Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Synthesis of New Crown Ethers Containing Appended Pyridine, 10-hydroxybenzoquinoline, 8-hydroxyquinoline and 2-amino-1-hydroxybiphenyl Sidearms

Hua-Can Song[a]; Jerald S. Bradshaw[b]; Yi-Wen Chen[a]; Guo-Ping Xue[b]; Wei-Ming Li[a]; Krzysztof E. Krakowiak[c]; Paul B. Savage[b]; Zun-Le Xu[a]; Reed M. Izatt[b]
[a] Department of Chemistry, Zhongshan University, Guangzhou, People's Republic of China [b] Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT, USA [c] IBC Advanced Technologies Inc., American Fork, UT, USA

Online publication date: 29 October 2010

To cite this Article Song, Hua-Can , Bradshaw, Jerald S. , Chen, Yi-Wen , Xue, Guo-Ping , Li, Wei-Ming , Krakowiak, Krzysztof E. , Savage, Paul B. , Xu, Zun-Le and Izatt, Reed M.(2002) 'Synthesis of New Crown Ethers Containing Appended Pyridine, 10-hydroxybenzoquinoline, 8-hydroxyquinoline and 2-amino-1-hydroxybiphenyl Sidearms', Supramolecular Chemistry, 14: 2, 263 — 269
To link to this Article: DOI: 10.1080/10610270290026176
URL: http://dx.doi.org/10.1080/10610270290026176

Supramolecular Chemistry, 2002 Vol. 14 (2-3), pp. 263–269

Taylor & Francis
Taylor & Francis Group

Synthesis of New Crown Ethers Containing Appended Pyridine, 10-hydroxybenzoquinoline, 8-hydroxyquinoline and 2-amino-1-hydroxybiphenyl Sidearms

HUA-CAN SONG[a,*], JERALD S. BRADSHAW[b], YI-WEN CHEN[a], GUO-PING XUE[b], WEI-MING LI[a], KRZYSZTOF E. KRAKOWIAK[c], PAUL B. SAVAGE[b], ZUN-LE XU[a] and REED M. IZATT[b]

[a]*Department of Chemistry, Zhongshan University, Guangzhou 510275 People's Republic of China;* [b]*Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602 USA;* [c]*IBC Advanced Technologies, Inc., 856 East Utah Valley Drive, American Fork, UT 84003 USA*

(Received 15 October 2001; In final form 30 November 2001)

Twelve crown ethers containing one or two arms were synthesized. Two methods were used to attach arms to the azacrown ethers. Ligands 4–12 were prepared by a nucleophilic substitution of secondary macrocyclic amine functions on RX (X = bromide or tosylate groups). Ligands 13–15 were obtained via a Mannich reaction of secondary macrocyclic amines with 5-chloro-8-hydroxyquinoline or a substituted-phenol. Diaza-18-crown-6 was treated with 2-bromomethyl-9-methyl-1,10-phenanthroline at the same conditions in which 4–8 and 10–12 were prepared. In this case, the main product was the diazacrown ether containing one arm.

Keywords: Lariat ethers; Syntheses; Substitution and Mannich reaction

INTRODUCTION

Contamination of water supplies by toxic metal ions is a major environmental concern [1]. The high toxicity of many transition and post-transition metal ions, especially Hg^{2+} and Pb^{2+}, is well-recognized [2]. There is a great need for monitoring the level of these metal ions in the environment. Currently, the methods to measure metal ion concentrations in waste streams are usually spectroscopic and wet chemical analysis techniques on samples removed from waste streams [3]. It would be an attractive alternative to monitor the concentrations of specific metal ions in a complex matrix continuously and remotely by using ion-selective sensory devices.

8-Hydroxyquinoline (HQ) has been used extensively as a chromogenic, extraction, and precipitation reagent in analysis and as a fluorescence reagent [4–7]. Introducing HQ fragments into the macrocycle framework can increase the rigidity of those ligands and improve their complexation ability and selectivity for metal ions or organic molecules [8–14]. In macrocyclic ligands containing HQ sidearms, ion coordination with the HQ fragments and the macrocyclic ether can provide interesting new metal ion complexation and fluoroionophoric properties.

Recently, chemical sensors based on the synthetic fluoroionophores and chromoionophores capable of signaling complexation of metal ions have been reported [15–20], however, most of them lacked metal ion selectivity. Many crown ethers have been found to interact selectively with metal ions, and some of them have been used to develop metal ion sensors [20–24]. 5-Chloro-8-hydroxyquinoline (CHQ) appended azacrown ethers in which CHQ was attached through its 7-position (**1**, Fig. 1) or its 2-position (**3**, Fig. 1) [25,26] demonstrated a much greater selectivity than their parent diaza-18-crown-6 ligand for metal ions. Compound **1** exhibited a stronger complexing ability for Mg^{2+} than for Ba^{2+} (log *K* value in methanol is 3.60 for Ba^{2+} and 6.82 for Mg^{2+}) and **3** has a strong complexing ability for Ba^{2+} (log *K* value in methanol is 12.2 for Ba^{2+}) and does not interact with Mg^{2+} [25]. Indeed, **1** is a very effective sensor for Mg^{2+} [27]. Diaza-18-crown-6 containing two 5-nitro-8-hydroxyquinoline units

*Corresponding author.

ISSN 1061-0278 print/ISSN 1029-0478 online © 2002 Taylor & Francis Ltd
DOI: 10.1080/10610270290026176

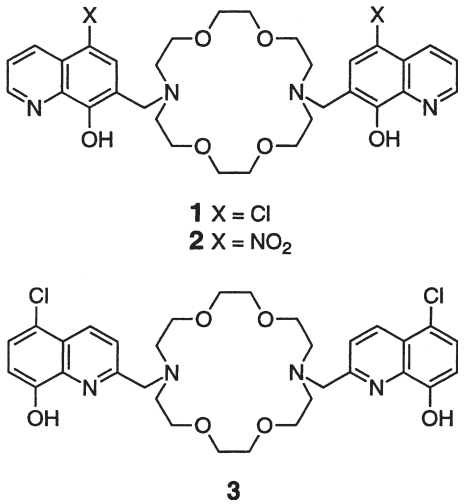
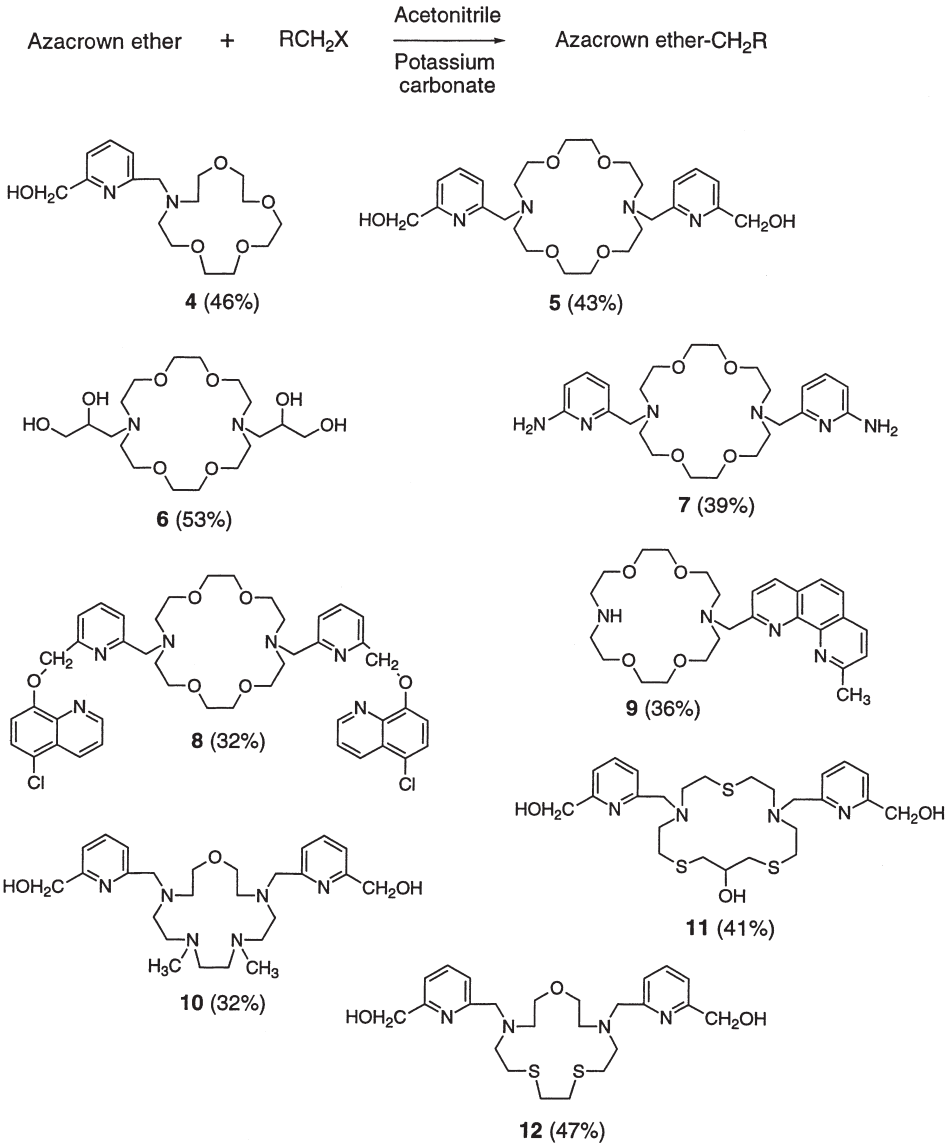


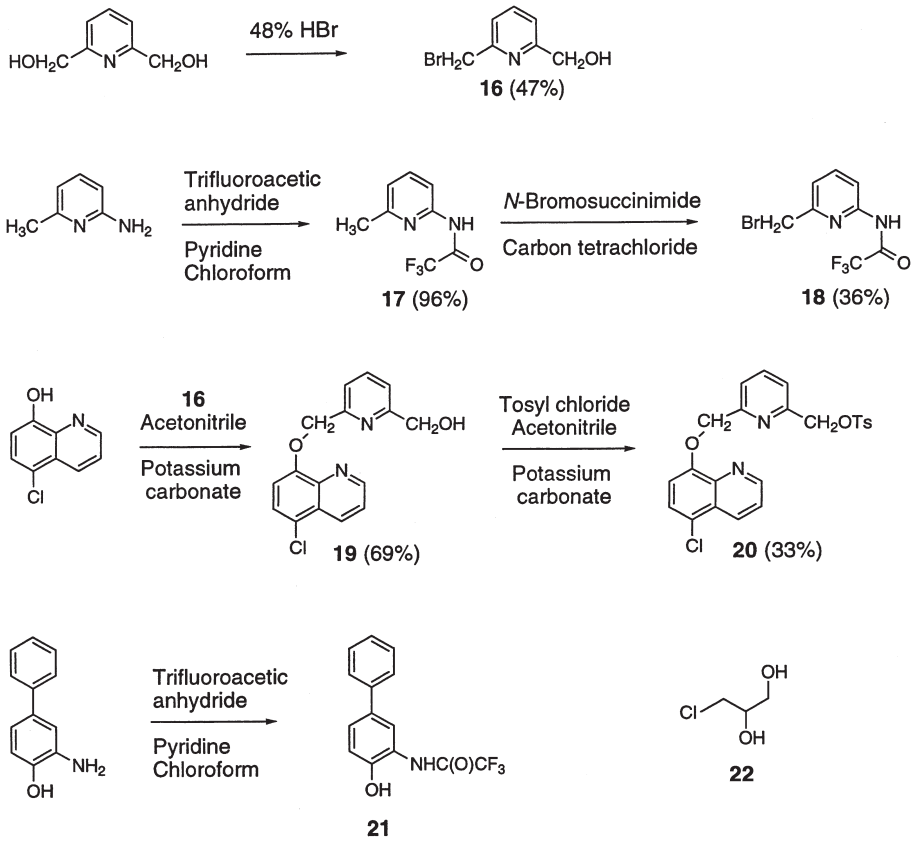
FIGURE 1 5-Chloro-8-hydroxyquinoline (CHQ)-substituted diaza-18-crown-6 ligands **1**–**3**.

connected through their 7-positions (**2**) has been shown to have high affinity and selectivity for Hg^{2+} ion and to be an effective chemosensor for Hg^{2+} [15].

The complexing ability and selectivity of the lariat crown ethers for metal ions can be varied by changing parameters such as the size of the crown ether ring and the type, number, and position of the complexing heteroatoms [28–36]. We now report the preparation of a series of new diazacrown ethers bearing substituted pyridine, 2,3-dihydroxypropane, 8-hydroxyquinoline and 2-amino-1-hydroxybiphenyl sidearms in order to investigate their affinity for metal ions and to further develop chromophoric and fluorophoric sensors. The metal ion affinities of these new ligands will be reported when that work is finished.



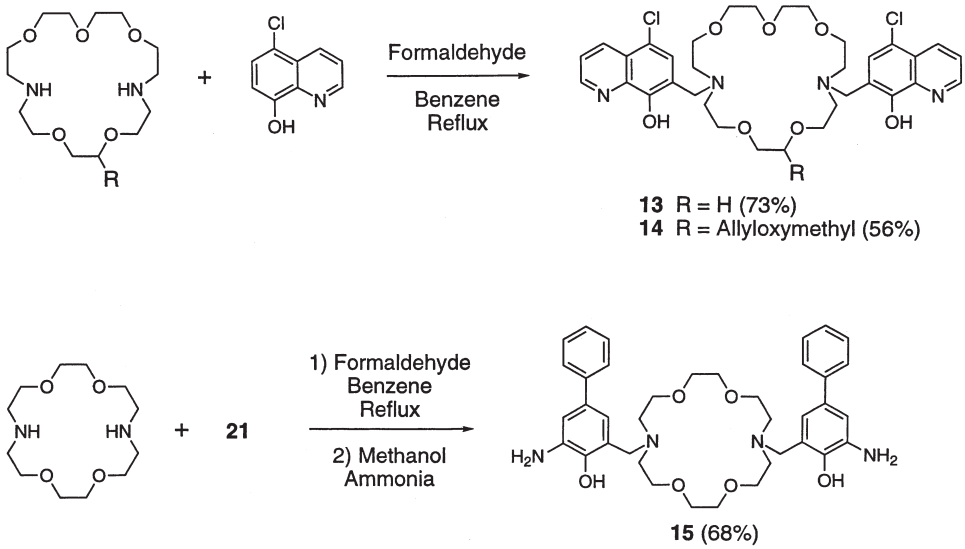
SCHEME 1 Preparation of Azacrown ethers containing side arms using RCH_2X.



SCHEME 2 Preparation of some intermediates.

RESULTS AND DISCUSSION

The preparation of ligands **4**–**12** was accomplished by normal nucleophilic substitution of the appropriate macrocyclic secondary amines on RX where X = bromide or tosylate groups (Scheme 1). Thus, refluxing a mixture of the appropriate azacrown ether, corresponding RX and triethylamine (or potassium carbonate) in acetonitrile gave the aromatic ring appended macrocycles **4**–**12**. It was reported that **10** could not be prepared by this method [37], however, the synthesis of **10** was accomplished by dropping a solution of 2-(bromomethyl)-6-(hydroxymethyl)pyridine (**16**) in acetonitrile into a solution of



SCHEME 3 Preparation of Azacrown ethers containing side arms by the Mannich reaction.

tetraaza-15-crown-5 and potassium carbonate in acetonitrile at 0°C over 3 h. After that the mixture was stirred at room temperature for 4 h and then refluxed for 6 h.

When the size and rigidity of side arms are large, introducing them into the diazacrown ether framework gave only monosubstituted products. For example, attaching 10-hydroxybenzoquinoline to diaza-18-crown-6 by a Mannich reaction using bis(methoxymethyl)diaza-18-crown-6 gave only monosubstituted 7-(10-hydroxybenzoquinolin-9-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 25% yield [36]. The same situation was found when we prepared **9** by nucleophilic substitution. Diaza-18-crown-6 was treated with 2.2 equiv. of 2-bromomethyl-9-methyl-1,10-phenanthroline under the same conditions in which **4**–**8** and **10**–**12** were prepared. The resulting mixture gave only **9**, the monosubstituted product. No disubstituted diaza-18-crown-6 product was observed in this reaction as shown by MS and ^{1}H and ^{13}C NMR data.

The intermediate bromide and tosylate compounds (**16**, **18**, and **21**) needed to form **4**, **5**, **8**, and **10**–**12** were prepared as shown in Scheme 2. 2-(Bromomethyl)-6-(hydroxymethyl)pyridine (**16**) was prepared in a yield of 47% by the reported method [38] except that the mixture was neutralized at −15°C.

Ligands **13**–**15** were obtained via a Mannich reaction of the secondary macrocyclic amines with 5-chloro-8-hydroxyquinoline or 1-hydroxy-2-(trifluoroacetamido)biphenyl (**21**) followed by hydrolysis of the trifluoroacetamido group as shown in Scheme 3. In general, the yield of nucleophilic substitutions to form crown ethers containing sidearms is lower than those using the Mannich reaction. Thus, all other things being equal, the Mannich reaction could be the best method for connecting phenolic sidearms to the azacrown ethers.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform, unless specified otherwise, on Varian NMR instruments. 5-Allyloxymethyl-1,10-diaza-4,5,13,16,19-pentaoxacycloheneicosane needed for the preparation of **14** was prepared in the same manner as the unsubstituted diaza-21-crown-7 [39] from allyloxytriethyleneglycol ditosylate [40] and tetraethylene glycol. Solvents and other starting materials were used as purchased.

2-(Bromomethyl)-6-(hydroxymethyl)pyridine (16) [38]

Ligand **16** was synthesized by refluxing a mixture of 10 g (72 mmol) of 2,6-pyridinedimethanol and 100 ml of 48% aqueous HBr for 1 h. The mixture was cooled to −15°C and neutralized by slow addition of 40% aqueous NaOH keeping the temperature of the mixture below −15°C. The mixture was then diluted to 300 ml, and extracted with 500 ml of methylene chloride in five portions. The residue was purified by chromatography on silica gel to give 6.76 g (47%) of **16**. The mp and NMR spectral data were identical to those reported in Ref. [38].

2-Trifluoroacetamido-6-picoline (17) [36]

To a solution of 2-amino-6-picoline (5.4 g, 50 mmol) and 7.9 g (100 mmol) of anhydrous pyridine in 80 ml of CH_2Cl_2 was added 22.8 g (11.5 mmol) of trifluoroacetic anhydride at 0–5°C over a 1 h period. The mixture was stirred at room temperature for 12 h. When most of solvent was evaporated under reduced pressure, the mixture was washed with water three times, and then dried (Na_2SO_4). The solvent was removed under reduced pressure to give **17** (96%); ^{1}H NMR (DMSO-d_6) δ: 2.40 (s, 3H), 6.69 (d, $J = 7.5$ Hz, 1H), 6.79 (d, $J = 9.0$ Hz, 1H), 7.79 (dd, $J = 6.9, 7.2$ Hz, 1H), 8.02 (s, 1H, NH). This material was used without further purification in the next step.

2-Bromomethyl-6-trifluoroacetamidopyridine (18)

A mixture of 2.04 g (10 mmol) of **17**, 1.80 g (10 mmol) of *N*-bromosuccinimide, and 0.3 g of benzoyl peroxide in 80 ml of CCl_4 was refluxed for 6 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography to give 1.01 g (36%) of pure **18**; ^{1}H NMR (DMSO-d_6) δ: 4.68 (s, 2H), 6.78 (d, $J = 7.2$ Hz, 1H), 7.08 (d, $J = 8.1$ Hz, 1H), 7.98 (dd, $J = 6.3, 6.6$ Hz, 1H), 8.15 (s, 1H, NH). *Anal.* Calcd. For $C_8H_6BrF_3N_2O$: C, 33.95; H 2.14. Found: C, 34.08; H, 2.08.

2-Hydroxymethyl-6-(5-chloroquinolin-8-yloxymethyl)pyridine (19)

To a solution of 3.58 g (20 mmol) of 5-chloro-8-hydoxyquinoline and 9.6 g (70 mmol) of K_2CO_3 in 150 ml of MeCN was added dropwise 4.5 g (21 mmol) of **16** in 30 ml of MeCN at room temperature during 2 h. The mixture was refluxed for 4 h and the solvent was distilled under reduced pressure. The residue was purified by chromatography to give 4.13 g (69%) of **19** as a low melting solid; ^{1}H NMR δ: 4.80 (s, 2H), 5.55 (s, 2H), 6.97 (d, $J = 8.8$ Hz, 1H), 7.19 (d, $J = 7.8$ Hz, 1H), 7.47 (d, $J = 8.8$ Hz, 1H), 7.52–7.63 (m, 2H), 7.71 (d, $J = 7.8$ Hz, 1H), 8.59 (d, $J = 8.8$ Hz, 1H), 9.02 (d, $J = 3.2$ Hz, 1H); HRMS for $C_{16}H_{14}ClN_2O_2$ $(M + H)^+$, calcd: 301.0744, found: 301.0734. This

material was used in the next step without further purification.

2-(*p*-Toluenesulfoxymethyl)-6-(5-chloroquinolin-8-yloxymethyl)pyridine (20)

To a solution of 1.49 g (5.0 mmol) of **19** and 2.4 g (17.5 mmol) of K_2CO_3 in 60 ml of MeCN was added dropwise 1.14 g (6.0 mmol) of *p*-toluenesulfonyl chloride in 25 ml of MeCN at room temperature and the resulting mixture was refluxed for 6 h. After removing the MeCN, the product (33%) was purified by chromatography; mp 105–107°C; ^{1}H NMR δ: 2.52 (s, 3H), 5.16 (s, 2H), 5.42 (s, 2H), 6.91 (d, $J = 9.0$ Hz, 1H), 7.33–7.38 (m, 3H), 7.41–7.71 (m, 4H), 7.87 (d, $J = 8.0$ Hz, 2H), 9.05 (d, $J = 10$ Hz, 2H); HRMS for $C_{33}H_{19}ClN_2O_4S$ $(M)^+$, calcd. 454.0754, found 454.0747. Ligand **8** prepared from **20** gave a satisfactory elemental analysis.

4-Phenyl-2-trifloroacetamidophenol (21)

Compound **21** was prepared as **17** above to give a quantitative yield; mp 244–245°C; ^{1}H NMR (DMSO-d_6) δ: 7.05 (d, $J = 8.8$ Hz, 1H), 7.30–7.62 (m, 7H), 10.11 (s, 1H, NH), 10.65 (s, 1H, OH); HRMS for $C_{14}H_{11}F_3NO_2(M + H)^+$, calcd. 282.0742, found 282.0763. Ligand **15**, prepared from **21**, gave a satisfactory elemental analysis.

General Procedure a to Synthesize Compounds 4–12 (Scheme 1)

To a mixture of 3.0 mmol of crown ether and 15.0 mmol (2.0 g) of K_2CO_3 in 40 ml of MeCN was added dropwise to a solution of 7.1 mmol of RX in 40 ml of MeCN over a 1.5 h period. After the mixture was refluxed for 6 h, the solid mixture was filtered and the solvent was distilled under reduced pressure. The product was purified by chromatography using a mixture of methylene chloride, methanol and ammonia (50:5:1) as eluent.

1-(6-Hydroxymethylpyridin-2-ylmethyl)-1-aza-4,7,10,13-tetraoxacyclopentadecane (4)

According to the general procedure A, compound **4** (0.47 g, 46%) was prepared from 0.73 g (3.6 mmol) of **16** and 0.66 g (3.0 mmol) of 1-aza-4,7,10,13-tetraoxacyclopentadecane; mp 126.5–127.5°C; ^{1}H NMR δ: 2.63 (s, 2H), 2.75 (s, 2H), 3.54–3.69 (m, 16H), 3.84 (s, 2H), 4.96 (s, 2H), 7.02 (d, $J = 4.8$ Hz, 1H), 7.06 (d, $J = 4.8$ Hz, 1H), 7.58 (t, $J = 7.4$ Hz, 1H); HRMS for $C_{17}H_{28}N_2O_5$ $(M)^+$: calcd. 340.1998, found: 340.2006. *Anal*. Calcd. for $C_{17}H_{28}N_2O_5$: C, 59.98; H, 8.29. Found: C, 60.12; H, 8.18.

1,10-Bis(6-hydroxymethylpyridin-2-ylmethyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (5)

Ligand **5** (0.65 g, 43%) was obtained as a low melting solid according to general procedure A from 3.0 mmol (0.79 g) of diaza-18-crown-6 and 7.1 mmol (1.43 g) of **16**; ^{1}H NMR δ: 2.62 (t, $J = 16$ Hz, 8H), 3.61 (m, 16H), 3.92 (s, 4H), 4.51 (s, 4H), 7.13 (d, $J = 6.0$ Hz, 2H), 7.18 (d, $J = 6.0$ Hz, 2H), 7.60 (t, $J = 6.8$ Hz, 2H); HRMS for $C_{26}H_{40}N_4O_6Na$ $(M)^+$: calcd. 527.2845, found 527.2831. *Anal*. Calcd. for $C_{26}H_{40}N_4O_6$: C, 61.88; H, 7.99. Found: C, 61.82; H, 8.08.

1,10-Bis(2,3-dihydroxypropyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (6)

Diaza-18-crown-6 (3.0 mmol, 0.79 g) 22 was treated with 7.1 mmol (0.78 g) of 3-chloro-1,2-propanol according to the general procedure A to give 0.65 g (53%) of **6** as a viscous oil; ^{1}H NMR δ: 2.82 (t, $J =$ 4.5 Hz, 8H), 3.60–3.64 (m, 26H); ^{13}C NMR δ: 48.3, 49.6, 62.9, 64.4, 66.8, 79.9, 70.3, 70.4, 70.7; HRMS for $C_{18}H_{38}N_2O_8Na$ $(M + Na)^+$, calcd. 433.2526, found 433.2503. *Anal*. Calcd. for $C_{18}H_{38}N_2O_8$: C, 52.67; H, 9.33. Found: C, 52.82: H, 9.19.

1,10-Bis(6-aminopyridin-2-ylmethyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (7)

Diaza-18-crown-6 (3.0 mmol, 0.79 g) and 7.1 mmol (2.01 g) of **18** was treated using Et_3N as base to remove HBr generated in the reaction according to general procedure A. After MeCN was removed, 50 ml of MeOH–NH_3 was added to the residue and the mixture was refluxed for 12 h. MeOH was distilled under reduced pressure and the residue was purified by chromatography to give 0.55 g (39%) of **7** as a low melting solid; ^{1}H NMR δ: 2.87 (s, 8H), 3.75 (m, 20H), 6.16 (s, 4H, NH_2), 6.73 (d, $J = 6.8$ Hz, 2H), 7.00 (d, $J = 7.8$ Hz, 2H), 7.60(m, 2H); HRMS for $C_{24}H_{38}N_6O_4Na$, calcd. 497.2852, found 497.2855. *Anal*. Calcd. for $C_{24}H_{38}N_6O_4$: C, 60.74; H, 8.07. Found: C, 60.71; H, 8.18.

1,7-Bis[6-(5-chloroquinolin-8-yloxymethyl)pyridin-2-ylmethyl]-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (8)

Ligand **8** (0.27 g, 32%) was isolated as a viscous oil from 0.99 g (2.1 mmol) of **20** and 0.26 g (1.0 mmol) of diaza-18-crown-6 according to the general procedure A; ^{1}H NMR δ: 2.83 (s, 8H), 3.50 (s, 8H), 3.59 (s, 8H), 3.96 (s, 4H), 5.50 (s, 4H), 7.01 (d, $J = 2.0$ Hz, 2H), 7.06 (s, 2H), 7.39–7.46 (m, 4H), 7.56–7.60 (m, 2H), 7.79 (d, $J = 8.0$ Hz, 2H), 8.52 (dd, $J = 1.6$, 1.6 Hz, 2H), 9.00 (dd, $J = 1.6$, 1.6 Hz, 2H); HRMS for $C_{44}H_{48}Cl_2N_6O_6$ $(M)^+$, calcd. 850.3012, found 850.3016. *Anal*. Calcd.

for $C_{44}H_{48}Cl_2N_6O_6$: C, 63.84; H, 5.84. Found: C, 63.69; H 5.97.

1-(9-Methyl-1,10-phenanthrolin-2-ylmethyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (9)

2-Bromomethyl-9-methyl-1,10-phenanthroline was synthesized from 2,9-dimethyl-1,10-phenanthroline [41]. This compound (3.6 mmol, 1.03 g) was treated with 1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (1.5 mmol, 0.39 g) in MeCN according to the general procedure A to give **9** (0.25 g, 36%); mp 130–131.5°C; ^{1}H NMR δ: 2.88 (t, $J = 2.7$ Hz, 4H), 2.94 (s, 3H), 3.00 (s, 4H), 3.50 (s, 4H), 3.56 (s, 4H), 3.63 (t, $J = 3.0$ Hz, 4H), 3.77 (s, 4H), 4.13 (s, 2H), 7.54 (d, $J = 4.8$ Hz, 1H), 7.75 (d, $J = 4.5$ Hz, 1H), 7.79 (d, $J = 4.8$ Hz, 1H), 7.82 (d, $J = 4.5$ Hz, 1H), 8.18 (d, $J = 4.8$ Hz, 1H), 8.34 (d, $J = 4.5$ Hz, 1H); HRMS for $C_{26}H_{37}N_4O_4$ $(M + H)^+$ (Fab), calcd. 469.2815, found 469.2810. *Anal*. Calcd. for $C_{26}H_{37}N_4O_4$: C, 66.64; H, 7.74. Found: C, 66.69; H, 7.67.

1,7-Bis(6-hydroxymethylpyridin-2-ylmethyl)-10,13-dimethyl-4-oxa-1,7,10,13-tetraazacyclopentadecane (10)

According to the general procedure A, compound **10** (0.23 g, 32%) was obtained as a viscous liquid from 0.15 mmol (0.37 g) of 10,13-dimethyl-4-oxa-1,7,10,13-tetraazacyclopentadecane [37] and 0.78 g (3.6 mmol) of **16** except the addition of **16** at 0°C during 3 h and stirring for 4 h at room temperature; ^{1}H NMR δ: 1.97 (s, 6H), 2.12–2.42 (m, 8H), 2.73 (m, 4H), 2.88 (m, 4H), 3.43–3.78 (m, 8H), 4.69 (s, 4H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 7.4$ Hz, 2H), 7.63 (t, $J = 7.6$ Hz, 2H). *Anal*. Calcd. for $C_{26}H_{42}N_6O_3$: C, 64.17; H, 8.70. Found: C, 64.02; H, 8.77.

12-Hydroxy-1,7-bis(6-hydroxymethylpyridin-2-ylmethyl)-1,7-diaza-4-oxa-10,14-dithiacyclohexadecane (11)

According to general procedures A, compound **11** (0.32 g, 41%) was obtained from 1.5 mmol (0.42 g) of 12-hydroxyl-1,7-diaza-4-oxa-10,14-dithiacyclohexadecane [37] except the addition of **16** at 0°C during 3 h and stirring for 4 h at room temperature, mp 106–107°C; ^{1}H NMR δ: 2.61 (m, 2H), 2.68 (d, $J = 3.9$ Hz, 4H), 2.78 (m, 14H), 3.80 (s, 4H), 3.91 (m, 1H), 4.71 (s, 4H), 7.11 (d, $J = 4.5$ Hz, 2H), 7.35 (d, $J = 4.5$ Hz, 2H), 7.64 (t, $J = 4.5$ Hz, 2H). *Anal*. Calcd. for $C_{25}H_{38}N_4O_4S_2$: C, 57.44; H, 7.33. Found: C, 57.32; H, 7.25.

1,7-Bis(6-hydroxymethylpyridin-2-ylmethyl)-1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (12)

This compound (0.69 g, 47%) was obtained as a viscous oil from 3.0 mmol (0.75 g) of diazadithia-15-crown-5 and 0.71 mmol (1.58 g) of **16** according to the general procedure **A**; ^{1}H NMR δ: 2.81–2.92 (m, 12H), 3.06 (m, 4H), 3.61 (t, $J = 4.6$ Hz, 4H), 3.89 (s, 4H), 4.70 (s, 4H), 7.13 (d, $J = 6.3$ Hz, 2H), 7.37 (d, $J = 6.0$ Hz, 2H), 7.63 (t, $J = 6.0$ Hz, 2H). *Anal*. Calcd. for $C_{24}H_{36}N_4O_3S_2$, C, 58.51; H, 7.36. Found: C, 58.35; H, 7.50.

General Procedure B for the Preparation of Compounds 13–15 (Scheme 3)

A mixture of 2.0 mmol of crown ether, 4.5 mmol (0.85 g) of 5-chloro-8-hydroxyquinoline and 6.0 mmol (0.19 g) of paraformaldehyde in 60 ml of anhydrous benzene was refluxed in an N_2 atmosphere for 12 h. The solvent was distilled under reduced pressure and the residue was isolated by chromatography.

1,10-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7,13,16,19-pentaoxa-cycloheneicosane (13)

According to the general procedure B, compound **13** (1.00 g, 73%) was synthesized as a viscous liquid from 0.61 g (2.0 mmol) of diaza-21-crown-7 [39] and 0.79 g (4.4 mmol) of 5-chloro-8-hydroxyquinoline; ^{1}H NMR δ: 2.95 (m, 8H), 3.65 (m, 12H), 3.72 (m, 8H), 4.06 (s, 4H), 7.35 (s, 2H), 7.47 (d, $J = 3.5$ Hz, 2H), 8.46 (d, $J = 4.0$ Hz, 2H), 8.91 (s, 2H); HRMS for $C_{34}H_{42}Cl_2N_4O_7Na$ $(M + Na)^+$, calcd. 711.2328, found 711.2345. *Anal*. Calcd. for $C_{34}H_{42}Cl_2N_4O_7$, C, 59.22; H, 6.14. Found: C, 59.05; H, 6.20.

5-Allyloxymethyl-1,10-bis(5-chloro-8-hydroxyquinolin-7-ylmethyl-1,10-diaza-4,7,13,16,19-pentaoxacycloheneicosane (14)

This compound (0.64 g, 56%) was prepared as a viscous liquid from 0.54 g (1.5 mmol) of 5-allyloxymethyl-1,10-diaza-4,7,13,16,19-pentaoxacycloheneicosane and 0.59 g (3.3 mmol) of 5-chloro-8-hydroxyquinoline according to the general procedure B; ^{1}H NMR δ: 2.87 (t, $J = 3.2$ Hz, 8H), 3.43 (d, $J = 2.8$ Hz, 3H), 3.61 (m, 16H), 3.88 (t, $J = 16$ Hz, 4H), 4.01 (d, $J = 18$ Hz, 4H), 5.06–5.30 (m, 2H), 5.71–5.91 (m, 1H), 7.35 (s, 2H), 7.46 (q, $J = 4.0$ Hz, 2H), 8.44 (dd, $J = 1.6$, 2.0 Hz, 2H), 8.90 (dd, $J = 1.4$, 1.4 Hz, 2H); HRMS for $C_{38}H_{48}Cl_2N_4O_8Na$ $(M + Na)^+$, calcd. 781.2747, found 781.2740. *Anal*. Calcd. for $C_{38}H_{48}Cl_2N_4O_8$, C,60.08; H, 6.37. Found: C, 59.95; H, 6.42.

1,10-Bis(3-amino-2-hydroxy-5-phenylbenzyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (15)

According to the general procedure B, a mixture of 0.79 g (3 mmol) of 1,10-diaza-18-crown-6, 1.77 g

(6.3 mmol) of **21** and 0.54 g (18 mmol) of paraformaldehyde in 80 ml of anhydrous benzene was refluxed for 12 h to give 1,10-bis(2-hydroxy-5-phenyl-3-trifluoroacetamidobenzyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane. Benzene was removed from the mixture under reduced pressure, 50 ml of MeOH–NH_3 was added to the residue, and the resulting mixture was stirred for 12 h at room temperature. After the solvent was removed under reduced pressure, product **15** (1.34 g, 68%) was isolated from the residue by chromatography; mp 160–161.5°C; ^{1}H NMR (DMSO-d_6) δ: 2.80 (s, 8H), 3.62 (m, 16H), 3.94 (s, 4H), 7.29–7.44 (m, 8H), 7.59 (d, $J = 7.2$ Hz, 6H); HRMS for $C_{38}H_{47}N_4O_6Na$ $(M - H + Na)^+$, calcd. 678.3393, found 678.3402. *Anal*. Calcd. for $C_{38}H_{48}N_4O_6$: C, 69.49; H, 7.37. Found: C, 69.55; H, 7.52.

Acknowledgements

The authors thank the Scientific and Technical Commission of Guangzhou, China and the US Office of Naval Research for financial support.

References

[1] Boudou, A. and Ribeyre, F. (1997) In: Sigel, H., ed, *Metal Ions in Biological Systems* (Marcel Dekker, New York) Vol. 34.
[2] Foulkes, E. (1990) *Biological Effects of Heavy Metals* (CRC Press, Boca Raton, FL) **Vols. 1 and 2**.
[3] Lester, J. (1987) *Heavy Metals in Wastewater and Sludge Treatment Processes* (CRC Press, Boca Raton, FL) Vol. 1.
[4] Sandell, E.B. and Onishi, H. (1978) *Photometric Determination of Traces of Metals, 4th Ed.*, p 415.
[5] Stary, J. (1964) *The Solvent Extraction of Metal Chelates* (Pergamon Press, New York).
[6] Welcher, F.J. (1947) *8-Hydroxyquinoline in Organic Analytical Reagents* (Van Nostrand Reinhold, Princeton, NJ) Vol. 1, p 264.
[7] Gordon, L., Salutsky, M.L. and Willard, H.H. (1959) *Precipitation from Homogeneous Solution* (Wiley, New York).
[8] Nishida, H., Katyama, Y., Katsuki, H., Nakamura, H., Takagi, M. and Ueno, K. (1982), *Chem. Lett.*, 1853.
[9] Alihodzic, S., Zinic, M., Klaic, B., Kiralj, R., Kojic-Prodic, B., Herceg, M. and Cimerman, Z. (1993), *Tetrahedron Lett.* **34**, 8345.
[10] Katayama, Y., Fukuda, R., Iwasaki, T., Nita, K. and Takagi, M. (1988), *Anal. Chim. Acta* **204**, 113.
[11] Chaptoeau, E., Czech, B.P., Gebauer, C.R., Kumar, A., Leong, K., Mytych, D.T. and Bartsch, R.A. (1991), *J. Org. Chem.* **56**, 2575.
[12] Zhang, X.X., Bordunov, A.V., Bradshaw, J.S., Dalley, N.K., Kou, X. and Izatt, R.M. (1995), *J. Am. Chem. Soc.* **117**, 11507.
[13] Bradshaw, J.S. and Izatt, R.M. (1977), *Acc. Chem. Res.* **30**, 338.
[14] Bordunov, A.V., Bradshaw, J.S., Zhang, X.X., Dalley, N.K., Kou, X. and Izatt, R.M. (1996), *Inorg. Chem.* **35**, 7229.
[15] Prodi, L., Bargossi, C., Montalti, M., Zaccheroni, N., Su, N., Bradshaw, J.S., Izatt, R.M. and Savage, P.B. (2000), *J. Am. Chem. Soc.* **122**, 6769.
[16] Rurack, K., Kollmannsberger, M., Resch-Genger, U. and Daub, J. (2000), *J. Am. Chem. Soc.* **122**, 968.
[17] Oehme, I., Prattes, S., Wolfveis, S.O. and Mohr, J.G. (1998), *Tetrahedron* **47**, 595.
[18] Chau, L.K. and Porter, D.M. (1990), *Anal. Chem.* **62**, 1964.
[19] Wang, K., Seiler, K., Rusterholz, P. and Simon, W. (1992), *Analyst* **117**, 57.
[20] Izatt, R.M., Pawlak, K., Bradshaw, J.S. and Bruening, R.L. (1995), *Chem. Rev.* **95**, 1231.
[21] Ueno, A., Ikeda, A., Ikeda, H., Ikeda, T. and Toda, F. (1999), *J. Org. Chem.* **64**, 382.
[22] Oguz, U. and Akkaya, U.E. (1998), *Tetrahedron Lett.* **39**, 5857.
[23] Unob, F., Asfari, Z. and Vicens, J. (1998), *Tetrahedron Lett.* **39**, 2951.
[24] Marquis, D., Desvergne, J.-P. and Bouas-Laurent, H. (1995), *J. Org. Chem.* **60**, 7984.
[25] Bordunov, A.V., Bradshaw, J.S., Zhang, X.X., Dalley, N.K., Kou, X. and Izatt, R.M. (1996), *Inorg. Chem.* **35**, 7229.
[26] Zhang, X.X., Bordunov, A.V., Bradshaw, J.S., Dalley, N.K., Kou, X. and Izatt, R.M. (1995), *J. Am. Chem. Soc.* **117**, 11507.
[27] Prodi, L., Boletta, F., Montalti, M., Zaccheroni, N., Savage, P.B., Bradshaw, J.S. and Izatt, R.M. (1998), *Tetrahedron Lett.* **39**, 5451.
[28] van Verggel, F.C.J.M., Verboom, W. and Reinhoudt, D.N. (1994), *Chem. Rev.* **94**, 279.
[29] Graf, E., Hosseini, M.W., DeCian, A. and Fischer, J. (1966), *J. Bull. Soc. Chim. Fr.* **133**, 743.
[30] Gokel, G.W. and Schall, O.F. (1996) In: Gokel, G.W., ed, *Comprehensive Supramolecular Chemistry, Ed. 1* (Pergamon, New York), p 97.
[31] Bradshaw, J.S., Song, H.-C., Xue, G.-P., Bronson, R.T., Chiara, J.A., Krakowiak, K.E., Savage, P.B. and Izatt, R.M. (2001), *Supramol. Chem.* **13**, 499.
[32] Xue, G.-P., Bradshaw, J.S., Song, H.-C., Bronson, R.T., Savage, P.B., Krakowiak, K.E., Izatt, R.M., Prodi, L., Montalti, M. and Zaccheroni, N. (2001), *Tetrahedron* **57**, 87.
[33] Su, N., Bradshaw, J.S., Zhang, X.X., Savage, P.B., Krakowiak, K.E. and Izatt, R.M. (1999), *J. Org Chem.* **64**, 3825.
[34] Bartsch, R.A., Bitalac, L.P., Cowey, C.L., Elshani, S., Goo, M.-J., Huber, F.J., Ivy, S.N., Jang, Y., Johnson, R.J., Kim, J.S., Luboch, E., McDonough, J.A., Pugia, M.J., Son, B. and Zhao, Q. (2000), *J. Heterocyclic Chem.* **37**, 1337.
[35] Habata, Y., Saeki, T., Akabori, S., Zhang, X.X. and Bradshaw, J.S. (2001), *J. Heterocyclic Chem.* **38**, 253.
[36] Su, N., Bradshaw, J.S., Zhang, X.X., Song, H.-C., Savage, P.B., Xue, G.-P., Krakowiak, K.E. and Izatt, R.M. (1999), *J. Org. Chem.* **64**, 8855.
[37] Yang, Z., Bradshaw, J.S., Zhang, X.X., Savage, P.B., Krakowiak, K.E., Dalley, N.K., Su, N., Bronson, R.T. and Izatt, R.M. (1999), *J. Org. Chem.* **64**, 3162.
[38] Newcomb, M., Timko, J.M., Walba, D.M. and Cram, D.J. (1977), *J. Am. Chem. Soc.* **99**, 6392.
[39] Krakowiak, K.E., Maas, G.E., Bradshaw, J.S., Hathaway, J.K. and Izatt, R.M. (1995), *J. Heterocyclic Chem.* **32**, 179.
[40] Babb, D.A., Czech, B.P. and Bartsch, R.A. (1986), *J. Heterocyclic Chem.* **23**, 609.
[41] Newkome, R.G., Theriot, J.K., Gupta, K.V., Fronczek, R.F. and Baker, R.G. (1989), *J. Org. Chem.* **54**, 1766.