A New Approach to the Synthesis of Phenol-Containing Macroheterocycles

Andrei V. Bordunov,*,† Nikolai G. Lukyanenko,‡ Victor N. Pastushok,‡ Krzysztof E. Krakowiak,§ Jerald S. Bradshaw,*,† N. Kent Dalley,† and Xiaolan Kou†

Department of Chemistry, Brigham Young University, Provo, Utah 84602-4672, A. V. Bogatsky Physico-Chemical Institute, Ukranian Academy of Sciences, 86 Chernomorskaya Doroga, Odessa, 270080 Ukraine, and IBC Advanced Technologies, Inc., P.O. Box 98, American Fork, Utah 84003

Received February 14, 1995®

A one-step method for the synthesis of new phenol-containing cryptands and cryptohemispherands by treating *N,N'*-bis(methoxymethyl)diazacrowns with the appropriate bis- and trisphenols is reported. This method, based on a special Mannich reaction, gives cyclized products without the need for protecting groups and high dilution conditions. Unusually high yields of cryptohemisherands were realized using a relatively high concentration of the starting materials (50 mmol/L) and in the absence of metal cations as template agents in the reaction mixture. These excellent yields can be explained by intramolecular hydrogen bonding which prevents polycondensation. This new method also allowed preparation of new phenol-containing cylindrical tricyclic ligands by first forming bisphenol-substituted diaza-18-crown-6 at 80 °C followed by its reaction with a second bis(methoxymethyl)-substituted diaza-18-crown-6 at 144 °C. Crystal structures of two cryptohemispherands are reported herein. A shorter internal distance between N and O atoms in **27** as compared to **6** (R = NO_2, $n = m = 2$) indicates intramolecular hydrogen bonding in phenol-containing macrocycle **27**.

Introduction

A great number of macroheterocycles containing phenolic rings as part of their molecular framework have been synthesized. Some of these include calixarenes,[1] oxacalixarenes,[2] azacalixarenes,[3] spherands,[4] cryptands,[5] crown ethers,[6] and azacrown ethers.[5a,7] The complexing properties of these macrocycles have been reviewed.[8]

Introducing phenolic units into the framework of mono- and polycyclic ligands is important for many reasons. First, phenolic groups with the OH functions directed inside the macrocycle cavity are potential complexing sites for metal cations and some organic substances. Phenol-containing cryptand **1** (see Figure 1) exhibited a stronger interaction with Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, and Cd^{2+} than did aliphatic cryptand **2**.[5a] Participation of internal phenolic groups in complexation was also observed when complexes of phenol-containing macrocyclic Schiff bases with UO_2^{2+} and transition metal ions were formed.[9] Three-dimensional macrocycle **3**,[10] containing internal catechol fragments, exhibited a very strong affinity toward Fe^{3+}. Phenolic OH groups of the calixarenes are able to interact with cations and neutral molecules to form intramolecular or intermolecular complexes.[1c] Due to this interaction, a number of calixarenes and azacalixarenes are efficient uranophiles.[3,11] Deprotonation of the phenolic groups in alkaline media is an additional factor in increasing their complexing ability and selectivity. The deprotonated forms of the calixarenes were found to be carriers for selective transport of Cs^+ ions through a liquid membrane.[12]

Second, the phenolic OH groups of a macrocyclic system as well as the *para*-position of the phenol ring can be functionalized with different substituents. These substituents can affect the complexing ability of the ligands. In addition, the phenolic units are appropriate sites for attaching the macrocycles to inorganic solid supports.[13] Phenolic fragments with free *para*-positions have been used for the introduction of chromophores and for the preparation of chromogenic complexing agents.[14]

† Brigham Young University.
‡ Ukranian Academy of Sciences.
§ IBC Advanced Technologies, Inc.
® Abstract published in *Advance ACS Abstracts,* July 1, 1995.

(1) (a) Gutsche, C. D. *Calixarenes*; Monographs in Supramolecular Chemistry, Royal Society of Chemistry, London, 1989. (b) Vicens, J., Bohmer, V., Eds.; *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Kluwer Academic Publishers: Holland, 1990. (c) Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D. *Inclusion Compounds*; Oxford University Press: New York, 1991.
(2) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536.
(3) Takemura H.; Yoshimura, K.; Khan, I. U.; Shinmyozu, T.; Inazu, T. *Tetrahedron Lett.* **1992**, *33*, 5775.
(4) Cram, D. J.; Carmack, R. A.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 571.
(5) (a) Czech, A.; Czech, B. P.; Bartsch, R. A.; Chang, C. A.; Ochaya, V. O. *J. Org. Chem.* **1988**, *53*, 5. (b) Czech, A.; Czech, B. P.; Desai, D. H.; Hallman, J. L.; Phillips, J. B.; Bartsch, R. A. *J. Heterocycl. Chem.* **1986**, *23*, 1355.
(6) (a) Browne, C. M.; Ferguson, G.; McKervey, M. A.; Mulholland, D. L.; O'Connor, T.; Parvez, M. *J. Am. Chem. Soc.* **1985**, *107*, 2703. (b) 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. (c) Van Der Leij, M.; Oosterink, H. J.; Hall, R. H.; Reinhoudt, D. N. *Tetrahedron* **1981**, *37*, 3661.
(7) Kimura, E.; Kimura, Y.; Yatsunami, T.; Shionoya, M., Koike, T. *J. Am. Chem. Soc.* **1987**, *109*, 6212.
(8) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem Rev.* **1991**, *91*, 1721.
(9) (a) Okawa, H.; Kida, S. *Bull. Chem. Soc. Jpn.* **1972**, *46*, 1759. (b) Mandal, S. K.; Nag, K. *J. Chem. Soc., Dalton Trans.* **1983**, 2429. (c) Casellato, U.; Fregona, D.; Sitran, S.; Tamburini, S.; Vigato, P. A.; Fenton, D. E. *Inorg. Chem. Acta* **1985**, *110*, 181.
(10) Kiggen, W.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 714.
(11) Shinkai, S.; Koreishi, H.; Ueda, K.; Arimura, T.; Manabe, O. *J. Am. Chem. Soc.* **1987**, *109*, 6371.
(12) (a) Izatt, R. M.; Lamb, J. D.; Hawkins, R. T.; Izatt, S. R.; Christensen, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 1782. (b) Izatt, R. M.; Hawkins, R. T.; Christensen, J. J. *J. Am. Chem. Soc.* **1985**, *107*, 63.
(13) (a) McDaniel, C. W.; Bradshaw, J. S., Krakowiak, K. E.; Izatt, R. M.; Savage, P. B.;Tarbet, B. J.; Bruening, R. L. *J. Heterocycl. Chem.* **1989**, *26*, 413. (b) Bradshaw, J. S.; Krakowiak, K. E.; Tarbet, B. J.; Bruening, R. L.; Biernat, J. F.; Bochenska, M.; Izatt, R. M., Christensen, J. J. *Pure Appl. Chem.* **1989**, *61*, 1619. (c) Bradshaw, J. S.; Izatt, R. M.; Christensen, J. J.; Krakowiak, K. E.; Tarbet, B. J.; Bruening, R. L., Lifson, S. *J. Inclusion Phenom.* **1989**, *7*, 127.

0022-3263/95/1960-4912$09.00/0

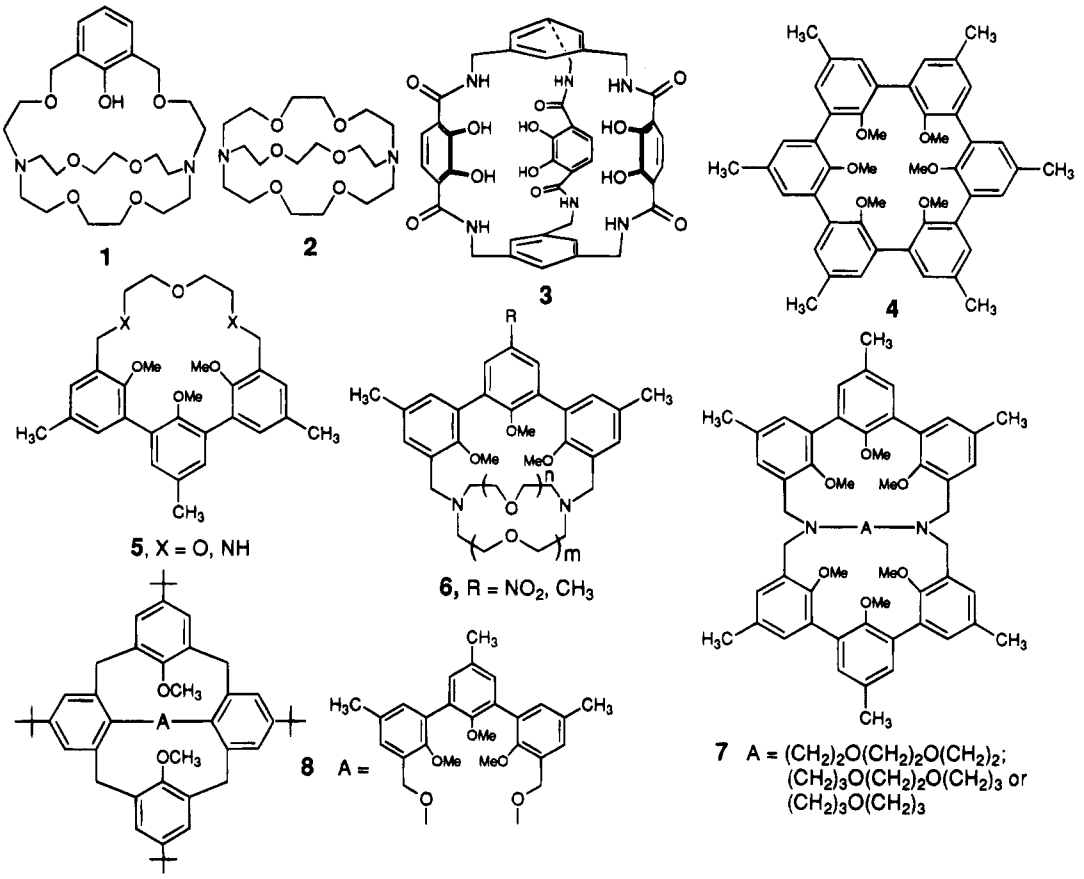


Figure 1. Macroheterocycles mentioned in this study.

Third, fully or partially preorganized, rigid ligands such as the spherands **4**,[15] hemispherands **5**,[16,17ac] cryptohemispherands **6**,[17] spherocryptands **7**,[17d] and calixaspherands **8**[18] have a high affinity for the alkali metal cations. The selectivity of complex formation allows the analytical determination of lithium, sodium and potassium cations in clinical chemistry.[19] Compounds **4**–**8** contain aromatic rings directly connected to each other which restricts free rotation in the molecule and, therefore, provides donating centers in fixed or almost fixed positions. Additional rigidity is possible due to formation of intramolecular hydrogen bonds between neighboring phenolic OH groups and between OH groups and other heteroatoms. In addition, the electron rich aromatic rings in the macrocycle cavity are sources of π-electrons which can interact with positively charged substances.[20]

A number of phenol-containing cryptands have been prepared by Bartsch and co-workers.[5,14a] They used a number of synthetic techniques including protection for the OH groups, reduction with $LiAlH_4$, and high dilution conditions in the cyclization step. We have recently reported a convenient way for introducing phenolic fragments to the cryptand cavity using *N,N'*-bis(methoxymethyl)diaza-18-crown-6 as the reagent in a special Mannich reaction.[21] We also reported the application of this method for the synthesis of monoaza-, diaza-, and bis(azacrown ether)s containing phenolic units.[21,22] This study continues our research on aminomethylation as a cyclization method for the synthesis of new polycyclic phenol-containing ligands.

(14) (a) Chapoteau, E.; Czech, B. P.; Gebauer, C. R.; Kumar, A.; Leong, K., Mytych, D. T.; Zazulak, W.; Desai, D. H.; Luboch, E.; Krzykawski, J.; Bartsch, R. A. *J. Org. Chem.* **1991**, *56*, 2575. (b) Kitazawa, S.; Kimura, K.; Shono, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3253.

(15) (a) Cram, D. J., Kaneda, T.; Helgeson, R. C.; Lein, G. M., *J. Am. Chem. Soc.* **1979**, *101*, 6752. (b) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Brown, S. B.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 3645. (c) Cram, D. J.; Lein, G. M. *J. Am. Chem. Soc.* **1985** *107*, 3657.

(16) (a) Artz, S. P.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 2160. (b) Lein, G. M.; Cram, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 448.

(17) (a) Cram, D. J.; Ho, S. P.; Knobler, C. R.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1986**, *108*, 2989. (b) Helgeson, R. C.; Czech, B. P.; Chapoteau, E.; Gegaurer, C. R.; Kumar, A.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6339. (c) Cram, D. J.; Ho, S. P. *J. Am. Chem. Soc.* **1986**, *108*, 2998. (d) Krakowiak, K. E.; Bradshaw, J. S.; Zhu, C.; Hathaway, J. K.; Dalley, N. K.; Izatt, R. M. *J. Org. Chem.* **1994**, *59*, 4082.

(18) (a) Reinhoudt, D. N.; Dijkstra, P. J.; in't Veld, P. J. A.; Bugge, K. E.; Harkema, S.; Ungaro, R.; Ghidini, E. *J. Am. Chem. Soc.* **1987**, *109*, 4761. (b) Dijkstra, P. J.; Brunink, J. A. J.; Bugge, K. E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567.

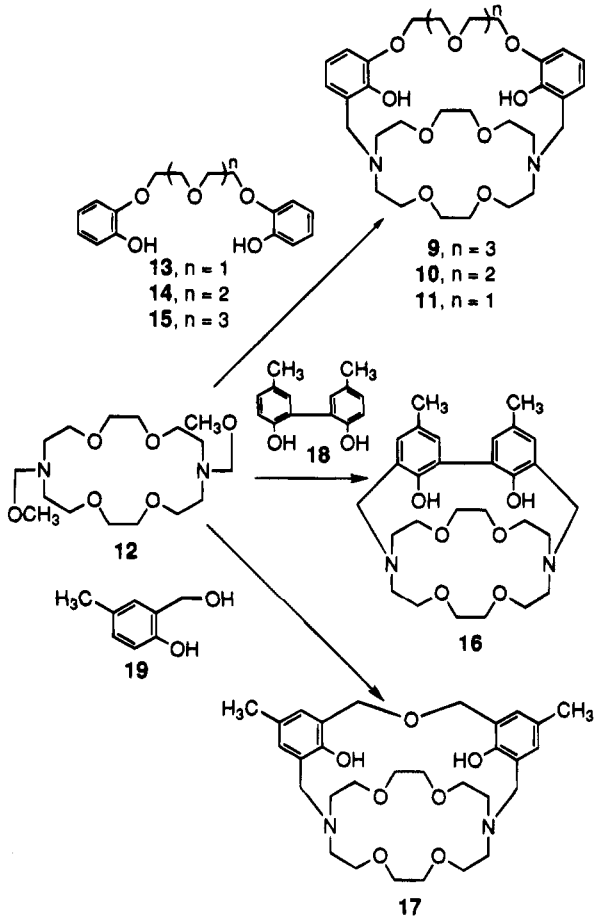
(19) (a) Cram, D. J.; Chapoteau, E.; Czech, B. P.; Gebauer, C. R.; Helgeson, R. C.; Kumar, A. *Novel Chromogenic Ionophores for Determination of Sodium and Potassium in Biological Fluids: Synthesis and Application*; Proceedings of The Fifth International Symposium on Inclusion Phenomena and Molecular Recognition; Atwood, J. L., Ed.; Plenum Press: New York, 1990. (b) Czech, B. P.; Chapoteau, E.; Kumar, A. U. S. Patent 5,817,103, 1993. (c) Czech, B. P.; Chapoteau, E.; Chimenti, M. Z.; Zazulak, W.; Gebauer, C. R.; Kumar, A. *Anal. Chim. Acta* **1992**, *263*, 159. (d) Czech, B. P.; Chapoteau, E.; Zazulak, W.; Gebauer, C . R.; Kumar, A. *Anal. Chim. Acta* **1990**, *241*, 127. (e) Zazulak, W.; Chapoteau, E.; Czech, B. P.; Kumar, A. *J. Org. Chem.* **1992**, *57*, 6720.

(20) (a) Araki, K.; Shimizu, H.; Shinkai, S. *Chem. Lett.* **1993**, *208*, 205. (b) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933. (c) Petti, M. A.; Shepodd, R. E.; Barrans, Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825. (d) Stauffer, D. A.; Dougherty, D. A. *Tetrahedron Lett.* **1988**, *29*, 6039.

(21) Lukyanenko, N. G.; Pastushok, V. N.; Bordunov, A. V. *Synthesis* **1991**, 241.

(22) Lukyanenko, N. G.; Pastushok, V. N.; Bordunov, A. V.; Vetrogon, V. I.; Vetrogon, N. I.; Bradshaw, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1489.

Scheme 1. Preparation of Macrobicycles 9–11, 16, and 17



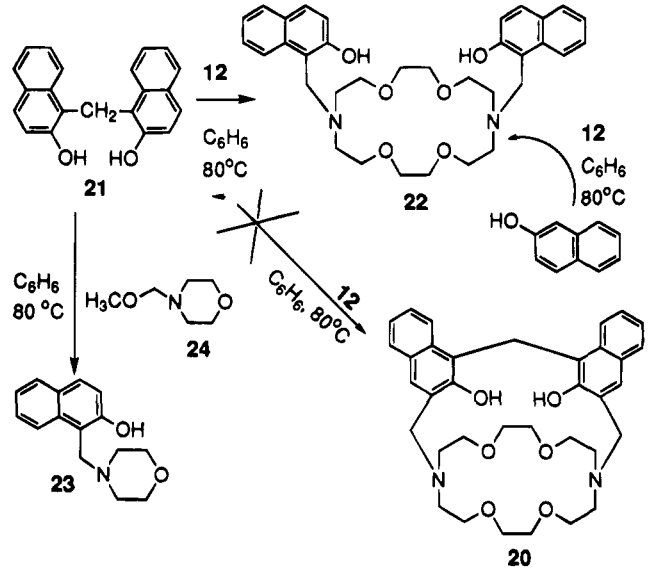
Results and Discussion

Synthesis of New Macrocycles. New bicyclic cryptands **9** and **10** (Scheme 1) were prepared in the same manner as that for **11**.[21] Refluxing equivalent amounts of *N,N'*-bis(methoxymethyl)diaza-18-crown-6 (**12**)[23] with bis(phenol)s **13** and **14** in xylene gave bisphenol-containing cryptands **9** and **10** in 28% and 36% yields, respectively. Reaction in benzene gave a complicated mixture of polycondensation products instead of the bicycles. Refluxing xylene was also used for the synthesis of cryptands **16** and **17** (Scheme 1). Reactant **12** reacted smoothly with 2,2'-dihydroxy-5,5'-dimethylbiphenyl (**18**) or 2-hydroxy-5-methylbenzyl alcohol (**19**). In the latter case, aminomethylation of the phenolic rings was accompanied by intramolecular dehydration of the CH_2OH groups to form the new ether linkage.

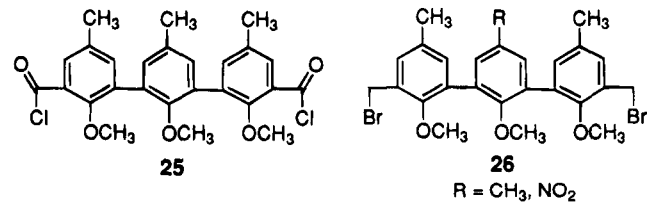
Using *N,N'*-bis(methoxymethyl)diazacrowns in preparing phenol-containing cryptands has three advantages. First, it is a one-step reaction. Second, no protecting groups are needed. Third, high dilution conditions are not necessary. The last point allows for an easy preparation of phenol-containing cryptands on a large scale. Moreover, this new method can be used to prepare polycyclic ligands containing phenols which are unsubstituted in the *para*-position and could be functionalized with chromophores.[14]

We attempted to prepare cryptand **20** by cyclization of 1,1'-methylenebis-2-naphthol (**21**) with **12** in refluxing benzene (Scheme 2). Lariat diazacrown **22** was obtained in that reaction. The structure of **22** was supported by NMR spectroscopy and mass spectrometry and by its synthesis from 2-naphthol and **12**. Aminomethylation of **21** by **12** proceeded on already occupied position 1 of the naphthol ring of **21** followed by loss of the benzyl group. This interaction is probably a general one for **21** and a methoxymethylamine since compound **23** was obtained from the reaction of **21** and *N*-(methoxymethyl)morpholine (**24**) (Scheme 2).

Scheme 2. Attempted Preparation of Macrobicycle 20



Cryptohemispherands **6** (see Figure 1) are highly selective reagents for the alkali metal cations.[17] Cryptohemispherand **6** (R = CH_3, $n = m = 2$) exhibited a strong affinity toward Cs^+ as compared with other alkali metal cations.[17c] High selectivity towards Na^+ was observed for cryptohemispherands **6** (R = CH_3, $n = m = 1$) and (R = CH_3, $n = 2$, $m = 1$).[17c] There are two main approaches to the synthesis of **6**; (1) acylation of diazacrown ethers with diacid dichloride **25** followed by reduction of the macrocyclic diamides, [17a] and (2) alkylation of the free diazacrown with bis(bromomethyl) compounds **26**.[17d] Both of these methods require a number of steps to prepare the starting rigid aromatic

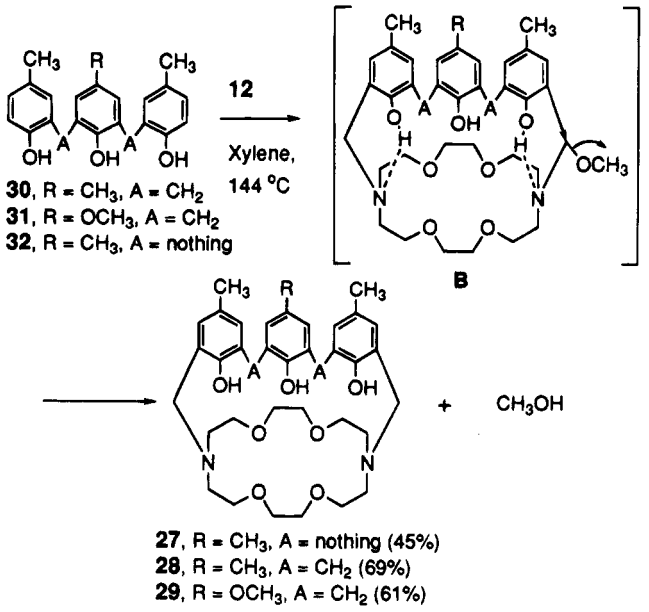


bridge, high dilution conditions, and, in the case of macrocylic diamide intermediates, an additional step to decompose the hydroborane complexes after reduction.

N,N'-Bis(methoxymethyl)-substituted **12** is a synthon for the cryptohemispherands such as **27-29** (Scheme 3). These bicyclic ligands were prepared by treating **12** with trisphenols **30-32** in refluxing xylene. Starting compounds **30** and **31** were synthesized by condensation of 2,6-bis(hydroxymethyl)-*p*-cresol (or 2,6-bis(hydroxymethyl)-*p*-methoxyphenol) with an excess of *p*-cresol in refluxing hexane with HCl as a catalyst. Application of **12** for the synthesis of **27–29** eliminates some steps included

(23) Bogatsky, A. V.; Lukyanenko, N. G.; Pastushok, V. N.; Kostyanovsky, R. G. *Dokl. Acad. Nauk. SSSR* **1982**, *265*, 619; *Chem. Abstr.* **1982**, *97*, 216146c.

Scheme 3. Preparation of Macrobicycles 27–29

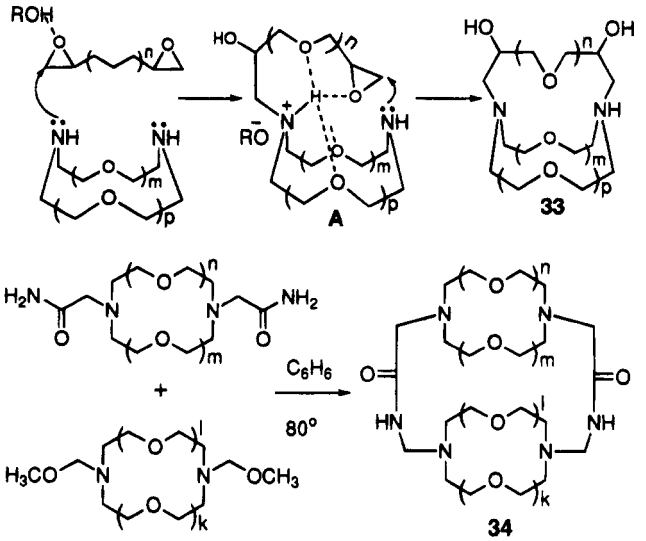


protection of the phenolic functional groups. Changing the anisole units of the cryptohemispherands to phenol units would allow a study of cation complexion by these phenolate-containing bicycles in basic water media. This possibility and the possibility of introducing chromogenic groups in these structures could make these new ligands very interesting ligating groups.

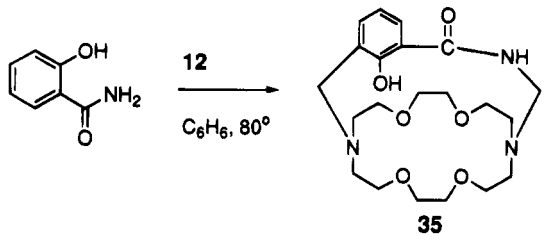
Macrocyclization reactions are accompanied by polycondensations which considerably decrease the yields of the final macrocyclic compounds. High dilution, high pressure techniques, and template syntheses are used to reduce polycondensation. The yields of **27–29** are unusually high even though none of the above methods for reducing polycondensation were used. Our reactions were carried out at atmospheric pressure, the concentrations of the starting reagents were 50 mmol/L, and metal cations were absent from the reaction mixture. High yields of hydroxy-containing cryptands **33** (97%, when $n = 1, m = p = 2$) were also reported[24] (see Scheme 4). The high yields for **33** were explained by intramolecular hydrogen bonding between the protonated amine and the epoxide in intermediate **A**. High yields also were reported for amide-containing tricyclic cryptands **34** (73%, when $n = m = l = k = 2$).[25] Intramolecular binding should also play a role in the formation of **27–29** as shown in intermediate **B** (Scheme 3). The acidity and position of the phenolic OH groups makes internal hydrogen bonding in the intermediate very probable. CPK models show that self assembly cyclization during the synthesis of **27–29** is possible. The exact location of hydrogen bonds in intermediate **B** are not known. According to CPK models, data from two-dimensional NMR spectroscopy,[26] and from the X-ray structure, the OH group of the middle phenolic ring cannot form a hydrogen bond with the azacrown ring. The more possible hydrogen bonding between the end OH groups and the azacrown nitrogen atoms in **B** probably restricts rotation and allows for an efficient intramolecular cyclization as shown.

Cyclization of salicylamide with **12** in refluxing benzene (Scheme 5) is another example of the intramolecular

Scheme 4. Preparation of Macroheterocycles 33 and 34



Scheme 5. Preparation of Macrobicycle 35



coordination of reagent and substance by hydrogen bonding. Two different functional groups of salicylamide are involved in aminomethylation with **12**. In spite of the different characteristics of the reaction centers, the yield of final cryptand **35** was 34%. In this case, special techniques to prevent polycondensation were not used. Concentration of the reagents was 50 mmol/L and no metal template cations were present.

N-(Methoxymethyl)azacrown ethers are effective aminomethylation reagents for various functional groups besides phenols and amides, such as for triazoles, imidazoles, nitroalkanes, imides, and sulfonamides. A number of lariat monoaza and diazacrown ethers containing those functional groups were prepared via aminomethylation.[27] The self-assembly cyclization of *N,N'*-bis(methoxymethyl)diazacrown ethers with appropriate reagents containing two of the above mentioned functional groups opens opportunities to obtain new polycyclic ligands with additional complexing centers inside the cavity.

The synthesis of new phenol-containing macrotricyclic ligands was also an object of our study. We used **12** in a two-step synthesis for the preparation of compounds **36** and **37** (Scheme 6). The first step was carried out as described for unsubstituted phenol[21] using 2 equiv of

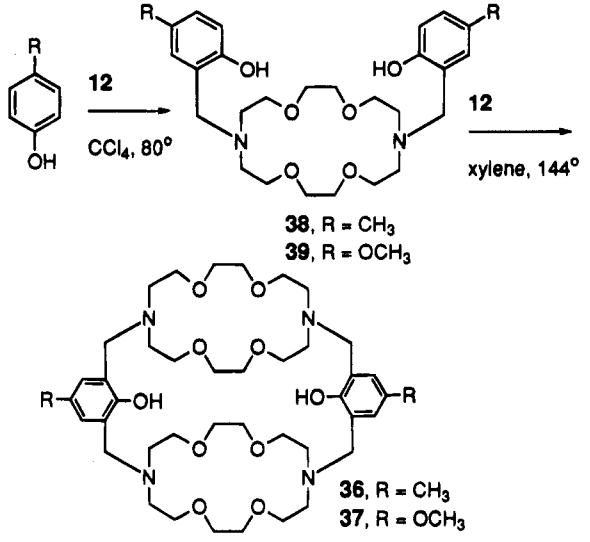
(24) Lukynenko, N. G.; Reder, A. S. *Zh. Org. Khim.* **1989**, *25*, 385; *Chem. Abstr.* **1989**, *111*, 232757r.

(25) Lukyanenko, N. G.; Pastushok, V. N.; Bordunov, A. V. *Zh. Org. Khim.* **1991**, *27*, 2630; *Chem. Abstr.* **1992**, *117*, 48529r.

(26) Kalyuskii, A. R.; Shapiro, Yu. E.; Bordunov, A. V.; Pastushok, V. N.; Lukyanenko, N. G. *Khim. Geterotsikl. Soedin.* **1993**, 406; *Chem. Abstr.* **1994**, *120*, 76716e.

(27) (a) Bogatsky, A. V.; Lukyanenko, N. G.; Pastushok, V. N.; Kostyanovsky, R. G. *Synthesis* **1983**, 992. (b) Lukyanenko, N. G.; Pastushok, V. N. *Zh. Org. Khim.* **1989**, *25*, 2435. *Chem. Abstr.* **1990**, *113*, 23882e. (c) Lukyanenko, N. G.; Kostyanovskii, R. G.; Pastushok, V. N., Bogatskii, A. V. *Khim. Geterotsikl Soedin.* **1986**, 413; *Chem. Abstr.* **1987**, *106*, 50175p. (d) Lukyanenko, N. G.; Pastushok, V. N.; Bordunov, A. V., Ivanov, E. I.; Kalayanov, G. D. *Khim. Geterotsikl Soedin.* **1993**, 270; *Chem. Abstr.* **1994**, *120*, 545262r.

Scheme 6. Preparation of Macrotricycles 36 and 37

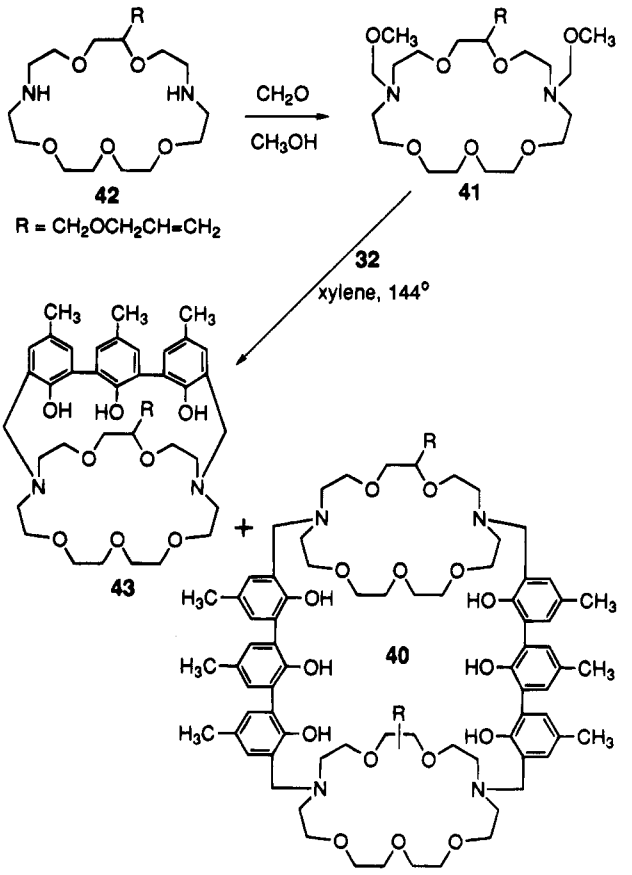


p-cresol or anisole with 1 equiv of **12**. This process gave intermediate lariat diazacrowns **38** and **39** in yields of 84% and 61%, respectively. The second diazacrown fragment could not be introduced by treating **38** or **39** with **12** at 80 °C. Tricycles **36** and **37** were synthesized by treating **38** and **39** with **12** in refluxing xylene (144 °C). The synthesis of **36** and **37** in one step by refluxing a mixture of *p*-cresol or anisole and **12** in xylene was unsuccessful.

Bis(allyloxymethyl)-containing tricyclic cryptand **40** was prepared as a mixture of isomers by a 2:2 cyclization of trisphenol **32** and (allyloxymethyl)-containing *N,N'*-bis(methoxymethyl)diaza-21-crown-7 (**41**) (Scheme 7). Compound **41** was used without purification after interaction of diazacrown **42** with formaldehyde in CH_3OH. We tried to demonstrate with this example the possibility of preparing cryptohemispherands with an alkene-containing sidearm which could be used to attach the macropolycycle to different inorganic supports.[13] Compound **40** was isolated in a 7% yield along with desired cryptohemishperand **43** (14%), the 1:1 cyclization product, using column chromatography, first on neutral alumina with toluene/THF as eluant and than on silica gel with MeOH/NH_4OH as eluant. **40** is probably a mixture of syn- and anti-isomers. We could not observe those isomers separately by accessible analytical methods. **43** is the first cryptohemispherand formed on a diaza-21-crown-7 ring. Cram and co-workers reported a cryptohemispherand on a diaza-15-crown-5 (**6**, R = CH_3, n = 2, m = 1) in two isomeric forms which could be converted one into the other.[17a] Due to a decreased rigidity of **43** compared to **6** (R = CH_3, n = 2, m = 1), the isomeric forms of **43** could not be observed. We did not observe 2:2 cyclization (to form the dimer of **27**) when trisphenol **32** and **12** were reacted under the same conditions (see Scheme 3). Possibly, the 18-membered diazacrown is more suitable for self-assembly cyclization to form the 1:1 condensation product (**27**, in this case).

X-ray Analysis. The structures of **27** and **43** (R = $CH_2OCH_2CH{=}CH_2$) were determined by X-ray diffraction. Experimental details, positional parameters, and structural data including bond lengths and angles for **27** and **43** are available.[28] Computer drawings of the compounds are shown in Figures 2 and 3. Both structures were solved by direct methods. It was found that

Scheme 7. Preparation of Macrobicycle 43 and Macrotricycle 40



nearly every atom of the diaza-18-crown-6 ring in **27** (Figure 2) was disordered. In the refinement process, the bond lengths for C–C and C–O bonds were refined to values of approximately 1.47 Å, and 1.42 Å, respectively. Under these circumstances, the final R value of 12.8% was fairly good, but some of the bond angles were not realistic. However, the atoms of the spherand portion of **27** were not disordered and, therefore, gave reliable information regarding that part of the structure. Crystals of **43** (Figure 3) were not stable in air and so a crystal was encased in a capillary tube. Even with that protection, the intensity of the standards dropped about 30% during data collection.

The major focus of the structural investigation is centered on the rigid spherand portion of the two molecules. It is interesting to compare their conformational differences and also to compare **27** and **43** with **6** (R = NO_2, m, n = 2)[17d] and the Cs·**6** (R = CH_3, m, n =2) complex.[17a] The chemical formula of the spherand portion of **6** is identical to that of **27** and **43** except that **6** (R = NO_2, m, n = 2) has methoxy groups instead of OH groups on the three benzenes and a NO_2 group rather than a CH_3 group on the *para*-position of the middle benzene ring. The sperand portion of the complex of **6** (R = CH_3, m, n = 2) with Cs^+ differs from **27** and **43** only in the presence of the methoxy groups instead of OH groups on the benzene rings and the complexed Cs^+ ion. However, the rigid spherand fragments of all four structures are similar.

(28) X-ray structure data and experimental details are available from the Cambridge Crystallographic Data Center. The experimental details, atomic coordinates, and structural data can be obtained on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1E2, U.K.

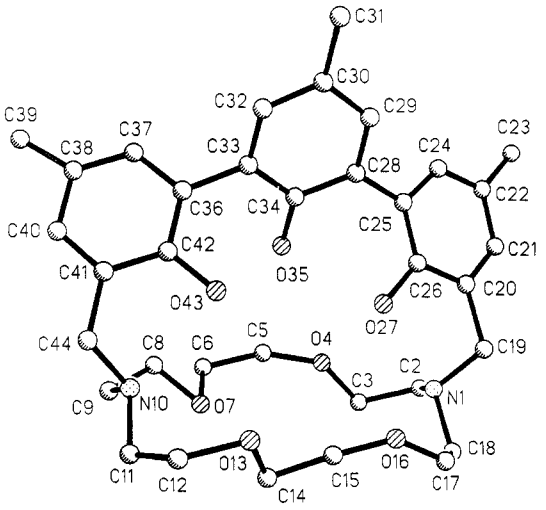


Figure 2. Computer drawing of **27** with atom labels. The hydrogen atoms and O4′, C5′, and O16′ are omitted for clarity.

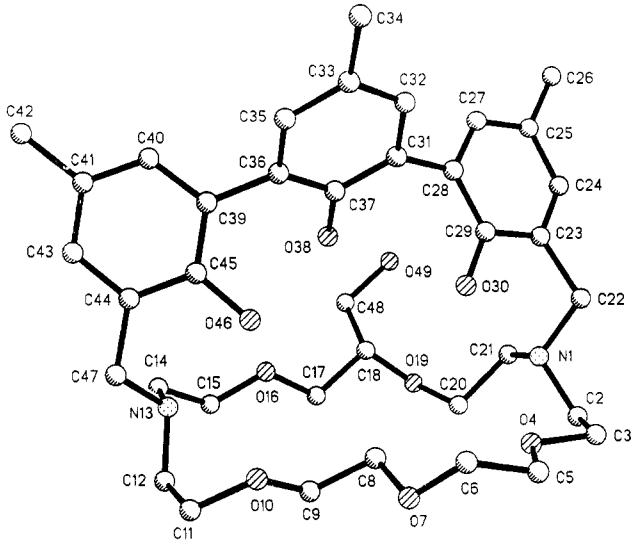


Figure 3. Computer drawing of **43** with atom labels. The hydrogen atoms and the terminal three atoms of the R group are omitted for clarity.

The dihedral angles between the least square planes of the benzene groups in the methoxy compounds have values ranging from 54.1° to 59.2° in **6** (R = NO_2, *m*, *n* = 2) and 55.7° to 56.5° in the Cs^+ complex of **6** (R = CH_3, *m*, *n* = 2). However, these values have a much wider range in the OH compounds in **27** and **43**. The dihedral angles between adjacent benzenes in **27** are 48.5° and 56° while in **43** they are 46.3° and 59.3°. The dihedral angles between the "end" benzene planes are 39.0° and 40.5° in **27** and **43**, respectively. It is of interest that the largest differences for **27** and **43** from **6** (R = NO_2, *m*, *n* = 2) and the Cs^+ complex of **6** (R = CH_3, *m*, *n* = 2) involve the dihedral angles between the outer benzenes. While the triangles formed by the three oxygens of the spherand in all four compounds are similar, i.e. they are located over the crown ring with the oxygens of the end benzene pointing in one direction relative to the page and the middle oxygen pointing in the other, there are significant differences. The interatomic distances between the oxygens of the terminal benzenes and the nearby nitrogens of the crown rings of **27** and **43** (see Figures 2 and 3) are shorter than in **6** (R = NO_2, *m*, *n* = 2) and in the Cs^+ complex of **6** (R = CH_3, *m*, *n* = 2). Specifically in **27**, the N1···O27 and N10···O43 are 2.69 and 2.80 Å, respectively, while in **43** N1···O30 and N13···O46 are 2.68 and 2.62 Å, respectively. By way of contrast, similar distances in **6** (R = NO_2, *m*, *n* = 2) are 3.08 and 3.21 Å. These values were not available for the Cs^+ complex. These shorter values and the presence of hydroxy groups rather than methoxy groups suggest possible hydrogen bonding. Unfortunately, it was not possible to locate these hydrogen atoms in either structure. The C–O···N angles neither support nor rule out the presence of such interaction. Figures 2 and 3 suggest that a hydrogen being directed toward the N atoms is sterically unlikely. However, all the O···N distances are short and three of the four significantly shorter than the sum of the Van der Waal radii for O and N (2.90 Å).

Little can be said regarding the conformation of the crown ring of **27** due to the disorder. The crown ring of **43** is not preorganized. The N···N ring interatomic distance in **27** is 7.06 Å and in **43** is 7.72 Å. This is to be expected because of the larger crown ring in **43**. The distance in **27** is 0.16 Å longer than that found in **6** (R = NO_2, *m*, *n* = 2) which contains the same uncomplexed crown as **27** and 0.39 Å longer than that found in the Cs^+ complex of **6** (R = CH_3, *m*, *n* = 2). These differences and that found in **43** point to greater flexibility in phenol-containing cryptohemispherands than that found in cryptohemispherands containing toluene groups in the spherand arm.

Experimental Section

Melting points of the prepared compounds are uncorrected. Proton NMR spectra were obtained at 100 and 250 MHz in $CDCl_3$. Mass spectra were recorded at 70 and 12 eV and on a FAB mass spectrometer. Starting materials and solvents were purchased from commercial sources where available. Compounds **12**,[23] **14**,[29] **15**,[29] and **32**[30] were prepared as reported.

2,6-Bis(2′-hydroxy-5′-methylbenzyl)-4-methylphenol (30). A mixture of 2,6-bis(hydroxymethyl)-4-methylphenol (3.36 g, 0.02 mol), *p*-cresol (21.6 g, 0.2 mol), and 30 mL of hexane was stirred and refluxed until the mixture became homogeneous. A few drops of HCl (36%) was added, and the reaction mixture was refluxed for 6 h, cooled, and filtered. The white crystals were washed with hot CH_3OH and recrystallized from CH_3CO_2H, mp 222–223 °C (44%); ^1H NMR (DMF) δ 2.09 (s, 3 H), 2.12 (s, 6 H), 3.89 (s, 4 H), 6.74- 6.93 (m, 8 H); MS, *m*/*z* 348 (M^+). Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.31; H, 6.90. Found: C, 79.28; H, 6.78.

2,6-Bis(2′-hydroxy-5′-methylbenzyl)-4-methoxyphenol (31). Compound **31** was prepared as above for **30** from 2,6-bis(hydroxymethyl)-4-methoxyphenol (3.68 g, 0.02 mol) and *p*-cresol (21.6 g, 0.2 mol); mp 223–224 °C (36%); ^1H NMR (DMF) δ 2.10 (s, 6 H), 3.80 (s, 3 H), 3.87 (s, 4 H), 6.71- 7.11 (m, 8 H); MS, *m*/*z* 364 (M^+). Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.82; H, 6.59. Found: C, 75.70; H, 6.68.

General Procedure for the preparation of Cryptands 9, 10, 16, 17, 27–29, and 35–37. A solution of *N*,*N*′-bis(methoxymethyl)diaza-18-crown-6 (**12**) (0.35 g, 1 mmol) in 20 mL of xylene (benzene, in the case of **35**) was refluxed with 1 mmol of the appropriate phenolic substance under Ar for 12 h (cryptands **9**, **10**, **16**, **27**, and **35**), for 24 h (cryptands **17**, **36**, and **37**) or for 4 h (cryptands **28** and **29**). After evaporation of the solvent under reduced pressure, the crude material was purified by column chromatography on neutral aluminum oxide using $C_6H_6/CHCl_3$: 2/1 then 1/1 as eluents. Specific details are as follows:

(29) Oepen, G.; Dix, J. P.; Vogtle F. *Liebigs Ann. Chem.* **1978**, 1592.
(30) Koening, K. E.; Lein, G. M.; Stückler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553.

44,45-Dihydroxy-8,11,14,17,20,30,33,38,41-nonaoxa-1,27-diazatetracyclo[25.8.8.1^{3,7}.1^{21,25}]pentatetraconta-3,5,7-(44),21,23,25(45)-hexaene (9) (Scheme 1). Macrocycle **9** was isolated as an oil (28%): ^{1}H NMR δ 2.71 (t, 8 H, J = 5.2), 3.51−3.55 (m, 16 H), 3.73 (s, 4 H), 3.97 (m, 12 H), 4.18 (m, 4 H), 6.60−6.77 (m, 6 H); MS, m/z 664 (M^+). Anal. Calcd for $C_{34}H_{52}N_2O_{11}$: C, 61.45; H, 7.83; N, 4.22. Found C, 61.70; H, 7.81; N, 4.01.

41,42-Dihydroxy-8,11,14,17,27,30,35,38-octaoxa-1,24-diazatetracyclo[22.8.8.1^{3,7}.1^{18,22}]ditetraconta-3,5,7(41),18,-20,22(42)-hexaene (10) (Scheme 1). Compound **10** was isolated as an oil (36%): ^{1}H NMR δ 2.70 (t, 8 H, J = 5.2), 3.61−3.65 (m, 16 H), 3.76 (s, 4 H), 3.84 (m, 8 H), 4.12 (m, 4 H), 6.55−6.74 (m, 6 H); MS, m/z 620 (M^+). Anal. Calcd for $C_{32}H_{48}N_2O_{10}$: C, 61.94; H, 7.74; N, 4.52. Found: C, 61.88; H, 7.79; N, 4.63.

31,32-Dihydroxy-5,10-dimethyl-17,20,25,28-tetraoxa-1,14-diazatetracyclo[12.8.8.1^{3,7}.1^{8,12}]ditriaconta-3,5,7(31),8,-10,12(32)-hexaene (16) (Scheme 1). Macrocycle **16** was isolated as a solid, mp 224−226 °C (25%): ^{1}HNMR δ 2.21 (s, 6 H), 2.57−2.85 (m, 8 H), 3.62−4.01 (m, 20 H), 6.73 (s, 2 H), 6.95 (s, 2 H), 10.30 (br, 2 H); MS, m/z 500 (M^+). Anal. Calcd for $C_{28}H_{40}N_2O_6$: C, 67.20; H, 8.00; N, 5.60. Found: C, 67.11; H, 8.22; N, 5.89.

34,35-Dihydroxy-5,13-dimethyl-9,20,23,28,31-pentaoxa-1,17−diazatetracyclo[15.8.8.1^{3,7}.1^{11,15}]pentatriaconta-3,5,7-(34),11,13,15(35)-hexaene (17) (Scheme 1). Compound **17** was a solid, mp 197−199 °C (12%): ^{1}H NMR δ 2.24 (s, 6 H), 2.58−2.76 (m, 8 H), 3.49−3.61 (m, 20 H), 4.42 (s, 4 H), 6.68−7.17 (m, 4 H); MS, m/z 544 (M^+). Anal. Calcd for $C_{30}H_{44}N_2O_7$: C, 66.18; H, 8.09; N, 5.15. Found: C, 66.04; H, 8.08; N, 5.09.

36,37,38-Trihydroxy-5,10,15-trimethyl-22,25,30,33-tetraoxa-1,19-diazapentacyclo[17.8.8.1^{3,7}.1^{8,12}.1^{13,17}]-octatriaconta-3,5,7(36),8,10,12(37),13,15,17(38)-nonaene (27) (Scheme 3). Compound **27** was isolated as a solid, mp 193−195 °C (45%): ^{1}H NMR δ 2.30 (s, 6 H), 2.37 (s, 3 H), 2.81 (m, 8 H), 3.59−3.80 (m, 20 H), 6.81−7.19 (m, 6 H); MS, m/z 607 [M + 1]$^+$. Anal. Calcd for $C_{35}H_{46}N_2O_7$: C, 69.31; H, 7.59; N, 4.62. Found: C, 69.19; H, 7.64; N, 4.47.

38,39,40-Trihydroxy-5,11,17-trimethyl-24,27,32,35-tetraoxa-1,21-diazapentacyclo[19.8.8.1^{3,7}.1^{9,13}.1^{15,19}]tetraconta-3,5,7(38),9,11,13(39),15,17,19(40)-nonaene (28) (Scheme 3). Ligand **28** was isolated as a solid, mp 140−142 °C (69%): ^{1}H NMR δ 2.06 (s, 6 H), 2.13 (s, 3 H), 2.55−2.79 (m, 8 H), 3.44−3.76 (m, 24 H), 6.52−6.88 (m, 6 H); m/z 634 (M^+). Anal. Calcd for $C_{37}H_{50}N_2O_7$: C, 70.03; H, 7.89; N, 4.42. Found: C, 70.09; H, 7.98; N, 4.55.

38,39,40-Trihydroxy-5,17-dimethyl-11-methoxy-24,27,-32,35-tetraoxa-1,21-diazapentacyclo[19.8.8.1^{3,7}.1^{9,13}.1^{15,19}]-tetraconta-3,5,7(38),9,11,13(39),15,17,19(40)-nonaene (29) (Scheme 3). Ligand **29** was isolated as a solid, mp 148−150 °C (61%): ^{1}H NMR δ 2.11 (s, 6 H), 2.61−2.82 (m, 8 H), 3.50−3.96 (m, 27 H), 6.60−6.90 (m, 6 H); MS, m/z 650 (M^+). Anal. Calcd for $C_{37}H_{50}N_2O_8$: C, 68.31; H, 7.69; N, 4.31. Found : C, 68.40; H, 7.81; N, 4.08.

28-Hydroxy-14,17,22,25-tetraoxa-1,9,11-triazatricyclo-[9.8.8.1^{3,7}]octacosa-3,5,7(28)-trien-8-one (35) (Scheme 5). Compound **35** was an oil (34%): ^{1}H NMR δ 2.62 (m, 4 H), 2.90 (m, 4 H), 3.23−3.63 (m, 18 H), 4.43 (d, 2 H, J = 5.8), 6.61−8.01 (m, 3 H), 9.30 (br, 1 H), 12.5 (s, 1 H); MS, m/z 423 (M^+). Anal. Calcd for $C_{21}H_{33}N_3O_6$: C, 59.57; H, 7.80; N, 9.93. Found: C, 59.69; H, 7.58; N, 9.74.

51,52-Dihydroxy-5,22-dimethyl-12,15,29,32,37,40,45,48-octaoxa-1,9,18,26-tetraazapentacyclo[24.8.8.8.1^{3,7}.1^{20,24}]-dipentaconta-3,5,7(51),20,22,24(52)-hexaene (36) (Scheme 6). Ligand **36** was an oil (16%): ^{1}H NMR δ 2.11 (s, 6 H), 2.80 (t, 16 H, J = 5.4), 3.50−3.74 (m, 40 H), 6.73 (s, 4 H); MS, m/z 788 (M^+). Anal. Calcd for $C_{42}H_{68}N_4O_{10}$: C, 63.96; H, 8.63; N, 7.11. Found: C, 63.84; H, 8.70; N, 7.33.

51,52-Dihydroxy-5,22-dimethoxy-12,15,29,32,37,40,45,-48-octaoxa-1,9,18,26-tetraazapentacyclo[24.8.8.8.1^{3,7}.1^{20,24}]-dipentaconta-3,5,7(51),20,22,24(52)-hexaene (37) (Scheme 6). Ligand **37** was an oil (14%): ^{1}H NMR δ 2.81 (t, 16 H, J = 5.4), 3.54−3.75 (m, 46 H), 6.80 (s, 4 H); MS, m/z 820 (M^+). Anal. Calcd for $C_{42}H_{68}N_4O_{12}$: C, 61.46; H, 8.29; N, 6.83. Found: C, 61.37; H, 8.06; N, 6.80.

7,16-Bis(2-hydroxy-1-naphthylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (22) (Scheme 2). 1-Naphthol (0.3 g, 2.1 mmol) or 1,1′-methylenebis-2-naphthol (21) (0.3 g, 1 mmol) was refluxed with **12** (0.35 g, 1 mmol) in 30 mL of benzene under Ar for 12 h. Compound **22** precipitated from the benzene solution after cooling the reaction mixture to rt. The solid product was separated and washed with hot CH_3OH. Compound **22** was recrystallized from 1,4-dioxane to give a 79% yield, 176−179 °C: ^{1}H NMR δ 3.00 (t, 8 H, J = 5.4), 3.61−3.80 (m, 16 H), 4.29 (s, 4 H), 7.08−7.89 (m, 12 H); MS, m/z 574 (M^+). Anal. Calcd for $C_{34}H_{42}N_2O_6$: C, 71.08; H, 7.32; N, 4.88. Found: C, 71.21; H, 7.30; N, 4.71.

7,16-Bis(2-hydroxy-5-methylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (38) (Scheme 6). Compound **38** was prepared as reported[21] from *p*-cresol (0.4 g, 3.7 mmol) and **12** (0.6 g, 1.7 mmol) to give a solid, mp 118−120 °C (84%): ^{1}H NMR δ 2.13 (s, 6 H), 2.72 (t, 8 H, J = 5.3), 3.49−3.91 (m, 20 H), 6.52−6.74 (m, 6 H), MS, m/z 502 (M^+). Anal. Calcd for $C_{28}H_{42}N_2O_6$: C, 66.93; H, 8.37; N, 5.58. Found: C, 66.99; H, 8.42; N, 5.39.

7,16-Bis(2-hydroxy-5-methoxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (39) (Scheme 6). Compound **39** was prepared as described[21] from anisole (0.5 g, 4 mmol) and **12** (0.6 g, 1.7 mmol) to give a solid, mp 134−135 °C (61%): ^{1}H NMR δ 2.75 (t, 8 H, J = 5.3), 3.50−3.89 (m, 26 H), 6.60−6.85 (m, 6 H), MS, m/z 534 (M^+). Anal. Calcd for $C_{28}H_{42}N_2O_8$: C, 62.92; H, 7.87; N, 5.24. Found: C, 62.81; H, 7.99; N, 5.00.

39,40,41-Trihydroxy-5,10,15-trimethyl-35-[(allyloxy)-methyl]-22,25,28,33,36-pentaoxa-1,19-diazapentacyclo-[17.11.8.1^{3,7}.1^{8,12}.1^{13,17}]monotetraconta-3,5,7(39),8,10,12-(40),13,15,17(41)-nonaene (43) and 2:2 adduct 40 (Scheme 7). Diazacrown **42** (2.2 g, 5.9 mmol) was mixed with 30 mL of a CH_3OH solution of formaldehyde (0.5 g, 16.7 mmol). The solution was kept overnight at 25 °C, and the solvent was evaporated under reduced pressure. The resulting oil was dissolved in 30 mL of xylene, and 1.9 g (5.9 mmol) of **32** was added to the solution. The reaction mixture was refluxed for 12 h. Xylene was evaporated under reduced pressure and the resulting oil was purified on neutral alumina using toluene/THF: 1/1 as eluent. Macrocycles **40** and **43** were separated on silica gel using CH_3OH/NH_4OH: 40/1 as eluent in yields of 7 and 14%, respectively. Cryptand **43** had the following properties: ^{1}H NMR δ 2.27 (s, 6 H), 2.36 (s, 3 H), 2.61−2.96 (m, 8 H), 3.30−3.96 (m, 27 H), 5.10−5.26 (m, 2 H), 5.81 (m, 1 H), 6.80−7.20 (m, 6 H); MS m/z 721 [M + 1]$^+$. The crystal structure of **43** can be seen in Figure 3. Macropolycycle **40** had the following properties: ^{1}H NMR δ 2.29 (s, 12 H), 2.36 (s, 6 H), 2.60−2.96 (m, 16 H), 3.34−3.98 (m, 54 H), 5.10−5.26 (m, 4 H), 5.81 (m, 2 H), 6.80−7.21 (m, 12 H); MS m/z 1441.9 (M + 1)$^+$.

Acknowledgment. This work was supported, in part, by U.S. Department of Energy, Chemical Sciences Division, Office of Basic Energy Science, Contract no. DE-FG02-86ER 13463.

JO950280E