Synthesis of Proton-Ionizable *p*-Nitrophenol-Containing Tetraazacrown and Diazadithiacrown Ethers from an Aromatic Building Block Prepared via the Einhorn Reaction

Kejiang Hu, Jerald S. Bradshaw,*,† Victor N. Pastushok,‡ Krzysztof E. Krakowiak,§ N. Kent Dalley, Xian Xin Zhang, and Reed M. Izatt

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602

Received March 4, 1998

A series of *p*-nitroanisole-containing tetraazacrown (**14**−**18**), diazacryptand (**22**), and diazadithiacrown (**23**−**25**) macrocycles has been prepared by treating the appropriate secondary diamine, diazacrown, or dimercaptan with 2,6-bis[(2-chloroacetamido)methyl]-4-nitroanisole (**BB**). Five of these *p*-nitroanisole-containing macrocycles were reported earlier. Four new bis(*p*-nitroanisole)-containing macrocycles resulting from a 2 + 2 macrocyclization of diamine or dimercaptan with **BB** were also isolated. Six of the *p*-nitroanisole-containing macrocycles (**16**, **17**, **22**−**25**) were converted to the *p*-nitrophenol-containing macrocycles (**27**−**32**) on treatment with LiI in refluxing pyridine. Thermodynamic quantities (log *K*, ΔH, and $T\Delta S$) for the interactions of four new compounds (**24**, **27**, **31**, and **32**) with Na^+, K^+, Ba^{2+}, Ag^+, and Pb^{2+} were evaluated by calorimetric titration at 25.0 °C in either 70% or absolute methanol solution. The compounds show strong interactions with Ag^+ and Pb^{2+} but very weak interactions with Na^+, K^+, and Ba^{2+}. Ligand **31** exhibited high selectivity for Ag^+ over Pb^{2+}. X-ray crystal structures were obtained for diazadithia macrocycle **23** and the Ag^+−**31** complex.

Introduction

Macrocyclic ligands containing proton-ionizable functions are of interest for many reasons. Proton-ionizable groups on ligands alleviate the need for a counteranion in metal ion transport through liquid membranes or in solvent extraction. Often the cation−crown complex stability is increased when the crown ether ligand is ionized.[1] Thus, formation of a macrocycle−cation complex is favored by basic conditions and dissociation of the complex is promoted by acidic conditions. The UV and fluorescence spectra can be different for the deprotonated forms of certain proton-ionizable ligands, and this property has been used for spectrophotometric determinations of metal ion concentrations.[2−4]

The proton-ionizable crown ethers can be classified as those containing the proton-ionizable group on side arms such as **1**−**6** (Figure 1) and as those containing the proton-ionizable group as part of the macroring such as **7**−**13**. Crown ethers containing attached proton-ionizable groups have been described in a review.[5] In general, these types of crown ethers were prepared to improve solvent extraction and transport of metal ions through liquid membranes.[1,6] Ligand **4** was prepared from the appropriate *o*-methoxyphenoxymethyl-substituted ethylene glycol[7] and **5** from a tartaric acid derivative.[8] The phenol-substituted azacrown ethers were usually prepared by treating the unsubstituted azacrown with the appropriate hydroxy-substituted benzyl halide.[9,10] A modified Mannich aminomethylation reaction has been developed to attach certain hydroxyaromatic compounds to the azacrown ethers.[11] 5-Chloro-8-hydroxyquinolin-7-ylmethyl-substituted **2** was prepared using the Mannich reaction by treating *N*,*N*′-bis(methoxymethyl)diaza-18-crown-6 with 5-chloro-8-hydroxyquinoline.[12] 5-Chloro-8-hydroxyquinolin-2-ylmethyl-substituted ligand **3** was prepared by treating diaza-18-crown-6 with 2-(bromomethyl)-5-chloro-8-methoxyquinoline followed by LiCl to convert the methoxy group to a hydroxy group.[12] It is most interesting to note that **2** and **3** have very different affinities for metal cations.[12,13] Ligand **2** with the 8-hydroxyquinoline substituted through its position 7 formed very stable complexes with Mg^{2+}, Ca^{2+}, Cu^{2+}, and Ni^{2+} but not with the alkali metal ions. Ligand **3** with the 8-hydroxyquinoline substituted through its position 2 formed very strong complexes with Ba^{2+} and K^+ (log *K* = 12.2 and 6.61, respectively), but not with Mg^{2+} or Cu^{2+}.

† Fax: 801-378-5474. E-mail: jerald_bradshaw@byu.edu.

‡ Present address: Physico-Chemical Institute of the National Academy of Sciences of Ukraine, 86 Chernomorskaya Doroga 270080, Odessa, Ukraine.

§ Present address: IBC Advanced Technologies, Inc., P.O. Box 98, American Fork, UT 84003.

(1) Bartsch, R. A.; Charewicz, W. A.; Kang, S. I.; Walkowiak, W. *ACS Symp. Ser.* **1987**, *347*, 86.

(2) Sakai, Y.; Kawano, N.; Nakamura, H.; Takagi, M. *Talanta* **1986**, *33*, 407.

(3) Nishida, H.; Tazaki, M.; Takagi, M.; Ueno, K. *Mikrochim. Acta* **1981**, *1*, 281.

(4) Nishida, H.; Katayama, Y.; Katsui, H.; Nakamura, H.; Takagi, M.; Ueno, K. *Chem. Lett.* **1982**, 1853.

(5) McDaniel, C. W.; Bradshaw, J. S.; Izatt, R. M. *Heterocycles* **1990**, *30*, 665.

(6) Bartsch, R. A.; Czech, B. P.; Kang, S. I.; Steward, L. E.; Walkowiak, W.; Charewicz, W. A.; Heo, G. S.; Son, B. *J. Am. Chem. Soc.* **1985**, *107*, 4997.

(7) Nakamura, H.; Nishida, H.; Takagi, M.; Ueno, K. *Anal. Chim. Acta* **1982**, *139*, 219.

(8) Frederic, L. A.; Fyles, T. M.; Gurprasad, N. P.; Whitfield, D. M. *Can. J. Chem.* **1981**, *59*, 1724.

(9) Gatto, V. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 8240.

(10) Czech, A.; Czech, B. P.; Bartsch, R. A.; Chang, C. A.; Ochaya, V. O. *J. Org. Chem.* **1988**, *53*, 5.

(11) For a review, see: Bordunov, A. V.; Bradshaw, J. S.; Pastushok, V. N.; Izatt, R. M. *SynLett.* **1996**, 933.

(12) Bordunov, A. V.; Bradshaw, J. S.; Zhang, X. X.; Dalley, N. K.; Kou, X.-L.; Izatt, R. M. *Inorg. Chem.* **1996**, *35*, 7229.

(13) Zhang, X. X.; Bordunov, A. V.; Bradshaw, J. S.; Dalley, N. K.; Kou, X.-L.; Izatt R. M. *J. Am. Chem. Soc.* **1995**, *117*, 11507.

S0022-3263(98)00414-9 CCC: $15.00
Published on Web 06/24/1998

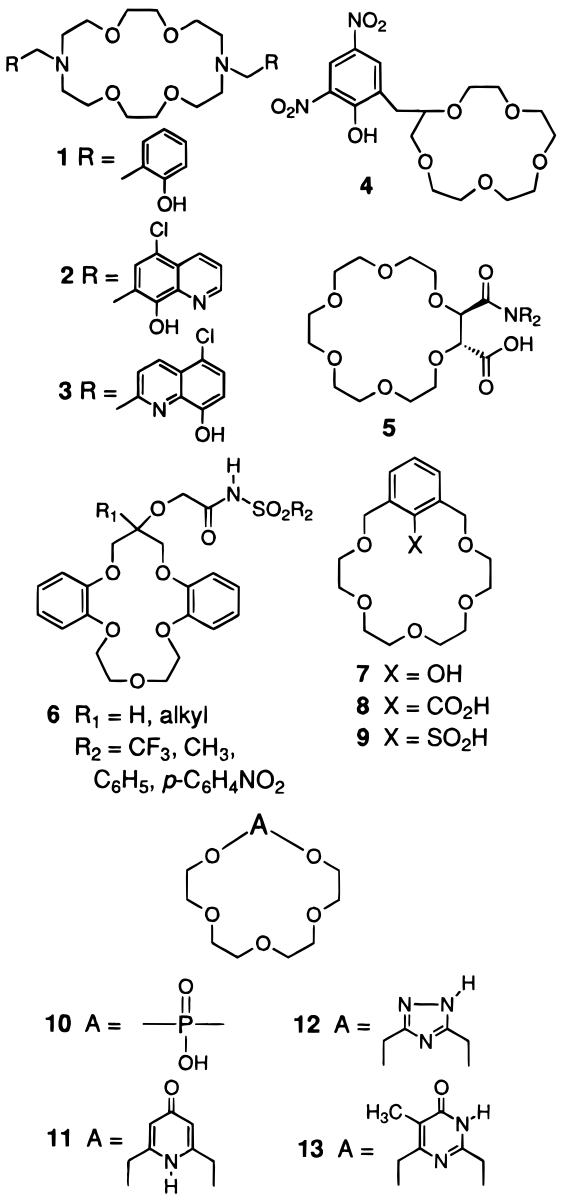


Figure 1. Proton-ionizable macrocycles.

^{1}H NMR and X-ray crystallography studies show that 2-quinolinyl-substituted **3** forms a cryptate-like structure when complexed with Ba^{2+}. Thus, the position of attachment of the proton-ionizable side arm has a profound effect on cation complexation.

Ligand **6**, containing a mixed carboxylic sulfonic imide group, has recently been developed as a ligand with a tuneable proton-ionizable group.[14] The ligand with $R_2 = CF_3$ is about 1000 times more acidic than a carboxylic acid in the same medium. The acidity is greatly decreased when $R_2 = CH_3$ or phenyl.

Macrocylic polyethers containing intraannular hydroxy, carboxylic, and sulfinic acid groups have been known for some time.[15−18] The proton-ionizable phosphate crowns (**10**)[19] and those containing the 4-pyridone (**11**),[20,21] triazole (**12**),[22,23] and pyrimidone (**13**)[24] subcyclic groups were prepared in our laboratory. Only a few benzopolyazacrown ethers containing intraannular hydroxy groups have been reported.[10,25−27] Treatment of *p*-chlorophenol with a bis secondary amine and formaldehyde gave the *N*,*N*′-bis(5-chloro-2-hydroxybenzyl)-diamine. This bis-phenol was then treated with the bis secondary amine and formaldehyde at a higher temperature to give the bis phenol-containing tetraazacrown ethers.[27]

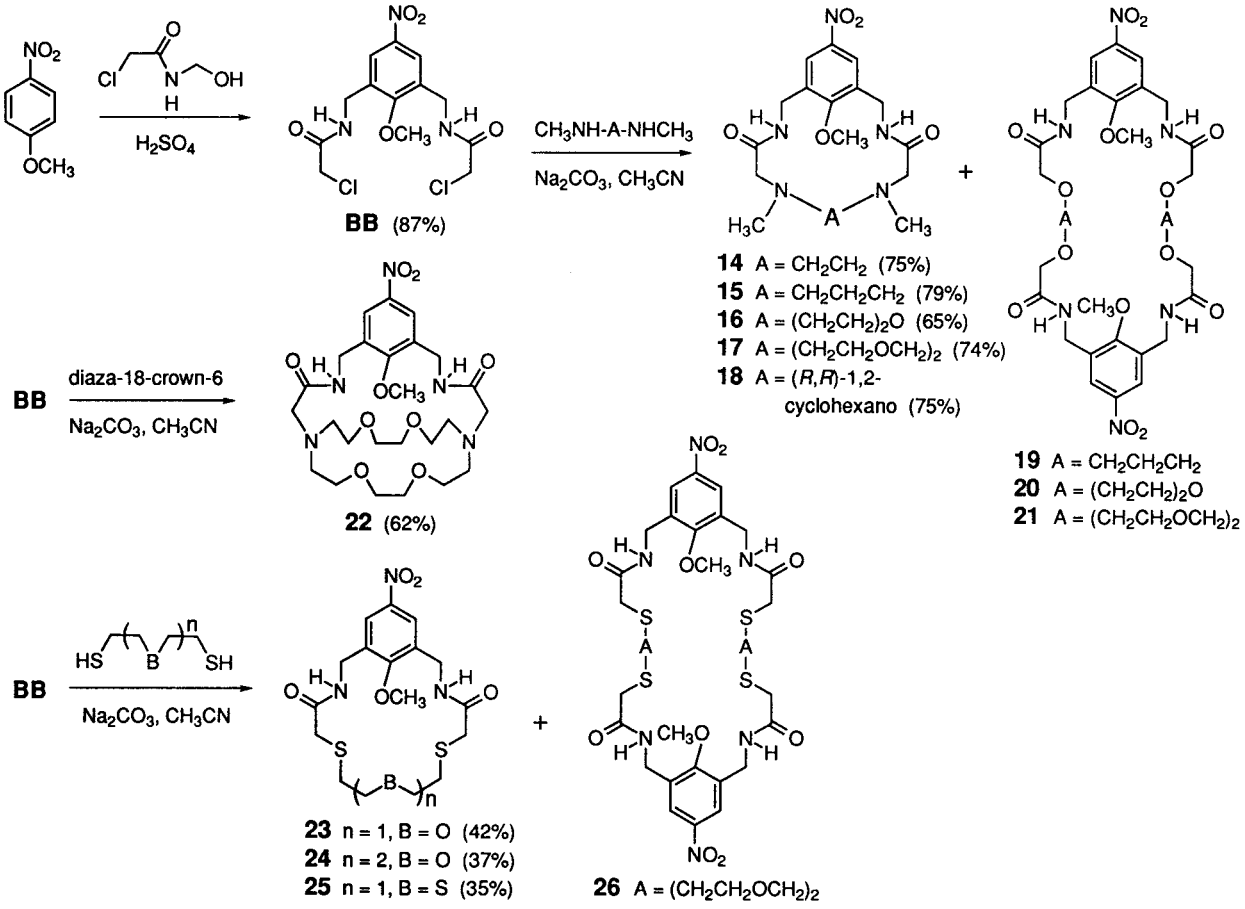
We recently reported the synthesis of four new tetraazacrown ethers (**14**−**17**) and a diazacryptand (**22**) each containing a *p*-nitroanisole group using the Einhorn reaction to prepare the *p*-nitroanisole building block (**BB**) (Scheme 1).[28] Herein, we report the synthesis of new *p*-nitroanisole-containing chiral tetraaza-15-crown-5 (*R*,*R*-**18**) and diazadi- and diazatrithia macrocyles **23**−**25** (Scheme 1). Four new 2 + 2 macrocyclization products (**19**−**21** and **26**) were also isolated from the reaction of **BB** with three of the secondary diamines and a dimercaptan. Six of the *p*-nitroanisole-containing macrocyles were converted to the *p*-nitrophenol-containing macrocycles **27**−**32**. Four of the new macrocyles exhibited excellent affinity for Ag^+. X-ray structures were obtained for sulfur-containing **23** and the $AgNO_3$ complex of **31**.

Results and Discussion

The use of the bis(α-chloroacetamide)s for the synthesis of the polyazacrown ethers has been reported.[29] Preparation of the bis(α-chloroacetamide)s was carried out by acylation of the appropriate diamines with chloroacetyl chloride. They were then treated with appropriate diamines followed by reduction of the two amide functions to form the azamacrocycles. We recently reported the synthesis of *p*-nitroanisole-containing bis(α-chloroacetamide) **BB** (Scheme 1) and its use to prepare some *p*-nitroanisole-containing tetraaza crown ethers **14**−**17** and cryptand **22**.[28] New *p*-nitroanisole-containing macrocycles **18** and **23**−**25** were prepared by treating **BB** with the appropriate diamines or dithiols and sodium carbonate in refluxing acetonitrile (Scheme 1). Starting

(14) Huber, V. J.; Ivy, S. N.; Lu, J.; Bartsch, R. A. *J. Chem. Soc., Chem. Commun.* **1997**, 1499.
(15) Browne, C. M.; Ferguson, G.; Mckervey, M. A.; Mulholland, D. L.; O′Connor, T.; Parvez, M. *J. Am. Chem. Soc.* **1985**, *107*, 2703.
(16) Chapoteau, E.; Czech, B. P.; Kumar, A.; Pose, A.; Bartsch, R. A.; Holwerda, R. A.; Dalley, N. K.; Wilson, B. E.; Weining, J. *J. Org. Chem.* **1989**, *54*, 861.
(17) Newcomb, M.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6405.
(18) Aarts, V. M. L. J.; van Staveren, C. J.; Gootenhuis, P. D. J.; van Eerden, J.; Kruise, L.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1986**, *108*, 5035.
(19) Bradshaw, J. S.; Huszthy, P.; Izatt, R. M. *J. Heterocycl. Chem.* **1986**, *23*, 1673.
(20) Bradshaw, J. S.; Colter, M. L.; Nakatsuji, Y.; Spencer, N. O.; Brown, M. F.; Izatt, R. M.; Arena, G.; Tse, P.-K.; Wilson, B. E.; Lamb, J. D.; Dalley, N. K.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1985**, *50*, 4865.
(21) Bradshaw, J. S.; Nakatsuji, Y.; Huszthy, P.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1986**, *23*, 353.
(22) Bradshaw, J. S.; Chamberlin, D. A.; Harrison, P. E.; Wilson, B. E.; Arena, G.; Dalley, N. K.; Lamb, J. D.; Izatt, R. M.; Morin, F. G.; Grant D. M. *J. Org. Chem.* **1985**, *50*, 3065.
(23) Bradshaw, J. S.; Nielsen, R. B.; Tse, P. K.; Arena, G.; Wilson, B. E.; Dalley, N. K.; Lamb, J. D.; Christensen, J. J.; Izatt, R. M. *J. Heterocycl. Chem.* **1986**, *23*, 361.
(24) Redd, J. T.; Bradshaw, J. S.; Huszthy, P.; Izatt, R. M.; Dalley, N. K. *J. Heterocycl. Chem.* **1998**, *35*, 1.
(25) Rogers, S. J.; Ng, C. Y.; Raymond, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 4094.
(26) Mandal, S. K.; Thompson, L. K.; Nag, K.; Charland, J. P.; Gabe, E. J. *Inorg. Chem.* **1987**, *26*, 1391.
(27) Pastushok, V. N.; Bordunov, A. V.; Bradshaw, J. S.; Izatt, R. M. *J. Org. Chem.* **1996**, *61*, 6888.
(28) Pastushok, V. N.; Hu, K.; Bradshaw, J. S.; Dalley, N. K.; Bordunov, V. N.; Lukyanenko, N. G. *J. Org. Chem.* **1997**, *62*, 212.
(29) Krakowiak, K. E.; Bradshaw, J. S.; Izatt, R. M. *SynLett.* **1993**, 611.

Scheme 1



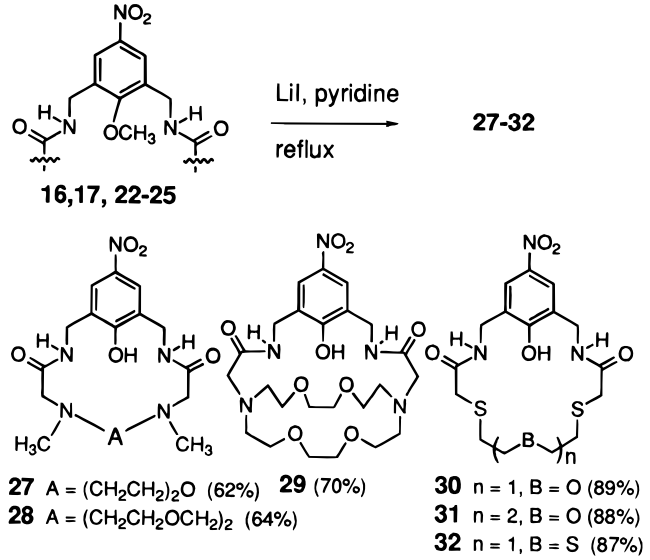
(*R*,*R*)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine used to prepare **18** was synthesized by a literature procedure.[30] Reactions were carried out under high dilution conditions to ensure high yields. Sulfur-containing macrocycles were insoluble in most solvents and, thus, were isolated in low yields.

As reported previously, compounds **14**−**16** exhibited conformational transformations caused by the intraannular methoxy group.[28] The free energies of activation ($\Delta G^{\ddagger}$) for these transformations were greater than 15 kcal/mol for **14**, 14.9 kcal/mol for **15**, and 12.1 kcal/mol for **16**. Compound **18** has the same number of atoms in the macrocyclic ring as **14**, but it has a more complicated ^{1}H NMR spectrum. Proton NMR peaks attributable to the hydrogen atoms on the carbons next to the anisole ring in **18** do not coalesce at a temperature of 140 °C; thus, the $\Delta G^{\ddagger}$ value for the conformational transformations of **18** must be greater than 16 kcal/mol. A satisfactory combustion analysis and a high-resolution mass analysis of all new *p*-nitroanisole-containing macrocycles were obtained.

Some interesting new 2 + 2 macrocyclization byproducts were found in along with **15**−**17** and **24** (compounds **19**−**21** and **26**, Scheme 1). No attempt was made to increase the yields of these new 2 + 2 macrocyclization products. One would expect a higher yield of these products if the cyclization reaction were run in more concentrated solutions. Compounds **19**−**21** and **26** were isolated directly from column chromatography, and they exhibited satisfactory high-resolution mass spectra.

(30) Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335.

Scheme 2



Macrocycles **16**, **17**, and **22**−**25** were successfully converted to the corresponding proton-ionizable *p*-nitrophenol-containing macrocycles (Scheme 2). Nucleophilic cleavage of the internal methoxy group of these macrocycles with lithium iodide occurred smoothly in refuxing pyridine.[5] The *p*-nitrophenol-containing ligands derived from **14** and **15** could not be isolated. The proposed structures of these proton-ionizable macrocycles are consistent with data provided by their ^{1}H NMR and mass spectra and either high-resolution MS or a satisfactory combustion analysis.

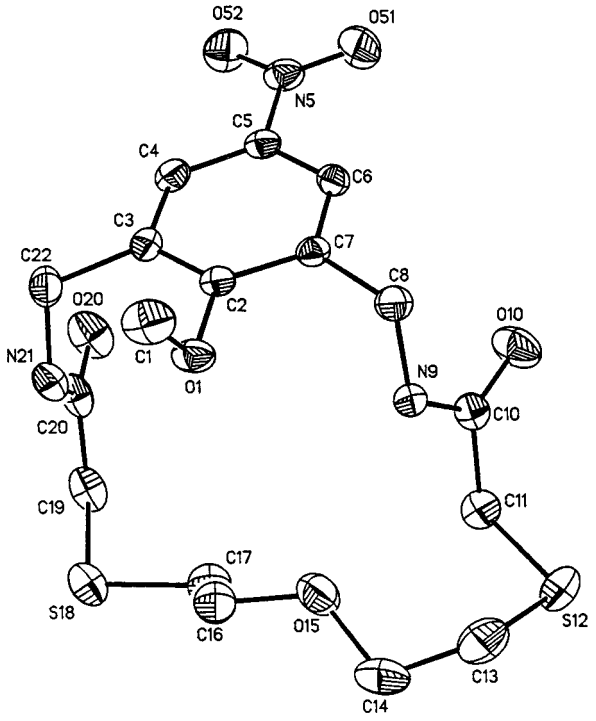


Figure 2. Structure of **23** with thermal ellipsoids drawn at the 35% probability level. Hydrogen atoms and C16′ and C17′, 0.4 occupancy sites of disordered atoms, are omitted for clarity.

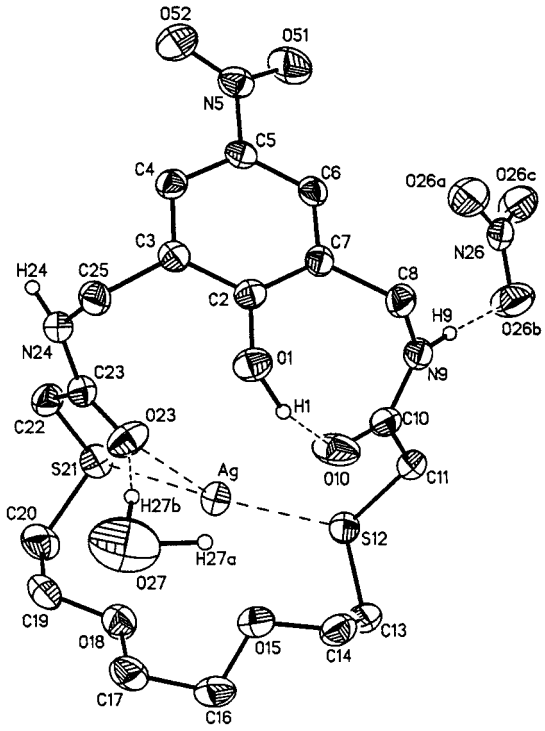


Figure 3. Structure of **31**−$AgNO_3$ with thermal ellipsoids drawn at the 40% probability level. Most hydrogen atoms are omitted for clarity.

The structures of **14**, **23**, and the $AgNO_3$ complex of **31** have been established by X-ray crystallographic studies. The structure of **14** was described previously.[28] Compound **23** (Figure 2) contains the same rigid portion that is present in **14**. Unlike **14**, both of the amide oxygens of **23** point in the same direction with respect to the macrocyclic ring. The ring of **23** is irregular in shape largely because of the presence of the two sulfur atoms in the macrocycle (Figure 2). Both of the sulfur atoms point out of the cavity, a structural feature found in many sulfur-containing macrocycles in which a sulfur atom is not involved in interactions with a cation in the cavity. The methoxy group of the anisole points out of the cavity in a manner similar to that found in **14**.

The complex **31**−$AgNO_3$ is shown in Figure 3. The interactions of Ag^+ with three donor atoms of the host affect the conformation of **31**. The ring of **31** differs from that of **23** only by the presence of an additional C−C−O group in the atom chain joining the two sulfur atoms. However, the shape of the ring of uncomplexed **23** differs considerably from that of **31** in its Ag^+ complex. The two short Ag−S interactions (2.493(1) Å to S12 and 2.587(1) Å to S21) indicate partial covalent character and explain the stability of the complex between Ag^+ and **31**. These forces shorten the distance between sulfur atoms causing the ligand to have an elliptical shape. The Ag^+ also interacts with one amide oxygen atom, O23 (2.498(3) Å). This interaction may be the cause of the deviation of the S−Ag−S angle (136.8°) from 180°. The other amide atom (O10) interacts with the phenol hydrogen and forms an intramolecular hydrogen bond. Both amide oxygens are on the same side of the ring. The structure contains a nitrate anion and a water of hydration, both of which interact with **31** through hydrogen bonding.

Interactions of diazadithiacrown ethers **24** and **31**, diazatrithiacrown ether **32**, and tetraazacrown ether **27** with Na^+, K^+, Ba^{2+}, Ag^+, and Pb^{2+} have been evaluated by a calorimetric titration technique[31] at 25 °C either in a 70:30 (v/v) CH_3OH/H_2O (70% CH_3OH) or in an absolute CH_3OH solution. The values of equilibrium constants (log *K*), enthalpy change (ΔH), and entropy change ($T\Delta S$) for these interactions are listed in Table 1. Interactions of K^+ and Ba^{2+} with **24** and **27** in 70% CH_3OH are very weak. Even in absolute CH_3OH, **24** and **27** interact very weakly with Na^+. No reaction heat was detected for these interactions. We did not evaluate thermodynamic quantities for the interactions of **31** and **32** with Na^+, K^+, and Ba^{2+}, since these interactions should also be weak. On the other hand, ligands **24**, **27**, and **31** form

Table 1. log *K*, ΔH (kJ/mol), and $T\Delta S$ (kJ/mol) Values for Interactions of Macrocyclic Ligands with Metal Ions in 70:30 (v/v) Methanol/Water at 25.0 °C

ligand	cation	log *K*	ΔH	$T\Delta S$
24	Na^+	*a*, *b*		
	K^+	*a*		
	Ba^{2+}	*a*		
	Ag^+	5.66 ± 0.05	−61.5 ± 0.4	−29.2
27	Na^+	*a*, *b*		
	K^+	*a*		
	Ba^{2+}	*a*		
	Ag^+	3.49 ± 0.03	−34.5 ± 0.6	−14.6
	Pb^{2+}	3.23 ± 0.07	−63.0 ± 0.3	−44.5
31	Ag^+	5.91 ± 0.10	−57.6 ± 0.2	−23.9
	Pb^{2+}	2.10 ± 0.08	−27.3 ± 0.8	−15.3
32	Ag^+	(yellow precipitate; thermodynamic quantities were not evaluated)		
	Pb^{2+}	1.94 ± 0.09	−38.6 ± 0.8	−27.5

[a] No measurable heat other than heat of dilution indicating that ΔH and/or log *K* is small. [b] In absolute MeOH.

(31) (a) Oscarson, J. L.; Izatt, R. M. In *Physical Methods of Chemistry, Vol. VI*: *Determination of Thermodynamic Properties*; Rossiter, B. W., Baetzold, R. C., Eds.; John Wiley & Sons: New York, 1992; Chapter 7. (b) Izatt, R. M.; Zhang, X. X.; An, H. Y.; Zhu, C. Y.; Bradshaw, J. S. *Inorg. Chem.* **1994**, *33*, 1007.

stable complexes with Ag^+ and Pb^{2+} in 70% CH_3OH. Trithia macrocycle **32** forms a precipitate with Ag^+ and complexes Pb^{2+} with a log K value of 1.94 in 70% CH_3OH.

Dithiacrown ether **24** shows a high selectivity for Ag^+ (log $K = 5.66$) over Na^+, K^+, and Ba^{2+}, and **31** shows a high selectivity for Ag^+ (log $K = 5.91$) over Pb^{2+} (log $K = 2.10$). The selectivity factor of Ag^+/Pb^{2+} by **31** is more than 3 orders of magnitude. Compound **27**, containing no sulfur donors, forms stable complexes with both Ag^+ and Pb^{2+} but shows no selectivity between the two. However, **27** demonstrates good selectivity for Ag^+ and Pb^{2+} over the alkali and alkaline-earth metal ions studied.

The high selectivity of **24** and **31** for Ag^+ is due to a proper preorganization of the ligands. Since Ag^+ prefers a linear coordination geometry and possesses a high affinity for soft sulfur atoms, the disposition of the two sulfur donor atoms in **24** and **31** provides an ideal coordination environment for Ag^+. The crystal structure of the **31**−$AgNO_3$ complex indicates that Ag^+ is strongly bound to two sulfur atoms and weakly bound to an amide oxygen atom (see above).

Data in Table 1 show that complexation of **24**, **27**, **31**, and **32** with Ag^+ and Pb^{2+} is enthalpy driven. All ΔH and $T\Delta S$ values are negative. The high selectivity of Ag^+ by **24** and **31** is attributed to an enthalpic effect (very favorable ΔH values). Although the **27**−Pb^{2+} interaction has a large negative ΔH value (−63.0 kJ/mol), the very negative $T\Delta S$ value (−44.5 kJ/mol) cancels the enthalpic contribution to the stability constant and indicates a large conformational change of **27** upon complexation with Pb^{2+}.

Experimental Section

The NMR spectra were obtained at 200 and 500 MHz. FAB was used to record the mass spectra. Starting materials were purchased from commercial chemical companies unless otherwise noted. 2,6-Bis[(2-chloroacetamido)methyl]-4-nitroanisole (**BB**) and macrocycles **14**−**17** and **22** were prepared as reported.[28]

Preparation of (7*R*,12*R*)-6,13-Dimethyl-22-methoxy-20-nitro-3,6,13,16-tetraazatricyclo[16.3.1.0.^{7,12}]docosa-1(22),-18,20-triene-4,15-dione (18) (Scheme 1). Macrocycle **18** was obtained by refluxing a mixture of 0.65 g (3 mmol) of (1*R*,2*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine[30] and 1.1 g (3 mmol) of diamide **BB** and 10 g (0.09 mol) of anhydrous Na_2CO_3 in 1 L of CH_3CN for 12 h under N_2. The Na_2CO_3 was then filtered, and the CH_3CN was evaporated. Compound **18** (0.86 g, 75%) was isolated as yellow prisms after flash column chromatography (silica gel, NH_3/CH_3OH/EtOAc: 1/1/18) and recrystallization in ethanol; $R_f = 0.38$; mp 253−5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16 (d, $J = 6.2$ Hz, 2H), 7.72 (broad s, 1H), 7.55 (d, $J = 6.4$ Hz, 1H), 4.96−4.65 (m, 2H), 4.37−4.16 (m, 2H), 3.94 (s, 3H), 3.10−2.80 (m, 4H), 2.62−2.30 (m, 2H), 2.27 (s, 3H), 1.80−1.60 (m, 4H), 1.45 (s, 3H), 1.24−1.02 (m, 4H); ^{13}C NMR (500 MHz) δ 171.3, 162.7, 143.6, 135.3, 132.2, 125.9, 124.5, 65.4, 64.2, 61.1, 60.6, 60.3, 42.0, 39.8, 34.2, 32.7, 25.2, 25.1, 24.5, 23.2; HRMS (FAB) calcd for $C_{21}H_{32}O_5N_5$ ($M^+ + H$) 434.2403, found 434.2423. Anal. Calcd for $C_{21}H_{31}N_5O_5$: 58.18; H, 7.21. Found: C, 58.25; H, 7.12.

21-Methoxy-19-nitro-9-oxa-6,12-dithia-3,15-diazabicyclo-[15.3.1]henicosa-1(21),12,19-triene-4,14-dione (23) (Scheme 1). Macrocycle **23** was obtained as above for **18** from 0.46 g (3 mmol) of 3-oxa-1,5-pentanedithiol and **BB**. Compound **23** (0.54 g, 42%) was isolated by flash chromatography (silica gel, EtOAc) and recrystallization from EtOH to give a white solid; $R_f = 0.54$ (1:20 MeOH/ EtAc); mp 196−7 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.70 (t, $J = 5.8$ Hz, 2H), 8.32 (s, 2H), 4.36 (d, $J = 5,8$ Hz, 4H), 3.96 (s, 3H), 3.08 (s, 4H), 2.73 (t, $J = 7.6$ Hz, 4H), 2.45 (t, $J = 7.6$ Hz, 4H); ^{13}C NMR δ 169.7, 161.7, 142.9, 134.2, 125.5, 70.1, 62.7, 36.7, 35.5, 30.9; MS m/z 430 $(M + 1)^+$. Anal. Calcd for $C_{17}H_{23}N_3O_6S_2$: C, 47.54; H, 5.40. Found: C, 47.48; H, 5.58.

24-Methoxy-22-nitro-9,12-dioxa-6,15-dithia-3,6,15,18-tetraazabicyclo[18.3.1]tetracosa-1(24),20,22-triene-4,17-dione (24) (Scheme 1). Macrocycle **24** was obtained as above for **18** from 0.56 g (3 mmol) of 3,5-dioxa-1,8-octanedithiol and **BB**. Compound **24** (0.52 g, 37%) was isolated as a white solid; mp: 168−9 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.73 (t, $J = 5.8$ Hz, 2H), 8.25 (s, 2H), 4.40 (d, $J = 5.8$ Hz, 4H), 3.90 (s, 3H), 3.24 (t, $J = 7.4$ Hz, 4H), 3.17 (s, 4H), 3.12 (s, 4H), 2.58 (t, $J = 7.4$ Hz, 4H); ^{13}C NMR δ 169.6, 160.9, 143.3, 134.6, 123.7, 69.5, 68.7, 62.1, 36.5, 35.0, 30.8; MS m/z 474 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{27}N_3O_7S_2$: C, 48.19; H 5.75. Found: C, 48.29; H, 5.84.

21-Methoxy-19-nitro-6,9,12-trithia-3,15-diazabicyclo-[15.3.1]henicosa-1(21),17,19-triene-4,14-dione (25) (Scheme 1). Macrocycle **25** was obtained as above for **18** from 0.46 g (3 mmol) of 3-thia-1,5-pentanedithiol and **BB**. Compound **25** (0.46 g, 35%) was isolated as a white solid: mp 209−10 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.71 (t, $J = 5.8$ Hz, 2H), 8.29 (s, 2H), 4.36 (d, $J = 5.8$ Hz, 4H), 3.96 (s, 3H), 3.11 (s, 4H), 2.51−2.34 (m, 4H), 2.16−2.09 (m, 4H); ^{13}C NMR δ 169.5, 161.5, 142.9, 134.2, 125.0, 62.6, 36.9, 34.8, 31.6, 31.3; MS m/z 446 $(M + 1)^+$. Anal. Calcd for $C_{17}H_{23}N_3O_5S_3$: C, 45.83; H, 5.20. Found: C, 46.00; H, 5.40.

6,10,24,28-Tetramethyl-37,38-dimethoxy-17,35-dinitro-3,6,-10,13,21,24,28,31-octaazatricyclo[31.3.1.1^{15,19}]octatriaconta-1(37),15,17,19(38),33,35-hexene-4,12,22,30-tetrone (19) (Scheme 1). New compound **19** (28 mg, 2.4%) was isolated as a byproduct during the preparation of **15**:[29] ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (broad s, 8H), 4.55 (d, $J = 6.2$ Hz, 8H), 3.88 (s, 6H), 3.13 (s, 8H), 2.51 (t, $J = 7.0$ Hz, 8H), 2.34 (s, 12H), 1.72 (t, $J = 7.0$ Hz, 4H); ^{13}C NMR δ 171.6, 161.1, 144.0, 134.0, 122.6, 61.6, 61.1, 56.0, 43.7, 37.3, 25.5; HRMS (FAB, NaOAc) calcd for $C_{36}H_{54}O_{10}N_{10}Na$ 809.3922, found 809.3924.

6,12,26,32-Tetramethyl-37,38-dimethoxy-17,35-dinitro-9,29-dioxa-3,6,12,15,23,26,28,31-octaazatricyclo[35.3.1.1^{17,21}]-dotetraconta-1(41),17,19,21(42),37,39-hexene-4,14,24,34-tetrone (20) (Scheme 1). New compound **20** (16 mg, 1.3%) was isolated as a byproduct in the preparation of **16**:[29] ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96 (broad s, 8H), 4.48 (d, $J = 6.0$ Hz, 8H), 3.83 (s, 6H), 3.50 (t, $J = 5.4$ Hz, 8H), 3.12 (s, 8H), 2.58 (t, $J = 5.4$ Hz, 8H), 2.34 (s, 12H); ^{13}C NMR δ 171.6, 160.9, 144.2, 134.1, 123.0, 68.8, 61.8, 61.3, 57.2, 43.6, 37.0; HRMS (FAB, NaOAc) calcd for $C_{38}H_{58}O_{12}N_{10}Na$ 869.4133, found 869.4135.

6,15,29,38-Tetramethyl-47,48-dimethoxy-22,45-dinitro-9,12,32,35-tetraoxa-3,6,15,18,26,29,38,41-octaazatricyclo-[40.3.1.1^{22,24}]octatetraconta-1(47),20,22,24(48),43,45-hexene-4,17,27,40-tetrone (21) (Scheme 1). New compound **21** (52 mg, 3.7%), an oil, was isolated as a byproduct in the preparation of **17**:[29] ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.19 (d, $J = 6.0$ Hz, 4H), 8.03 (s, 4H), 4.51 (d, $J = 6.0$ Hz, 8H), 3.89 (s, 6H), 3.50 (t, $J = 4.8$ Hz, 8H), 3.15 (s, 16H), 2.63 (t, $J = 4.8$ Hz, 8H), 2.39 (s, 12 H); ^{13}C NMR δ 171.6, 160.8, 144.3, 134.2, 122.7, 70.2, 68.8, 61.6, 61.2, 57.2, 43.6, 37.1; HRMS (FAB, NaOAc) calcd for $C_{42}H_{66}O_{14}N_{10}Na$ 957.4658, found 957.4673.

47,48-Dimethoxy-22,45-dinitro-9,12,32,35-tetraoxa-6,-15,29,38-tetrathia-3,18,26,41-tetraazatricyclo[40.3.1.1^{22,24}]-octatetraconta-1(47),20,22,24(48),43,45-hexene-4,17,27,40-tetrone (26) (Scheme 1). New compound **26** (60 mg, 4.2%) was isolated as a byproduct in the preparation of **24**: mp 203−4 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.65 (t, $J = 5.8$ Hz, 4H), 8.07 (s, 4H), 4.38 (d, $J = 5.8$ Hz, 8H), 3.85 (s, 6H), 3.52 (t, $J = 6.8$ Hz, 8H), 3.43 (s, 8H), 3.22 (s, 8H), 2.71 (t, $J = 6.8$ Hz, 8H); ^{13}C NMR δ 169.8, 160.5, 143.5, 134.5, 122.4, 69.57, 69.3, 61.5, 36.8, 34.5, 31.0; HRMS (FAB, NaOAc) calcd for $C_{38}H_{54}O_{14}N_6S_4Na$ 969.2479, found 969.2476. Anal. Calcd for $C_{38}H_{54}N_6O_{14}S_4$: C, 48.19; H, 5.75. Found: C, 48.26; H, 5.82.

General Procedure for the Preparation of Proton-Ionizable Macrocycles Containing the *p*-Nitrophenol Fragment (Scheme 2). Macrocycles containing the *p*-nitroanisole fragment and 8 equiv of LiI were added to 5−20 mL of anhydrous pyridine. The mixture was refluxed for 8−18

h under N_2. Pyridine was evaporated under vaccum. The solid residue was treated with 5−20 mL of a 1 N HCl solution. After the mixture was stirred for 20 min, it was extracted twice with 5 mL portions of ether. The aqueous phase was titrated carefully with saturated sodium bicarbonate until it was slightly basic. The basic solution was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to give white to light yellow solids. Further purification of these compounds was achieved by recrystallization in ethanol.

6,12-Dimethyl-21-hydroxy-19-nitro-9-oxa-3,6,12,15-tetraazabicyclo[15.3.1]henicosa-1(21),17,19-triene-4,14-dione (27) (Scheme 2). Macrocycle **27** was synthesized from **16** (50 mg, 0.12 mmol) according to the general procedure. Compound **27** was recrystallized from ethanol as a light yellow solid (30 mg, 62%): mp 212−3 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.32 (t, J = 5.2 Hz, 2H), 8.10 (s, 2H), 4.95 (broad, 1H), 4.46 (d, J = 5.2 Hz, 4H), 3.26 (t, J = 5.8 Hz, 4H), 3.01 (s, 4H), 2.44 (t, J = 5.8 Hz, 4H), 2.29 (s, 6H); ^{13}C NMR δ 171.0, 162.8, 137.2, 126.9, 126.5, 68.4, 60.8, 56.4, 44.2, 38.8; MS m/z 410 (M + 1)$^+$. Anal. Calcd for $C_{18}H_{27}N_5O_6$: C, 52.80; H, 6.65. Found: C, 52.70; H, 6.62.

6,15-Dimethyl-24-hydroxy-22-nitro-9,12-dioxa-3,6,15,-18-tetraazabicyclo[18.3.1]-tetracosa-1(24),20,22-triene-4,-17-dione (28) (Scheme 2). Macrocycle **28** was synthesized from **17** (0.81 g, 1.7 mmol) according to the general procedure. Compound **28** was obtained after column chromatography as a yellow oil (0.50 g, 64%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.28 (t, J = 6.0 Hz, 2H), 8.12 (s, 2H), 4.50 (d, J = 6.0 Hz, 4H), 3.36 (t, J = 5.0 Hz, 4H), 3.19 (s, 4H), 3.05 (s, 4H), 2.57 (t, J = 5.0 Hz, 4H), 2.40 (s, 6H); ^{13}C NMR δ 173.7, 161.0, 139.8, 126.7, 126.5, 70.0, 69.9, 60.8, 57.3, 45.2, 38.9; HRMS (FAB) calcd for $C_{20}H_{32}N_5O_7$ (M$^+$ + H) 454.2302, obsd 454.2305.

32-Hydroxy-8-nitro-18,21,26,29-tetraoxa-1,4,12,15-tetraazatricyclo[13.8.8.1^{6,10}]dotriaconta-6,8,10(32)-triene-3,13,-dione (29) (Scheme 2). Macrocycle **29** was converted from **22** (554 mg, 1.0 mmol) according to the general procedure. Compound **29** was recrystallized from ethanol as a yellow solid (0.38 g, 70%): mp 178−9 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18 (broad s, 2H), 8.09 (s, 2H), 4.38 (d, J = 4.0 Hz, 4H), 3.42−3.18 (m, 17H), 3.13 (s, 4H), 2.70−2.50 (m, 4H), 2.50 (s, 4H); ^{13}C NMR δ 172.8, 160.3, 140.7, 126.7, 126.7, 70.5, 69.5, 59.5, 56.1, 39.7; HRMS (FAB) calcd for $C_{24}H_{38}N_5O_9$ (M$^+$ + H) 540.2669, found 540.2661.

21-Hydroxy-19-nitro-9-oxa-6,12-dithia-3,15-diazabicyclo-[15.3.1]henicosa-1(21),17,19-triene-4,14-dione (30) (Scheme 2). Macrocycle **30** was converted from **23** (0.20 g, 0.47 mmol) according to the general procedure. Compound **30** was recrystallized from ethanol as a yellow solid (0.17 g, 89%): mp 264−6 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.41 (s, 1H), 8.89 (t, J = 5.4 Hz, 2H), 8.22 (s, 2H), 4.32 (d, J = 5.4 Hz, 4H), 3.20 (s, 4H), 3.04 (t, J = 6.8 Hz, 4H), 2.51 (t, J = 6.8 Hz, 4H); ^{13}C NMR δ 171.4, 160.7, 13.8.7, 126.9, 126.6, 69.7, 38.3, 35.3, 31.3; MS m/z 416 (M + 1)$^+$. Anal. Calcd for $C_{16}H_{21}N_3O_6S_2$: C, 46.25; H, 5.09. Found: C, 46.40; H, 5.23.

24-Hydroxy-22-nitro-9,12-dioxa-6,15-dithia-3,6,15,18-tetraazabicyclo[18.3.1]tetracosa-1(24),20,22-triene-4,17-dione (31) (Scheme 1). Macrocycle **31** was converted from **24** (0.26 g, 0.54 mmol) according to the general procedure. Compound **31** was recrystallized from ethanol as a yellow solid (0.22 g, 88%): mp 167−8 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.26 (s, 1H), 8.83 (t, J = 5.6 Hz, 2H), 8.17 (s, 2H), 4.34 (d, J = 5.6 Hz, 4H), 3.34 (t, J = 7.4 Hz, 4H), 3.25 (s, 4H), 3.18 (s, 4H), 2.59 (t, J = 7.4 Hz, 4H); ^{13}C NMR δ 171.1, 159.9, 139.1, 127.7, 125.4, 70.1, 68.8, 38.0, 34.8, 30.8; MS m/z 460 (M + 1)$^+$, 482 (M + Na)$^+$. Anal. Calcd for $C_{18}H_{25}N_3O_7S_2$: C, 47.05; H, 5.48. Found: C, 47.15; H, 5.56.

21-Hydroxy-19-nitro-6,9,12-trithia-3,15-diazabicyclo-[15.3.1]henicosa-1(21),17,19-triene-4,14-dione (32) (Scheme 1). Macrocycle **32** was converted from **25** (0.23 g, 0.52 mmol) according to the general procedure. Compound **32** was recrystallized from ethanol as a yellow solid (0.19 g, 87%): mp 233−4 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.32 (s, 1H), 8.93 (t, J = 5.6 Hz, 2H), 8.20 (s, 2H), 4.33 (d, J = 5.6 Hz, 4H), 3.22 (s, 4H), 2.80−2.42 (m, 4H), 2.38−2.30 (m, 4H); ^{13}C NMR (500 MHz) δ 170.9, 160.2, 138.9, 126.8, 126.4, 38.2, 34.5, 32.0, 31.0; MS m/z 432 (M + 1)$^+$, 454 (M + Na)$^+$. Anal. Calcd for $C_{16}H_{21}N_3O_5S_3$: C, 44.53; H, 4.90. Found: C, 44.44; H, 4.76.

X-ray Structure Determinations. Crystal data, experimental details, atomic coordinates and thermal parameters, and bond lengths and angles have been deposited in the Cambridge Crystallographic Data Center. These data can be obtained on request from the Director, Cambridge Crystallographia Data Center, University Chemical Laboratory, Linsfield Road, Cambridge CB2 1EW, U.K.

Determination of Thermodynamic Quantities. log K, ΔH, and $T\Delta S$ values were determined as described earlier[31] in 70% or absolute CH_3OH solutions at 25.0 ± 0.1 °C by titration calorimetry using a Tronac Model 450 calorimeter equipped with a 20 mL reaction vessel. The metal ion solutions were titrated into the macrocyclic ligand solutions, and the titrations were carried out to a 2-fold excess of the metal ions. The titration experiments showed that all interactions studied had a 1:1 cation−ligand ratio. The method used to process the calorimetric data and to calculate the log K and ΔH values has been described.[32]

Acknowledgment. The authors thank the Department of Energy, Office of Basic Energy Sciences, Grant DE-FG02-86ER-13463 (proton-ionizable ligands), and the Office of Naval Research (chiral ligands) for their financial support.

Supporting Information Available: Tables listing structure determination information, positional and thermal parameters for all atoms, anisotropic thermal parameters for non-hydrogen atoms, and bond angles and lengths for **23** and **31**−$AgNO_3$ (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980414Z

(32) Eatough, D. J.; Christensen, J. J.; Izatt, R. M. *Thermochim. Acta* **1972**, *3*, 219 and 233.