Synthesis of Diazadibenzo-18-Crown-6 Ligands with Appended Chromophoric and Fluorophoric Groups as Potential Metal Ion Chemosensors

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In honor of Professor Jerald S. Bradshaw

Six new diazadibenzo-18-crown-6 ligands substituted with two each of 8-hydroxyquinoline (**7**), 8-aminoquinoline (attached through its C-2 or C-7 position) (**12** and **13**), 8-methoxyquinoline (**18**), 5-chloro-8-methoxyquinoline (**19**), and dansylamidoethyl (**21**) side arms were synthesized as potential metal ion chemosensors and potential reagents for the selective extraction of certain metal ions from aqueous solutions. Ligands **7**, **12**, **13**, **18**, and **19** were synthesized by reductive amination of diazadibenzo-18-crown-6 (**5**) and the appropriate quinolinecarboxaldehydes. Bis(dansylamidoethyl)-substituted ligand **21** was synthesized by treating diazacrown ether **5** with *N*-dansylaziridine (**20**).

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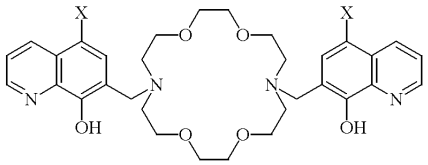
Introduction.

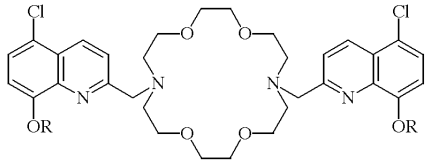
Decades of research expanding the number of macrocyclic ligands that form complexes with metal cations have led to a wealth of information about selective macrocycle-ion interactions [1]. This information has been applied in the development of multiple chromophore and fluorophore appended macrocycles, which complex metal cations and respond to complexation *via* changes in absorbance or fluorescence properties [2]. These appended macrocycles constitute a large number of selective metal ion chemosensors that would be very useful for measuring and monitoring metal ion concentrations in environmental and biological systems.

We have prepared and studied several series of macrocyclic ligands with appended chromophores and fluorophores for use as selective metal-ion chemosensors [3]. 8-Hydroxy- and 8-methoxyquinoline-substituted diaza-18-crown-6 ligands (**1**-**4**, Figure 1) developed in our laboratory exhibit significantly improved affinity and selectivity for certain metal ions compared to unsubstituted diaza-18-crown-6 [3e,3f]. Also, these ligands have important luminescent properties when complexed with certain metal ions. Ligand **1**, with the two 5-chloro-8-hydroxyquinoline (CHQ) substituents attached through the quinoline C-7 position, has a high affinity for Mg^{2+} and lower affinity for the other alkaline earth and alkali metal ions [3f]. Ligand **3** with the CHQ attached through its C-2 position, on the other hand, exhibits a very strong affinity for Ba^{2+} and no affinity for Mg^{2+}. Ligands **1** and **2** have proven to be effective chemosensors for Mg^{2+} and Hg^{2+}, respectively [4,5]. As an efficient chemosensor, ligand **4** selectively binds and responds to Cd^{2+} as shown by an increase in fluorescence [6]. A number of other diaza-18-crown-6 ligands with substituents such as 8-aminoquinoline [7], 8-(benzenesulfonamido)quinoline [8] and dansylamidoethyl [3b] fluorophores have also been prepared and studied in our laboratory. Up to now, most of our work has concentrated on the synthesis and study of *N*-functionalized derivatives of diaza-18-crown-6 as metal ion chemosensors [2a].

In this paper, we report the synthesis of six new diazadibenzo-18-crown-6 ligands containing two 8-hydroxyquinoline (**7**), 8-aminoquinoline (attached through its C-2 or C-7 position) (**12** and **13**), 8-methoxyquinoline (**18**), 5-chloro-8-methoxyquinoline (**19**), and dansylamidoethyl (**21**) fluorophores. The new crown ether ligands are based on a diazadibenzo-18-crown-6 platform. In comparison to the ligands based on diaza-18-crown-6 framework (*e.g.* compounds **1**-**4**), the presence of the benzo groups in the new ligands should increase the rigidity of the crown ether ring, reduce the basicity of the ring oxygen atoms, and increase the overall



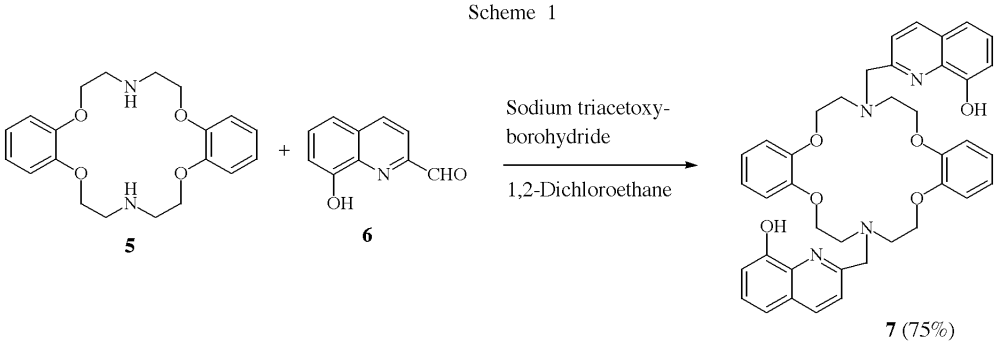
1 X = Cl
2 X = NO_2



3 R = H
4 R = CH_3

Figure 1. 5-Chloro(or Nitro)-8-hydroxy-quinoline-substituted Diaza-18-crown-6 Ligands 1-4.

Scheme 1



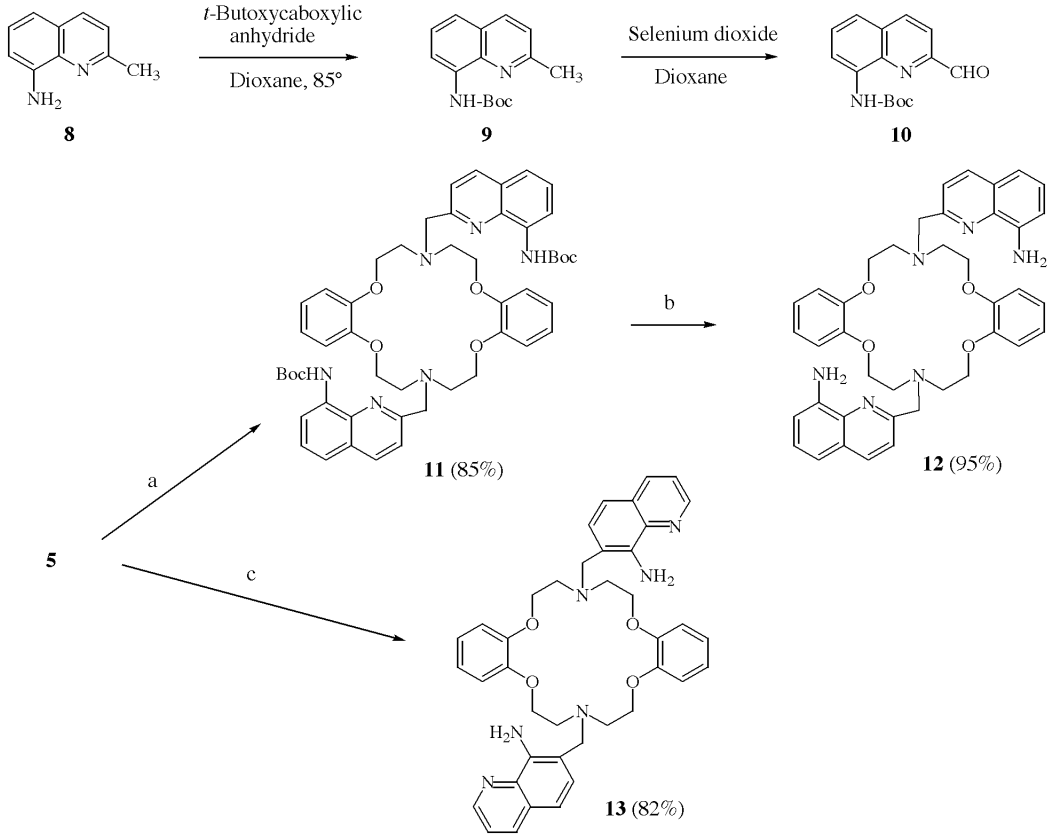
lipophilicity of the ligands [9]. An increase in lipophilicity of these new compounds may make them useful for the selective extraction of certain metal ions.

Results and Discussion.

Reductive amination [10] is a convenient method to synthesize *N*-functionalized azacrown ethers. Treatment of the azacrown ethers with the appropriate aldehydes in the presence of sodium triacetoxyborohydride in 1,2-dichloroethane yields the *N*-functionalized azacrown ethers in one step [6,7,11]. Compounds **7**, **12**, **13**, **18**, and **19** were synthesized by reductive amination (Schemes 1-3). Diazadibenzo-18-crown-6 (**5**) was treated with commercially available 8-hydroxy-2-quinolinecarboxaldehyde (**6**) to give ligand **7** in a 75% yield (Scheme 1).

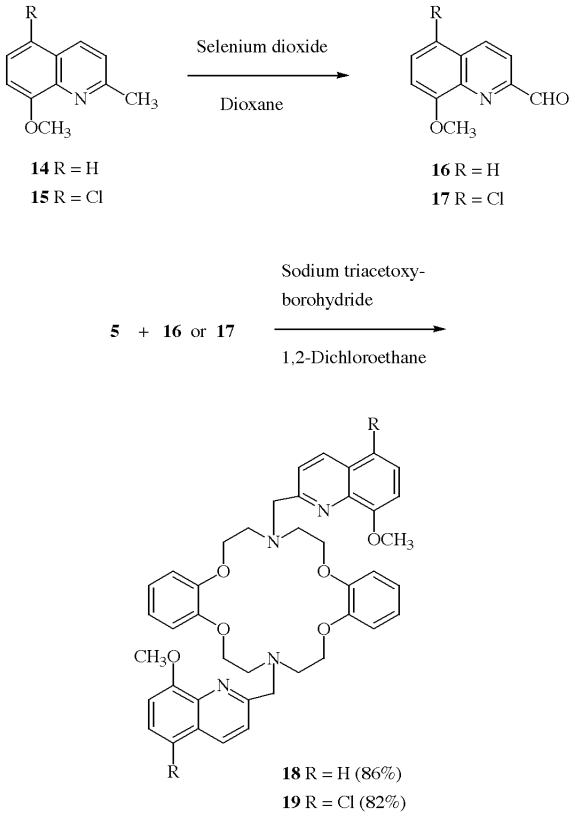
The synthetic strategy for the synthesis of ligands **12** and **13** is outlined in Scheme 2. The preparation of key aldehyde precursor **10** began with commercially available

Scheme 2



a) **10**, sodium triacetoxyborohydride, 1,2-dichloroethane; b) 4.0 *M* hydrochloric acid, dioxane; c) 8-amino-7-quinolinecarboxaldehyde, sodium triacetoxyborohydride, dichloroethane.

Scheme 3

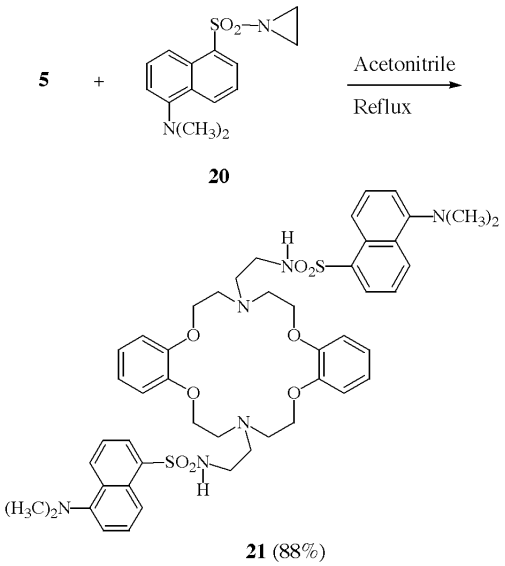


8-aminoquinaldine (**8**). Treatment of **8** with *t*-butoxycarboxylic anhydride in dioxane at 85-90° gave Boc-protected **9** in an 88% yield. Oxidation of **9** was accomplished with selenium dioxide in dioxane to provide aldehyde **10** in a 90 % yield. Finally, compounds **11** and **13** were obtained in good yields using the reductive amination procedure from **10** and 8-amino-7-quinolinecarboxaldehyde [12], respectively. Removal of the Boc protecting groups was easily accomplished in an excellent yield (95 %) using 4.0 *M* hydrochloric acid in dioxane to give ligand **12**.

5-Chloro-8-methoxyquinaldine (**15**), needed to prepare bis(5-chloro-8-methoxyquinolin-2-ylmethyl)-substituted ligand **19**, was synthesized as described [3f]. Key intermediate quinolinecarboxaldehydes **16** and **17** were prepared by oxidation of commercially available **14** and **15** with selenium dioxide in dioxane. Ligands **18** and **19** were prepared by reductive amination of aldehydes **16** and **17**, respectively, and crown **5** (Scheme 3). Bis(dansylamidoethyl)-substituted ligand **21** was easily prepared by treating *N*-dansylaziridine **20** [3a] with **5** using our reported method (Scheme 4) [3a,3b].

In summary, six new diazadibenzo-18-crown-6 ligands substituted with two each of 8-hydroxyquinoline (**7**), 8-aminoquinoline (attached through its C-2 or C-7 position) (**12** and **13**), 8-methoxyquinoline (**18**), 5-chloro-8-methoxyquinoline (**19**) and dansylamidoethyl (**21**) side arms were synthesized as potential metal ion chemosensors and potential reagents for the selective extraction of certain metal ions. A report on the affinities of some of these new ligands for metal ions and their possible use as sensors for metal ions will be reported in due course.

Scheme 4



EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Varian Gemini 200 MHz spectrometer. Tetramethylsilane was used as the internal standard. The ms spectra were obtained on a Finnegan 8430 high resolution mass spectrometer using the fast atom bombardment (fab) and chemical ionization (ci) methods. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. All solvents were purified by standard procedures. Starting materials were used without further purification. 8-Amino-7-quinolinecarboxaldehyde [12] and diazadibenzo-18-crown-6 (**5**) [13] were prepared as reported.

N,*N*'-Bis[8-hydroxy-2-quinolinylmethyl]-4,13-diazadibenzo-18-crown-6 (**7**) (Scheme 1).

A mixture of **5** (537 mg, 1.5 mmole) and 8-hydroxyquinoline-2-carboxaldehyde (**6**) (571 mg, 3.3 mmole) in 25 ml of 1,2-dichloroethane was stirred with sodium triacetoxyborohydride (848 mg, 4.0 mmole) under nitrogen at room temperature for 5 hours. The reaction was then quenched with saturated sodium carbonate (15 ml) and the mixture was extracted with methylene chloride (3 x 10 ml). The combined methylene chloride extracts were dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by recrystallization from methylene chloride/ethanol (1:3) to give 756 mg (75%) of **7** as a white solid, mp 191-193°;

^{1}H nmr (deuteriochloroform): δ = 3.41 (t, 8H), 4.14 (s, 4H), 4.17 (t, 8H), 6.87 (m, 8H), 7.17 - 7.45 (m, 6H), 7.73 (d, 2H), 8.15 (d, 2H); hrms (fab): m/z = 673.3036 (M^+), calcd, 673.3028.

Anal. Calcd. for $C_{40}H_{40}N_4O_6 \cdot 1.5H_2O$: C, 68.65; H, 6.19. Found: C, 68.66; H, 6.04.

8-(*t*-Butoxycarbonylamino)quinaldine (**9**) (Scheme 2).

8-Aminoquinaldine (**8**) (3.95 g, 25 mmole) was stirred with di-*t*-butyldicarbonate (10.9 g, 50 mmole) in 70 ml of dioxane at 85-90° for two days. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride/hexane (1:1) as eluent to give 5.68 g (88%) of **9** as white crystals, mp 72-73°; ^{1}H nmr (deuteriochloroform): δ = 1.59 (s, 9H), 2.73 (s, 3H), 7.25-7.47 (m, 3H), 7.99 (d, 1H), 8.38 (dd, 1H), 9.06 (d, 1H); hrms (ci): m/z = 259.1430 [$(M+H)^+$], calcd. 259.1448.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02. Found: C, 70.00; H, 6.87.

8-(*t*-Butoxycarbonylamino)-2-quinolinecarboxaldehyde (**10**) (Scheme 2).

To a stirred suspension of freshly sublimed selenium dioxide (3.33 g, 30 mmole) in 150 ml of dioxane at 50-55° was added a solution of **9** (4.34 g, 16.8 mmole) in 50 ml of dioxane during the course of 3 hours. The mixture was heated to 80-85° overnight, filtered, and the dioxane was removed under reduced pressure. The residue was purified by column chromatography on silica gel with methylene chloride as eluent to give 4.11 g (90%) of **10** as green crystals, mp 129-131°; ^{1}H mnr (deuteriochloroform): δ = 1.62 (s, 9H), 7.47 - 7.70 (m, 2H), 8.05 (d, 1H), 8.29 (d, 1H), 8.52 (dd, 1H), 9.0 (s, 1H), 10.26 (s, 1H); hrms (ci): m/z = 273.1229 [$(M+H)^+$], calcd. 273.1240.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92. Found: C, 66.06; H, 5.82.

N,*N*'-Bis[(8-*t*-butoxycarbonylamino)-2-quinolinylmethyl]-4,13-diazadibenzo-18-crown-6 (**11**) (Scheme 2).

Macrocycle **11** was prepared as above for **7** from **5** (537 mg, 1.5 mmole) and **10** (897.6 mg, 3.3 mmole). Crude compound **11** was purified by recrystallization from chloroform/ethanol (1:1) to give 1.1 g (85%) of **11** as white crystals, mp 215-216°; ^{1}H nmr (deuteriochloroform): δ = 1.59 (s, 18H), 3.38 (t, 8H), 4.14 (s, 4H), 4.16 (t, 8H), 6.82 (m, 8H), 7.37-7.51 (m, 4H), 7.73 (d, 2H), 8.10 (d, 2H), 8.39 (d, 2H), 8.99 (s, 2H); hrms (fab): m/z = 893.4203 [$(M+Ha)^+$]. Calcd. 893.4217.

Anal. Calcd. for $C_{50}H_{58}N_6O_8$: C, 68.94; H, 6.71. Found: C, 68.70; H, 6.65.

N,*N*'-Bis(8-aminoquinolin-2-ylmethyl)-4,13-diazadibenzo-18-crown-6 (**12**) (Scheme 2).

Compound **11** (870 mg, 1.0 mmole) was treated with 4.0 *M* hydrochloric acid in 50 ml of dioxane and the mixture was allowed to stir for 12 hours. A chilled solution of 3 *N* sodium hydroxide (80 ml) was added dropwise to the mixture. Solid **12** was filtered and recrystallized from dimethylformamide/ethanol (3:1) to give a 95 % yield of the pure product, mp 193-195°; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 3.25 (t, 8H), 4.02 (s, 4H), 4.05 (t, 8H), 5.82 (s, 4H), 6.77 -6.91 (m, 10H), 7.03 (dd, 2H), 7.23 (d, 2H), 7.63 (d, 2H), 8.14 (d, 2H); hrms (fab): m/z = 693.3170 [$(M+Na)^+$], calcd. 693.3169.

Anal. Calcd. for $C_{40}H_{42}N_6O_4$: C, 71.62; H, 6.31. Found: C, 71.40; H, 6.44.

N,*N*'-Bis(8-aminoquinolin-7-ylmethyl)-4,13-diazadibenzo-18-crown-6 (**13**) (Scheme 2).

Macrocycle **13** was prepared as above for **7** from **5** (537 mg, 1.5 mmole) and 567.6 mg (3.3 mmole) of 8-amino-7-quinolinecarboxaldehyde. Crude **13** was purified by recrystallization from dimethylformamide/ethanol (5:1) to give 824 mg (82%) of **13** as a yellow solid, mp 220-221°; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 3.20 (t, 8H), 4.01 (s, 4H), 4.04 (t, 8H), 5.82 (s, 4H), 6.78-6.82 (m, 10H), 7.04 (d, 2H), 7.26 (d, 2H), 7.43 (dd, 2H), 8.08 (d, 2H); hrms (fab): m/z = 693.3150 [$(M+Na)^+$], calcd. 693.3169.

Anal. Calcd. for $C_{40}H_{42}N_6O_4$: C, 71.62; H, 6.31. Found: C, 71.38; H, 6.44.

8-Methoxy-2-quinolinecarboxaldehyde (**16**) (Scheme 3).

Compound **16** was prepared as above for **10** from 8-methoxyquinaldine (**14**) (2.91 g, 16.8 mmole) and selenium dioxide (3.33 g, 30 mmole). Crude compound **16** was purified by column chromatography on silica gel using methylene chloride/hexane (3:1) as eluent to give 2.89 g (92%) of **16** as yellow crystals, mp 103-104°; ^{1}H nmr (deuteriochloroform): δ = 4.17 (s, 3H), 7.17 (d, 1H), 7.49 (d, 1H), 7.62 (t, 1H), 8.08 (t, 1H), 8.30 (d, 1H), 10.33 (s, 1H); ms(ci): m/z = 188 [$(M+1)^+$].

Anal. Calcd. for $C_{11}H_9NO_2$: C. 70.58; H, 4.85. Found: C, 70.36; H, 4.62.

5-Chloro-8-methoxy-2-quinolinecarboxaldehyde (**17**) (Scheme 3).

Compound **17** was prepared as above for **10** from 5-chloro-8-methoxyquinaldine **15** (3.49 g, 16.8 mmole) and selenium dioxide (3.33 g, 30 mmole). Crude **17** was purified by column chromatography on silica gel using methylene chloride/hexane (3:1) as eluent to give 3.35 g (90%) of **17** as yellow crystals, mp 163-164°: ^{1}H nmr (deuteriochloroform): δ = 4.15 (s, 3H), 7.07 (d, 1H), 7.67 (d, 1H), 8.14 (d, 1H), 8.66 (d, 1H), 10.31 (s, 1H); ms (ci); m/z = 222 (M^+).

Anal. Calcd. for $C_{11}H_8NO_2Cl$: C, 59.66; H, 3.64. Found: C, 59.79; H, 3.77.

N,*N*'-Bis(8-methoxyquinolin-2-ylmethyl)-4,13-diazadibenzo-18-crown-6 (**18**) (Scheme 3).

Macrocycle **18** was prepared as above for **7** from **5** (537 mg, 1.5 mmole) and **16** (617 mg, 3.3 mmole). Crude **18** was purified by recrystallization from methylene chloride/ethanol (2:1) to give 903 mg (86%) of **18** as a white solid, mp 196-197°; ^{1}H nmr (deuteriochloroform): δ = 3.36 (t, 8H), 4.08 (s, 6H), 4.15 (t, 8H), 4.21 (s, 4H), 6.78-6.81 (m, 8H), 7.05 (dd, 2H), 7.39 - 7.44 (m, 4H), 7.82 (d, 2H), 8.10 (d, 2H); hrms (fab): m/z = 723.3152 [$(M + Na)^+$], calcd. 723.3161.

Anal. Calcd. for $C_{42}H_{44}N_4O_6$: C, 71.98; H, 6.33. Found: C, 71.81; H, 6.15.

N,*N*'-Bis(5-chloro-8-methoxyquinolin-2-ylmethyl)-4,13-diazadibenzo-18-crown-6 (**19**) (Scheme 3).

Macrocycle **19** was prepared as above for **7** from **5** (537 mg, 1.5 mmole) and **17** (729 mg, 3.3 mmole). Crude **19** was purified by recrystallization from chloroform/ethanol (2:1) to give 946 mg (82%) of **19** as a white solid, mp 204-206°; ^{1}H nmr (deuteriochloroform): δ = 3.37 (t, 8H), 4.08 (s, 6H), 4.16 (t, 8H), 4.24

(s, 4H), 6.82 (m, 8H), 7.0 (d, 2H), 7.51 (d, 2H), 7.96 (d, 2H), 8.50 (d, 2H); hrms (fab): m/z = 791.2373 [(M + Na)$^+$], calcd. 791.2383.

Anal. Calcd. for $C_{42}H_{42}N_4O_6Cl_2$•1.5H_2O: C, 63.31; H, 5.69. Found: C, 63.57; H, 5.72.

N,*N'*-Bis(dansylamidoethyl)-4,13-diazadibenzo-18-crown-6 (**21**) (Scheme 4).

N-Dansylarizidine (**20**) (662 mg, 2.4 mmole) in dry acetonitrile (20 ml) was added drop- wise over 30 minutes to a refluxing solution of **5** (358 mg, 1.0 mmole) in 30 ml of dry acetonitrile under nitrogen. The mixture was stirred at reflux for 5 hours. After evaporation of the solvent, the crude product was purified by recrystallization from chloroform/ethanol (1:1) to give 801 mg (88%) of **21** as a green solid, mp 79-81°; ^{1}H nmr (deuteriochloroform): δ = 2.59 (t, 4H), 2.85 (s, 12H), 2.91 (m, 12H), 3.80 (t, 8H), 5.58 (br, 2H), 6.70 (dd, 4H), 6.89 (dd, 4H), 7.13 (d, 2H), 7.48 (t, 4H), 8.24 (m, 4H), 8.51 (d, 2H); hrms (fab): m/z = 933.3673 [(M + Na)$^+$]. Calcd. 933.3659.

Anal. Calcd. for $C_{48}H_{58}N_6O_8S_2$: C, 63.27; H, 6.42. Found: C, 63.12; H, 6.46.

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REFERENCES AND NOTES

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[1a] R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, J. J. Christensen, and D. Sen, *Chem. Rev.*, **85**, 271 (1985); [b] R. M. Izatt, K. Pawlak, J. S. Bradshaw, and R. L. Bruening, *Chem. Rev.*, **91**, 1721 (1991); [c] R. M. Izatt, K. Pawlak, J. S. Bradshaw, and R. L. Bruening, *Chem. Rev.*, **95,** 1231 (1995); [d] Y. Inoue and G. W. Gokel, Cation Binding by Macrocycles; Marcel Dekker: New York, 1990.

[2a] G.-P. Xue, B. P. Savage, J. S. Bradshaw, X. X. Zhang, and R. M. Izatt, Functionalized Macrocyclic Ligands as Sensory Molecules for Metal Ions, In Advances in Supramolecular Chemistry, Vol. **7**. G. W. Gokel Ed.; JAI Press, New York, NY, 2000, pp 99-137; [b] P. Bühlmann, E. Pretsch, and E. Bakker, *Chem. Rev.*, **98**, 1593 (1998).

[3a] G.-P. Xue, J. S. Bradshaw, J. A. Chiara, P. B. Savage, K. E. Krakowiak, R. M. Izatt, L. Prodi, M. Montalti, and N. Zaccheroni, *Synlett*., 1181 (2000); [b] G.-P. Xue, J. S. Bradshaw, H.-C. Song, R. T. Bronson, P. B. Savage, K. E. Krakowiak, R. M. Izatt, L. Prodi, M. Montalti, and N. Zaccheroni, *Tetrahedron*, **57**, 87 (2001); [c] N. Su, J. S. Bradshaw, X. X. Zhang, H.-C. Song, P. B. Savage, G.-P. Xue, K. E. Krakowiak, and R. M. Izatt, *J. Org. Chem.*, **64**, 8855 (1999); [d] N. Su, J. S. Bradshaw, P. B. Savage, K. E. Krakowiak, and R. M. Izatt, *J. Org. Chem.*, **64**, 3825 (1999); [e] X. X. Zhang, A. V. Bordunov, J. S. Bradshaw, N. K. Dalley, X.-L. Kou, and R. M. Izatt, *J. Am. Chem. Soc.*, **117**, 11507 (1995); [f] A.V. Bordunov, J. S. Bradshaw, X. X. Zhang, N. K. Dalley, X.-L. Kou, and R. M. Izatt, *Inorg. Chem.*, **35**, 7229 (1996).

[4] L. Prodi, F. Bolletta, M. Montalti, N. Zaccheroni, P. B. Savage, J. S. Bradshaw, and R. M. Izatt, *Tetrahedron Lett.*, **39**, 5451 (1998).

[5] L. Prodi, C. Bargossi, M. Montalti, N. Zaccheroni, N. Su, J. S. Bradshaw, R. M. Izatt, and P. B. Savage, *J. Am. Chem. Soc.*, **122**, 6769 (2000).

[6] L. Prodi, M. Montalti, N. Zaccheroni, P. B. Savage, J. S. Bradshaw, and R. M. Izatt, *Tetrahedron Lett.*, **42**, 2941 (2001).

[7] G.-P. Xue, J. S. Bradshaw, N. K. Dalley, P. B. Savage, K. E. Krakowiak, R. M. Izatt, L. Prodi, M. Montalti, and N. Zaccheroni, *Tetrahedron Lett.*, **57**, 7623 (2001).

[8] G.-P. Xue, J. S. Bradshaw, N. K. Dalley, P. B. Savage, R. M. Izatt, L. Prodi, M. Montalti, and N. Zaccheroni, *Tetrahedron Lett.*, submitted.

[9] J. L. Hallman, N. A. R. Nabulsi, M. D. Utterback, B. Strzelbicka, and R. A. Bartsch, *Anal. Chem.*, **67**, 4101 (1995).

[10] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanof, and R. D. Shah, *J. Org. Chem.*, **61**, 3849 (1996).

[11] Z. Yang, J. S. Bradshaw, X. X. Zhang, P. B. Savage, K. E. Krakowiak, N. K. Dalley, N. Su, R. T. Bronson, and R. M. Izatt, *J. Org. Chem.*, **64**, 3162 (1999).

[12] E. C. Riesgo, X.-Q. Jin, and R. P. Thummel, *J. Org. Chem.*, **61**, 3017 (1996).

[13] S. A. G. Högberg and D. J. Cram, *J. Org. Chem.*, **40**, 151 (1975).