Syntheses of Diazadithiacrown Ethers Containing Two 8-Hydroxyquinoline Side Arms

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Ten new diazadithiacrown ethers containing two 8-hydroxyquinoline (HQ) sidearms attached through the HQ 7-positions and four new diazadithiacrown ethers containing two HQ sidearms attached through the HQ 2-positions have been prepared. Some of these new ligands also contain a hydroxymethyl substituent. The starting macrocyclic diazadithiacrown ethers were obtained by treatment of a bis(-chloroamide) with the appropriate dimercaptan using K₂CO₃ as the base followed by reduction of the resulting macrocyclic dithiadiamide by BH₃·THF or by NaBH₄ in the presence of BF₃-ether as a catalyst. HQ-containing ligands 23-32 were synthesized by a Mannich reaction of the secondary macrocyclic diamines with the substituted-8-hydroxyquinoline. HQ-containing ligands 33-36 were prepared by reductive amination of the secondary macrocyclic diamines with 8-hydroxyquinoline-2-carbaldehyde.
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Introduction

In general, the complexing ability and selectivity of lariat ethers for metal ions can be varied by changing certain parameters such as the acidity of the phenolic OH group; the size of the crown ether ring; type, number, and position of the complexing crown ether heteroatoms; the stereochemistry imposed by the arms which connect the phenolic group to the macroring; and the pH of media. For example, diaza-18-crown-6 containing two 5-chloro-8-hydroxyquinoline (CHQ) groups attached through the CHQ 7-position (1, Figure 1) exhibits a stronger affinity for Mg2+ than for Ba2+ (log K value in MeOH for Mg2+ is 6.82, for Ba2+ 3.60) and its isomer, diaza-18-crown-6 bearing two CHQ groups attached through the CHQ 2-position (4), has a stronger affinity for Ba2+ than for Mg2+ (log K value in MeOH for Ba2+ is 12.2).1 Ligands 3 and 5, the HQ analogs of 1 and 4, respectively (1 and 4 with the chlorine atoms removed), do not exhibit the same complexing properties as do 1 and 4.5 Increasing the number of macroring nitrogen atoms and changing the size of macroring could change the affinity of the ligand toward the heavy metal ions. For example, for ligand 5, the log K value in MeOH for Cu2+ is 4.39 while its tetraaza-15-crown-5 analog (6) has a log K value for Cu2+ of 15.5.3 Ligand 2, which has a 5-nitro substituent on each 8-hydroxyquinoline, has a high affinity and selectivity for Hg2+ and has proven to be a chemosensor for Hg2+.4 Diazad-18-crown-6 with two 4-methyl(or nitro)-6-aminophenol groups attached through the phenol 2-positions (7 and 8) form dinuclear complexes with one Cu2+ complexed to the two 6-aminophenols and one Na+ in the macroring cavity.5

Diazadithia(ortrithia)crown ethers 9 containing two HQ side arms have also been synthesized.6-7 These new azathia ligands have poor solubilities in MeOH and, therefore, their complexing properties with metal ions cannot be conveniently studied. A few of ligands 9 have a hydroxymethyl substituent attached to the macroring and are thereby more soluble in methanol. Herein, we report the synthesis of a series of new diazadithiacrown ethers bearing two 5-substituent(or 2-methyl)-HQ side-arms. Some of these new ligands contain a hydroxymethyl group on the macroring. A report on the affinities of some of these new ligands for metal ions and their possible use as sensors for metal ions will be reported in due course.
Results and Discussion

The CHQ and HQ side arms are best attached to the diazadithiacrown ethers through macroring NH groups. Macrocyclic ligands containing two secondary amine functions have conveniently been prepared by the crab-like synthesis using bis(α-chloroamide)s. The NH functions of the secondary bis(α-chloroamide)s are unreactive toward alkylation agents including thiols. In the present case, bis(α-chloroamide)s 10-12 were treated with the appropriate dimercaptans using K$_2$CO$_3$ as the base to form macrocyclic diamides 13-15 in yields of 46%-61% as shown in Scheme 1. The macrocyclic diamides were in turn reduced to the desired diazadithiacrown ethers 16, 17, and 22 by either B$_2$H$_6$-THF or the NaBH$_4$-BF$_3$-THF complex (Scheme 1). Ligands 18-21 shown in Scheme 1 were prepared as reported. Satisfactory elemental analyses were obtained for the new macrocyclic diamides or for new HQ and CHQ armed ligands 23-36 prepared from them.

The Mannich aminomethylation reaction has been used to attach HQ and CHQ groups to the azacrown ethers through HQ and CHQ 7-positions. In the present case, the appropriate diazadithiacrown ether (16-22) and the appropriate HQ derivative were treated with paraformaldehyde in refluxing benzene in the one-step aminomethylation reaction to give the bis(2- or 5-substituted-8-quinolin-7-ylmethyl)-substituted ligands 23-32 (Scheme 2).

The products of the Mannich reaction of the diazadithiacrown ethers with HQ (23 and 27) and 8-hydroxyquinoline (26) were mixtures. Each of these two starting materials has no substituent on the quinoline 5-position. Thus, both the 5 and 7 positions could be aminomethylated under these reaction conditions. Although we did not look for the side products in these reactions, we recently showed by a careful $^1$H NMR analysis that when diazatricithiacrown ether 18 was treated with 8-hydroxyquinoline, the product mixture proved to be about 90% of the desired product where both quinoline substituents were attached through the 8-hydroxyquinoline 7-position, about 9% of the product with one 8-hydroxyquinoline attached through its 7-position and the other through its 5-position and the remaining product had both 8-hydroxyquinoline groups attached through their 5-positions. Thus, we suspect that products 23, 26 and 27 are mixtures where the HQ groups are attached through their 7-and 5-positions.

HQ has been attached to diaza-18-crown-6 and a series of tetraaza-15(16)-crown-5 ligands through the HQ 2-position by a reductive amination process using NaBH$_2$(OAc)$_3$. In the present case, 8-hydroxyquinoline-2-carboxaldehyde and the appropriate ligand (16-18 or 20) were treated with NaBH$_2$(OAc)$_3$ to form the bis(8-hydroxyquinolin-2-ylmethyl)-substituted ligands 33-36 in yields of 46% - 66% (Scheme 3). It is important to note that the hydroxy group of HQ did not have to be protected for this reaction as previously reported.
Figure 1. Compounds Mentioned in the Introduction.

Scheme 1. Preparation of Diazadithiacrown Ethers 16, 17 and 22.
Scheme 2. Preparation of 8-Hydroxyquinoline-substituted Diazadithiacrown Ethers 23-32 by the Mannich Reaction.

References