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NOVEL SYNTHESES OF MONOFUNCTIONALIZED TRIAZA-CROWNS AND CYCLAMS WITH A SECONDARY AMINE GROUP ON A SIDE CHAIN

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Abstract: Several monofunctionalized triaza-crowns and cyclams each containing a secondary amine group on a side chain have been prepared in good yields in few steps from readily available starting materials. The X-ray crystal structure of the complex of silver ion with 1-(2-ethylamino)ethyl-4,7,10,13-tetraethyl-1,4,7,10,13-pentaazacyclopentadecane (4) shows that the nitrogen atom of the side chain interacts strongly with the silver ion.

Cyclams containing one reactive functional group have been attached to antibody cells which were then concentrated into tumors so that the tumor could be located by γ-scintigraphy or positron emission tomography after complexing the cyclam with ^{64}Cu, ^{99}Tc or ^{111}In ions[1,2] In addition, certain cyclams containing a secondary amine on a side group formed complexes with metal ions wherein the nitrogen of the side group interacted with the metal ion.[3-5] Up to now, there has been no simple method to prepare macrocycles with a secondary amine function on a side chain. We now report new and convenient methods to prepare per-N-alkyl-substituted triaza-crowns 1 and 2 and cyclams 3 and 4, each containing a secondary amine pendant group, without using high dilution techniques or nitrogen protecting groups (Scheme 1). An X-ray crystal structure of the complex of new cyclam 4 with silver ion shows that the amine on the side chain is interacting with the metal ion (Figure 1). The secondary amine group on the side chain of our new ligands could also be useful for attaching the aza-crown or cyclam to a solid support. Aza-crowns attached to silica gel are useful for the removal of unwanted heavy metal ions from aqueous solutions.[6,7] Other monofunctionalized macrocycles have been used to form cyclams and crown ethers with pendant arms.[8-10] Convenient two or three step syntheses have been reported for the preparation of crowns and cryptands without functional groups.[7,11] However, the usual process to prepare monofunctionalized aza-crowns or cyclams has required many steps, high dilution techniques and the use of nitrogen protecting groups.[2,8,12,13]

Our new methods to prepare triaza-crowns and cyclams containing secondary amine side groups use simple ring closure reactions of easily synthesized dihalides or a diacid and oligoethylene polyamines (Scheme I). In pathway 1 to form triaza-crowns 1 and 2, the two

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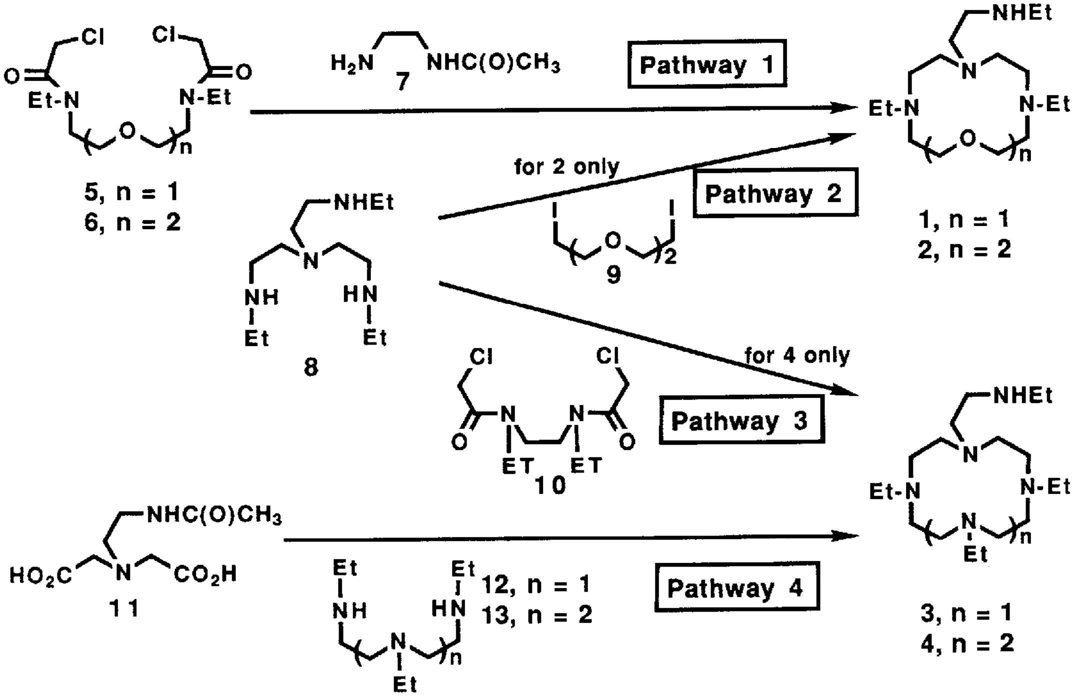
Scheme I. Preparation of New Crowns and Cyclams



Reaction Conditions

Pathway 1: 1) CH_3CN, 0° to 80°, Na_2CO_3; 2) $BH_3 \cdot THF$, THF

Pathway 2: 1) CH_3CN, 0° to reflux, Na_2CO_3, NaI

Pathway 3: 1) CH_3CN, -10° to 25°, Na_2CO_3; 2) $BH_3 \cdot THF$, THF

Pathway 4: 1) DMF, DCC, 1-hydroxybenzotriazole; 2) $BH_3 \cdot THF$, THF

reactants were first mixed in a small amount of acetonitrile in the presence of sodium carbonate at low temperature for a few hours. The reaction mixture was then stirred at room temperature for 24 hours and then at 80°C for 16 to 24 hours. Mixing at the initial low temperature should provide an ordered association of the reactants, especially where intermolecular hydrogen bonding is possible. This ordered association could lead to higher yields of the cyclized products. Others have also synthesized nitrogen-containing macrocycles in high yields without high dilution using reactants that could form a 1:1 product-like complex through hydrogen bonding.[14-16] Reactants 5 and 6, used in pathway 1, were prepared in one step from the corresponding N,N'-diethyldiamines[17,18] and chloroacetyl chloride in stirred chloroform and water in the presence of potassium carbonate at 0-5°C. The two cyclic triamides produced in the first step of pathway 1 were reduced by the borane-THF complex in the usual manner. The reduction products were dissolved a small amount of water and an ammonium hydroxide solution was added until the pH of the mixture was about 10. This mixture was extracted with chloroform to give 1 (26% overall)[19] and 2 (35% overall)[19] as oils. Triaza-crown 2 was also prepared as shown in pathway 2. Compound 8 (bp 85°C/0.5mm) used in pathway 2 was prepared from the available <u>tris</u>-(2-aminoethyl)amine (Fluka) by first forming the <u>tris</u>-acetamide (mp 107°C) with acetic anhydride followed by reduction with lithium aluminum hydride. The process of pathway 2 led directly to 2 as the sodium iodide complex which was recrystallized from THF to give a 34% overall yield (mp 157-158°C).

Cyclams 3 and 4 were prepared as shown in pathways 3 and 4. Cyclam 4[19] was formed in pathway 3 as an oil in 25% overall yield by reacting 8 with 10[20], first at 0°C, then at room temperature followed by reduction. In pathway 4, both 3 and 4 were formed by first reacting diacid 11[21] with 12 (Alfa) or 13[22] (can be purchased from Phaltz and Bauer) in DMF using dicyclohexylcarbodiimide and 1-hydroxybenzotriazole as activators. The resulting triamides were chromatographed on neutral alumina (THF) and reduced by the borane-THF complex. The reduced products were treated with ammonium hydroxide as above to give cyclams 3 (19% overall)[19] and 4 (23% overall)[19] as oils.

It is interesting to note that in the ^{1}H NMR spectra for 1-4, the peaks attributed to the methyl hydrogens of the ethyl group attached to the nitrogen atom of the pendant arm were shifted downfield (δ 1.0 to δ 1.1) from the peaks attributed to the methyl hydrogens of the other N-ethyl groups. This shift reflects the different environments for the two types of N-ethyl substituents.

The X-ray crystal structure of the 4-silver perchlorate complex is shown in Figure 1. It is of particular interest that the side chain nitrogen atom (N 73) is strongly associated with the silver ion. The silver-nitrogen atom distances in the crystal structure are Ag-N13, 2.392

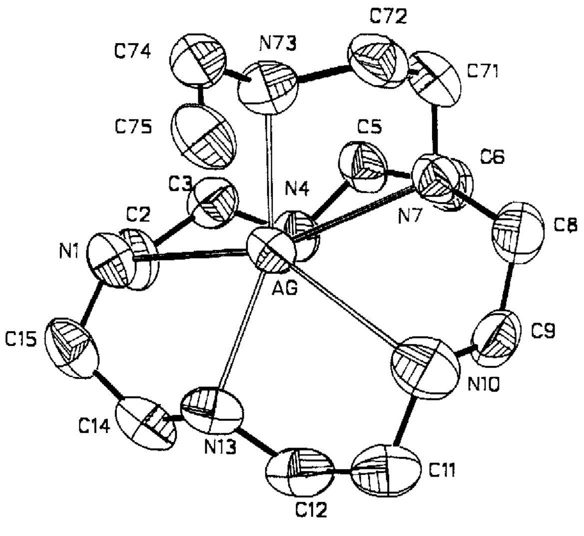


Figure 1. Computer drawing of the silver-4 complex. All hydrogen atoms; the ethyl side chains on N1, N4, N10 and N13; and the anion are omitted for clarity. X-ray intensity data were collected from a 0.30 x 0.55 x 0.35 mm crystal mounted on a Nicolet R3 diffractometer (Mo Kα, λ = 0.71069 Å). The crystal was monoclinic Cc, Z = 4, a = 14.079(9), b = 13.185(6), c = 15.528(5) Å, β = 90.42(5)°, 2844 unique observed reflexions with F > 3σ(F). Structure refinement was done by using a cascading blocked least squares procedure with anisotropic temperature for all atoms except hydrogens. Disorder in the ethyl group bonded to N10 was resolved. However, the disorder of C74 and C75 could not be resolved.

(10) Å; Ag-N73, 2.426(10) Å; Ag-N7, 2.518(8) Å; Ag-N1, 2.543(10) Å; Ag-N4, 2.671(10) Å; and Ag-N10, 2.911(10) Å. The silver-side chain nitrogen atom distance is one of the shorter distances indicating a strong interaction. This crystal structure is the first one reported for a cyclam-15-metal complex with an interacting side chain. Similar metal ion complexes with a cyclam-14 containing a side chain have been reported.[3-5]

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