New Tetraazacrown Ethers Containing Two Pyridine, Quinoline, 8-Hydroxyquinoline, or 8-Aminoquinoline Sidearms

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A series of macrocyclic tetraazacrown ethers containing two pyridine, quinoline, 8-hydroxyquinoline, or 8-aminoquinoline sidearms has been prepared. Crab-like cyclization of bis(α-chloroacetamide)s and diamines followed by reduction of the cyclic diamides was used to synthesize the selected crown ethers containing two unsubstituted macroring nitrogen atoms. The preparation of the macrocycles with sidearms was accomplished by reductive amination of the proper aldehydes with the crown ethers using sodium triacetoxyborohydride ($NaBH(OAc)_3$) as the reducing agent. The 8-hydroxyquinoline- and 8-aminoquinoline-containing macrocycles were synthesized by reductive amination of 8-acetoxyquinoline-2-carboxaldehyde or 8-nitroquinoline-2-carboxaldehyde followed by removing the acetate groups or reducing the nitro groups to amino groups, respectively. Complexation of ligand **22** with Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} was evaluated potentiometrically in aqueous solution (0.10 M Me_4NCl) at 25 °C. Ligand **22** formed very stable complexes with these metal ions. The UV−vis spectra of **22** and its complexes were examined in an aqueous acetic acid buffer solution (pH 5). The **22**−Cu^{2+} complex provided a new absorption band at 258 nm.

Introduction

The high toxicity of many transition and post-transition metals is well-recognized,[1] and, consequently, there is a great need for monitoring the levels of these metal ions in the environment. Currently, metal ion concentrations in waste streams are usually measured by spectroscopic or wet chemical methods on samples removed from waste streams.[2] An attractive alternative would be to monitor the concentration of specific metal ions in a complex matrix continuously and remotely by using ion-selective sensory devices.

Chemical sensors employing fiber optic technology could prove useful for the in-situ detection and quantification of metal ions provided synthetic fluoroionophores (FIPs) and chromoionophores (CIPs) capable of signaling the complexation of metal ions with useful selectivity are developed. Optical sensors for metal ions have been reported;[3−7] however, they have generally lacked ion selectivity. A number of optical sensors have been based on ion-chelating dyes, which have been used in the spectrophotometric determination of various metal ions. A number of CIP and FIP dyes, including zincon,[4] 8-hydroxyquinoline-5-sulfonic acid,[5] calcichrome,[6] and lipophilized PAR (**1**, see Figure 1),[7] have been immobilized on solid supports yielding metal ion sensors. These systems responded well with many metal ions but did not display significant ion selectivity.

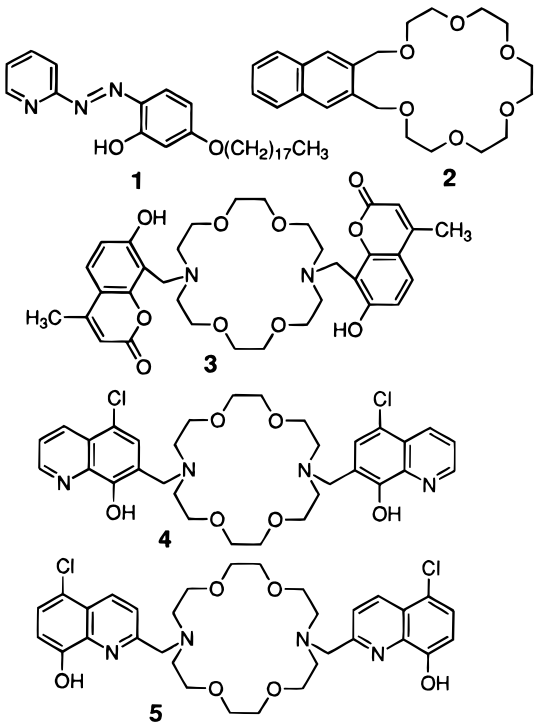

Figure 1. Compounds mentioned in the Introduction.

The critical requirement for the design of an ion-specific fluorescent chemosensor is the selective binding of the target ion by the chemosensor. Many macrocyclic ligands are known to interact selectively with many metal ions,[8] and some of these have been used to develop

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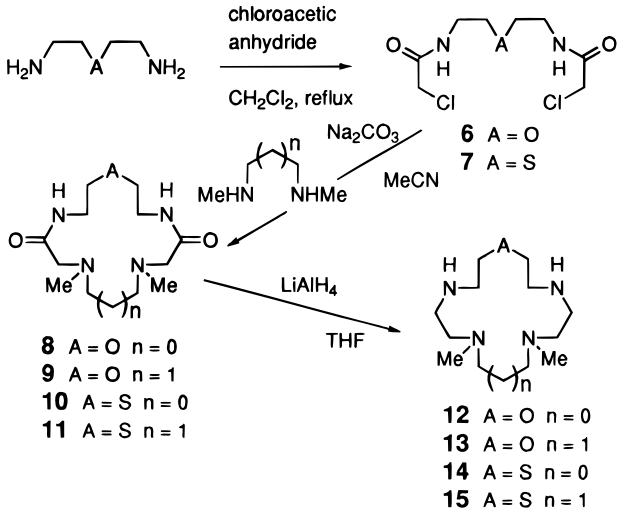
metal ion sensors.[9−15] The first such application was reported by Sousa and Larson in the preparation of some naphthalenocrown ether ligands (see **2**, for example).[9] The observed fluorescence changes for these naphthalene-containing ligands upon binding alkali metal ions in ethanol were attributed to a heavy atom effect (for Cs^+ and Rb^+) and a complexation-induced change in triplet energy relative to ground and excited singlet state energies.

A number of crown ether-containing FIPs have been prepared with various fluorophore sidearms including anthracene, coumarin, merocyanine, and benzoxazinone groups.[10−15] Crown ethers containing oximic and Schiff-base sidearms have also been prepared.[11] Improvements in metal ion complexing ability and selectivity have been observed when proton-ionizable chromophoric or fluorophoric units are attached to the crown ring as sidearms.[12] For example, diprotonic and fluorogenic crown ether **3**, developed by Takagi and co-workers,[13] has proven particularly effective toward Ca^{2+}, Ba^{2+}, and other divalent cations. New 5-chloro-8-hydroxyquinoline (CHQ)-substituted azacrown ethers where CHQ was attached through its 7-position (**4**) or its 2-position (**5**) have been synthesized in our laboratory.[14,15] The ion selectivities demonstrated by **4** and **5** were much greater than those of the parent diaza-18-crown-6 macrocycle.[15] Particularly striking is the selectivity of compound **4** for Ni(II) over Cu(II) (log K = 11.4 and 10.1, respectively, in methanol) and its strong complexing ability with Mg^{2+} and Ca^{2+}. Indeed, ligand **4** is a very effective sensor for Mg^{2+} ions.[16]

Scheme 1. Syntheses of Tetraazacrown Ethers with Two Unsubstituted Nitrogens



Compound **5**, with attachment of CHQ through its 2-position, displays strong complexation in methanol with K^+ and Ba^{2+} (log K = 6.61 and 12.2, respectively) but not with Mg^{2+} or Cu^{2+}. The crystal structure of the complex of Ba^{2+} with **5** shows that both 8-CHQ groups are bidentate chelators of Ba^{2+}, and both are juxtaposed on the same side of the complex forming a cryptate-like structure.[15]

This report describes the preparation of new 8-hydroxyquinoline-(8-HQ) and 8-aminoquinoline-substituted tetraazacrown ethers designed to selectively bind transition and post-transition metal ions with a concomitant modulation in the absorption and fluorescence spectra of the compounds. Tetraazacrown ethers have been shown to selectively complex the target group of metal ions.[8] Preliminary complexation studies of one of these new ligands (**22**) with various metal ions in aqueous solution showed that **22** forms very stable complexes and the **22**−Cu^{2+} complex gave a new band at 258 nm in its UV absorption spectrum.

Results and Discussion

Synthesis of Tetraazacrown Ethers with Two Unsubstituted Macroring Nitrogen Atoms. A convenient way to functionalize the polyazacrown ethers with FIP or CIP groups is via attachment to ring NH groups. To allow attachment of two FIP or CIP groups, it was necessary to prepare macrocycles containing two secondary amine groups. Application of crab-like bis(α-chloroacetamide)s for the synthesis of azacrown ethers with one or two secondary macroring nitrogen atoms has been reported.[17,18] In these syntheses, bis(α-chloroacetamide)s were prepared by acylating the appropriate diamines with chloroacetyl chloride or chloroacetic anhydride. The bis(α-chloroamide)s were then treated with bis-secondary amines in MeCN using a carbonate base to form macrocyclic diamides **8**−**11** (Scheme 1). These diamides were reduced to form the four tetraazacrown ethers containing two secondary ring nitrogen atoms (**12**−**15**) as shown in Scheme 1. The crab-like bis(α-

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chloroacetamide)s **6** and **7** were prepared in almost quantitative yields. The amide portions of the bis(α-chloroamide)s work as protecting groups for the nitrogen atoms, and they increase the reactivity of the chloro-substituted carbon toward nucleophilic substitution.[18] Compounds **6** and **7** were reacted with two different bis-secondary amines by a cyclization reaction to form the four macrocyclic diamides **8**−**11** in 57−73% yields.

The crab-like cyclization reactions were carried out without using high dilution techniques and at room temperature. The relativley high yields may be attributable to hydrogen bonding between the amide oxygen atoms of the bis(α-chloroamide) and the amine hydrogen atoms of the bis-secondary amines which would keep the two chloride units in the positions needed for the cyclization reaction.[17]

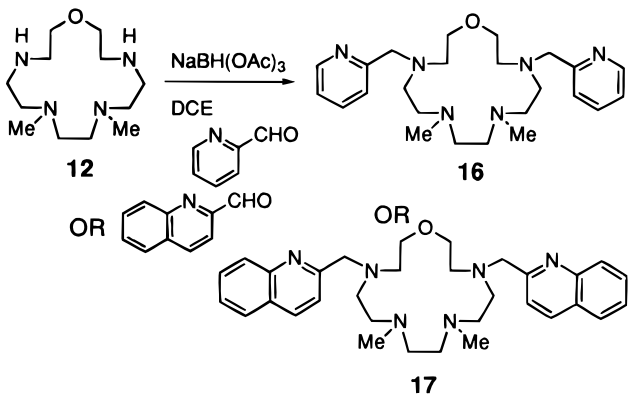
Reduction of **8**−**11** with $LiAlH_4$ gave the four tetraaza-crown ethers (**12**−**15**) in 71−83% yields. Reduction can also be achieved by using diborane in THF. Diborane reduction results in the formation of a borane complex which requires a complex workup procedure.[18] To avoid the relatively more complicated workup, reduction was done by $LiAlH_4$ and gave the products in good yields. A satisfactory elemental analysis was obtained for at least one 8-hydroxy- or 8-amine-substituted quinoline derivative of each of **12**−**15**.

Synthesis of Quinoline Derivative-Containing Tetraazacrown Ethers. We have reported two methods of attaching 5-chloro-8-hydroxyquinoline to diaza-18-crown-6 (to form **4** and **5**).[14] Ligand **5** was prepared by a nucleophilic substitution of the secondary nitrogens on the macrocycle ring on halomethyl-substituted 8-methoxyquinoline followed by removal of the methyl groups.[14] Ligand **4** was prepared by conversion of the secondary amines of the macrocycle to (methoxymethyl)amines which are active electrophilic reagents in the Mannich reaction and react readily with the electron rich phenolic side of 5-chloro-8-hydroxyquinoline.[14] We attempted to prepare the quinoline derivative-containing tetraaza macrocycles by these two methods. Unfortunately, no desired products were obtained.

Reactions of aldehydes with primary or secondary amines in the presence of reducing agents to give secondary or tertiary amines, respectively, known as reductive amination, are useful methods to alkylate amine groups. Direct reductive amination of aldehydes with amines using sodium triacetoxyborohydride ($NaBH(OAc)_3$) as a reducing agent has been developed for a wide variety of substrates.[19] Compared to other hydride reducing agents such as sodium cyanoborohydride ($NaBH_3CN$), $NaBH(OAc)_3$ is mild, less toxic, and exhibits remarkable selectivity as a reducing agent.[19]

To investigate the feasibility of synthesizing the quinoline derivative-containing tetraazamacrocycles by reductive amination, macrocycle **12** was treated with 2-pyridinecarbaldehyde and 2-quinolinecarboxaldehyde in the presence of $NaBH(OAc)_3$ to form pyridine- and quinoline-substituted tetraaza-15-crown-5 ligands **16** and **17** in 87% and 82% yields, respectively (Scheme 2). Although $NaBH(OAc)_3$ is a very mild reducing agent, a small amount of alcohol reduction product from the aldehyde was observed. Reductive amination of 8-hydroxyquinoline-2-carboxaldehyde with a tetraazacrown ether did not occur,

Scheme 2. Syntheses of Pyridine- and Quinoline-Substituted Crown Ethers via Reductive Amination



possibly because of the presence of the phenolic OH group. However, when macrocycles **12**−**15** were treated with 8-acetoxyquinoline-2-carboxaldehyde in the presence of $NaBH(OAc)_3$, 8-acetoxyquinoline-substituted macrocycles **18**−**21** were formed in good yields (Scheme 3). Products **18**−**21** could not be purified by chromatography because they were hydrolyzed by the solvent system used, and, thus, were treated without purification with KOH to form **22**−**25** in 71−78% yields. When working up 8-HQ-substituted macrocycles **22**−**25** following hydrolysis of the acetates, the solution was adjusted to pH ∼ 10. In this pH range, the tetraazacrown ethers contain one or more molecules of HCl as demonstrated by the elemental analyses for **22**, **23,** and **25**.

Another approach to prepare 8-HQ-substituted **22** is shown in Scheme 4. The 8-HQ pendant arms were attached to the aliphatic nitrogen by stepwise reductive amination before cyclization to form **26**. Compound **26** was cyclized with crab-like bis(α-chloroamide) **27** to give the intermediate macrocyclic diamide **28**. To avoid deprotonation of the phenolic OH group, triethylamine was used instead of Na_2CO_3 in the cyclization reaction. The resulting bisamide was reduced by the borane−THF complex to give **22** in a 27% overall yield. Aqueous HCl needed to be added to the reaction mixture to destroy the complex with borane. Treatment of the diamide with $LiAlH_4$ gave a lower yield. Compared to the approach in Scheme 3, both the cyclization and reduction steps (Scheme 4) gave lower yields. Thus, the direct attachment of the quinolinecarbaldehyde to the secondary amines of the macrocycle ring is a more convenient way to prepare macrocycles with quinoline derivatives as sidearms.

In the complex of CHQ-containing **5** with Ba^{2+}, the cation is coordinated by all nitrogen and oxygen atoms of the ligand.[15] To compare the effect of the hydroxy oxygen atom of 8-hydroxyquinoline in metal ion complexation with that of an amine nitrogen atom, a series of macrocycles containing 8-aminoquinoline sidearms was also prepared (see Scheme 5). 8-Nitroquinoline-2-carbaldehyde was reacted with the NH groups on the macrocycles by reductive amination to form compounds **29**−**32**. Even though an excess amount of 8-nitroquinoline-carbaldehyde was used, some monosubstituted products were obtained. Decomposition of the 8-nitroquinoline-substituted compounds was observed within a couple of days so the nitro macrocycles were reduced immediately after purification. The nitro groups of compounds **29** and **30** were reduced by catalytic hydrogenation using plati-

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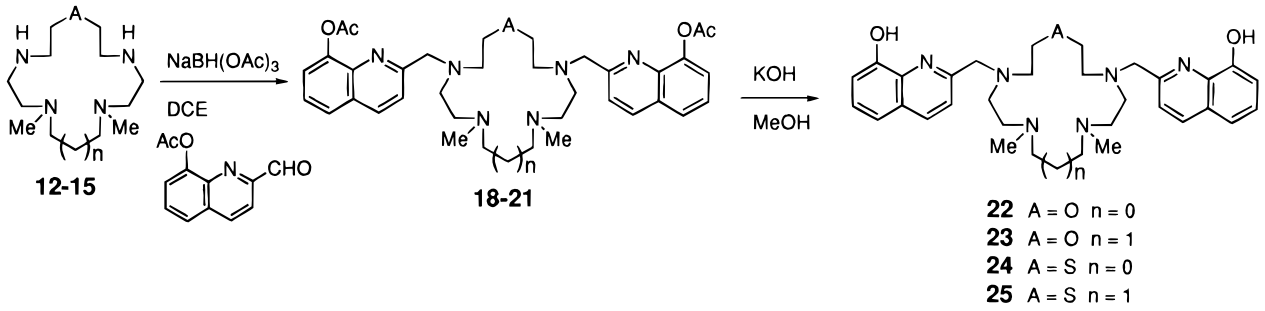
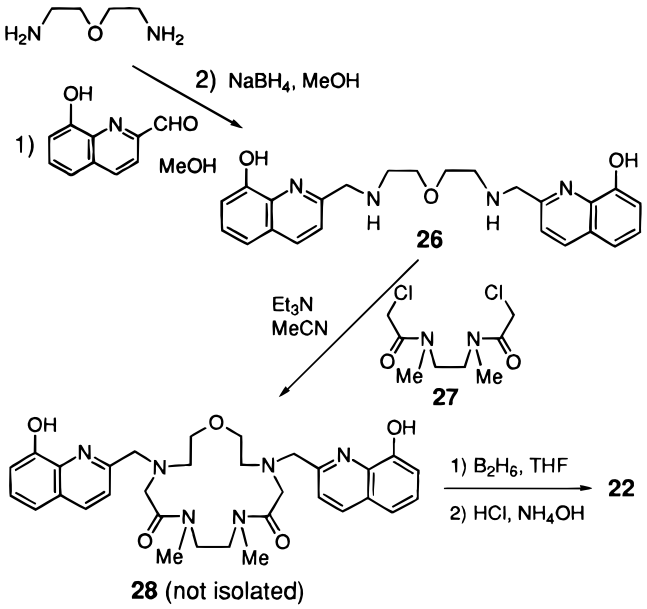
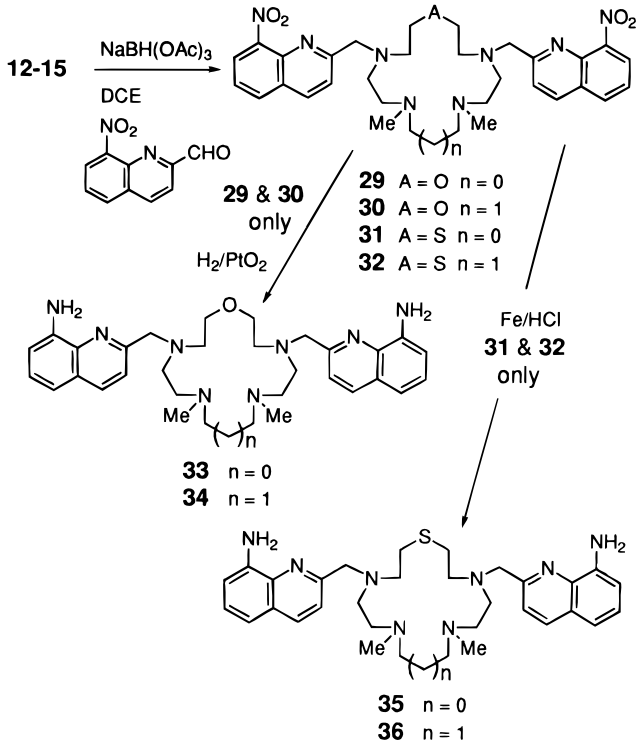
Scheme 3. Syntheses of 8-Hydroxyquinoline-Substituted Tetraazacrown Ethers via Reductive Amination



Scheme 4. Alternate Synthesis of 22



Scheme 5. Syntheses of 8-Aminoquinoline-Substituted Tetraazacrown Ethers



num oxide as the catalyst to form **33** and **34** in 52% and 63% yield, respectively. Reduction of **31** and **32** was achieved using iron and HCl to form **35** and **36** in low yields. Decomposition of starting **31** and **32** was observed under this condition.

The NMR spectra for the substituted macrocycles were consistent with the proposed structures. The OH proton signals of compounds **22**−**25** were not observed in $CDCl_3$. In DMSO-d_6, the OH protons could be observed as a very broad peak at $\delta > 10$ ppm. All new isolated macrocyclic compounds had satisfactory molecular weights as determined by HRMS. All of the 8-hydroxy- and 8-aminoquinoline-substituted ligands except **24** also had satisfactory elemental analyses.

Protonation and Complexation Studies of Ligand 22. Protonation constants of 8-hydroxyquinoline-containing tetraazacrown ether **22** and stability constants for the interactions of **22** with Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} were determined by a potentiometric titration technique[20] at 25 °C in aqueous solution. The ionic strength was kept constant with 0.10 M tetramethylammonium chloride. The overall reactions are expressed by the general equation:

$$pM^{2+} + qH^{+} + rL^{2-} \rightleftharpoons M_pH_qL_r^{(2p+q-2r)} \quad (1)$$

where M is the metal ion and L is the ligand. The overall equilibrium constant can be defined as

$$\beta_{pqr} = [M_pH_qL_r^{(2p+q-2r)}]/[M^{2+}]^p[H^{+}]^q[L^{2-}]^r \quad (2)$$

Table 1. Logarithms of Protonation Constants of Macrocyclic Ligand 22 in Aqueous Solution (0.10 M Me_4NCl) at 25.0 °C

reaction	log β
$H^+ + L^{2-} \rightleftharpoons HL^-$	9.55 ± 0.05
$2H^+ + L^{2-} \rightleftharpoons H_2L$	16.85 ± 0.08
$3H^+ + L^{2-} \rightleftharpoons H_3L^+$	19.87 ± 0.09
$4H^+ + L^{2-} \rightleftharpoons H_4L^{2+}$	21.31 ± 0.14

The values of the protonation constants of the ligands and stability constants of the metal ion complexes (log β_{pqr}) are listed in Tables 1 and 2, respectively.

Four protonation constants can be calculated for compound **22**. The first two protonation constants (log $K_1 = 9.55$ and log $K_2 = 7.30$ (16.85 − 9.55), Table 1) and the last two constants (log $K_3 = 3.02$ and log $K_4 = 1.44$) are close to each other. A large decrease in protonation constants is seen between the second and the third protonation steps. Since the first protonation constant of **22** (log $K_1 = 9.55$) is close to the log K_1 value of free

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Table 2. Overall Stability Constants[a] of Metal Ion Complexes with Macrocyclic Ligand 22 in Aqueous Solution (0.10 *M* Me_4NCl) at 25.0 °C

			log β_{pqr}					
p	*q*	*r*	Cu^{2+}	Co^{2+}	Ni^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}
1	0	1	15.52 ± 0.08	12.34 ± 0.04	13.46 ± 0.03	12.41 ± 0.03	15.33 ± 0.02	13.65 ± 0.03
1	1	1	18.55 ± 0.12		16.15 ± 0.18	15.55 ± 0.09	17.50 ± 0.05	16.93 ± 0.03
1	−1	1	8.53 ± 0.19	6.44 ± 0.06	7.49 ± 0.12	6.49 ± 0.05	9.62 ± 0.07	8.22 ± 0.08
2	0	1	18.92 ± 0.22					
1	0	2		20.19 ± 0.06				
1	−2	1			−3.59 ± 0.25			

[a] The equilibria of the reactions are defined by the general equation: $pM^{2+} + qH^{+} + rL^{2-} \rightleftharpoons M_pH_qL_r^{(2p+q-2r)}$. M = metal; L = ligand. A minus *q* value refers to OH^- group.

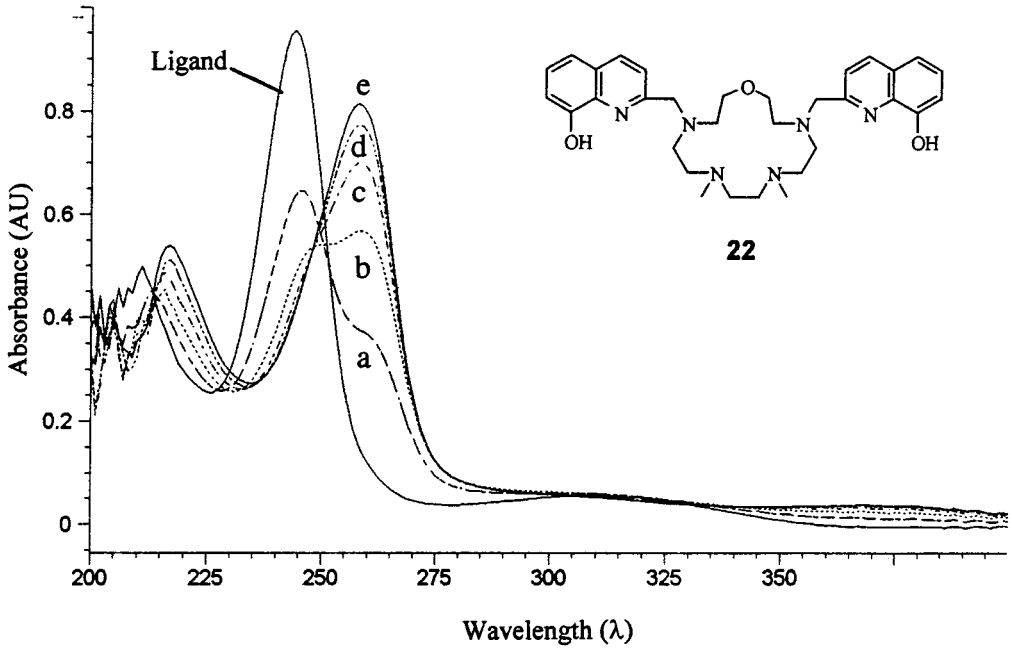

Figure 2. UV−visible spectra of free **22** and its Cu^{2+} complexes in an aqueous buffered solution. [**22**] = 0.977 × 10^{-5} M, [buffer] = 5.0 × 10^{-2} M acetic acid (pH = 4.7). The labels a−e indicate 1−5 equiv of Cu^{2+} added to the ligand successively.

8-hydroxyquinoline (9.65 at 25 °C, μ = 0.1),[21] the first two protonation constants of **22** are due to protonation of OH groups of the 8-hydroxyquinoline portion, and the last two are attributed to protonation of the nitrogen atoms of the ligand. Therefore, the fully deprotonated ligand (L^{2-}) is capable of forming a neutral complex with a divalent cation which may be coordinated by both the 8-hydroxyquinolines and the macroring.

Data in Table 2 show that each metal ion studied forms several types of complexes with the ligand. The 1:1 complexes ML ($p = 1$, $q = 0$, $r = 1$ in eq 1) and $M(OH)L^-$ ($p = 1$, $q = -1$, $r = 1$) are observed in each case. The complexes of ligand **22** with Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} are very stable in aqueous solution. The large stability constants (log β_{ML} > 12 and log β_{MHL} > 15) are shown in Table 2. The most stable complexes were observed for Cu^{2+}. The values of log β_{CuL} and log β_{CuHL} are 15.5 and 18.6, respectively. Cd^{2+} also forms very stable complexes with ligand **22** (log β_{CdL} = 15.3 and log β_{CdHL} = 17.5). Therefore, not only the fully deprotonated form of **22** (L^{2-}) but also the monoprotonated ligand (HL^-) forms very stable complexes with the metal ions studied (except for Co^{2+}). In the case of Co^{2+}, the complex $CoHL^+$ was not detected. However, Co^{2+} forms a 1:2 (M:L) complex with **22** (log β_{CoL_2} = 20.2). A dinuclear complex with Cu^{2+}, Cu_2L^{2+}, was also observed. The equilibrium constants of the complexes containing hydrolysis products of the metal ions, $M(OH)L^-$, range from 6.44 (log $\beta_{Co(OH)L}$) to 9.62 (log $\beta_{Cd(OH)L}$). The Ni^{2+} forms a second type of hydrolysis complex, $Ni(OH)_2L^{2-}$, which has a very low equilibrium constant (Table 2).

UV−Visible Spectra. The UV spectra of free and complexed ligand **22** are shown in Figures 2 and 3. The free **22** has an absorption maximum at 244 nm. Upon addition of Cu^{2+}, a new peak develops at 258 nm (Figure 2). Other metal ions (Zn^{2+}, Pb^{2+}, Cd^{2+}, Ag^+, Hg^{2+}, Co^{2+}, and Ni^{2+}) were also titrated with **22**, but none produced a new peak or significantly interfered with the new **22**−Cu^{2+} complex peak at 258 nm (Figure 3). Thus, the 258 nm peak for the **22**−Cu^{2+} complex could be used for sensing purposes.

Experimental Section

The ^1H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and 50 or 75 MHz in $CDCl_3$ unless otherwise noted. MS spectra were determined using chemical ionization (CI) and fast atom bombardment (FAB) methods. All starting materials were either purchased from commercial sources or synthesized by known methods: 8-acetoxyquinoline-2-carbaldehyde[22] and 8-nitroquinoline-2-carbaldehyde.[23]

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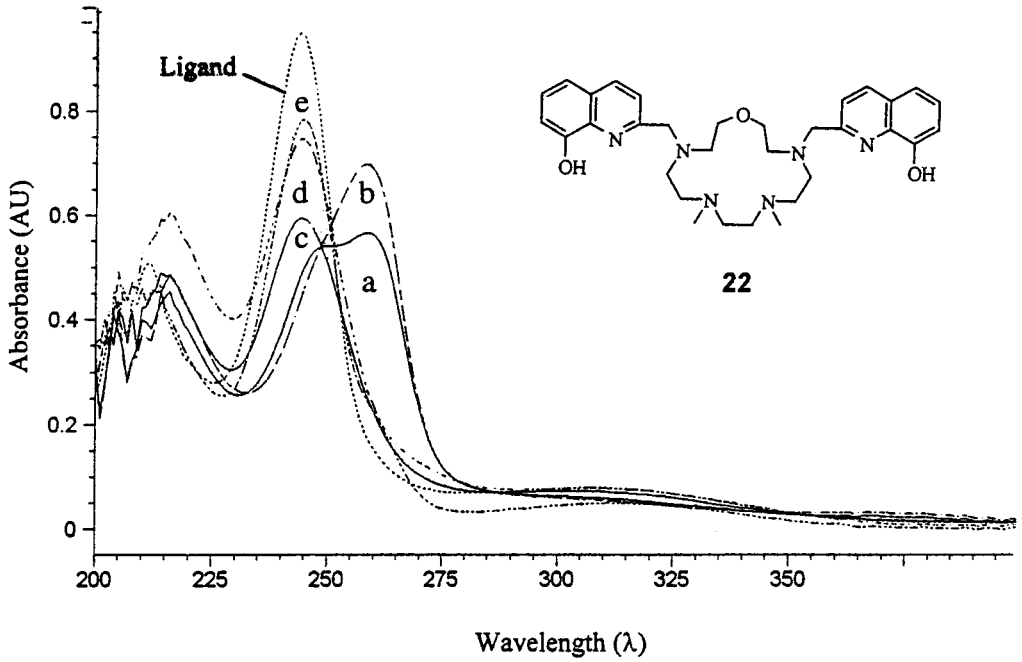

Figure 3. UV−visible spectra of free and complexed **22** in acetic acid buffer solution (pH = 4.7). (a and b) Cu^{2+} (1 and 2 equiv, respectively), (c) Zn^{2+}, (d) Pb^{2+}, and (e) Cd^{2+} (2 equiv each). [**22**] = 0.977×10^{-5} M and [buffer] = 5.0×10^{-2} M acetic acid.

Bis[2-(α-chloroacetamido)ethyl] Ether (6) (Scheme 1). Chloroacetic anhydride (4.1 g, 24 mmol) in 10 mL of CH_2Cl_2 was added dropwise through a dropping funnel to a stirred solution of 2,2′-oxybis(ethylamine) (0.94 g, 10 mmol) at 0−5 °C over a 1-h period. The mixture was stirred for additional 1 h at room temperature. Saturated aqueous $NaHCO_3$ was added to neutralize the reaction mixture. The organic layer was separated and washed twice with 20 mL portions of saturated aqueous $NaHCO_3$ and then twice with portions of water. The organic layer was dried (Na_2SO_4), and the solvent was evaporated under vacuum to give a crude product (2.52 g, 98%). The crude bis-α-chloroamide product was used to prepare the appropriate macrocycles without further purification; mp = 81−2 °C; ^{1}H NMR δ 6.94 (br s, 2H), 4.07 (s, 4H), 3.61−3.50 (m, 8H); ^{13}C NMR δ 166.3, 69.5, 42.9, 39.7; MS (CI) *m/z* 257 (M^+); HRMS (CI) calcd for $C_8H_{15}{}^{35}Cl_2N_2O_3$ (MH^+): 257.0460, found: 257.0472.

Bis[2-(α-chloroacetamido)ethyl] Sulfide (7) (Scheme 1). Compound **7** was synthesized from 2,2′-thiobis(ethylamine) (1.2 g, 10 mmol) and chloroacetic anhydride (4.1 g, 24 mmol) as above for **6**. A white precipitate formed gradually during the reaction. When the reaction was completed, the solution was cooled to 0 °C to complete the precipitation. The solid was filtered and washed with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4), and the solvent was evaporated to produce another portion of the product. Crude product **7** (2.71 g, 99%) was used without further purification; mp = 108−9 °C; ^{1}H NMR δ 6.99 (br s, 2H), 4.08 (s, 4H), 3.58−3.51 (m, 4H), 2.75 (t, J = 6.6 Hz, 4H); ^{13}C NMR δ 168.6, 42.9, 39.9, 31.4; MS (CI) *m/z* 273 (M^+); HRMS (CI) calcd for $C_8H_{15}{}^{35}Cl_2N_2O_2S$ (MH^+): 273.0231, found: 273.0235.

General Procedure A: Cyclization of Bis(α-chloroamide)s 6 or 7 with Diamines (Scheme 1). A mixture of 3.89 mmol of **6** or **7**, 3.89 mmol of the appropriate diamine, and 1.5 g of Na_2CO_3 was stirred at reflux in 150 mL of MeCN for 24 h. The mixture was filtered, the solvent evaporated, and 50 mL of $CHCl_3$ added. The mixture was again filtered and evaporated. The crude cyclic diamide product was purified by flash chromatography on silica gel (40:5:1/CH_2Cl_2:MeOH:NH_4OH).

(23) Tadros, W. M.; Shoeb, H. A.; Kira, M. A.; Yousif, F.; Ekladios, E. M.; Ibrahim, S. A. *Ind. J. Chem.* **1975**, *13*, 1366.

1,4-Dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane-6,14-dione (8) (Scheme 1). Macrocyclic diamide **8** was obtained according to general procedure A from 1.00 g (3.9 mmol) of **6** and 0.34 g (3.8 mmol) of *N,N′*-dimethylethylenediamine. Compound **8** (0.86 g, 81%) was isolated after column chromatography and recrystallization in EtOAc as white crystals; mp = 151 °C; ^{1}H NMR δ 7.72 (br s, 2H), 3.58−3.47 (m, 8H), 3.03 (s, 4H), 2.57 (s, 4H), 2.27 (s, 6H); ^{13}C NMR δ 170.8, 69.3, 61.9, 55.6, 42.8, 38.5; MS (FAB) *m/z* 295 (MNa^+); HRMS (FAB) calcd for $C_{12}H_{25}N_4O_3$ (MH^+): 273.1926, found: 273.1927. Anal. Calcd for $C_{12}H_{24}N_4O_3$: C, 52.92; H, 8.88; Found: C, 52.70; H, 8.68.

1,5-Dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecane-7,15-dione (9) (Scheme 1). Macrocyclic diamide **9** was obtained according to general procedure A from 2.57 g (0.01 mol) of **6** and 1.02 g (0.01 mol) of *N,N′*-dimethyl-1,3-propanediamine. Compound **9** (1.86 g, 65%) was isolated after column chromatography and recrystallization in EtOAc as white crystals; mp = 84−5 °C; ^{1}H NMR δ 7.46 (br s, 2H), 3.55−3.44 (m, 8H), 3.02 (s, 4H), 2.44 (t, J = 7.1 Hz, 4H), 2.31 (s, 6H), 1.63 (p, J = 7.1 Hz, 2H); ^{13}C NMR δ 171.1, 69.9, 62.1, 55.1, 43.4, 39.1, 26.2; MS (FAB) *m/z* 287 (MH^+), 309 (MNa^+); HRMS (FAB) calcd for $C_{13}H_{27}N_4O_3$ (MH^+): 287.2083, found: 287.2066. Anal. Calcd for $C_{13}H_{26}N_4O_3$: C, 54.52; H, 9.15; Found: C, 54.74; H, 8.93.

1,4-Dimethyl-1,4,7,13-tetraaza-10-thiacyclopentadecan-6,14-dione (10) (Scheme 1). Macrocyclic diamide **10** was obtained according to general procedure A from 2.72 g (0.01 mol) of **7** and 0.88 g (0.01 mol) of *N,N′*-dimethylethylenediamine. Compound **10** (1.64 g, 57%) was isolated after column chromatography and recrystallization in EtOAc as white crystals; mp = 151−152 °C; ^{1}H NMR δ 7.99 (br s, 2H), 3.49−3.44 (m, 4H), 3.05 (s, 4H), 2.75−2.71 (m, 4H), 2.56 (s, 4H), 2.34 (s, 6H); ^{13}C NMR δ 170.9, 61.9, 61.9, 55.9, 43.5, 36.5, 32.1; MS (FAB) *m/z* 289 (MH^+), 311 (MNa^+); HRMS (FAB) calcd for $C_{12}H_{25}N_4O_2S$ (MH^+): 289.1698, found: 289.1693. Anal. Calcd for $C_{12}H_{24}N_4O_2S$: C, 49.97; H, 8.39; Found: C, 50.17; H, 8.16.

1,5-Dimethyl-1,5,8,14-tetraaza-11-thiacyclohexadecane-6,14-dione (11) (Scheme 1). Macrocyclic diamide **11** was obtained according to general procedure A from 2.72 g (0.01 mol) of **7** and 1.02 g (0.01 mol) of *N,N′*-dimethyl-1,3-propanediamine. Compound **11** (1.84 g, 61%) was isolated after column chromatography and recrystallization in EtOAc as white crystals; mp = 128 °C; ^{1}H NMR δ 7.59 (br s, 2H), 3.52−3.46

(m, 4H), 3.00 (s, 4H), 2.79−2.75 (m, 4H), 2.45 (t, J = 7.1 Hz,, 4H), 2.31 (s, 6H), 1.70 (p, J = 7.1 Hz, 2H); ^{13}C NMR δ 171.0, 62.2, 55.7, 43.2, 37.2, 32.8, 26.2; MS (FAB) m/z 203 (MH^+), 325 (MNa^+); HRMS (FAB) calcd for $C_{13}H_{27}N_4O_2S$ (MH^+): 303.1855, found: 303.1872. Anal. Calcd for $C_{13}H_{26}N_4O_2S$: C, 51.63; H, 8.66; Found: C, 51.74; H, 8.44.

General Procedure B: Lithium Aluminum Hydride Reduction. The macrocyclic diamide was dissolved in dry THF, and the solution was cooled in an ice bath. $LiAlH_4$ was carefully added to the solution. The mixture was refluxed in an oil bath. The reaction was monitored by TLC (40:4:1/CH_2Cl_2:MeOH:NH_4OH). When the reaction was completed, the mixture was cooled in an ice bath, and then water, 15% NaOH solution, and more water were added. The white precipitate was filtered, and the solid was washed with CH_2Cl_2. The combined organic solutions were evaporated to give the crude reduced product which was purified by flash chromatography on silica gel (50−100:5:1/CH_2Cl_2:MeOH:NH_4OH) to give the products as oils.

1,4-Dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (12) (Scheme 1). $LiAlH_4$ (170 mg, 4.4 mmol) was added slowly to a solution of **8** (300 mg, 1.1 mmol) in 6 mL of dry THF at 0 °C. The resulting mixture was refluxing for 10 h and worked up as general procedure B. Macrocyclic diamine **12** (193 mg, 72%) was obtained as an oil; ^{1}H NMR δ 3.46 (dd, J = 4.8, 4.5 Hz, 4H), 2.83 (br s, 2H), 2.63 (dd, J = 4.8, 4.5 Hz, 4H), 2.52−2.49 (m, 4H), 2.39−2.35 (m, 4H), 2.27 (s, 4H), 2.05 (s, 6H); ^{13}C NMR δ 69.5, 57.4, 55.6, 49.4, 46.8, 41.9; MS (FAB) m/z 245 (MH^+), 267 (MNa^+); HRMS (FAB) calcd for $C_{12}H_{29}N_4O$ (MH^+): 245.2341, found: 245.2328.

1,5-Dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecane (13) (Scheme 1). $LiAlH_4$ (260 mg, 6.8 mmol) was added slowly to a solution of **9** (500 mg, 1.7 mmol) in 6 mL of dry THF at 0 °C. The resulting mixture was refluxing for 48 h and worked up as general procedure B. Macrocyclic diamine **7** (333 mg, 76%) was obtained as an oil; ^{1}H NMR δ 3.48 (dd, J = 4.8, 4.5 Hz, 4H), 3.10 (br s, 2H), 2.68 (dd, J = 4.8, 4.5 Hz, 4H), 2.61−2.58 (m, 4H), 2.42−2.39 (m, 4H), 2.28 (t, J = 6.6 Hz, 4H), 2.08 (s, 6H), 1.48 (p, J = 6.6 Hz, 2H); ^{13}C NMR δ 70.0, 57.5, 54.5, 49.2, 46.6, 42.4, 25.8; MS (FAB) m/z 259 (MH^+); HRMS (FAB) calcd for $C_{13}H_{31}N_4O$ (MH^+): 259.2498, found: 259.2489.

1,4-Dimethyl-1,4,7,13-tetraaza-10-thiacyclopentadecane (14) (Scheme 1). $LiAlH_4$ (1.6 g, 4 mol) was added slowly to a solution of **10** (3.0 g, 10 mol) in 90 mL of dry THF at 0 °C. The resulting mixture was refluxing for 24 h and worked up as general procedure B. Macrocyclic diamine **14** (2.24 g, 83%) was obtained as an oil; ^{1}H NMR δ 2.88 (br s, 2H), 2.68−2.67 (m, 8H), 2.64−2.56 (m, 4H), 2.45−2.42 (m, 4H), 2.35 (s, 4H), 2.14 (s, 6H); ^{13}C NMR δ 57.2, 55.7, 48.0, 46.7, 42.7, 33.3; MS (FAB) m/z 261 (MH^+), 283 (MNa^+); HRMS (FAB) calcd for $C_{12}H_{29}N_4S$ (MH^+): 261.2113, found: 261.2100.

1,5-Dimethyl-1,5,8,14-tetraaza-11-thiacyclohexadecane (15) (Scheme 1). $LiAlH_4$ (1.31 g, 34 mmol) was added slowly to a solution of **11** (2.6 g, 8.6 mmol) in 100 mL of dry THF at 0 °C. The resulting mixture was refluxing for 18 h and worked up as general procedure B. Macrocyclic diamine **15** (1.67 g, 71%) was obtained as an oil; ^{1}H NMR δ 2.78−2.74 (m, 4H), 2.70−2.66 (m, 4H), 2.67 (br s, 2H), 2.62−2.59 (m, 4H), 2.42 (m, 4H), 2.34 (t, J = 12.6 Hz, 4H), 2.12 (s, 6H), 1.52 (p, J = 6.9 Hz, 2H); ^{13}C NMR δ 57.1, 54.3, 48.1, 46.3, 42.5, 32.6, 25.1; MS (FAB) m/z 275 (MH^+), 297 (MNa^+); HRMS (FAB) calcd for $C_{13}H_{31}N_4S$ (MH^+): 275.2269, found: 275.2286.

General Procedure C: Reductive Amination of Pyridine- or Quinolinecarboxaldehyde with Tetraazacrown Ethers (Schemes 2 and 3). A mixture of the pyridine- or quinolinecarboxaldehyde and the macrocyclic diamine in $ClCH_2CH_2Cl$ was stirred with 1.3−1.6 equiv of $NaBH(OAc)_3$ under a N_2 atmosphere at room temperature. The reaction was monitored by TLC. When the reaction was completed, 1 N HCl was added to terminate the reaction. Then 1 N NaOH was added to adjust the pH value of the solution to pH 10−12. The solution was then extracted several times by portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH) to give the product.

7,13-Bis(2-pyridinylmethyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (16) (Scheme 2). Compound **16** (185 mg, 87%) was obtained as an oil according to general procedure C from 2-pyridinecarboxaldehyde (110 mg, 1 mmol) and **12** (122 mg, 0.5 mmol); ^{1}H NMR δ 8.49 (d, J = 7.1 Hz, 2H), 7.63 (t, J = 6.8 Hz, 2H), 7.54 (d, J = 7.1 Hz, 2H), 7.13 (t, J = 6.8 Hz, 2H), 3.79 (s, 4H), 3.52 (t, J = 6.1 Hz, 4H), 2.83−2.77 (m, 8H), 2.62−2.56 (m, 8H), 2.22 (s, 6H); ^{13}C NMR δ 160.3, 149.1, 136.5, 123.3, 122.0, 70.5, 61.6, 55.4, 55.2, 54.2, 53.0, 44.5; MS (FAB) m/z 449 (MNa^+); HRMS (FAB) Calcd for $C_{24}H_{39}N_6O$ (MH^+): 427.3185, found: 427.3181.

7,13-Bis(2-quinolinylmethyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (17) (Scheme 2). Compound **17** (216 mg, 82%) was obtained as an oil according to general procedure C from 2-quinolinecarboxaldehyde (157 mg, 1 mmol) and **12** (122 mg, 0.5 mmol); ^{1}H NMR δ 8.03 (d, J = 8.3 Hz, 2H), 7.93 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H), 7.54−7.51 (m, 4H), 7.41−7.36 (m, 2H), 3.84 (s, 4H), 3.40−3.35 (m, 4H), 2.86−2.71 (m, 16H), 2.38 (s, 6H); ^{13}C NMR δ 160.3, 147.5, 136.6, 129.5, 128.8, 127.6, 127.3, 126.2, 121.2, 69.7, 61.7, 54.7, 54.4, 53.2, 51.8, 43.0; MS (FAB) m/z 549 (MNa^+); HRMS (FAB) calcd for $C_{32}H_{43}N_6O$ (MH^+): 527.3498, found: 527.3506. Anal. Calcd for $C_{32}H_{42}N_6O$: C, 72.97; H, 8.04. Found: C, 72.74, H, 8.18.

7,13-Bis((8-acetoxy-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (18) (Scheme 3). Compound **18** (210 mg, 82%) was obtained as an oil according to general procedure C from 8-acetoxyquinoline-2-carboxaldehyde (172 mg, 0.8 mmol) and **12** (98 mg, 0.4 mmol); ^{1}H NMR δ 8.06 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 8.1, 1.5 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 7.4, 8.1 Hz, 2H), 7.35 (dd, J = 7.4, 1.5 Hz, 2H), 3.93 (s, 4H), 3.47 (t, J = 4.2 Hz, 4H), 2.89 (t, J = 6.3 Hz, 4H), 2.78−2.75 (m, 12H), 2.42 (s, 6H), 2.32 (s, 6H); ^{13}C NMR δ 169.8, 160.3, 147.4, 140.3, 136.3, 128.6, 125.8, 125.7, 122.2, 121.3, 70.1, 61.5, 55.0, 54.0, 53.9, 52.1, 43.5, 21.1; MS (FAB) m/z 665 (MNa^+); HRMS (FAB) calcd for $C_{36}H_{47}N_6O_5$ (MH^+): 643.3608, found: 643.3582.

8,14-Bis((8-acetoxy-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecane (19) (Scheme 3). Compound **19** (279 mg, 85%) was obtained as an oil according to general procedure C from 8-acetoxyquinolin-2-carboxaldehyde (215 mg, 1 mmol) and **13** (129 mg, 0.5 mmol); ^{1}H NMR δ 8.09 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.66 (dd, J = 8.3, 1.5 Hz, 2H), 7.46 (dd, J = 7.6, 8.3 Hz, 2H), 7.38 (dd, J = 7.6, 1.5 Hz, 2H), 3.95 (s, 4H), 3.53 (t, J = 4.6 Hz, 4H), 2.89 (t, J = 6.4 Hz, 4H), 2.81 (t, J = 5.1 Hz, 4H), 2.64 (m, 8H), 2.46 (s, 6H), 2.29 (s, 6H), 1.76 (p, J = 6.6 Hz, 2H); ^{13}C NMR δ 169.9, 160.9, 147.4, 140.3, 136.3, 128.7. 125.8, 125.8, 122.1, 121.3, 70.0, 61.5, 55.4, 55.0, 54.1, 52.0, 42.8, 21.1; MS (FAB) m/z 657 (MH^+), 679 (MNa^+); HRMS (FAB) Calcd for $C_{37}H_{49}N_6O_5$ (MH^+): 657.3764, found: 657.3745.

7,13-Bis((8-acetoxy-2-quinolinylmethyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-thiacyclopentadecane (20) (Scheme 3). Compound **20** (336 mg, 88%) was obtained as an oil according to general procedure C from 8-acetoxyquinoline-2-carboxaldehyde (250 mg, 1.2 mmol) and **14** (150 mg, 0.6 mmol); ^{1}H NMR δ 8.10 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.67 (dd, J = 8.1, 1.5 Hz, 2H), 7.46 (dd, J = 7.5, 8.1 Hz, 2H), 7.40 (dd, J = 7.5, 1.5 Hz, 2H), 3.95 (s, 4H), 2.92−2.87 (m, 4H), 2.77−2.70 (m, 8H), 2.63−2.58 (m, 8H), 2.48 (s, 6H), 2.21 (s, 6H); ^{13}C NMR δ 169.9, 160.7, 147.4, 140.4, 136.3, 128.7, 125.8, 125.7, 122.0, 121.3, 61.8, 55.9, 55.7, 54.9, 51.9, 43.5, 29.6, 21.1; MS (FAB) m/z 681 (MNa^+); HRMS (FAB) calcd for $C_{36}H_{47}N_6O_4S$ (MH^+): 659.3379, found: 659.3382.

8,14-Bis((8-acetoxy-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-thiacyclopentadecane (21) (Scheme 3). Compound **21** (269 mg, 80%) was obtained as an oil according to general procedure C from 8-acetoxyquinoline-2-carboxaldehyde (215 mg, 1 mmol) and **15** (137 mg, 0.5 mmol); ^{1}H NMR δ 8.10 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.67 (dd, J = 8.1, 1.5 Hz, 2H), 7.47 (dd, J = 7.5, 8.1 Hz, 2H), 7.39 (dd, J = 7.5, 1.5 Hz, 2H), 3.95 (s, 4H), 2.90−2.85 (m, 4H), 2.74−2.71 (m, 8H), 2.57−2.46 (m, 14H), 2.18 (s, 6H), 1.68 (p,

J = 6.6 Hz, 2H); ^{13}C NMR δ 169.9, 160.9, 147.4, 140.4, 136.3, 128.7, 125.7, 121.9, 121.3, 61.7, 55.6, 55.4, 54.8, 52.0, 43.3, 29.9, 25.3, 21.1; MS (FAB) m/z 673 (MH^+), 695 (MNa^+); HRMS (FAB) calcd for $C_{37}H_{49}N_6O_4S$ (MH^+): 673.3536, found: 673.3542.

General Procedure D: Removal of Acetate Groups on Macrocyclic Compounds 18−21. A solution of the 8-acetoxy-2-quinolinylmethyl-substituted macrocyclic compound in MeOH was cooled to 0 °C and stirred vigorously while 10% aqueous KOH was slowly added. The mixture was stirred at room temperature for 30 min and neutralized with 3 N HCl to pH 8. The solution was then extracted several times by portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product. The crude product was purified by flash chromatography on silical gel (70−100:5:1/CH_2Cl_2:MeOH:NH_4OH) to give the product.

7,13-Bis((8-hydroxy-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (22) (Scheme 3). Compound **22** (154 mg, 92%) was obtained as an oil according to general procedure D from **18** (193 mg, 0.3 mmol); ^{1}H NMR (CD_3OD) δ 8.20 (d, J = 12.0 Hz, 2H), 7.41−7.35 (m, 6H), 7.24−7.19 (m, 2H), 4.08 (s, 4H), 3.73 (s, 4H), 3.91 (t, J = 8.6 Hz, 4H), 3.08 (t, J = 8.6 Hz, 4H), 2.88 (s, 6H), 2.67 (s, 8H); ^{13}C NMR (CD_3OD) δ 159.3, 153.2, 139.4, 139.2, 130.5, 128.5, 122.2, 120.3, 113.8, 68.0, 59.4, 58.3, 56.8, 52.6, 51.0, 42.9; MS (FAB) m/z 582 (MNa^+), 604 ($M + Na^+ - H^+$), 626 ($M + 2Na^+ - 2H^+$); HRMS (FAB) calcd for $C_{32}H_{43}N_6O_3$ (MH^+): 559.3396, found: 559.3377. Anal. Calcd for $C_{32}H_{42}N_6O_3 \cdot 6HCl \cdot 2.5H_2O$: C, 46.73; H, 6.49. Found: C, 46.82; H, 6.45.

8,14-Bis((8-hydroxy-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecane (23) (Scheme 3). Compound **23** (376 mg, 94%) was obtained as an oil according to general procedure D from **19** (460 mg, 0.7 mmol); ^{1}H NMR δ 8.06 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.36 (dd, J = 7.8, 7.3 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 7.3 Hz, 2H), 3.92 (s, 4H), 3.55 (t, J = 5.1 Hz, 4H), 2.87−2.81 (m, 8H), 2.60 (t, J = 6.9 Hz, 4H), 2.49 (t, J = 6.9 Hz, 4H), 2.20 (s, 6H), 1.65 (p, J = 6.9 Hz, 2H); ^{13}C NMR δ 158.7, 152.4, 137.7, 136.4, 127.7, 127.2, 122.1, 117.6, 110.2, 69.9, 61.7, 55.9, 55.3, 54.4, 53.0, 43.5, 25.0; MS (FAB) m/z 595 (MNa^+), 617 ($M + Na^+ - H^+$) 639 ($M + 2Na^+ - 2H^+$); HRMS (FAB) calcd for $C_{33}H_{45}N_6O_3$ (MH^+): 573.3553, found: 573.3568. Anal. Calcd for $C_{33}H_{44}N_6O \cdot 6HCl \cdot 2.5H_2O$: C, 47.38; H, 6.63. Found: C, 47.12; H, 6.55.

7,13-Bis((8-hydroxy-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-thiacyclopentadecane (24) (Scheme 3). Compound **24** (258 mg, 90%) was obtained as an oil according to general procedure D from **20** (320 mg, 0.5 mmol); ^{1}H NMR δ 8.08 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.41 (dd, J = 7.6, 8.1 Hz, 2H), 7.29 (dd, J = 1.2, 8.3 Hz, 2H), 7.15 (dd, J = 1.2, 7.6 Hz, 2H), 3.93 (s, 4H), 2.91−2.86 (m, 4H), 2.75−2.70 (m, 8H), 2.60−2.55 (m, 8H), 2.18 (s, 6H); ^{13}C NMR δ 158.4, 152.4, 137.6, 136.5, 127.7, 127.4, 122.0, 117.7, 110.3, 61.8, 56.1, 55.9, 55.2, 52.5, 43.3, 29.5; MS (FAB) m/z 597 (MNa^+), 619 ($M + 2Na^+ - H^+$), 641 ($M + 3Na^+ - H^+$); HRMS (FAB) calcd for $C_{32}H_{43}N_6O_2S$ (MH^+): 575.3168, found: 575.3151.

8,14-Bis((8-hydroxy-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-thiacyclohexadecane (25) (Scheme 3). Compound **25** (327 mg, 89%) was obtained as an oil according to general procedure D from **21** (420 mg, 0.6 mmol); ^{1}H NMR δ 8.08 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.15 (d, J = 7.5 Hz, 2H), 3.94 (s, 4H), 2.87−2.84 (m, 4H), 2.74−2.67 (m, 8H), 2.54 (t, J = 6.6 Hz, 4H), 2.47 (t, J = 6.9 Hz, 4H), 2.17 (s, 6H), 1.68 (p, J = 6.9 Hz, 2H); ^{13}C NMR δ 158.5, 152.3, 137.6, 136.5, 127.7, 127.3, 122.1, 117.8, 110.2, 61.6, 55.7, 55.4, 54.9, 52.3, 43.4, 29.8, 25.4; MS (FAB) m/z 589 (MH^+), 611 ($M + Na^+ - H^+$), 633 ($M + 2Na^+ - 2H^+$); HRMS (FAB) calcd for $C_{33}H_{45}N_6O_2S$ (MH^+): 589.3324, found: 589.3340. Anal. Calcd for $C_{33}H_{44}N_6O_2S \cdot 2HCl \cdot H_2O$: C, 58.31; H, 7.12, N, 12.36. Found: C, 58.39; H, 7.08, N, 12.53.

***N,N′*-Bis((8-hydroxy-2-quinolinyl)methyl)-3-oxa-1,5-pentanediamine (26)** (Scheme 4). To a solution of 8-hydroxyquinoline-2-carbaldehyde (173 mg, 1 mmol) in MeOH (10 mL) was added a solution of oxybis(ethyldiamine) (52 mg, 0.5 mmol) in MeOH. The reaction mixture was warmed in a water bath for 1 h. The solution was then concentrated to 5 mL and cooled in an ice bath. A solution of $NaBH_4$ in MeOH was added to the reaction mixture at room temperature. The reaction mixture was stirred for 1 h, filtered, and MeOH was removed under reduced pressure. The yellow powder obtained was dissolved in 30% aqueous HOAc and neutralized with aqueous Na_2CO_3. The solution was extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated to give the crude product. The crude product was purified by flash chromatography to give the product (167 mg, 80%) as a yellow oil; ^{1}H NMR δ 7.93 (d, J = 8.5 Hz, 2H), 7.34 (dd, J = 8.0, 7.8 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.20 (dd, J = 8.0, 1.2 Hz, 2H), 7.10 (dd, J = 7.8, 1.2 Hz, 2H), 6.10 (br s, 4H), 4.11, (s, 4H), 3.67 (t, J = 5.0 Hz, 4H), 2.93 (t, J = 5.0 Hz, 4H); ^{13}C NMR δ 157.6, 152.7, 137.8, 136.4, 127.6, 127.2, 121.0, 117.6, 110.7, 70.2, 54.6, 48.6; MS (FAB) m/z 419 (MH^+); HRMS (FAB) calcd for $C_{24}H_{27}N_4O_3$ (MH^+): 419.2083, found: 419.2077.

7,13-Bis((8-hydroxy-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (22) (Scheme 4). Compound **28** was prepared according to procedure A from 0.65 (1.55 mmol) of **26**, 0.37 g (1.55 mmol) of **27** (prepared as above for **6** from *N,N′*-dimethylethylenediamine), 1.25 g of Et_3N (instead of Na_2CO_3), and 50 mL of MeCN. Macrocyclic diamide **28** was not purified. Crude **28** was reduced according to procedure B with $LiAlH_4$ to give 230 mg (27% overall) of **22** which exhibited the same physical and spectral properties as **22** prepared above (Scheme 3).

7,13-Bis((8-nitro-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (29) (Scheme 5). Compound **29** (169 mg, 55%) was obtained as an oil according to general procedure C from **12** (122 mg, 0.5 mmol) and 8-nitroquinoline-2-carboxaldehyde (274 mg, 1.4 mmol); ^{1}H NMR δ 8.20 (d, J = 8.7 Hz, 2H), 7.99 (dd, J = 8.3, 1.2 Hz, 2H), 7.96 (dd, J = 7.6, 1.2 Hz, 2H), 7.89 (d, J = 8.7 Hz, 2H), 7.55 (dd, J = 7.6, 8.3 Hz, 2H), 4.00 (s, 4H), 3.51 (t, J = 4.8 Hz, 4H), 2.91 (t, J = 6.6 Hz, 4H), 2.82 (t, J = 4.8 Hz, 4H), 2.71−2.66 (m, 8H), 2.28 (s, 6H); ^{13}C NMR δ 164.1, 148.3, 138.9, 136.2, 131.7, 128.3, 124.8, 123.3, 123.2, 70.2, 61.7, 55.3, 54.9, 54.5, 52.9, 44.2; MS (FAB) m/z 639 (MNa^+); HRMS (FAB) calcd for $C_{32}H_{41}N_8O_5$ (MH^+): 617.3199, found: 617.3211.

8,14-Bis((8-nitro-2-quinolinylmethyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecane (30) (Scheme 5). Compound **30** (164 mg, 52%) was obtained as an oil according to general procedure C from **13** (129 mg, 0.5 mmol) and 8-nitroquinoline-2-carboxaldehyde (274 mg, 1.4 mmol); ^{1}H NMR δ 8.19 (d, J = 8.6 Hz, 2H), 7.99 (dd, J = 8.3, 1.2 Hz, 2H), 7.96 (dd, J = 7.6, 1.2 Hz, 2H), 7.89 (d, J = 8.6 Hz, 2H), 7.55 (dd, J = 7.6, 8.3 Hz, 2H), 3.99 (s, 4H), 3.53 (t, J = 4.9 Hz, 4H), 2.90−2.78 (m, 8H), 2.60 (t, J = 6.6 Hz, 4H), 2.53 (t, J = 6.8 Hz, 4H), 2.23 (s, 6H), 1.69 (p, J = 6.6 Hz, 2H); ^{13}C NMR δ 164.3, 148.3, 138.9, 136.2, 131.7, 128.3, 124.7, 123.3, 123.2, 69.9, 61.6, 55.9, 55.1, 54.4, 52.7, 43.3, 24.9; MS (FAB) m/z 631 (MH^+), 653 (MNa^+); HRMS (FAB) calcd for $C_{33}H_{43}N_8O_5$ (MH^+): 631.3356, found: 631.3353.

7,13-Bis((8-nitro-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-thiacyclopentadecane (31) (Scheme 5). Compound **31** (200 mg, 63%) was obtained as an oil according to general procedure C from **14** (130 mg, 0.5 mmol) and 8-nitroquinoline-2-carboxaldehyde (274 mg, 1.4 mmol); ^{1}H NMR δ 8.18 (d, J = 8.7 Hz, 2H), 7.97 (dd, J = 8.1, 1.5 Hz, 2H), 7.94 (dd, J = 7.8, 1.5 Hz, 2H), 7.84 (d, J = 8.7 Hz, 2H), 7.53 (dd, J = 7.8, 8.1 Hz, 2H), 3.97 (s, 4H), 2.89−2.79 (m, 4H), 2.76−2.68 (m, 8H), 2.64−2.58 (m, 8H), 2.22 (s, 6H); ^{13}C NMR δ 163.8, 148.3, 138.9, 136.2, 131.6, 128.3, 124.8, 123.3, 123.0, 61.6, 55.8, 55.6, 54.9, 51.9, 43.5, 29.7; MS (FAB) m/z 633 (MH^+), 655 (MNa^+); HRMS (FAB) calcd for $C_{32}H_{40}N_8O_4Na$ (MNa^+): 655.2791, found 655.2797.

8,14-Bis((8-nitro-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-thiacyclohexadecane (32) (Scheme 5). Compound **32** (165 mg, 51%) was obtained as an oil according to general procedure C from **15** (137 mg, 0.5 mmol) and 8-nitroquinoline-2-carboxaldehyde (274 mg, 1.4 mmol); ^{1}H NMR δ 8.19 (d, J = 8.6 Hz, 2H), 7.99 (dd, J = 8.3, 1.2 Hz, 2H), 7.96 (dd, J = 8.3, 1.2 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H), 7.55 (dd, J = 7.8, 8.2 Hz, 2H), 3.99 (s, 4H), 2.90−2.85 (m, 4H),

2.78−2.68 (m, 8H), 2.56 (t, J = 6.6 Hz, 4H), 2.49 (t, J = 7.0 Hz, 4H), 2.19 (s, 6H), 1.69 (p, J = 7.0 Hz, 2H); ^{13}C NMR δ 164.0, 148.3, 138.9, 136.2, 131.7, 128.3, 124.8, 123.4, 123.0, 61.5, 55.6, 55.4, 54.9, 52.1, 43.4, 30.0, 25.3; MS (FAB) m/z 647 (MH^+), 669 (MNa^+); HRMS (FAB) calcd for $C_{33}H_{43}N_8O_4S$ (MH^+): 647.3128, found: 647.3122.

General Procedure E: Catalytic Hydrogenation of Nitroquinoline-Substituted Macrocycles. To a solution of 8-nitro-2-quinolinylmethyl-substituted macrocycle in 100 mL of MeOH in a 500 mL pressure vessel was added 0.3 g of PtO_2 (Adam's catalyst). The head and fittings were attached, and the vessel was connected to a H_2 cylinder. The system was alternately evacuated and pressurized with H_2 to 40−50 psi three times. After a final evacuation, H_2 was introduced into the vessel until the pressure reached 100 psi. The reaction was allowed to proceed overnight. The vessel was vented, the catalyst was removed by filtration, and the reaction mixture was washed with MeOH. The filtrates were combined, and the solvent was removed under reduced pressure to give a yellow oil. The product was purified by chromatography on silica gel (40:5:1/CH_2Cl_2:MeOH:NH_4OH).

7,13-Bis((8-amino-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (33) (Scheme 5). Compound **33** (130 mg, 88%) was obtained as an oil according to general procedure E from **29** (160 mg, 0.26 mmol); ^{1}H NMR δ 8.00 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.26 (dd, J = 8.3, 7.6 Hz, 2H), 7.12 (dd, J = 8.3, 1.2 Hz, 2H), 6.91 (dd, J = 7.6, 1.2 Hz, 2H), 5.00 (br s, 4H), 3.95 (s, 4H), 3.53 (t, J = 4.6 Hz, 4H), 2.93 (t, J = 6.4 Hz, 4H), 2.70 (m, 12H), 2.31 (s, 6H); ^{13}C NMR δ 143.9, 137.7, 136.4, 127.9, 127.0, 121.8, 116.0, 110.3, 70.4, 62.0, 55.4, 54.7, 54.2, 52.7, 44.1; MS (FAB) m/z 579 (MNa^+); HRMS (FAB) Calcd for $C_{32}H_{45}N_8O$ (MH^+): 557.3716, found: 557.3715. Anal. calcd for $C_{32}H_{44}N_8O\cdot 1HCl\cdot 1.5H_2O$: C, 61.97; H, 7.80. Found: C, 62.09; H, 7.45.

8,14-Bis((8-amino-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecane (34) (Scheme 5). Compound **34** (106 mg, 81%) was obtained as an oil according to general procedure E from **30** (145 mg, 0.23 mmol); ^{1}H NMR δ 7.99 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.28 (dd, J = 8.1, 7.6 Hz, 2H), 7.11 (d, J = 8.1, Hz, 2H), 6.90 (d, J = 7.6 Hz, 2H), 4.97 (s, 4H), 3.95 (s, 4H), 3.56 (t, J = 5.1 Hz, 4H), 2.89−2.82 (m, 8H), 2.60 (t, J = 6.8 Hz, 4H), 2.49 (t, J = 6.8 Hz, 4H), 2.21 (s, 6H), 1.65 (p, J = 6.6 H, 2H); ^{13}C NMR δ 158.1, 143.8, 137.6, 136.3, 127.9, 126.9, 121.7, 116.0, 110.2, 70.2, 62.0, 56.1, 55.4, 54.1, 52.9, 43.5, 25.3; MS (FAB) m/z 571 (MH^+), 593 (MNa^+); HRMS (FAB) Calcd for $C_{33}H_{47}N_8O$ (MH^+): 571.3873, found: 571.3857. Anal. calcd for $C_{33}H_{46}N_8O$: C, 69.44; H, 8.12. Found: C, 69.26; H, 7.94.

General Procedure F: Reduction of Nitroquinoline-substututed Macrocycles by Reduced Iron and Hydrochloric Acid. A mixture of 8-nitro-2-quinolinylmethyl-substituted macrocycle, reduced Fe (400 mg), 5 mL of 95% EtOH, 1 mL of water, and 0.1 mL of concentrated HCl was refluxed for 1 h. The Fe was removed by filtration and washed with portions of hot 95% EtOH. The filtrate and washings were evaporated. The residue was dissolved in CH_2Cl_2 and washed with aqueous Na_2CO_3. The organic layer was separated and dried (Na_2SO_4). The crude product was purified by chromatography on silica gel (40:5:1/CH_2Cl_2:MeOH:NH_4OH).

7,13-Bis((8-amino-2-quinolinylmethyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-thiacyclohexadecane (35) (Scheme 5). Compound **35** (43 mg, 36%) was obtained as an oil according to general procedure F from **31** (130 mg, 0.21 mmol); ^{1}H NMR δ 8.00 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.30 (dd, J = 8.3, 7.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.92 (d, 7.3 Hz, 2H), 4.97 (br s, 4H), 3.94 (s, 4H), 2.93−2.88 (m, 4H), 2.78−2.70 m, 8H), 2.63−2.56 (m, 8H), 2.21 (s, 6H); ^{13}C NMR δ 157.7, 143.9, 137.7, 136.4, 128.0, 127.0, 121.6, 116.1, 110.3, 62.1, 56.0, 55.0, 52.3, 43.6, 29.4; MS (FAB) m/z 595 (MNa^+); HRMS (FAB) calcd for $C_{32}H_{44}N_8SNa$ (MNa^+): 595.3307, found: 595.3310. Anal. Calcd for $C_{32}H_{44}N_8S\cdot 1.5\ HCl\cdot 0.5H_2O$: C, 60.38; H, 7.36. Found: C, 60.69; H, 7.10.

8,14-Bis((8-amino-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-thiacyclohexadecane (36) (Scheme 5). Compound **36** (41 mg, 33%) was obtained as an oil according to general procedure F from **32** (135 mg, 0.21 mmol); ^{1}H NMR δ 8.00 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.28 (dd, J = 8.3, 7.3 Hz, 2H), 7.12 (dd, J = 8.3, 1.0 Hz, 2H), 6.90 (dd, J = 7.3, 1.0 Hz, 2H), 4.96 (br s, 4H), 3.94 (s, 4H), 2.90−2.85 (m, 4H), 2.75−2.68 (m, 8H), 2.54 (t, J = 7.1 Hz, 4H), 2.46 (t, J = 7.1 Hz, 4H), 2.18 (s, 6H), 1.67 (p, J = 6.8 Hz, 2H); ^{13}C NMR δ 157.7, 143.9, 137.6, 136.4, 128.0,127.0, 121.6, 116.1, 110.3, 61.9, 55.7, 55.4, 54.9, 52.3, 43.5, 29.7, 25.5; MS (FAB) m/z 587 (MH^+), 609 (MNa^+); HRMS (FAB) calcd for $C_{33}H_{47}N_8S$ (MH^+): 587.3644, found: 587.3638. Anal. Calcd for $C_{33}H_{46}N_8S\cdot 2HCl$: C, 60.08; H, 7.23. Found: C, 60.09; H, 6.86.

Determination of Protonation and Stability Constants. The protonation and stability constants were determined by potentiometric titration in aqueous solution at 25 °C. The titrations were carried out at a constant ionic strength of 0.10 M Me_4NCl using an automatic microprocessor-controlled potentiometric titrator.[24] Temperature was controlled within ± 0.1 °C using a jacketed cell through which water from a constant-temperature bath was circulated. Potentials to within ± 0.1 mV were measured using an Orion Model 701A Digital Ion Analyzer in conjunction with a Cole-Parmer combination electrode (Ag/AgCl reference cell). The electrode was calibrated by two precision buffer solutions, pH 4.000 ± 0.002 and 7.000 ± 0.002 at 25.0 °C (Cole-Parmer). Calculations were performed with the SUPERQUAD program[25] using an IBM computer. Compound **22** was used as its adduct with HCl (**22**·6HCl) which had good solubility in aqueous solution (0.01 M).

UV−Visible Spectral Measurements. UV−visible spectra were recorded at 23 ± 1 °C in a 1-cm quartz cell using a Hewlett-Packard 8452A Diode Array spectophotmeter. Both ligand and metal ions were prepared in aqueous acetic acid buffer (pH = 4.7). Concentrations of acetic acid and sodium acetate were 5.00×10^{-2} M and 5.00×10^{-2} *M*, respectively, and concentration of ligand **22** was 1.00×10^{-5} M. The metal ion concentrations were 1−5 times the ligand concentration.

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Supporting Information Available: NMR spectra for **6**, **7**, **12**−**15**, **16**, **18**−**21**, **24**, **26**, and **29**−**32**, discussion and figures for the X-ray crystal structures of **9** and **10**, and tables listing crystal data and structure determination information, positional and thermal parameters for all atoms, anisotropic thermal parameters for non-hydrogen atoms, and bond distances and angles for **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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