Synthetic Route To Produce Phenol-Containing Azamacropolycycles

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Introduction

The study of synthetic macrocyclic compounds is an important area of chemistry. The molecular topology of the macrocyclic ligands can be synthetically modulated in order to bind many different chemical species.[1−3] Much effort has been devoted to the design and synthesis of receptors able to coordinate metal ions into their macrocyclic cavity,[4] with the aim of studying their function as selective complexing agents and ionophores.[5−9] The lithium ion is one of the most important targets, due to its actual and potential applications in medicine and technology.[10] In this field, it has been shown that small aza-cages with a macrobicyclic arrangement are able to selectively encapsulate Li^+ in aqueous solution.[11−17] Ligands able to selectively bind a specific metal ion and undergo a concomitant color change are worthwhile subjects in host−guest chemistry, and many contain the phenolic function in the macrocyclic framework, which serves as the base of chromoionophores. To date, the macrocycles bearing phenolic groups, selective for the alkali metal ions synthesized, have been based exclusively upon crown ether or oxaazacrown ether derivatives, and very few examples have a macropolycyclic framework.[7d,8b−d] So far, no macropolycyclic receptors showing only nitrogen donors in the macrocyclic base of the phenol ionophores have been synthesized.

In this study we report a synthetic procedure which can be used to obtain, from the same polyazacycloalkane base (1,7-dimethyl-1,4,7,10-tetraazacyclododecane), two polycyclic phenol ligands with different molecular frameworks: the face-to-face phenol-containing azacrown with cylindrical molecular shape $\mathbf{L_1}$ and the small cage $\mathbf{L_2}$. Both compounds can be utilized in designing new phenol-containing azamacrocycles and studies of selective chromoionophores.

Results and Discussion

All of the new compounds were fully characterized using standard techniques (see Experimental Section). The procedure used to obtain both compounds $\mathbf{L_1}$ and $\mathbf{L_2}$ employs the same azamacrocyclic base **1** previously synthesized.[18a,b] The other reagents **2** and **3**, utilized in the cyclization, originate from 2,6-dimethylanisole, modified following the synthetic scheme reported by Czech et al.[7d]

The first step in producing the face-to-face diphenol-containing azamacrocycle $\mathbf{L_1}$ was the synthesis of the tetraamide **4**, which was obtained by reaction, in benzene and under high-dilution conditions, of **1** with 1 equiv of diacyclic chloride **2** in the presence of triethylamine as base (Scheme 1). From this reaction, after purification by column chromatography and recrystallization from CH_3CN, only compound **4**, which was the product of a 2 + 2 cyclization in low yield (26%), was isolated. The

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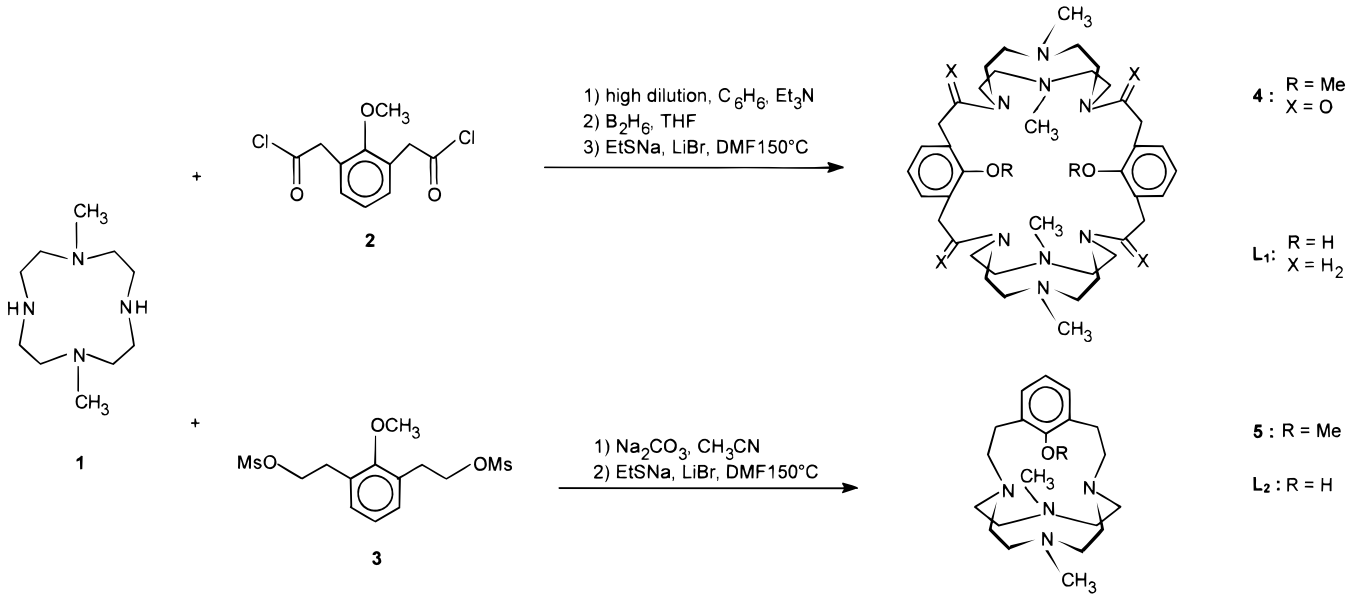
Scheme 1



reduction of the macrocyclic polyamides can be accomplished with either diborane or $LiAlH_4$. In our case, the polyamide intermediate **4** was treated with BH_3 in THF to reduce the amide functions. An attempt to destroy the tetrahydroborane adduct was not successful in both acid and basic aqueous solutions. In both cases, one hydroborane group remained bound to the macrocycle. After destruction of the excess BH_3 and evaporation of the solvent, the crude product was refluxed in an aqueous NaOH solution, and the only product isolated was treated with EtSNa in boiling DMF, in the presence of anhydrous LiBr, to remove the methyl groups. Under these conditions, the product lost the ethereal methyl groups, and the borane adduct was destroyed. The compound $\mathbf{L_1}$ obtained was purified as a tetrahydrochloride salt.

A simpler method was used to obtain the small cage $\mathbf{L_2}$. In this case the 2,6-dimethylanisole was transformed into its dimesyl derivative **3**, which has a lesser stereochemistry requirement and is more flexible than **2**. In this way, it was possible to obtain the small methylated phenol-containing cage **5** directly. The cyclization reaction of macrocyclic base **1** with 1 equiv of the reagent **3** in the presence of an alkaline carbonate base which, after chromatographic purification, afforded the cage **5** derived by a 1 + 1 cyclization, with a very high yield (58%). Cage **5** was further purified by transformation into its diperchlorate salt (**5**·$2HClO_4$) by treatment of the free amine with perchloric acid in ethanol. No template effect was found when different alkaline carbonates were used. **5**·$2HClO_4$ was treated with EtSNa in boiling DMF in the presence of anhydrous LiBr to remove the methyl group, affording, after chromatographic purification, $\mathbf{L_2}$ which was purified by treatment with perchloric acid in ethanol to obtain $\mathbf{L_2}$ as a diperchlorate salt.

The difference in the synthetic routes used to obtain $\mathbf{L_1}$ or $\mathbf{L_2}$ lies in the two 2,6-dimethylanisole derivatives used; accordingly, the cyclization scheme (2 + 2 or 1 + 1 to obtain $\mathbf{L_1}$ or $\mathbf{L_2}$, respectively) can be attributed mainly to the greater rigidity and stereochemistry requirements of **2** with respect to those of **3**.

In conclusion, using the same macrocyclic fragment, it is possible to profoundly influence the cyclization scheme by introducing only slight variations in the other synthetic molecules employed.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded (25 °C) at 200.13 and 50.33 MHz, respectively. Fast atom bombardment (FAB) mass spectra were determined using *m*-nitrobenzyl alcohol (NOBA) as matrix. Compounds **1**−**3** were synthesized as previously described.[18a,7d]

Cryptand Tetraamide (4). A solution (500 cm^3) of diacid chloride **2** (5.2 g, 20 mmol) in freshly distilled anhydrous benzene and a solution (500 cm^3) of 1,7-dimethyl-1,4,7,10-tetraazacyclododecane **1** (4.0 g, 20 mmol) and triethylamine (5.0 g, 50 mmol) in freshly distilled benzene were added simultaneously at room temperature with two syringe pumps to 1.5 dm^3 of vigorously stirred anhydrous benzene. The addition was completed in 8 h after which the solution was stirred for a further 6 h. The solvent was evaporated under vacuum, and the crude product was chromatographed on neutral alumina with CH_2Cl_2−MeOH 95:5 as eluent to afford **4** (R_f = 0.69 on neutral alumina TLC plates) as a yellowish oil, which was then recrystallized with hot CH_3CN to give a white solid (1.8 g, 24%); mp 160−162 °C; ^1H NMR ($CDCl_3$): 2.23 (s, 12H), 2.33 (m, 16H), 3.45 (m, 16H), 3.66 (s, 8H), 3.75 (s, 6H), 7.04 (dd, 2H, J_{HH} = 7.5 and 7.2 Hz), 7.13 (d, 4H, J_{HH} = 7.5 Hz); ^{13}C NMR: 29.7, 44.7, 49.7, 53.7, 62.1, 123.9, 129.0, 132.2, 155.8, 172.3; MS *m*/*z* (FAB) 778 ([M + H]$^+$). Anal. Calcd for $C_{42}H_{64}N_8O_6$: C 64.91; H, 8.30; N, 14.43. Found: C, 65.0; H, 8.4; N, 14.3.

Cryptand $\mathbf{L_1}$. A sample of the BH_3·THF adduct (100 cm^3 of a solution of 0.1 mol BH_3 in THF) was added dropwise, under nitrogen atmosphere, to a solution of tetraamide **4** (2 g, 2.6 mmol) in dry THF (40 cm^3) cooled to 0 °C. After removal of the cooling bath, the reaction mixture was allowed to warm to room temperature and then refluxed for 4 h. The solution was cooled again and the excess diborane was destroyed with a few drops of water. The solution was evaporated under vacuum and the residue dissolved in NaOH (6 mol dm^{-3}, 15 cm^3) and extracted with CH_2Cl_2. The organic solution was dried (Na_2SO_4) and evaporated to dryness to afford the tetraboron adduct as a yellowish oil. A mixture of the tetraboron adduct (1.4 g, 1.8 mmol), EtSNa (0.76 g, 9 mmol), and LiBr (0.46 g, 5.4 mmol) in dry DMF (25 cm^3) was heated at 150−155 °C for 6 h. The solution was evaporated under vacuum, and the crude product was chromatographed on neutral alumina with CH_2Cl_2−MeOH 10:1 as eluent (R_f = 0.47 on neutral alumina TLC plates). The pure product was dissolved in ethanol and treated with 37% HCl to give the dihydrated hydrochloride salt of $\mathbf{L_1}$ ($\mathbf{L_1}$·4HCl·$2H_2O$) as a white solid (0.82 g, 50%); ^1H NMR (D_2O, pH = 3): 2.80 (s,

12H) 2.84 (m, 16H), 2.95 (m, 16H), 3.15 (m, 8H), 3.32 (m, 8H), 7.02 (dd, 2H, J_{HH} = 7.9 and 7.5 Hz), 7.19 (d, 4H, J_{HH} = 7.9 Hz); ^{13}C NMR: 28.6, 43.9, 49.5, 53.7, 56.1, 124.3, 130.4, 130.9, 152.7. MS *m*/*z* (FAB) 694 [M + H$^+$]. Anal. Calcd for $C_{40}H_{76}N_8O_4Cl_4$: C, 54.91; H, 8.76; N, 12.81. Found: C, 54.7; H, 8.7; N, 12.8.

Cryptand (5·2HClO$_4$). Amine **1** (1 g, 5 mmol) and Na_2CO_3 (0.5 g, 47 mmol) were suspended in refluxing CH_3CN (100 cm^3). To this mixture, a solution of **3** (1.76 g, 5 mmol) in CH_3CN (100 cm^3) was added dropwise over 6 h, after which the suspension was refluxed for 72 h and then filtered. The solution was evaporated under vacuum to yield the crude product which was chromatographed on neutral alumina with CH_3Cl−MeOH 10:0.5 as eluent (R_f = 0.39 on neutral alumina TLC plates). Eluted fractions gave an oil, which was dissolved in ethanol and treated with 65% perchloric acid to give the diperchlorate salt as a white solid (1.62 g, 58%). ^{1}H NMR (D_2O, pH = 3): 2.74−2.88 (b, 6H) 2.93−3.41 (b, 24H), 3.77 (s, 3H), 7.17 (dd, 1H, J_{HH} = 7.6 and 7.4 Hz), 7.23 (d, 2H, J_{HH} = 7.6 Hz) ^{13}C NMR: 28.8, 43.6, 44.3, 49.2, 51.2, 57.54, 58.8, 59.5, 64.3, 128.9, 131.8, 135.7, 158.9; MS *m*/*z* (FAB) 360 ([M + H$^+$]). Anal. Calcd for $C_{21}H_{38}N_4O_9Cl_2$: C, 44.98; H, 6.84; N, 10.00. Found: C, 44.8; H, 6.8; N, 9.9.

Cryptand L$_2$·2HClO$_4$. A solution of cryptand **5** (1 g, 1.8 mmol), EtSNa (0.76 g, 9 mmol), and LiBr (0.46 g, 5.4 mmol) in dry DMF (50 cm^3) was heated at 150 °C for 6 h. The solvent was evaporated under vacuum, and the residue was suspended in CH_2Cl_2 and filtered. The organic layer was evaporated and the crude product was chromatographed on neutral alumina with CH_2Cl_2−MeOH 10:1 as eluent; (R_f = 0.57 on neutral alumina TLC plates). The crude product was dissolved in ethanol and treated with 65% perchloric acid to give the diperchlorate salt as a white solid (0.5 g, 51%). ^{1}H NMR (D_2O, pH = 4): 2.23 (s, 3H) 2.52 (m, 6H), 2.78 (m, 8H), 2.93−3.26 (b, 9H), 3.37 (m, 4H), 7.12 (dd, 1H, J_{HH} = 7.2 and 6.9 Hz), 7.22 (d, 2H, J_{HH} = 7.2 Hz); ^{13}C NMR: 28.5, 44.5, 44.8, 49.4, 51.0, 55.1, 57.0, 58.3, 126.0, 130.2, 132.7, 152.5. Anal. Calcd for $C_{20}H_{36}N_4O_9Cl_2$: C, 43.88; H, 6.63; N, 10.23. Found: C, 44.0; H, 6.5; N, 10.3.

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Supporting Information Available: ^{1}H AND ^{13}C NMR spectra (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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