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Synthesis of N-(bisphosphonomethyl)aza-15-Crown-5 and N-(bisphosphonomethyl)-aza-18-Crown-6 Ethers as Artificial Ion Channels: An Approach to Channel-Type Molecular Structures

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Synthesis of N-(bisphosphonomethyl)-aza-15-Crown-5 and N-(bisphosphonomethyl)-aza-18-Crown-6 Ethers as Artificial Ion Channels: An Approach to Channel-Type Molecular Structures

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We report the synthesis and characterization of 2 new N-(bisphosphonomethyl)-aza-15-crown-5 <u>**1a**</u> and N-(bisphosphonomethyl)-aza-18-Crown-6 ethers <u>**1b**</u> designed to further investigate the supramolecular assemblies based on exocyclic functional groups of crown ethers.

INTRODUCTION

The integration of macrocyclic ligands as aza-15-crown-5 or aza-18crown-6 ether substituents into a gem-*bis*phosphonic structure should leads to a new class of compounds with a wide range of potential applications: osteoporosis and Paget disease treatment, extraction and separation of isotopes, and complexing agents of actinides.^{1.2,3}

Clearfield et al.⁴ described the synthesis of supramolecular assemblies based on exocyclic functional groups of crown ethers resulting in unprecedented branched structures.

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The main goal of this study is to synthesise new structures as $\underline{1}$ to afterwards investigate the supramolecular assemblies based on exocyclic functional groups of crown ethers with better chelating properties than Clearfield structures owing to the *bis*phosphonic ligand and the variation of the length between the nitrogen atom and the methylene *bis*phosphonic group.

In this article, we report the first synthesis of 1,1-bis(diethylphosphono)-1-(4',7',10',13'-tetraoxa-1'-azacyclopentadec-1'-yl)methane <u>**1a**</u> and the 1,1-*bis*(diethylphosphono)-1-(4',7',10',13',16'-pentaoxa-1'-azacyclooctadec-1'-yl) methane **1b** (Figure 1).

RESULTS AND DISCUSSION

Synthesis of Crown Ethers

The first step is the preparation of 1-aza-[15-5]-crown ether $\underline{2a}$ and 1-aza-[18-6]-crown ether $\underline{2b}$ (Scheme 1). The tosylation of the tri- or tetraethylene glycol was performed in good yield (>90%) using *p*-toluenesulfonylchloride in THF and a solution of KOH in water.⁵

The monoaza-[15-5]- and [18-6]-crown ethers $\underline{2a}$ and $\underline{2b}$ then were obtained in moderated yields (25–50%) using the one-step synthesis described by Maeda and colleagues⁶ by the treatment of di(2-hydroxyethyl)amine with the corresponding tosylates in *t*BuONa/*t*BuOH.



SCHEME 1 Preparation of 1-aza-[15-5]-crown ether <u>2a</u> and 1-aza-[18-6]crown ether <u>2b</u>.^{5,6}

Synthesis of Substituted Crown Ether Gem-bisphosphonates

The crown ether-substituted methane-gem-bisphosphonic esters <u>1a</u> and <u>1b</u> were synthesized starting from crown ethers, triethylorthoformate, and diethyl phosphite. The reaction, performed at 140– 160°C, in closed Wheaton tubes (5 mL) under dry nitrogen atmosphere, without solvent, allowed, in one step, to get the crown ether-substituted methane-gem-bisphosphonic esters <u>1a</u> and <u>1b</u> (Scheme 2). Purifications were achieved by chromatography on alumina to give the compounds with 40–49% yields.



SCHEME 2 Synthesis of crown ethers-subtituted gem-*bis*phosphonates $\underline{1a}$ and $\underline{1b}$.

In summary, we described in this article the first synthesis of crown ether-substituted gem-*bis*phosphonic ethyl esters. The synthesis of crown ether-subtituted homologs $\underline{1}$, with a variation of the length between the nitrogen atom and the *bis*phosphonic groups, as well as the investigations of the supramolecular assemblies of these structures are in progress.

EXPERIMENTAL PART

All reactions involving air- or moisture-sensitive reagents or intermediates were carried out under dry nitrogen in flame-dried glassware. Reagents and solvents were distilled before use and stored under nitrogen over sodium wires (THF) or molecular sieves (dichloromethane). All reactions were monitored by ³¹P NMR. NMR spectra were recorded on BRUKER AC 200, or 250 (¹H frequency: 200.13 or 250.13 MHz; ¹³C frequency: 50.32 or 62.89 MHz, ³¹P frequency: 81.02 or 101.25 MHz, respectively). Chemical shifts are given in δ units with respect to TMS (¹H, ¹³C NMR) or H₃PO₄ 85% (³¹P), and coupling constants are expressed in Hz.

Triethylene Glycol Di(toluene-p-sulphonate)

In a 250-mL flask containing 100 mL of THF, were added *p*-toluenesulfonylchloride (42.0 g, 220 mmol) (recrystallized in pentane) and triethylene glycol (11.0 g, 73.2 mmol). A solution of KOH (26.2 g in 25 mL of water, 467 mmol) is added. The addition was performed for 3 h at 0°C. After this addition, the mixture was allowed to stand to ambient temperature for 7 h. Then the reaction is poured into 150 mL of a mixture of ice/CH₂Cl₂ (70/30). The water phase was extracted 3 times with 50 mL of CH₂Cl₂. The organic phases, dried over MgSO₄ and evaporated under vacuum, gave 31.3 g (68.3 mmol) of a yellow oil (yield = 93%).

¹H NMR (CDCl₃, 200 MHz): $\delta = 7.74$ (d, J = 8.2, 4H, H_{ar}), 7.30 (d, J = 8.2, 4H, H_{ar}), 4.10 (t, J = 4.7, 4H, TsO-CH₂), 3.61 (t, J = 4.7, 4H, TsO-CH₂–CH₂–), 3.48 (s, 8H, O–CH₂–CH₂–O), 2.40 (s, 6H, CH₃) ¹³C NMR (CDCl₃, 50 MHz): $\delta = 144.9$ (C_{ar}), 129.8 (C_{ar}), 70.6 (TsO-CH₂–CH₂–O–), 69.3 (O–CH₂–CH₂-O-), 68.7 (TsO-CH₂–CH₂–O-).

Tetraethylene Glycol Di(toluene-p-sulphonate)

In a 250-mL flask containing 100 mL of THF, *p*-toluenesulfonicchloride (41.4 g, 217 mmol) (recrystallized in pentane) and tetraethylene glycol (14.1 g, 72.6 mmol) were added. Then is added a to solution of KOH (26.2 g in 25 mL of water, 467 mmol). The addition was performed for 3 h at 0°C. After this addition, the mixture was allowed to stand to ambient temperature for 7 h. Then the reaction is poured into 150 mL of a mixture of ice/CH₂Cl₂ (70/30). The water phase was extracted 3 times with 50 mL of CH₂Cl₂. The organic phases, dried over MgSO₄ and evaporated under vacuum, gave 35 g of a yellow oil (yield = 96%).

¹H NMR (CDCl₃, 200 MHz): $\delta = 7.74$ (d, J = 8.2, 4H, H_{ar}), 7.29 (d, J = 8.2, 4H, H_{ar}), 4.11 (t, J = 4.7, 4H, TsO-CH₂), 3.63 (t, J = 4.7, 4H,

TsO–CH₂–CH₂–), 3.51 (s, 8H, O–CH₂–CH₂–O), 2.40 (s, 6H, CH₃) ¹³C NMR (CDCl₃, 50 MHz): δ = 144.8 (C_{ar}), 132.9 (C_{ar}), 129.8 (CH_{ar}), 127.9 (CH_{ar}), 70.7 (TsO–CH₂–CH₂–O–), 70.5 and 69.3 (O–CH₂–CH₂–O-), 68.6 (TsO–CH₂–CH₂–O–).

1-Aza [15-5] Crown ether 2a

At room temperature, in a 2-L flask, containing sodium terbutoxide (prepared by a 12-h reaction of Na [8.8 g, 383 mmol] in 1.5 L of *t*BuOH, at 50°C), were added drop by drop, simultaneously, triethylene glycol di(toluene-*p*-sulphonate) (32 g, 69.8 mmol) in 100 mL of dioxane and diethanolamine (8.10 g, 77.0 mmol) in 100 mL of *t*BuOH.

After the addition, the reaction was continued for 3 h at 40°C. Then the reaction mixture was filtered and the solvent was evaporated. Water (80 mL) was added to the residue and the solution was extracted once with hexane to remove hexane-soluble materials and then was extracted several times with dichloromethane. The dichloromethane extracts were combined, the solvent was evapored, and the residue was distilled (kugelrohr) to give a colorless liquid (4.55 g, Yield = 25%).

¹H NMR (CDCl₃, 200 MHz): δ = 3.38 and 3.49 (m, 16H, OC*H*₂), 2.86 (bs, 1H, N*H*), 2.58 (m, 4H, NC*H*₂).

¹³C NMR (CDCl₃, 50 MHz): $\delta = 70.1, 69.8, 69.7 (OCH₂), 48.8 (NCH₂).$

1-Aza [18-6] Crown ether 2b

At room temperature, in a 2-L flask containing tBuOK (30.7 g, 274 mmol) in 1.5-L of tBuOH, triethylene glycol di(toluene-*p*-sulphonate) (46 g, 91.5 mmol) are added simultaneously, drop by drop, in 100 mL of dioxanne and diethanolamine (9.6 g, 91.3 mmol) in 100 mL of tBuOH.

After the addition, the reaction was continued for 1 h at 40°C. Then the reaction mixture was filtered and the solvent was evaporated. Water (30 mL) was added to the residue and the solution was extracted once with hexane to remove hexane-soluble materials and then it was extracted several times with dichloromethane. The dichloromethane extracts were combined, the solvent was evapored off, and the residue was distilled (kugelrohr) to give a white solid (5.86 g, Yield = 24%). m.p. = 48° C.

¹H NMR (CDCl₃, 200 MHz): $\delta = 3.61$ (m, 20H, OCH₂), 2.78 (m, 4H, NCH₂), 1.14 (s, 1H, NH)

¹³C NMR (CDCl₃, 50 MHz): δ = 70.7, 70.5, 70.4, 70.2 (OCH₂), 49.1 (NCH₂).

1,1-Bis(diethylphosphono)-(4',7',10',13'-tetraoxa-1'azacyclopentadec-1'-yl)methane 1a

General Procedure

Under dry nitrogen atmosphere, in a closed Wheaton tube (5 mL), without solvent, 1-aza [15-5] crown ether (0.50 g, 2.28 mmol), triethylorthoformate (0.60 mL, 0.53 g, 3.61 mmol) and diethyl phosphite (0.56 mL, 0.60 g, 4.35 mmol) were added. The reaction mixture was heated at $150-160^{\circ}$ C for 2–3 h.

Then, triethylorthoformate was evapored under vaccum at 90°C. Purification was achieved by chromatography on alumina $(CH_3CN/CH_2Cl_2: 0/100 \rightarrow 40/60)$ to give 0.46 g a yellow oil (0.91 mmol, Yield = 25%).

³¹P (DMSO-d₆), 101 MHz): $\delta = 20.3$.

¹H NMR (CDCl₃, 200 MHz): $\delta = 4.17$ (m, 8H, OCH₂CH₃), 3.58 (m, 16H, OCH₂), 3.38 (t, 1H, ²J_{PH} = 25.2, PCHP), 3.09 (t, ³J_{HH} = 6.1, 4H, OCH₂CH₂N), 1.28 (t, ³J_{HH} = 7.03, 12H, OCH₂CH₃).

¹³C NMR (CDCl₃, 50 MHz): $\delta = 71.1$, 70.9, 70.4, 70.0 (OCH₂ crown ether), 62.8 and 62.2 (OCH₂CH₃), 60.8 (PCHP, t, ¹J_{CP} = 140), 55.5 (OCH₂CH₂N), 16.3 (OCH₂CH₃). HRMS(FAB+): calcd for C₁₉H₄₂NO₁₀P₂: 506.2284. Found: 506.2304.

1,1-Bis(diethylphosphono)-(4',7',10',13',16'-pentaoxa-1'azacyclooctadec-1'-yl)methane 1b

Under dry nitrogen atmosphere, in a closed Wheaton tube (5 mL), without solvent, 1-aza [18-6] crown ether (0.44 g, 1.67 mmol), triethylorthoformate (0.50 mL, 0.45 g, 3.01 mmol) and diethyl phosphite (0.41 mL, 0.44 g, 3.18 mmol) were added. The reaction mixture was heated at $150-160^{\circ}$ C for 2–3 h.

Then, triethylorthoformate was evapored under vaccum at 90°C. Purification was achieved by chromatography on alumina (CH₃CN/CH₂Cl₂: 0/100 \rightarrow 40/60) to give 0.45 g of yellow oil (0.82 mmol, Yield = 49%).

³¹P (DMSO-d₆, 101 MHz): $\delta = 20.4$.

¹H NMR (CDCl₃, 200 MHz): $\delta = 4.04$ (m, 8H, OCH₂CH₃), 3.48 (m, 20H, OCH₂), 3.41 (t, 1H, ²J_{PH} = 24.8, PCHP), 2.97 (t, ³J_{HH} = 5.8, 4H, OCH₂CH₂N), $\delta = 1.18$ (t, ³J_{HH} = 6.0 Hz, 12H, OCH₂CH₃).

¹³C NMR (CDCl₃, 50 MHz): δ = 71.7, 70.8, 70.5, 70.4, 69.7 (OCH₂ crown ether), 62.8 and 62.2 (OCH₂CH₃), 61.8 (PCHP, t, ¹J_{CP} = 142), 54.2 (OCH₂CH₂N), 16.3 (OCH₂CH₃). HRMS(FAB+): calcd for C₂₁H₄₆NO₁₁P₂: 550.2546. Found: 550.2567.

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