Synthesis of New Receptors Highly Selective for Ammonium Cations

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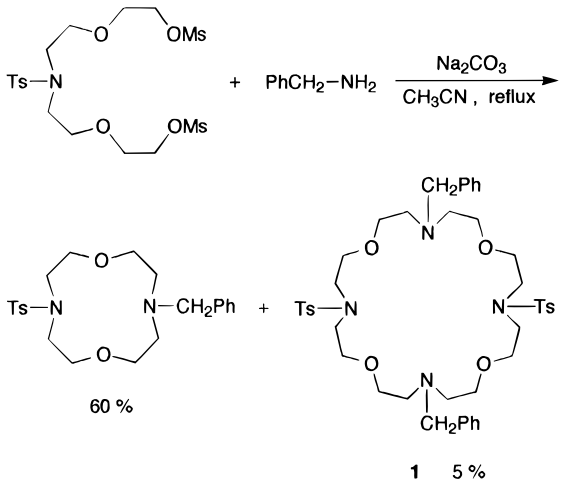
Introduction

The design of macrocyclic and macropolycyclic ligands featuring high selectivity for complexation of ammonium cations has received an enormous interest since the beginning of studies of molecular recognition using artificial receptors.[1] Complexation of ammonium cations occurs through specific hydrogen-bonding interactions; hence a receptor capable of forming highly stable and selective complexes should have complementarity with these substrates in terms of nature, number, and topology of binding sites.[2] It is well-known that macrocyclic polyethers are capable of complexing both alkali and ammonium salts though the stability and selectivity of complexes is in favor of alkali cations.[3] The replacement of one or more oxygen binding sites with nitrogen atoms strongly increases the selectivity for ammonium to the detriment of alkali cations,[4] in fact $^{+}N-H\cdots N$ hydrogen bonding is stronger than $^{+}N-H\cdots O$.[5]

The importance of topological arrangement of nitrogen donor sites is well documented; indeed the strongest $^{+}NH_4$ complex is obtained with a spherical macrotricyclic cryptand featuring four nitrogens situated at the corners of a tetrahedron.[6] Cylindrical macrotricyclic cryptands, in which two 1,7,10,16-tetraoxa-4,13-diazacyclooctadecane, [18]-N_2O_4, are connected through two lateral bridges, form complexes with α-ω bisammonium salts $[H_3N(CH_2)_nNH_3]^{2+}$ whose stability and selectivity strongly depend on the complementarity between the length of the bridging chains and the spacer between the two NH_3^+ groups.[7−9]

In previous studies, concerning the synthesis of new macropolycyclic lipophilic receptors capable of forming very stable and selective complexes with sodium cation, we have isolated, in only 5% yield, a new compound: 4,16-di-*p*-toluenesulfonyl-10,22-dibenzyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane (**1**) deriving from a two plus two condensation pathway (eq 1).[10]



The main features of **1** are (i) the presence of eight binding sites, four nitrogens and four oxygens, alternating in a 24-membered macrocyclic structure; (ii) the four nitrogen atoms are protected by two benzyl and two *p*-toluenesulfonyl groups, alternate to each other, whose selective deprotection allows a suitable building block for the synthesis of more sophisticated polycyclic receptors with new topological arrangements of binding sites. To our knowledge there are no reports, in the very large literature on polyoxapolyazacoronands, dealing with the preparation and study of complexation of tetraaza-macrocyclic receptors like **1** and of its derivatives.[11]

In the present paper we report: (i) a new and high-yielding synthetic procedure allowing **1** as the only macrocyclic product, thus making easier its isolation and purification; (ii) the synthesis of a new macrobicyclic lipophilic receptor **14** using **1** as building block; and (iii) the study of the complexation capabilities of these new receptors, with ammonium cations and amino acid ester hydrochlorides, under solid/liquid two-phase conditions.

Results and Discussion

New synthetic routes allowing **1** and its tetratosyl-amido derivative **11** are reported in Schemes 1 and 2. Starting from the already reported dimethanesulfonyl derivative **4**, it is possible to obtain, through Gabriel's procedure and subsequent treatment of the resulting amine **5** with *p*-toluenesulfonyl chloride, the 6-*p*-toluenesulfonyl-3,9-dioxa-1,6,11-triazaundecane **6** in quantitative yield. Condensation of **6** with 2 molar equiv of benzaldehyde gave the diimino derivative **7** which was hydrogenated at room temperature and atmospheric pressure in the presence of PtO_2 affording **8** in 95% overall yield. Condensation of **8** with 1 molar equiv of **4**, under usual conditions (CH_3CN and Na_2CO_3 solid as base, at reflux for 48 h), afforded the desired macrocycle **1** in 45% yield after purification by column chromatography.[12] Reductive detosylation of **1** with $LiAlH_4$ in refluxing THF allowed quantitatively the 4,16-dibenzyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacoronand, **2**.

The synthesis of the fully deprotected tetraazacoronand **3** is reported in Scheme 2.

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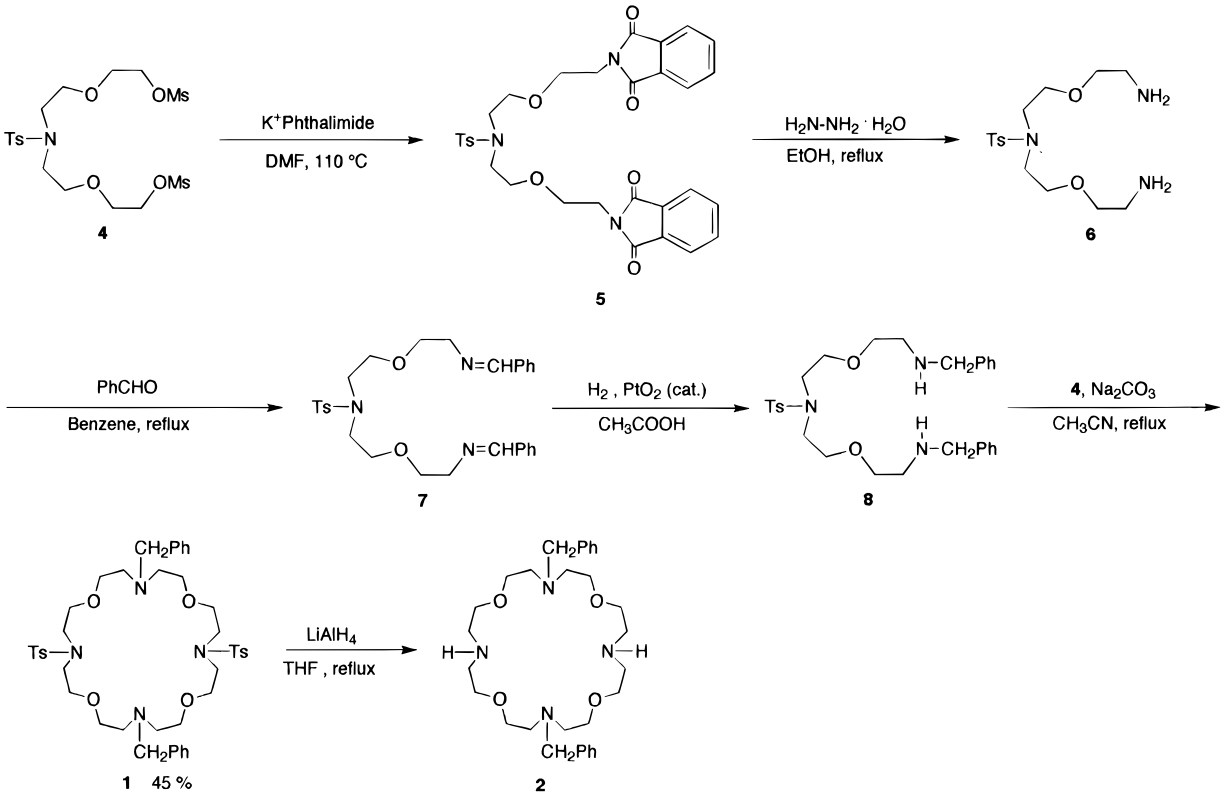
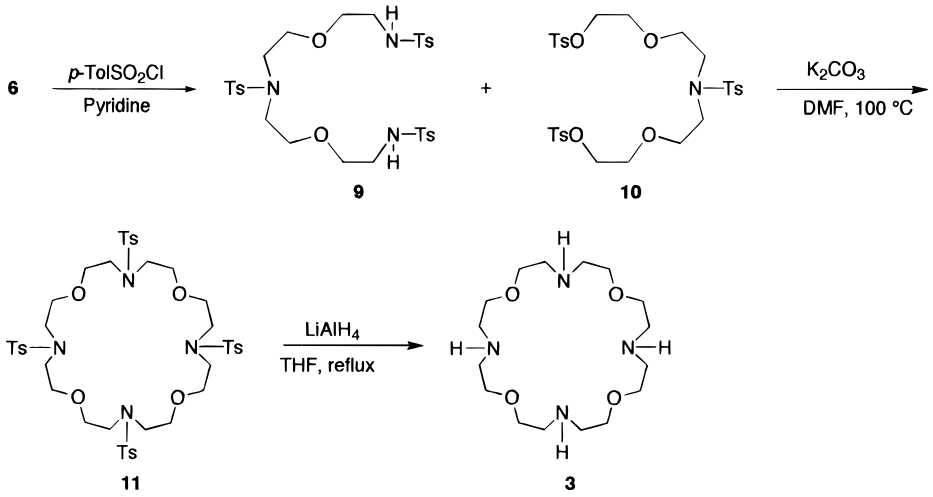
(10) Anelli, P. L.; Montanari, F.; Quici, S.; Ciani, G.; Sironi, A. *J. Org. Chem.* **1988**, *53*, 5292.
(11) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Azacrown Macrocycles. Heterocyclic Compounds*; Interscience Publ., J. Wiley: New York, 1993; Vol. 51.
(12) Unexpectedly when the condensation was carried out with the di-*p*-toluenesulfonyl derivative **10** (Scheme 2), the isolated yield of **1** was very low.
(13) Quici, S.; Manfredi, A.; Raimondi, L.; Sironi, A. *J. Org. Chem.* **1995**, *60*, 6379.

S0022-3263(95)02283-3 CCC: $12.00

Scheme 1



Scheme 2



The tetratosyl derivative **11**, prepared by condensation of **9** and **10** in DMF at 100 °C and isolated in 50% yield after column chromatography, was reacted with $LiAlH_4$ in THF at reflux for 48 h, giving pure **3** in quantitative yield.

The preparation of a macrobicyclic receptor using tetraoxatetraaza coronand **1** as building block (Scheme 3) was achieved in three steps, namely (i) catalytic debenzylation of **1** which afford **12**; (ii) condensation of **12** with 2-benzyl-1,3-propanediol bis(*p*-toluenesulfonate), which provided the ditosylamido macrobicycle **13** in 60% yield, after column chromatography; (iii) reductive detosylation of **13** to give, quantitatively, **14**.

Complexation experiments were carried out in solid/liquid two-phase conditions by equilibrating, with magnetic stirring, equimolecular amounts of the ligand dissolved in CH_2Cl_2 and solid ammonium, amino acid ester hydrochlorides, or alkali metal salts for 2 h at rt (see the Experimental Section). Values of the extent of complexation of **2**, **3**, and **14** are reported in Table 1, in comparison with those obtained by using [18]-N_2O_4 **15** as ligand.

As expected, the tetraazamacrocyclic ligands are better complexing agents for ammonium cations than the diaza derivative. This efficiency is demonstrated by comparing, in the series of ammonium halides, the extents of complexation of ligand **3** (94% for NH_4Cl and 100% for NH_4Br and NH_4I) and those of **15** which are 6%, 8%, and 15% for NH_4Cl, NH_4Br, and NH_4I, respectively. A small increase in the extent of complexation is observed with the latter ligand when amino acid ester hydrochlorides are used, and this is likely due to the higher overall lipophilic character of the cation. An alternative explanation of the increased affinity of the amino acid ester hydrochlorides is a possible role of an additional hydrogen bond to the ester unit from the macrocycles.

Scheme 3

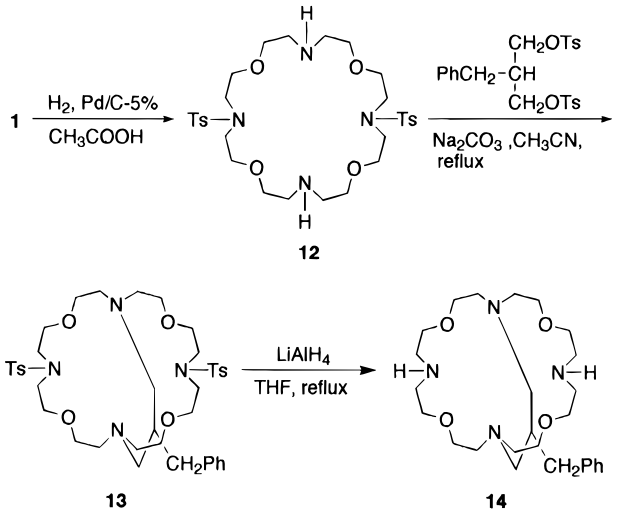


Table 1. Extents of Complexation of 2, 3, 14, and 15 under Solid/Liquid Two-Phase Conditions

	ligand (*E* (%))[b]			
salts[a]	**2**	**3**	**14**	**15**
NH_4Cl	53	94	40	6
NH_4Br	75	100	67	8
NH_4I	92	100	90	15
A	100	100	98	17
B	100	100	95	33
C	100	100	100	20
NaCl	17	17	11	3
NaBr	44	35	54	15
KCl	23	17	11	2
KBr	17	16	10	6

[a] A = L-serine methyl ester hydrochloride; B = L-cysteine methyl ester hydrochloride; C = glycine methyl ester hydrochloride. [b] E (%) = $[M\subset L)^+X^-]/[L]_0$.

Values of extents of complexation of receptors **2**, **3**, and **14** with ammonium halides likely depend on a combination of several factors, namely (i) the nature of binding sites responsible of hydrogen bonding (i.e., two tertiary and two secondary amines for **2** and **14** and four secondary amines in the case of **3**), (ii) the flexibility/rigidity balance which is in the order **3** > **2** > **14**, and (iii) the lipophilicity of the counterion I > Br > Cl. The data here reported are not sufficient to discriminate which one of these factors is responsible for the decreased extent of complexation of receptors **2** and **14** with respect to **3**. Nevertheless the results obtained clearly evidence that the novel [24]-N_4O_4 macrocycles exhibit a good selectivity for complexation of ammonium and amine salts in comparison with the [18]-N_2O_4 ligand. Although all measurements were carried out at a fixed time, and the dependence of extraction with time has not been considered, we do not believe that the lower extraction capability of **15** is due to a slower complexation process. This seems more likely in the case of rigid macropolycyclic receptors which require major conformational changes in order to have maximum interactions between binding sites and substrate. Indeed it must be stressed that in all the experiments a solid salt/ligand ratio = 1 was used; thus no mass effect could be expected and the reported values evidence the real strength of the receptor for complexation.

In order to gain insights about complexation of alkali cations we have investigated Na^+ and K^+ by using, for both, chloride and bromide salts. In the case of NaCl, KCl, and KBr the obtained values are quite low, ranging from 10% to 23% solubilization for tetraaza macrocycles and from 2% to 6% for [18]-N_2O_4. The extents of complexation observed for NaBr (15%, 35%, 44%, and 54% for **15**, **3**, **2**, and **14**, respectively), likely seem to reflect the flexibility/rigidity balance **3** > **2** > **14**; indeed higher rigidity tends to reduce the molecular cavity and allows preference for small cations. In fact, in any case, Na^+ is favored over K^+, the highest values being observed for the more rigid macrobicyclic system **14**.

Experimental Section[14]

1,11-Diphthalimido-6-*p*-toluenesulfonyl-3,9-dioxa-6-azaundecane (5). A solution of 6-*p*-toluenesulfonyl-3,9-dioxa-1,11-undecanediol bis(methanesulfonate) **4** (10.38 g, 20.6 mmol) and potassium phthalimide (8.4 g, 45.3 mmol) in 250 mL of dry DMF was stirred at 110 °C for 2 days. The reaction mixture was allowed to cool to rt, and the solvent was evaporated under reduced pressure. The residue was dissolved in 150 mL of CH_2Cl_2, and the white potassium methanesulfonate precipitate was filtered off. Evaporation of the solvent afforded a thick orange oily residue which was crystallized with 96% EtOH to give **5** (10 g, 80%) as a white solid: mp = 108−110 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.28 (t, 4H, J = 5.8 Hz), 3.45−3.60 (m, 8H), 3.81 (t, 4H, J = 5.8 Hz), 7.20 (d, 2H, J = 8.2 Hz), 7.61 (d, 2H, J = 8.2 Hz), 7.65−7.75 (m, 4H), 7.80−7.90 (m, 4H). Anal. Calcd for $C_{31}H_{31}N_3O_8S$: C, 61.48; H, 5.16; N, 6.94. Found: C, 61.12; H, 5.00; N, 6.78.

6-*p*-Toluenesulfonyl-3,9-dioxa-1,6,11-triazaundecane (6). A solution of diphthalimido derivative **5** (3.18 g, 5.25 mmol) in 100 mL of EtOH and hydrazine hydrate (2.7 mL, 52.5 mmol) was heated to reflux with stirring for 5 h, with formation of phthalhydrazide as a heavy white precipitate. The reaction mixture was allowed to cool to rt and filtered, and the precipitate was carefully washed with 20 mL of cold EtOH. Evaporation of the combined filtrates under reduced pressure afforded 1.78 g (98%) of **6** as a light yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.75 (t, 4H, J = 5.2 Hz), 3.34 (t, 4H, J = 6.0 Hz), 3.37 (t, 4H, J = 5.2 Hz), 3.56 (t, 4H, J = 6.0 Hz), 7.25 (d, 2H, J = 8.2 Hz), 7.66 (d, 2H, J = 8.2 Hz). Anal. Calcd for $C_{15}H_{27}N_3O_4S$: C, 52.15; H, 7.88; N, 12.16. Found: C, 52.40; H, 7.79; N, 11.80.

1,11-Bis(benzylimino)-6-*p*-toluenesulfonyl-3,9-dioxa-1,6,11-triazaundecane (7). A solution of diamine **6** (5.44 g, 15.7 mmol) and benzaldehyde (3.33 g, 31.4 mmol) in 100 mL of benzene was heated to reflux in a Dean−Stark apparatus, with stirring, for 4 h. During this time the theoretical amounts of H_2O (0.56 mL) separated. The solvent was evaporated under reduced pressure to afford 8.1 g (quantitative yield) of **7** as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.31 (t, 4H, J = 6.0 Hz), 3.53 (t, 4H, J = 6.0 Hz), 3.58−3.64 (m, 4H), 3.64−3.70 (m, 4H), 7.20 (d, 2H, J = 8.2 Hz), 7.32−7.39 (m, 6H), 7.62 (d, 2H, J = 8.2 Hz), 7.66−7.71 (m, 4H), 8.20 (s, 2H). Anal. Calcd for $C_{29}H_{35}N_3O_4S$: C, 66.77; H, 6.76; N, 8.05. Found: C, 66.52; H, 6.48; N, 7.92.

1,11-Dibenzyl-6-*p*-toluenesulfonyl-3,9-dioxa-1,6,11-triazaundecane (8). A solution of the diimino derivative **7** (8.2 g, 15.7 mmol) in 120 mL of CH_3COOH was hydrogenated at rt and atmospheric pressure in the presence of PtO_2 (100 mg, 0.44 mmol). The reaction was complete in 6 h, during which time a theoretical amount of H_2 (700 mL) was absorbed. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure. The residue was dissolved in 100 mL of H_2O, the pH was made alkaline with 30% aqueous NaOH and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were dried over $MgSO_4$ and evaporated to afford 8.0 g (quantitative yield) of **8** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.70 (br s, 2H, D_2O exchange), 2.35 (s, 3H), 2.73 (t, 4H, J = 5.2 Hz), 3.35 (t, 4H, J = 6.0 Hz), 3.49 (t, 4H, J = 5.2 Hz), 3.56 (t, 4H, J = 6.0 Hz), 3.77 (s, 4H), 7.20−7.35 (m, 12H), 7.68 (d, 2H, J = 8.2 Hz). Anal. Calcd for $C_{29}H_{39}N_3O_4S$: C, 66.26; H, 7.48; N, 7.99. Found: C, 65.94; H, 7.18; N, 7.85.

(14) See refs 10 and 13 for a listing of general experimental details.

4,16-Di-*p*-toluenesulfonyl-10,22-dibenzyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane (1). Solid Na_2CO_3 (10.1 g, 95.1 mmol) was added to a solution of the bis(benzylamino) derivative **8** (10 g, 19 mmol) and the diol bis(methanesulfonate) **4** (9.6 g, 19 mmol) in 220 mL of CH_3CN, and the resulting suspension was stirred at reflux for 4 days. The reaction mixture was allowed to cool to rt and filtered through Celite and the solvent evaporated to afford 16.5 g of the crude product, as an orange viscous oil. Purification by column chromatography (SiO_2, CH_2Cl_2/CH_3OH = 95:5 v/v) afforded 7.1 g (45%) of pure **1**: mp = 128−130 °C; ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 6H), 2.70 (t, 8H, J = 5.8 Hz), 3.34 (t, 8H, J = 5.8 Hz), 3.56 (t, 8H, J = 5.8 Hz), 3.63 (s, 4H), 7.20−7.30 (m, 14H), 7.66 (d, 2H, J = 8.2 Hz); MS-FAB(+) m/z 836 (M^+), calcd for $C_{44}H_{60}N_4O_8S_2$ 836. Anal. Calcd for $C_{44}H_{60}N_4O_8S_2$: C, 63.13; H, 7.22; N, 6.69. Found: C, 62.85; H, 6.91; N, 6.52.

4,16-Dibenzyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane (2). A solution of **1** (0.5 g, 0.6 mmol) in 30 mL of dry THF was slowly added to a magnetically stirred suspension of $LiAlH_4$ (0.23 g, 5.97 mmol) in 30 mL of dry THF in an inert atmosphere. After the addition was complete, the reaction mixture was refluxed and stirred for 4 days and then allowed to cool to rt, and the excess $LiAlH_4$ was decomposed with the stoicheometric amounts of H_2O. The aluminum oxide was filtered off and carefully washed with 50 mL of THF and the solvent evaporated to afford 320 mg (quantitative yield) of **2** as a colorless viscous oil: ^{1}H NMR ($CDCl_3$) δ 2.00 (br s, 2H, D_2O exchange), 2.50−2.90 (m, 16H), 3.30−3.60 (m, 16 H), 3.70 (s, 4H), 7.00−7.30 (m, 10H); MS-FAB(+) m/z 528 (M^+), calcd for $C_{30}H_{48}N_4O_4$ 528. Anal. Calcd for $C_{30}H_{48}N_4O_4$: C, 68.15; H, 9.15; N, 10.60. Found: C, 67.95; H, 8.98; N, 10.37.

1,6,11-Tri-*p*-toluenesulfonyl-3,9-dioxa-1,6,11-triazaundecane (9). A solution of *p*-toluenesulfonyl chloride (2.06 g, 10 8 mmol) in 10 mL of dry pyridine was slowly added to a magnetically stirred solution of the diamine **6** in 30 mL of dry pyridine, keeping the temperature below 5 °C. After the addition was complete, the reaction mixture was stirred at 0 °C for further 2 h and then was left overnight in the refrigerator. The mixture was poured in 100 g of crushed ice containing 40 mL of 37% aqueous HCl and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with 50 mL of H_2O and 50 mL of 5% aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated to afford 3.55 g of a viscous brown oil. Purification by column chromatography (SiO_2, CH_2Cl_2/CH_3OH, 99:1 v/v) gave 2.17 g (64%) of **9** as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 6H), 2.38 (s, 3H), 3.04 (t, 2H, J = 5.2 Hz), 3.06 (t, 2H, J = 5.2 Hz), 3.21 (t, 4H, J = 5.2 Hz), 3.42 (t, 4H, J = 4.9 Hz), 3.50 (t, 4H, J = 5.2 Hz), 5.67 (t, 2H, D_2O exchange, J = 6.0 Hz), 7.25 (d, 4H, J = 8.2 Hz), 7.27 (d, 2H, J = 8.2 Hz), 7.64 (d, 2H, J = 8.2 Hz), 7.71 (d, 4H, J = 8.2 Hz). Anal. Calcd for $C_{29}H_{39}N_3O_8S_3$: C, 53.27; H, 6.01; N, 6.43. Found: C, 53.02; H, 5.80; N, 6.22.

4,10,16,22-Tetra-*p*-toluenesulfonyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane (11). Solid K_2CO_3 (2.16 g, 15.65 mmol) was added to a solution of tri-*p*-toluenesulfonamido derivative **9** (2.05 g, 3.13 mmol) and the bis(*p*-toluenesulfonate) **10** (2.06 g, 3.13 mmol) in 60 mL of DMF, and the resulting suspension was stirred at 100 °C for 4 days. After this time the reaction mixture was allowed to cool to rt and filtered through Celite, the precipitate was carefully washed with 20 mL of DMF, and the filtrates were evaporated to dryness under reduced pressure to afford 3.1 g of a deep orange viscous oil. Purification by column chromatography (SiO_2, CH_2Cl_2/CH_3OH, 97:3 v/v) afforded an oily product which solidified with acetone giving **11** as a white solid: mp =149.5−151 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 12H), 3.29 (t, 16H, J = 5.8 Hz), 3.53 (t, 16H, J = 5.8 Hz), 7.29 (d, 8H, J = 8.2 Hz), 7.66 (d, 8H, J = 8.2 Hz); MS-FAB(+) m/z 964 (M^+), calcd for $C_{44}H_{60}N_4O_{12}S_4$ 964. Anal. Calcd for $C_{44}H_{60}N_4O_{12}S_4$: C, 54.75; H, 6.27; N, 5.80. Found: C, 53.60; H, 6.15; N, 5.71.

1,7,13,19-Tetraoxa-4,10,16,22-tetraazacyclotetracosane (3). A solution of **11** (3.68 g, 3.81 mmol) in 100 mL of dry THF was slowly added to a stirred suspension of $LiAlH_4$ (1.37 g, 76.24 mmol) in 40 mL of dry THF in an inert atmosphere. After the addition was complete, the reaction mixture was refluxed and stirred for 4 days and then allowed to cool to rt, and the excess $LiAlH_4$ was decomposed with the stoicheometric amounts of H_2O. The aluminum oxide was filtered off and carefully washed with 80 mL of THF and the solvent evaporated to afford 1.30 g (quantitative yield) of **3** as a pale yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 2.20−2.40 (br s, 4H, D_2O exchange), 2.73 (t, 16H, J = 5.0 Hz), 3.51 (t, 16 H, J = 5.0 Hz); MS-FAB(+) m/z 348 (M^+), calcd for $C_{16}H_{36}N_4O_4$ 348. Anal. Calcd for $C_{16}H_{36}N_4O_4$: C, 55.15; H, 10.41; N, 16.07. Found: C, 55.05; H, 10.50; N, 16.11.

4,16-Di-*p*-toluenesulfonyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane (12). A solution of **1** (2.6 g, 3.1 mmol) in 50 mL of CH_3COOH was hydrogenated at rt and atmospheric pressure in the presence of Pd/C, 5% (300 mg). The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure. The residue was dissolved in 100 mL of CH_2Cl_2 and washed with 10% aqueous Na_2CO_3 and the solvent evaporated to give 1.77 g (87%) of **12** as a white solid: mp = 95−96 °C; ^{1}H NMR ($CDCl_3$) δ 1.74 (br s, 2H, D_2O exchange), 2.40 (s, 6H), 2.73 (t, 8H, J = 5.0 Hz), 3.36 (t, 8H, J = 6.0 Hz), 3.49 (t, 8H, J = 5.0 Hz), 3.58 (t, 8H, J = 6.0 Hz), 7.27 (d, 4H, J = 8.2 Hz), 7.67 (d, 2H, J = 8.2 Hz); MS-FAB(+) m/z 656 (M^+), calcd for $C_{30}H_{48}N_4O_8S_2$ 656. Anal. Calcd for $C_{30}H_{48}N_4O_8S_2$: C, 54.86; H, 7.37; N, 8.53. Found: C, 55.05; H, 7.50; N, 8.42.

26-Benzyl-7,19-di-*p*-toluenesulfonyl-4,10,16,22-tetraoxa-1,7,13,19-tetraazabicyclo[12.12.3]heptacosane (13). Solid Na_2CO_3 (1.57 g, 14.8 mmol) was added to a solution of **12** (0.97 g, 1.48 mmol) and 2-benzyl-1,3-propanediol bis(*p*-toluenesulfonate)[13] (0.70 g, 1.48 mmol) in 80 mL of CH_3CN, and the resulting suspension was stirred at reflux for 6 days. The reaction mixture was allowed to cool to rt and filtered through Celite. The Celite was carefully washed with 50 mL of CH_2Cl_2, and the combined filtrates were evaporated. Purification of the residue by column chromatography (SiO_2, $CHCl_3/CH_3OH$ = 90:10 v/v) gave 0.48 g of pure **13**: mp = 167−170 °C; ^{1}H NMR ($CDCl_3$) δ 1.95−2.05 (m, 1H), 2.40 (s, 3H), 2.42 (s, 3H), 2.50−2.90 (m, 14H), 3.15−3.95 (m, 24H), 7.10−7.40 (m, 9H), 7.60−7.72 (m, 4H); MS-FAB(+) m/z = 810 ($M + 1 + Na^+$), 787 ($M^+ + 1$), calcd for $C_{40}H_{58}N_4O_8S_2Na$ 809. Anal. Calcd for $C_{40}H_{58}N_4O_8S_2$: C, 61.04; H, 7.43; N, 7.12. Found: C, 60.92; H, 7.30; N, 6.87.

26-Benzyl-4,10,16,22-tetraoxa-1,7,13,19-tetraazabicyclo-[12.12.3]heptacosane (14). A solution of **13** (0.45 g, 0.57 mmol) in 30 mL of dry THF was slowly added to a stirred suspension of $LiAlH_4$ (0.22 g, 5.70 mmol) in 20 mL of dry THF in an inert atmosphere. The reaction mixture was refluxed and stirred for 3 days and then cooled to rt, and the excess $LiAlH_4$ was decomposed with the stoicheometric amounts of H_2O. The aluminum oxide was filtered off and carefully washed with 50 mL of THF and the solvent evaporated to afford 270 mg (quantitative yield) of pure **14** as viscous oil: ^{1}H NMR ($CDCl_3$) δ 1.90−2.10 (m, 1H), 2.20−3.00 (m, 24H), 3.45−3.65 (m, 16 H), 7.00−7.30 (m, 5H); MS-FAB(+) m/z 501 ($M + Na^+$), 478 (M^+), calcd for $C_{26}H_{46}N_4O_4Na$ 501. Anal. Calcd for $C_{26}H_{46}N_4O_4$: C, 65.24; H, 9.69; N, 11.70. Found: C, 65.03; H, 9.55; N, 11.58.

Determination of the Extent of Complexation. Into a 20 mL centrifuge test tube were introduced 5 mL of a 1.53 × 10^{-2} M solution of the ligand (L) as free base in CH_2Cl_2, 7.65 × 10^{-2} mmol of the solid salt, and a small magnetic stir bar. The tube was stoppered to prevent evaporation, stirred for 2 h at 20 °C, and then centrifuged at 3000 rpm for 10 min. A 3 mL aliquot of the organic solution was diluted with 30 mL of CH_3OH, acidified with 1 mL of 6 N HNO_3, and potentially titrated with 1 × 10^{-2} N aqueous $AgNO_3$. Extents of complexation percent, E (%), are the ratio between the concentration of complexed ligand $[(M\subset L)^+X^-]$, which correspond to the amount of halide measured in the organic phase, and the initial concentration of the ligand used $[L]_0$ (eq 2).

$$E\ (\%) = [(M\subset L)^+X^-]/[L]_0 \qquad (2)$$

Experiments in the absence of ligands showed that all the salts used are totally insoluble in CH_2Cl_2. Results are reported in Table 1, values are within ±5% error.

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