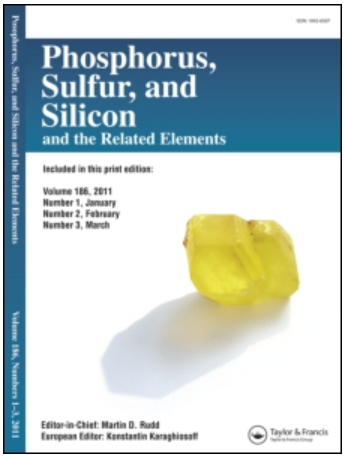

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Synthesis of N-(bisphosphonomethyl)-aza-15-Crown-5 and N-(bisphosphonomethyl)-aza-18-Crown-6 Ethers as Artificial Ion Channels: An Approach to Channel-Type Molecular Structures

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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 ***1a*** *and N-(bisphosphonomethyl)-aza-18-Crown-6 ethers* ***1b*** *designed to further investigate the supramolecular assemblies based on exocyclic functional groups of crown ethers.*

Keywords Aza-18-Crown-6 ether; aza-15-Crown-5 ether; gem-bisphosphonates; supramolecular assemblies

INTRODUCTION

The integration of macrocyclic ligands as aza-15-crown-5 or aza-18-crown-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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We are very grateful to Professor H. GROβ, who drawed our attention to the potential interest of structures such as **1**.

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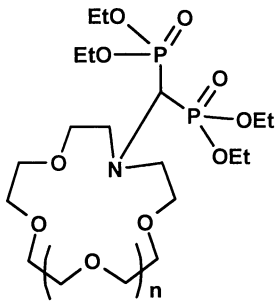
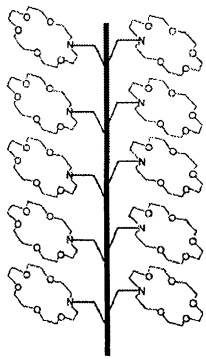


1a n = 1
1b n = 2

(a)



A schematic representation of "macrocyclic leaflets" formed by self-assembly of *N*-(phosphonomethyl)-aza-18-crown-6-ethers[4]

(b)

FIGURE 1

The main goal of this study is to synthesise new structures as **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.

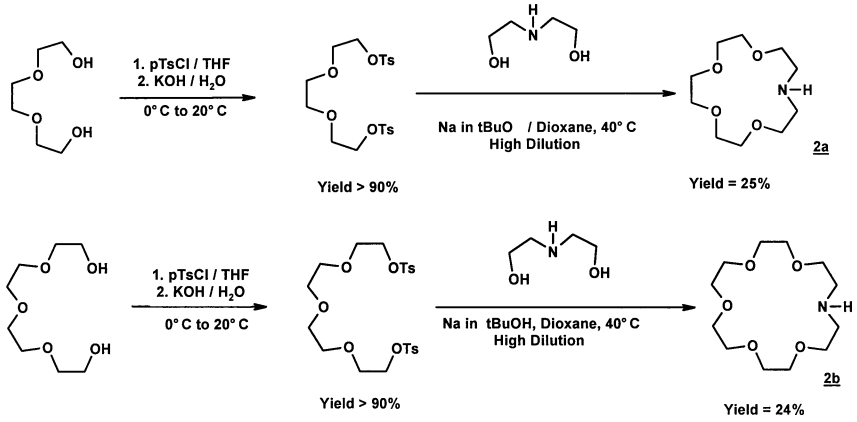
In this article, we report the first synthesis of 1,1-bis(diethylphosphono)-1-(4′,7′,10′,13′-tetraoxa-1′-azacyclopentadec-1′-yl)methane **1a** and the 1,1-*bis*(diethylphosphono)-1-(4′,7′,10′,13′,16′-pentaoxa-1′-azacyclooctadec-1′-yl) methane **1b** (Figure 1).

RESULTS AND DISCUSSION

Synthesis of Crown Ethers

The first step is the preparation of 1-aza-[15-5]-crown ether **2a** and 1-aza-[18-6]-crown ether **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]

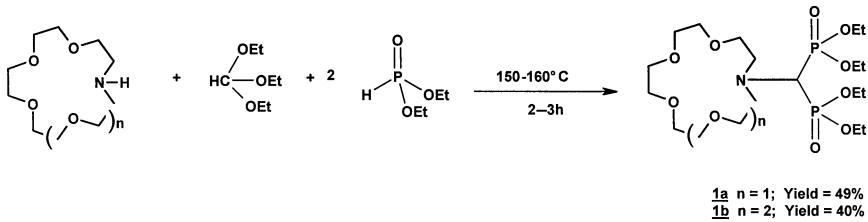
The monoaza-[15-5]- and [18-6]-crown ethers **2a** and **2b** then were obtained in moderated yields (25–50%) using the one-step synthesis described by Maeda and colleagues[6] by the treatment of di(2-hydroxyethyl)amine with the corresponding tosylates in *t*BuONa/*t*BuOH.



SCHEME 1 Preparation of 1-aza-[15-5]-crown ether **2a** and 1-aza-[18-6]-crown ether **2b**.[5,6]

Synthesis of Substituted Crown Ether Gem-*bis*phosphonates

The crown ether-substituted methane-gem-bisphosphonic esters **1a** and **1b** 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 **1a** and **1b** (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 **1a** and **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 **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 ^{31}P NMR. NMR spectra were recorded on BRUKER AC 200, or 250 (^{1}H frequency: 200.13 or 250.13 MHz; ^{13}C frequency: 50.32 or 62.89 MHz, ^{31}P frequency: 81.02 or 101.25 MHz, respectively). Chemical shifts are given in δ units with respect to TMS (^{1}H, ^{13}C NMR) or H_3PO_4 85% (^{31}P), 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/CH_2Cl_2 (70/30). The water phase was extracted 3 times with 50 mL of CH_2Cl_2. The organic phases, dried over $MgSO_4$ and evaporated under vacuum, gave 31.3 g (68.3 mmol) of a yellow oil (yield = 93%).

^{1}H NMR ($CDCl_3$, 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-CH_2), 3.61 (t, J = 4.7, 4H, TsO-CH_2—CH_2–), 3.48 (s, 8H, O—CH_2—CH_2—O), 2.40 (s, 6H, CH_3) ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 144.9$ (C_{ar}), 129.8 (C_{ar}), 70.6 (TsO-*C*H_2—*C*H_2—O—), 69.3 (O—*C*H_2—*C*H_2-O-), 68.7 (TsO-*C*H_2—*C*H_2-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/CH_2Cl_2 (70/30). The water phase was extracted 3 times with 50 mL of CH_2Cl_2. The organic phases, dried over $MgSO_4$ and evaporated under vacuum, gave 35 g of a yellow oil (yield = 96%).

^{1}H NMR ($CDCl_3$, 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-CH_2), 3.63 (t, J = 4.7, 4H,

TsO—CH_2—CH_2—), 3.51 (s, 8H, O—CH_2—CH_2—O), 2.40 (s, 6H, CH_3) ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 144.8 (C_{ar}), 132.9 (C_{ar}), 129.8 (CH_{ar}), 127.9 (CH_{ar}), 70.7 (TsO—CH_2—CH_2—O—), 70.5 and 69.3 (O—CH_2—CH_2—O-), 68.6 (TsO—CH_2—CH_2—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%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.38 and 3.49 (m, 16H, OCH_2), 2.86 (bs, 1H, N*H*), 2.58 (m, 4H, NCH_2).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 70.1, 69.8, 69.7 (OCH_2), 48.8 (NCH_2).

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

At room temperature, in a 2-L flask containing *t*BuOK (30.7 g, 274 mmol) in 1.5-L of *t*BuOH, 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 *t*BuOH.

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.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.61 (m, 20H, OCH_2), 2.78 (m, 4H, NCH_2), 1.14 (s, 1H, N*H*)

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 70.7, 70.5, 70.4, 70.2 (OCH_2), 49.1 (NCH_2).

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°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 → 40/60) to give 0.46 g a yellow oil (0.91 mmol, Yield = 25%).

^{31}P (DMSO-d_6), 101 MHz): $\delta = 20.3$.

^1H NMR ($CDCl_3$, 200 MHz): $\delta = 4.17$ (m, 8H, OCH_2CH_3), 3.58 (m, 16H, OCH_2), 3.38 (t, 1H, $^2J_{PH} = 25.2$, PCHP), 3.09 (t, $^3J_{HH} = 6.1$, 4H, OCH_2CH_2N), 1.28 (t, $^3J_{HH} = 7.03$, 12H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 71.1$, 70.9, 70.4, 70.0 (OCH_2 crown ether), 62.8 and 62.2 (OCH_2CH_3), 60.8 (PCHP, t, $^1J_{CP} = 140$), 55.5 (OCH_2CH_2N), 16.3 (OCH_2CH_3). HRMS(FAB+): calcd for $C_{19}H_{42}NO_{10}P_2$: 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°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 → 40/60) to give 0.45 g of yellow oil (0.82 mmol, Yield = 49%).

^{31}P (DMSO-d_6, 101 MHz): $\delta = 20.4$.

^1H NMR ($CDCl_3$, 200 MHz): $\delta = 4.04$ (m, 8H, OCH_2CH_3), 3.48 (m, 20H, OCH_2), 3.41 (t, 1H, $^2J_{PH} = 24.8$, PCHP), 2.97 (t, $^3J_{HH} = 5.8$, 4H, OCH_2CH_2N), $\delta = 1.18$ (t, $^3J_{HH} = 6.0$ Hz, 12H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 71.7$, 70.8, 70.5, 70.4, 69.7 (OCH_2 crown ether), 62.8 and 62.2 (OCH_2CH_3), 61.8 (PCHP, t, $^1J_{CP} = 142$), 54.2 (OCH_2CH_2N), 16.3 (OCH_2CH_3). HRMS(FAB+): calcd for $C_{21}H_{46}NO_{11}P_2$: 550.2546. Found: 550.2567.

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