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A CONVENIENT SYNTHESIS OF SPHERICAL CRYPTANDS BY A QUATERNIZATION-DEALKYLATION PROCEDURE.

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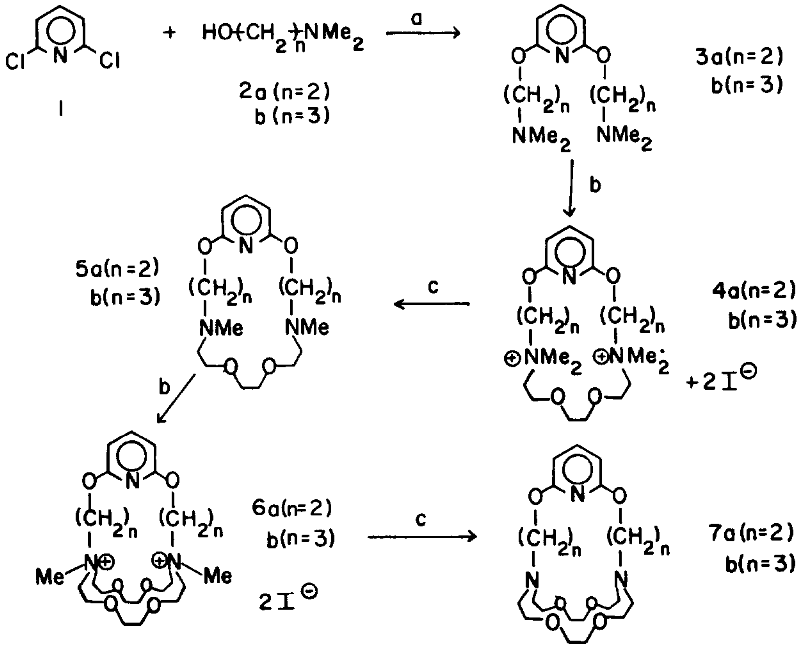
Summary. The construction of spherical cryptands has been accomplished from bis-diamines by a stepwise quaternization-demethylation sequence. Cryptands with diverse bridges can be easily prepared by this procedure.

Spherical cryptands[1] are generally prepared by the high-dilution condensation[2] of diamines with bis-acid chlorides. The resultant bis-amides are subsequently reduced with diborane[3] to give the corresponding macrocyclic or -bicyclic compounds. Although the yields of cryptands prepared by this sequence are generally high, the ability to prepare polyfunctionalized bridges can be limited by the reagents used.

Quaternary ammonium macrocycles[4,5] and cryptands[5] have been synthesized by an alkylation procedure, but to the best of our knowledge no reports of dealkylation and/or N-bridge manipulation, other than ring cleavage,[6] are known. Since quaternary ammonium halides have been easily and quantitatively demethylated using L-Selectride® and Super-Hydride® to give the free amines[7], the quaternization-demethylation sequence can be considered to be a viable pathway to macrocyclic systems. We herein demonstrate this procedure by the general preparation of pyridine aza-crown ethers and their subsequent transformation to the related cryptands, which are normally difficult to prepare by known procedures. This reaction sequence in a broad sense permits the synthesis of bridges which are different and/or functionalized.

The disubstituted pyridine derivatives 3 are readily prepared from 2,6-dichloropyridine and the salt of aminoalcohol 2 according to described procedures.[8] Treatment (reflux, 3 days) of 3a with bis(2-iodoethoxy)ethane, prepared by the Finkelstein reaction of the corresponding chloride,[9] in acetonitrile gave (41%) the bis-quaternary salt 4a[10] [mp 208-209°C (dec); NMR δ 3.25 (s, NMe_2)]. In this bis-alkylation procedure both bis(2-iodoethoxy)ethane and chloro analog were used; the former was preferred based on generally higher yields in cyclization and diminished hygroscopic properties of the iodide salt. Although not a problem with these ammonium macrocycles, it must be noted that certain bis-ammonium compounds with separated (13-15Å) cationic centers usually possess curare properties![11] Macrocycle 4b[10] [mp 178-179°C (dec)] was prepared in an analogous manner.



Reagents: (a) NaH, xylene, reflux 24 hrs; (b) CH_3CN, bis(2-iodoethoxy) ethane, reflux 48 hrs; (c) L-Selectride®, THF, reflux 2 hrs.

The bis-quaternary macrocycles 4 were normally not isolated but rather directly demethylated[7] to give the desired azacrown ethers 5a[10] [oil; 40% (overall); NMR ($CDCl_3$) δ 2.28 (N-Me)] and 5b[10] [oil; 43% (overall); NMR ($CDCl_3$) δ 2.30 (NMe)]. Purification of these azacrown ethers was best accomplished by thick layer chromatography on alumina eluting with cyclohexane-ethyl acetate (1:1); thus, any residual salts and traces of bridge-fragmented contaminants were efficiently removed.[12] Attempted distillation of these macrocycles resulted in partial decomposition.

The quaternization step was repeated using the appropriate dihalide; therefore, 5a gave 6a[10] [mp 232-233°C (dec); NMR (D_2O) δ 3.37 (s, N-Me)] and 5b gave 6b[10] [mp 202-203°C (dec), NMR (D_2O) δ 3.23 (s, N-Me)]. Since the NMR of 6a exhibited a singlet for the N-methyl group, it was assumed that quaternization of 5a proceeded to give an exo-exo ammonium configuration. In order to confirm this configuration a single crystal was grown from acetonitrile; Figure 1 validates the exo-exo orientation as determined by x-ray analysis.

Crystal data[13]: Crystals of $[C_{23}H_{41}N_3O_6]^{2+}2I^-\cdot CH_3CN$ are monoclinic, space group $P2_1/n$, a=11.355(2), b=23.291(3), c=12.161(6)Å, β=97.72(1)°, Z=4. Data were collected using MoK_α radiation on an Enraf-Nonius CAD4 diffractometer to θ=22° and were corrected for absorption. The structure was solved by location of the iodine atoms from a Patterson map, completed by Fourier methods, and refined by full-matrix least squares to R=0.030 for 3081 observed data.

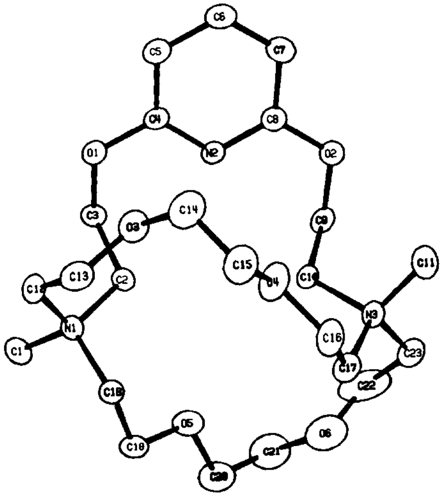


Figure Caption: Distances and angles averaged over chemically equivalent bonds are: N1-C1 1.488, N1-C2 1.521, C2-C3 1.500, C3-O1 1.432, C4-O1 1.360, C4-N2 1.333, C4-C5 1.371, C13-O3 1.420 N1-N3 5.732Å; C1-N1-C2 109.3°, C2-N1-C18 109.7°, C3-O1-C4 117.5°, N1-C2-C3 116.2°, C4-N2-C8 117.0°, N2-C4-C5 123.8°, C4-C5-C6 117.1°, C5-C6-C7 121.2°, C13-O3-C14 113.7°, C18-C19-O5 111.2°. Standard deviations in individual values are 0.005-0.009 Å and 0.3-0.6 degrees.

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