this reaction resulted from the intramolecular attack by a neighboring ring nitrogen atom forming **13a** in a very low yield. A trace amount of another compound which has very similar properties to those of **13a** was also observed. This material could be a result of the attack of the other ring nitrogen atom on the epithio intermediate.

Synthesis of 8-Hydroxyquinoline-Substituted Ligands. Ligands **14**−**16** with the CHQ units attached at the CHQ 7-position were formed using Mannich reaction conditions as shown in Scheme 3.[5d,9] The best results were achieved by first forming the *N*,*N*′-bis(methoxymethyl)diazacrown ethers by stirring the diaza crowns in methanol and a slight excess of paraformaldahyde.[9] After removal of methanol and addition of benzene to the mixtures, CHQ was added and the mixtures were refluxed. Benzene proved to be a good reaction solvent since there were few side products. Products **14**−**16** were purified using radial chromatography.

Compounds **17**−**19** (Scheme 4) were obtained in good yields using a reductive amination procedure.[5a,b] Ligands **17**−**19** with the 8-hydroxyquinoline sidearms attached at their 2-positions were more readily isolated than compounds **14**−**16** with CHQ units attached at their 7-positions.

UV−**Vis Studies.** Due to the low solubilities of the ligands in methanol, stability constants of **15**, **18**, and **19** could be determined by UV−vis spectrophotometry. Addition of metal ions to solutions of these ligands caused a decrease in intensity of the UV−vis absorption as well as formation of a new peak leading to at least one isosbestic point. Spectral variations in the UV−vis of **19** exhibited evidence of the formation of a second complex. In the case of Zn^{2+} and **19** (Figure 2), the first series of spectral lines passed through two isosbestic points at 226.5 and 253 nm until $C_M/C_L \approx 1$, then a new isosbestic point at 261 nm was observed at higher values of C_M/C_L. These spectral changes were interpreted as the result of formation of both mono- and binuclear complexes. The stoichiometry of complexation was found from interpretation of the spectrophotometric data and is given in Table 1. Whenever there was ambiguity in choosing the best stoichiometry, the simplest one was chosen if there is no other clear evidence to support another one.

All three ligands formed strong mononuclear complexes ($\log \beta \geq 5$) with the metal ions studied. The complexes of **18**, for example, were of sufficient thermodynamic stability that equilibrium constants for their formation could not be determined accurately by UV−vis spectro-

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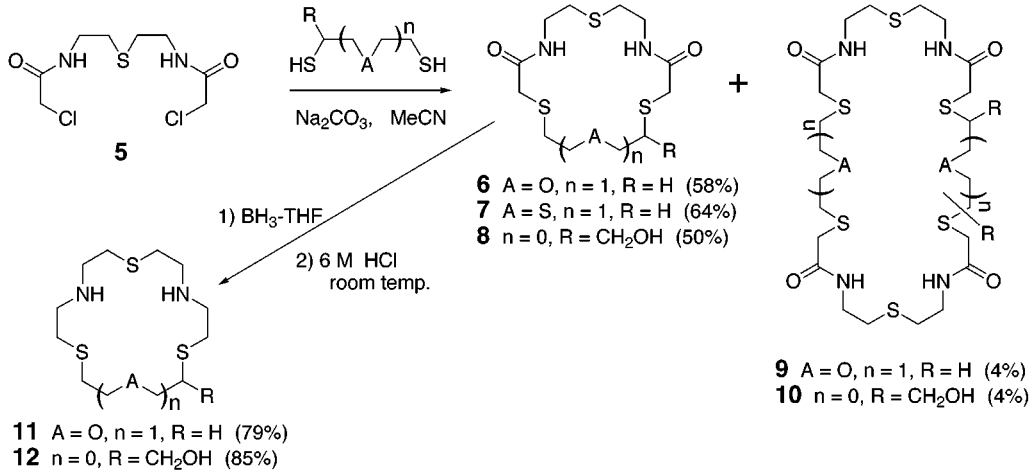
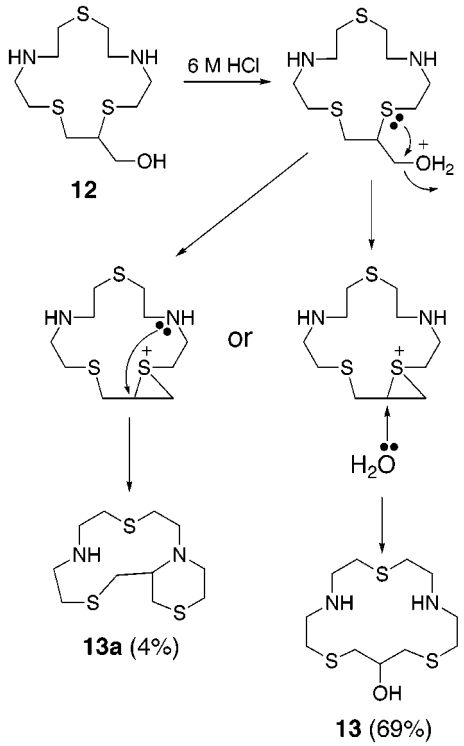
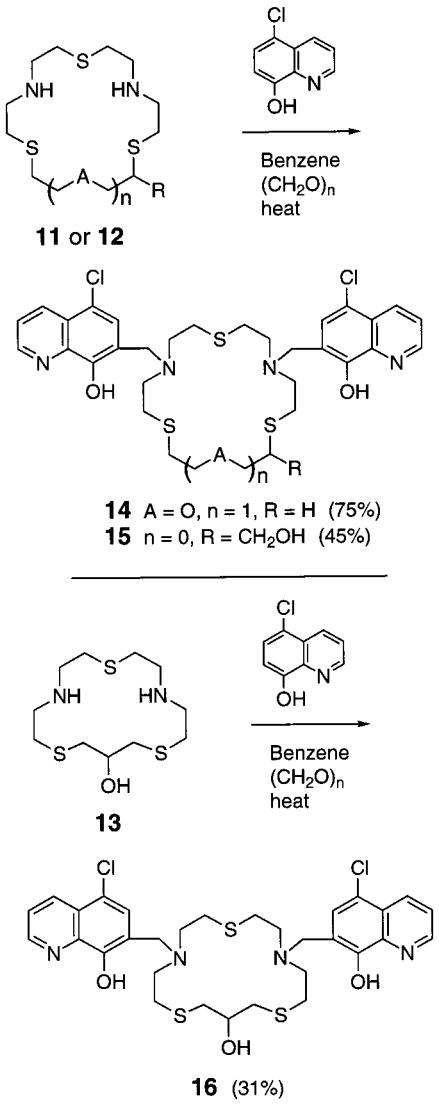
Scheme 1



Scheme 2



Scheme 3

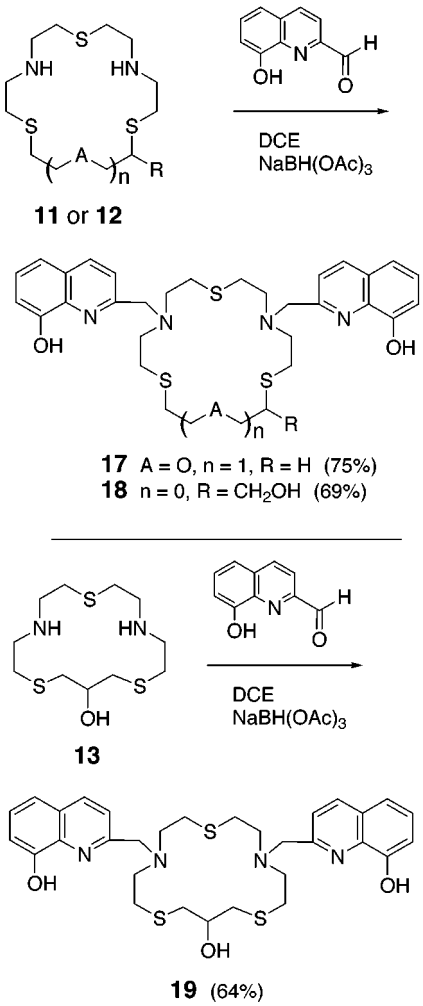


photometry. Only a lower limit of log β values could be given (log $\beta \geq 7$).

Among the three ligands studied, **18** possesses the highest affinity toward transition metal ions. The higher constants for the formation of complexes of **18** over those of **15** with a given cation can be explained by participation of quinoline nitrogen atoms in complexation. This demonstrates how the attachment site of the quinoline to the crown can effect complexation. When attached at the 7-position, the quinoline nitrogen atoms may not bind metal ions as effectively. Crown size effects can be seen by comparison of **18** and **19**. Although complexes formed by **19** with Ni^{2+} and Cu^{2+} are less stable than those formed by **18**, **19** can accommodate two cations. No comparison between **18** and **19** can be made for the other cations as only the lower limit of log β can be assigned.

Preliminary Fluorescence Studies. Among the transition metal ions studied, complexes of ligands **15**, **16**, **18**, and **19** with Cd^{2+}, Zn^{2+}, and Pb^{2+} gave emission wavelengths as shown in Table 2. Compounds **15** and **16** containing CHQ groups attached at the quinoline 7-positions, formed strongly fluorescent complexes of the type ML_2 with Cd^{2+}. However, the Cd^{2+} complexes of **18** and **19** with the 8-HQ sidearms attached through quinoline 7-positions, exhibited weaker fluorescence intensities at

Scheme 4



longer wavelengths and formed complexes of the type ML. Presumably, the fluorescence properties of the Cd^{2+} complexes were influenced by sidearm orientation.

Complexes with Zn^{2+} gave different results. Compounds **16** and **19** containing 16-membered rings gave strong emission bands, but **15** and **18** with 15-membered rings showed relatively weak fluorescence intensites with Zn^{2+}. Figures 3 and 4 illustrate the fluorescence spectra of the complexes formed by the interactions of Zn^{2+} with **16** and **19**, respectively. Interestingly, Figures 3 and 4 show that ML and M_2L complexes have emission maxima at different wavelengths (540 and 500 nm, respectively). Figures 5 and 6 illustrate the titration curves of **16** and **19** with Zn^{2+} showing a sharp endpoint for **16** at a 2:1 metal/ligand ratio. Figure 6 shows that **19** forms more than one type of complex with Zn^{2+}. It appears that **19** does not bind the second Zn^{2+} as strongly as does **16**. The fluorescence spectra of the **18**-M^{2+} complexes were similar to those of 8-HQ with the same metal ions. These results suggest a lack of crown participation in complexation by **18**. Complexes of Pb^{2+} with all ligands gave weak fluorescent responses while forming ML complexes. 8-Hydroxyquinoline and 5-chloro-8-hydroxyquinoline exhibited low fluorescence intensities with Cd^{2+}, Zn^{2+}, and Pb^{2+} relative to the ligands studied.

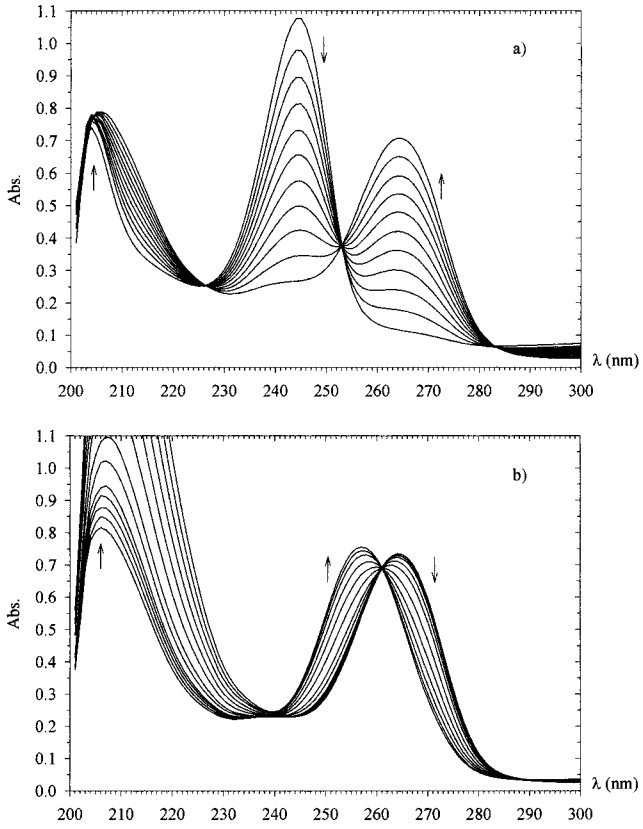


Figure 2. Spectral changes in the UV−vis absorption of **19** ($C_L = 1 \times 10^{-5}$ M) upon addition of $Zn(NO_3)_2$ in MeOH: (a) $0 < C_M/C_L < 1$; (b) $1.2 < C_M/C_L < 10.1$.

Experimental Section

The ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz in either DMSO-d_6 or $CDCl_3$. MS spectra were determined using chemical ionization (CI) and fast atom bombardment (FAB) methods. All starting materials were purchased from commercial sources or synthesized by known methods.

UV−vis spectral measurements were carried out using a previously described procedure.[10] The ligand stock solutions were prepared by dissolution of a weighed amount of ligand in methanol (HPLC grade, Fisher Scientific). Titrations of the ligand ($C_L \approx (1-2) \times 10^{-5}$ M) by metal ion solutions were performed directly in the spectrophotometric cell of 1 cm path length. The resulting spectra were recorded from 190 to 1100 nm at room temperature with an HP 8453 spectrophotometer after each addition of metal salt. The final metal-to-ligand ratios were varied between 5 and 25. The ionic strength was kept constant at 0.01 M by addition of sodium acetate (certified, Fisher Scientific). The process results in apparent equilibrium constants as a result of the high NaOAc concentration. The metal salts were the following: $Co(NO_3)_2$ (certified A.C.S., spectrum), $Ni(NO_3)_2 \cdot 6H_2O$ (Baker's Analyzed), $Cu(NO_3)_2$, and $Zn(NO_3)_2$ (certified A.C.S., Fisher Scientific), $Pb(NO_3)_2$ and $Cd(NO_3)_2 \cdot 4H_2O$ (AR, Mallinckrodt), and $Hg(NO_3)_2 \cdot H_2O$. The concentrations of stock solutions of metal salts were determined by complexometric titration with EDTA in the presence of the appropriate indicator.[11] The spectral variations recorded have been interpreted by the program Sirko.[12]

Since the UV spectra of the complexes exhibited low intensity absorption at longer wavelengths, the fluorescence

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Table 1. Stability Constants for the Formation of Metal Ion Complexes (log β_{xy})[a] in MeOH[b]

	15	**18**	**19**	**19**	**8-HQ**[c]	**8-HQ**[c]	**CHQ**[d]	**CHQ**[d]
log β	ML	ML	ML	M_2L	ML	ML_2	ML	ML_2
Co^{2+}	≥7	≥7	≥7		4.5 ± 0.2	11.6 ± 0.3	5.6 ± 0.3	11.7 ± 0.1
Ni^{2+}	6.82 ± 0.03	≥7	5.93 ± 0.06	12.7 ± 0.2		11.8 ± 0.2		11.7 ± 0.1
Cu^{2+}	6.7 ± 0.2	≥7	6.72 ± 0.05	11.4 ± 0.2	5.7 ± 0.1	13.3 ± 0.4	≥7	≥14
Zn^{2+}	6.8 ± 0.1	≥7	≥7	≥11	6.1 ± 0.2	10.4 ± 0.1	6.17 ± 0.07	10.8 ± 0.05
Cd^{2+}	5.18 ± 0.06	≥7	≥7		4.24 ± 0.06	9.2 ± 0.2		9.5 ± 0.2
Hg^{2+}	4.92 ± 0.02	≥7[e]	≥7	≥14	4.30 ± 0.01	8.60 ± 0.01	4.50 ± 0.03	9.29 ± 0.06
Pb^{2+}	5.44 ± 0.01	≥7	≥7		5.58 ± 0.01		5.3 ± 0.3	

[a] Corresponding to the general equilibrium: $xM^n + yL \rightleftharpoons M_xL_y^{xn+}$ (room temperature, I = 0.01 M NaOAc). [b] Mean values of $n \geq 2$ independent determinations, with the standard deviation σ_{n-1} on the mean. [c] 8-HQ = 8-hydroxyquinoline. [d] CHQ = 5-chloro-8-hydroxyquinoline. [e] Value of one determination only.

Table 2. Fluorescence Properties of 8-Hydroxyquinoline, 5-Chloro-8-hydroxyquinoline, 15, 16, 18, and 19 in Methanol Containing 0.01 M NaOAc

	Cd^{2+}						Zn^{2+}						Pb^{2+}					
ligand	8-HQ[a]	CHQ[a]	**15**	**16**	**18**	**19**	8-HQ[a]	CHQ[a]	**15**	**16**	**18**	**19**	8-HQ[a]	CHQ[a]	**15**	**16**	**18**	**19**
wavelength[b] (nm)	540	548	513	511	544	540	541	545	515	511	541	500	531	552	517	521	520	530
maximum intensity[c]	17	29	335	265	15	36	15	22	74	188	20	240	3	6	9	11	3	8
complexation	1:1	1:1	1:2	1:2	1:1	1:1	1:1	1:1	2:1	2:1	1:1	2:1	d	d	1:1	1:1	1:1	1:1

[a] 8-HQ and CHQ are defined in Table 1. [b] Wavelength of maximum intensity. [c] Intensity of 10 μM of each ligand. [d] Could not be determined from the fluorescence data.

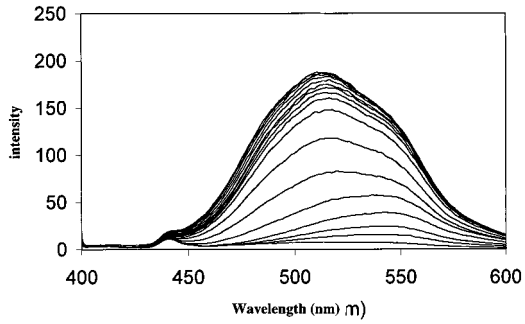

Figure 3. Fluorescence spectra of the **16**−Zn^{2+} complex: [**16**] = 10 μM, Zn^{2+} = 0.25−5 equiv.

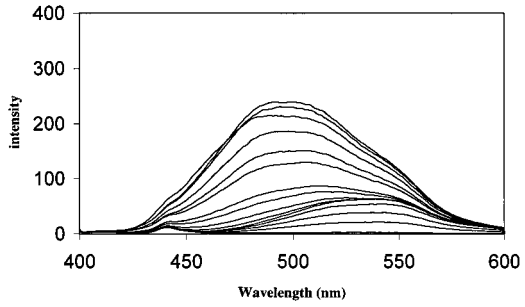

Figure 4. Fluorescence spectra of the **19**−Zn^{2+} complex:; [**19**] = 10 μM, Zn^{2+} = 0.25−5 equiv.

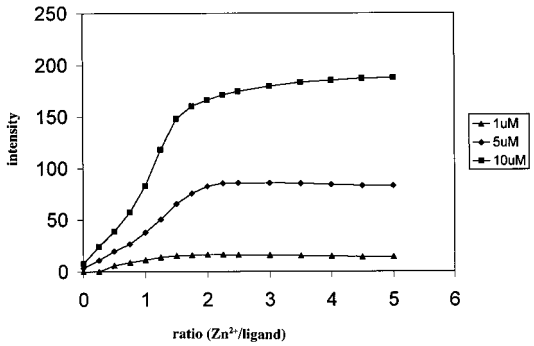

Figure 5. Fluorescence intensity (550 nm) of **16** (1−10 μM) titrated with Zn^{2+} (10−100 μM) in MeOH containing 0.01 M NaOAc.

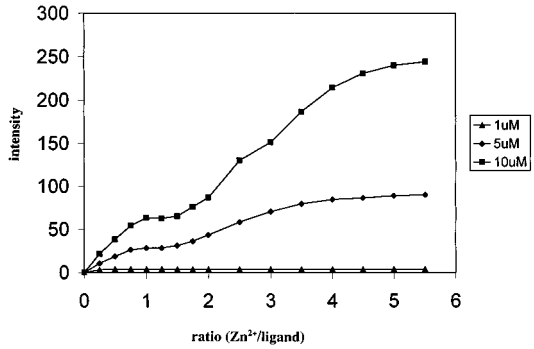

Figure 6. Fluorescence intensity (550 nm) of **19** (1−10 μM) titrated with Zn^{2+} (10−100 μM) in MeOH containing 0.01 M NaOAc.

spectra were measured using λ_{ex} = 390 nm at wavelengths between 400 and 600 nm with a Perkin-Elmer LS50B Fluorimeter. Fluorescence intensities were measured in methanol containing 0.01 M NaOAc. The titrations were performed with titrant (metal ions; 10−100 μM) and titrate (ligand; 1−10 μM). The metal ion sources were identical to those used to perform the UV−vis studies.

General Procedure A: Cyclization of 5 with Dimercaptans (Scheme 1). A mixture of **5**[5b] and a slight excess of the appropriate dimercaptan along with 4 equiv of K_2CO_3 were stirred at reflux in MeCN (60−150 mL/mmol of **5**) for 48 h under nitrogen gas. The mixture was then filtered hot, and the solvent was removed by evaporation. The crude cyclic diamides were purified by flash chromatography on silica gel using a CH_2Cl_2/MeOH/NH_4OH solvent system. The insolubility of the desired products often required the absorption of the crude product onto a small amount of silica gel, for loading purposes, to obtain good separations.

7,13-Diaza-1-oxa-4,10,16-trithiacyclooctadecane-6,14-dione (6). Compound **6** (1.81 g, 58%) was obtained as a white solid following general procedure A from 2.50 g (9.20 mmol) of **5**, 1.29 g (9.30 mmol) of 2,2′-oxydiethanethiol, and 5.10 g of K_2CO_3 in 1500 mL of MeCN after refluxing for 48 h: R_f 0.25 (silica gel, 100:4:0.4 of CH_2Cl_2/MeOH/NH_4OH); mp = 146−47 °C; ^{1}H NMR δ 8.07 (br t, J = 5.1 Hz, 2 H), 3.58 (t, J = 6.6 Hz, 4 H), 3.30 (dt, J_1 = 5.9 Hz, J_2 = 5.9 Hz, 4 H), 3.19 (s, 4 H), 2.80−2.65 (m, 8 H); ^{13}C NMR δ 169.1, 69.8, 39.2, 35.1, 31.7, 31.1; HRMS (FAB) calcd for $C_{12}H_{22}N_2O_3S_3Na$ (M + Na^+)

361.0690, found 361.0687. Anal. Calcd for $C_{12}H_{22}N_2O_3S_3$: C, 42.58; H, 6.55. Found: C, 42.72; H, 6.37.

10,16-Diaza-1,4,7,13-tetrathiacyclooctane-9,17-dione (7). Compound **7** (2.50 g, 64%) was obtained as a white solid following general procedure A from 3.00 g (10.99 mmol) of **5**, 1.12 g (11.00 mmol) of 2-mercaptoethyl sulfide, and 4.90 g of K_2CO_3 in 600 mL of MeCN after refluxing for 48 h: R_f 0.3 (silica gel, 100:5:0.5 of CH_2Cl_2/MeOH/NH_4OH); mp = 138−40 °C; ^{1}H NMR δ 8.21 (br t, J = 5.5 Hz, 2 H), 3.30 (dt, J_1 = 6.2 Hz, J_2 = 5.1 Hz, 4 H), 3.19 (s, 4 H), 2.75 (s, 8 H), 2.66 (t, J = 6.2 Hz, 4 H); ^{13}C NMR δ 169.4, 39.2, 34.5, 32.3, 31.7, 30.9; HRMS (FAB) calcd for $C_{12}H_{22}N_2S_4Na$ (M + Na^+) 377.0462, found 377.0449. Anal. Calcd for $C_{12}H_{22}N_2O_2S_4$: C, 40.05; H, 6.25. Found: C, 40.48; H, 6.12.

3-Hydroxymethyl-7,13-diaza-1,4,10-trithiacyclopentadecane-6,14-dione (8). Compound **8** (1.50 g, 50%) was also isolated as a white solid following general procedure A from 2.50 g (9.20 mmol) of **5**, 1.19 g (9.30 mmol) of 2,3-dimercaptopropanol, and 5.10 g of K_2CO_3 in 1500 mL of MeCN after refluxing for 48 h: R_f 0.3 (silica gel, 100:10:1 of CH_2Cl_2/MeOH/NH_4OH); mp = 132−34 °C; ^{1}H NMR δ 8.15 (t, J = 5.3 Hz, 2 H), 4.84 (t, J = 4.0 Hz, 1 H), 3.7−2.6 (m, 17 H); ^{13}C NMR δ 170.0, 169.7, 61.6, 47.9, 38.6, 38.4, 35.1, 34.2, 34.1, 31.6, 31.5; HRMS (FAB) calcd for $C_{11}H_{20}N_2O_3S_3Na$ (M + Na^+) 347.0525, found 347.0529. Anal. Calcd for $C_{11}H_{20}N_2O_3S_3$: C, 40.72; H, 6.21. Found: C, 40.53; H, 6.07.

7,13,25,31-Tetraaza-1,19-dioxa-4,10,16,22,28,34-hexathiacyclohexatricontane-6,14,24,32-tetraone (9). Following general procedure A, compound **9** (156 mg, 4%) was carefully isolated as a side product using 3.20 g (11.76 mmol) of **5**, 1.63 g (11.76 mmol) of 2,2′-oxydiethanethiol, and 5.20 g of K_2CO_3 in 640 mL of MeCN after refluxing for 48 h: R_f 0.2 (silica gel, 100:4:0.4 of CH_2Cl_2/MeOH/NH_4OH); mp = 153−54 °C; ^{1}H NMR δ 8.14 (br t, J = 5.1 Hz, 4 H), 3.57 (t, J = 6.6 Hz, 8 H), 3.26 (dt, J_1 = 6.2 Hz, J_2 = 6.2 Hz, 8 H), 3.16 (s, 8 H), 2.73 (t, J = 6.6 Hz, 8 H), 2.60 (t, J = 6.6 Hz, 8 H); ^{13}C NMR δ 169.1, 69.5, 38.7, 34.8, 31.1, 30.5; HRMS (FAB) calcd for $C_{24}H_{44}N_4O_6S_6$-Na (M + Na^+) 699.1483, found 699.1470. Anal. Calcd for $C_{24}H_{44}N_4O_6S_6$: C, 42.58; H, 6.55. Found: C, 42.67; H, 6.63.

3,17(18)-Bis(hydroxymethyl)-7,13,21,27-tetraaza-1,4,-10,16,18,24-hexthiacyclononaicosane-6,14,20,28-tetraone (10). Following general procedure A, compound **10** (120 mg, 4%) was also isolated as a side product from 1.25 g (4.60 mmol) of **5**, 0.58 g (4.65 mmol) of 2,3-dimercaptopropanol, and 2.10 g of K_2CO_3 in 800 mL of MeCN after refluxing for 48 h: R_f 0.2 (silica gel, 100:10:1 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 8.16 (t, J = 3.0 Hz, 4 H), 4.91 (t, J = 3.6 Hz, 2 H), 3.7−3.5 (m, 4 H), 3.4−2.5 (m, 30 H); HRMS (FAB) calcd for $C_{22}H_{40}N_4O_6S_6$-Na (M + Na^+) 671.1170, found 671.1154.

General Procedure B: Borane−THF Reduction (Scheme 1). The macrocylic diamides were dissolved in dry THF (5 mL/mmol of macrocycle). After the mixture was cooled in an ice bath, the borane−THF complex (1 M) was added (10 mmol/mmol of macrocycle) and the resulting mixture was refluxed for approximately 72 h. After being quenched with water (1 mL/20 mmol of the borane−THF complex), the solvent was removed by evaporation and 6 M HCl (10 mL/mmol of macrocycle) was used to dissolve the crude solid. The mixture was stirred at room temperature until gas ceased to be evolved (approximately 10 min). After the solution was cooled in an ice bath, NaOH (50% w/w) was added until a pH of 14−15 was reached, the resulting solution was then extracted with CH_2Cl_2 and dried (Na_2SO_4), and solvent was removed by evaporation. The crude product was purified by flash chromatography on silica gel using a CH_2Cl_2/MeOH/NH_4OH solvent system.

7,13-Diaza-4,10,16-trithia-1-oxacyclooctadecane (11). Compound **11** (2.08 g, 79%) was prepared as clear oil following general procedure B from 2.86 g (8.46 mmol) of **6** and 85 mL (85 mmol) of BH_3−THF along with 50 mL of dry THF: R_f 0.25 (silica gel, 100:7:0.5 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 3.70 (t, J = 5.9 Hz, 4H), 3.3−3.0 (m, 20 H), 2.85 (br s, 2 H); ^{13}C NMR δ 71.5, 48.5, 48.2, 33.2, 33.1, 32.2; HRMS (FAB) calcd for $C_{12}H_{27}N_2OS_3$ (M + H^+) 311.1285, found 311.1299. Anal. Calcd for $C_{12}H_{26}N_2OS_3$: C, 46.41; H, 8.44. Found: C, 46.58, H, 8.23.

2-Hydroxymethyl-7,14-diaza-1,4,10-trithiacyclopentadencane (12). Compound **12** (3.70 g, 85%) was isolated as a white solid following general procedure B from 4.80 g (14.8 mmol) of **8**, 150 mL (150 mmol) of BH_3−THF, and 60 mL of dry THF: mp = 75−78 °C; R_f 0.3 (silica gel, 100:13:2 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 3.70 (d, J = 5.1 Hz, 2 H),3.2, 3.1−2.2 (m, 21 H); ^{13}C NMR δ 64.2, 49.3, 48.1, 48.1, 47.8, 47.6, 35.5, 33.9, 33.5, 33.5, 32.2; HRMS (FAB) calcd for $C_{11}H_{25}N_2OS_3$ (M + H^+) 297.1130, found 297.1116. Anal. Calcd for $C_{11}H_{24}N_2OS_3$: C, 44.56; H, 8.16. Found: C, 44.65, H, 8.08.

3-Hydroxy-8,14-diaza-1,5,11-trithiacyclohexadecane (13) (Scheme 2). Rearranged product **13** was obtained by refluxing 101 mg (3.41 mmol) of **12** in 250 mL of 6 M HCl for 4 h. After being cooled to room temperature, the resulting solution was neutralized with 50% w/w NaOH and then evaporated to approximately 100 mL. NaOH 50% w/w was again added until a pH of 13−14 was reached, and then crude **13** was extracted with CH_2Cl_2 (3 × 100 mL). The combined, unwashed organic layer was dried (Na_2SO_4). Purification was done by flash chromatography on silica gel (100:20:3 of CH_2Cl_2/MeOH/NEt_3) to yield 69 mg (69%) of **13** as a clear solid: mp = 78−80 °C; R_f 0.3 (silica gel, 100:10:1 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 3.91 (tt, J_1 = 3.6 Hz, J_2 = 8.0 Hz, 1 H), 3.0−4.0 (br s, 3 H), 2.76−2.94 (m, 18 H), 2.64 (dd, J_1 = 8.0 Hz, J_2 = 14.2 Hz, 2 H), 3.2, 3.1, 2.2 (m, 21 H); ^{13}C NMR δ 71.5, 48.8, 47.8, 39.6, 33.8, 32.4; HRMS (FAB) calcd for $C_{11}H_{25}N_2OS_3$ (M + H^+) 297.1130, found 297.1120. Anal. Calcd for $C_{11}H_{24}N_2OS_3$: C, 44.56; H, 8.16. Found: C, 44.38, H, 7.95.

1,7-Diaza-4,10,14-trithiabicyclo[10.4.0]hexadecane (13a). Compound **13a** (25 mg, 4%) was isolated as a side product of the reaction to form **13** as a clear oil: R_f 0.5 (silica gel, 100:10:1 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 2.2−3.5 (m, 22 H); ^{13}C NMR 57.4, 51.2, 49.8, 49.0, 46.6, 33.0, 32.6, 32.3, 30.2, 27.5, 22.3; HRMS (EI$^+$) calcd for $C_{11}H_{22}N_2S_3$ (M^+) 278.0945, found 278.0947.

General Procedure C: Attachment of 5-Chloro-8-hydroxyquinoline at the 7-Position Using the Mannich Reaction (Scheme 3). The macrocyclic diamine and an excess of paraformaldehyde (2.1 equiv) were first mixed in MeOH (60 mL/1 mmol of macrocycle) and stirred overnight. MeOH was then removed, and benzene was added (60 mL/mmol of macrocycle). 5-Chloro-8-hydroxyquinoline (2.1 equiv) was then added, and the solution was refluxed for 24 h. The resulting solution was then filtered hot, and the solvent was removed by evaporation. The crude products were purified by radial arm chromatography using a CH_2Cl_2/MeOH/NH_4OH solvent system.

7,14-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-7,14-diaza-4,10,16-trithia-1-oxacyclooctadecane (14). Compound **14** (840 mg, 75%) was formed as a fluffy white solid following general procedure C from 500 mg (1.61 mmol) of **11**, 120 mg (3.93 mmol) of paraformaldehyde, and 690 mg (3.85 mmol) of 5-chloro-8-hydroxyquinoline in 20 mL of benzene and refluxed for 24 h: mp = 147−50 °C; R_f 0.5 (silica gel, 100:5:0.5 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 10.2−9.2 (brs, 2 H), 8.87 (dd, J_1 = 4.2 Hz, J_2 = 1.3 Hz, 2 H), 8.46 (dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 2 H), 7.50−7.47 (m, 4 H) 3.90 (s, 4 H), 3.70 (t, J = 6.0 Hz, 4 H), 3.00−2.70 (m, 20 H); ^{13}C NMR δ 151.1, 149.1, 139.4, 133.0, 128.0, 126.0, 122.2, 120.3, 119.6, 71.8, 54.9, 53.9, 53.7, 32.0, 30.2, 29.9; HRMS (FAB) calcd for $C_{32}H_{38}{}^{35}Cl_2N_4O_3S_3$-Na (M + Na^+) 715.1381, found 715.1396. Anal. Calcd for $C_{32}H_{38}{}^{35}Cl_2N_4O_3S_3$: C, 55.40; H, 5.52. Found: C, 55.38, H, 5.50.

8,13-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-3-hydroxymethyl-8,13-diaza-1,3,10-trithiacyclopentadecane (15). Compound **15** (210 mg, 45%) was isolated as a fluffy white solid following general procedure C from 200 mg (0.67 mmol) of **12**, 49 mg (1.62 mmol) of paraformaldehyde, and 291 mg (1.62 mmol) of 5-chloro-8-hydroxyquinoline in 25 mL of benzene and refluxed for 24 h: mp = 75−80 °C; R_f 0.6 (silica gel, 100:4:0.5 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 8.90 (dd, J_1 = 4.0 Hz, J_2 =1.1 Hz, 2 H), 8.48 (d, J = 8.8 Hz, 2 H), 8.4−7.4 (brs, 2 H), 7.55−7.49 (m, 4 H), 3.92 (s, 4 H),), 3.85 (dd, J_1

= 11.7 Hz, J_2 = 4.8 Hz, 1 H), 3.67 (dd, J_1 = 11.4 Hz, J_2 = 6.2 Hz, 1H), 3.1−2.6 (m, 20 H); ^{13}C NMR δ 151.0, 150.9, 149.2, 149.2, 139.4, 139.4, 133.2, 133.2, 128.3, 128.1, 126.1, 126.1, 122.4, 122.4, 120.5, 120.5, 119.6, 119.6, 64.0, 55.1, 54.7, 54.5, 54.1, 53.9, 53.9, 49.7, 35.1, 30.5, 29.9, 29.9, 29.4; HRMS (FAB) calcd for $C_{31}H_{36}{}^{35}Cl_2N_4O_3S_3Na$ (M + Na^+) 701.1224, found 701.1212. Anal. Calcd for $C_{31}H_{36}{}^{35}Cl_2N_4O_3S_3$: C, 54.78; H, 5.34. Found: C, 54.54, H, 5.41.

8,14-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-3-hydroxy-8,14-diaza-1,5,11-trithiacyclohexadecane (16). Compound **16** (70 mg, 31%) was made following general procedure C from 98 mg (0.33 mmol) of **13**, 20 mg (0.68 mmol) of paraformaldehyde, and 124 mg (0.69 mmol) of 5-chloro-8-hydroxyquinoline in 20 mL of benzene and refluxed for 24 h: mp = 70−75 °C; R_f 0.5 (silica gel, 100:7:0.5 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 8.86 (d, J = 4.0 Hz, 2 H), 8.48 (d, J = 8.8 Hz, 2 H), 8.4−7.4 (brs, 2 H), 7.55−7.48 (m, 4 H), 3.93−3.80 (m, 5 H), 3.0−2.6 (m, 21 H); ^{13}C NMR δ 150.9, 149.2, 139.4, 133.2, 128.4, 126.1, 122.4, 120.4, 119.5, 71.1, 54.3, 54.3, 54.0, 38.3, 30.4, 29.6; HRMS (FAB) calcd for $C_{31}H_{37}{}^{35}Cl_2N_4O_3S_3Na$ (M + H^+) 679.1405, found 679.1407. Anal. Calcd for $C_{31}H_{36}{}^{35}Cl_2N_4O_3S_3$: C, 54.78; H, 5.34. Found: C, 54.68, H, 5.13.

General Procedure D: Attachment of 8-Hydroxyquinoline at the 2-Position by Reductive Amination Using 8-Hydroxyquinoline-2-carboxaldehyde (Scheme 4). A mixture of 8-hydroxyquinoline-2-carboxaldehyde and the macrocyclic diamine in DCE (15 mL/mmol of macrocycle) was stirred with 1.3−1.6 equiv of $NaBH(OAc)_3$ under a nitrogen atmosphere at room temperature for 4−6 h. The reaction was then quenched with saturated $NaHCO_4$ and extracted with CH_2Cl_2 several times. The combined CH_2Cl_2 extracts were then dried (Na_2SO_4) and filtered, and the solvent was removed by evaporation to give the crude product. The crude product was purified by radial arm chromatography with a CH_2Cl_2/MeOH/NH_4OH solvent system.

7,13-Bis(8-hydroxyquinolin-2-ylmethyl)-7,13-diaza-4,10,16-trithia-1-oxacyclooctadecane (17). Compound **17** (240 mg, 32%) was isolated following general procedure D as an off-white solid from 367 mg (1.18 mmol) of **11**, 306 mg (1.77 mmol) of 8-hydroxyquinolin-2-carboxaldehyde (>2 equiv was used to maximize yield), and sodium triactetoxyborohydride (526 mg, 2.48 mmol) in 15 mL of DCE and stirring for 4 h: mp = 55−60 °C; R_f 0.8 (silica gel, 100:7:0.5 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 8.5−8.0 (brs 2 H), 8.10 (d, J = 8.4 Hz, 2 H), 7.69 (d, J = 8.4 Hz, 2 H), 7.42 (dd, J_1 = 8.4 Hz, J_2 = 7.7 Hz, 2 H), 7.30 (dd, J_1 = 8.1 Hz, J_2 =1.1 Hz, 2 H), 7.15 (dd, J_1 = 7.7 Hz, J_2 =1.1 Hz, 2 H), 3.95 (s, 4 H), 3.70 (t, J = 6.2 Hz, 4 H) 2.89−2.68 (m, 20 H); ^{13}C NMR δ 158.4, 152.1, 137.5, 136.7, 127.7, 127.4, 122.1, 117.9, 110.2, 71.8, 61.1, 54.6, 54.4, 32.1, 30.9, 30.7; HRMS (FAB) calcd for $C_{32}H_{40}N_4O_3S_3Na$ (M + Na^+) 647.2160, found 647.2156. Anal. Calcd for $C_{32}H_{40}N_4O_3S_3$: C, 61.51; H, 6.45. Found: C, 61.42, H, 6.42.

3-Hydroxymethyl-7,13-bis(8-hydroxyquinolin-2-ylmethyl)-7,13-diaza-1,4,10-trithiacyclopentadecane (18). Compound **18** (393 mg, 69%) was prepared following general procedure D as a greenish/white solid from 275 mg (0.93 mmol) of **12**, 337 mg (1.95 mmol) of 8-hydroxyquinolin-2-carboxaldehyde, and sodium triactetoxyborohydride (530 mg, 2.50 mmol) in 12 mL of DCE and stirred for 5 h: mp = 60−65 °C; R_f 0.7 (silica gel, 100:7:1 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 8.8−7.8 (brs, 2 H), 8.11 (d, J = 8.4 Hz, 2 H), 7.62 (dd, J_1 = 8.8 Hz, J_2 = 8.4 Hz, 2 H), 7.42 (dd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 7.16 (d, J = 7.7 Hz, 2 H), 3.96 (s, 4 H), 3.90 (dd, J_1 = 11.7 Hz, J_2 = 4.4 Hz, 2 H) 3.69 (dd, J_1 = 11.4 Hz, J_2 = 6.6 Hz, 2 H), 3.2−2.6 (m, 21 H); ^{13}C NMR δ 158.1, 157.6, 152.4, 152.2, 137.7, 137.5, 136.8, 136.7, 127.8, 127.8, 127.6, 127.5, 122.0, 122.0, 117.9, 117.8, 110.5, 110.3, 64.4, 61.5, 61.5, 55.5, 55.0, 54.6, 54.4, 49.8, 35.3, 31.0, 30.3, 30.2, 29.9; HRMS (FAB) calcd for $C_{31}H_{40}N_4O_3S_3Na$ (M + Na^+) 633.2004, found 633.1988. Anal. Calcd for $C_{31}H_{40}N_4O_3S_3$: C, 60.95; H, 6.27. Found: C, 60.93, H, 6.43.

3-Hydroxy-8,14-bis(8-hydroxyquinolin-2-ylmethyl)-8,14-diaza-1,5,11-trithiacyclohexadecane (19). Compound **19** (130 mg, 64%) was obtained following general procedure D as a greenish/white solid from 97 mg (0.33 mmol) of **13**, 119 mg (0.69 mmol) of 8-hydroxyquinolin-2-carboxaldehyde, and sodium triactetoxyborohydride (189 mg, 0.89 mmol) in 4.5 mL of DCE and stirred for 4 h: mp = 60−63 °C; R_f 0.8 (silica gel, 100:7:0.5 of CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR δ 9.1−8.3 (brs, 2 H), 8.09 (d, J = 8.8 Hz, 2 H), 7.54 (d, J = 8.4 Hz, 2 H), 7.46 (dd J_1 = 8.1 Hz, J_2 = 7.7 Hz, 2 H), 7.28 (d, J = 8.1 Hz, 2 H), 7.16 (d J = 7.3 Hz, 2 H), 4.01 (d J = 14.7 Hz, 2 H) 4.00 (m, 1 H), 3.89 (d, J = 14.7, 2 H) 3.0−2.6 (m, 21 H); ^{13}C NMR δ 157.4, 152.6, 137.8, 136.7, 127.8, 127.6, 121.8, 117.8, 110.6, 72.5, 61.1, 55.5, 55.0, 38.6, 31.3, 29.9; HRMS (FAB) calcd for $C_{31}H_{38}N_4O_3S_3Na$ (M + Na^+) 633.1925, found 633.1932. Anal. Calcd for $C_{31}H_{38}N_4O_3S_3$: C, 60.95; H, 6.27. Found: C, 60.81, H, 6.17.

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