Proton-Ionizable Crown Compounds. 20. The Synthesis of Polyazatriazolo-, Polyazabistriazolo- and Bispyridono-Crown Ligands Containing Lipophilic Hydrocarbon Substituents

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Four new macrocyclic polyaza-crown compounds containing a triazole subcyclic group and two to five lipophilic hydrocarbon substituents have been prepared from the appropriate polyamine and *N*-THP-protected 2,5-triazoledimethyl dichloride. *N,N,N',N'*-Tetrabenzyltetraazabistriazolo-18-crown-6 was prepared from *N,N'*-dibenzylethylenediamine and *N*-THP-protected 2,5-triazoledimethyl dichloride. Biscyclohexano-bispyridono-18-crown-6 was prepared from *trans*-1,2-cyclohexanediol and THP-protected 4-hydroxy-2,6-pyridinedimethyl ditosylate.

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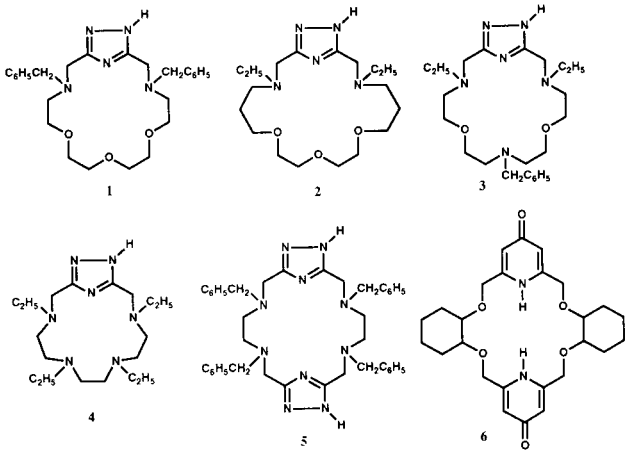
Introduction.

Proton-ionizable crown compounds, particularly those where the proton-ionizable moiety is part of the macroring, are of interest to us. The proton-ionizable macrocyclic ligands allow a proton-coupled transport of metal ions through various membrane systems [2-6]. The transport of these metal ions is *p*H dependent so that transport can be turned on or off by adjusting the *p*H [2,7,8]. In our previous work, we have studied macrocycles containing pyridono- (pK_a = 10.98) [2,4,9-12], triazolo- (pK_a = 9.55) [12-17], sulfonamido- (pK_a = 9 and 12) [18-21] and dialkylhydrogenphosphate- (p*K*a = 4-5) [22,23] crown ligands. No pyridono- or triazolo-crowns containing two of the proton-ionizable moieties have been prepared. These bispyridono- and bistriazolo-crowns would be of interest for the complexation and proton-driven transport of divalent metal ions.

This work describes the synthesis of triazolo-crowns containing lipophilic groups substituted at tertiary amine units in the ring (**1-4**, Figure 1), one bistriazolo-crown with four lipophilic tertiary amine units in the ring (**1-4**, Figure), one bistriazolo-crown with four lipophilic tertiary amine units in the ring **5** and a bispyridono-crown containing two lipophilic cyclohexano units **6**. We previously have reported the synthesis of triazolo-crowns containing lipophilic groups substituted on ring carbon atoms [15] and triazolo-crowns containing lipophilic groups attached to chiral carbon atoms on the macroring [17].

Figure 1. New Proton-Ionizable Crown Compounds



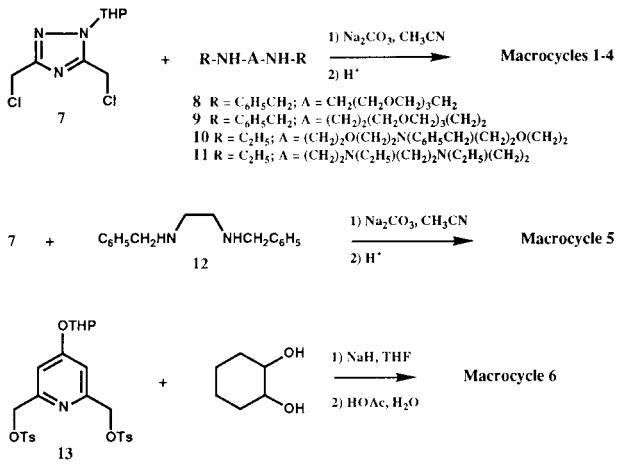
Results and Discussion.

The new triazolo-, bistriazolo- and bispyridono-crowns were prepared as shown in Scheme I. The monotriazolo-crowns **1-4** were isolated as oils in 36-62% yields by straight-forward techniques. Bistriazolo-crown **5** (22%) and bispyridono-crown **6** (8%) were purified by chromatography and recrystallization. The structures proposed for these new macrocyclic compounds are consistent with data obtained from their ir and ^{1}H nmr spectra and combustion analyses.

The starting materials used to prepare the new macrocycles were purchased or prepared as reported. Ditosylate **13** was prepared in a much higher yield than that reported previously [10] by using powdered potassium hydroxide as base in THF. Indeed, this procedure appears to be a superior method for the preparation of all types of tosylate and ditosylate esters [24]. Others have reported a similar tosylation reaction except that they used water/THF as a solvent [25,26]. Since acidic conditions were not used, this procedure is useful for the preparation of acid-labile tosylates. Thus, in our case, the THP-protected compound was readily prepared.

The triazolo- and 4-pyridono-containing macrocycles have proved to be effective agents for the proton-driven transport of a variety of metal ions [2,4,12,16]. Macrocycles **5** and **6** which contain two proton-ionizable triazole and two 4-pyridone units, respectively, should be carriers for the proton-driven transport of divalent cations. A report of the transport properties of these interesting new macrocycles will be published when the work is finished.

Scheme I. Preparation of New Proton-Ionizable Crowns



EXPERIMENTAL

Infrared (ir) spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer. The proton magnetic resonance (^{1}H nmr) spectra were obtained on a Varian Gemini 200 spectrometer using deuteriochloroform as the solvent. Molecular weights were determined by the electron impact method on a Finnegan 8430 high resolution mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Starting compounds **7** [14], **8** [27], **9** [27], **10** [28] were prepared as reported. The other starting materials were purchased.

Preparation of 4-(Tetrahydro-2-pyranoxy)-2,6-pyridinedimethyl Ditosylate (**13**).

Solid 4-(tetrahydro-2-pyranoxy)-2,6-pyridinedimethanol (20.62 g, 0.086 mole) was added to a stirred mixture of 24.3 g (0.038 mole) of solid potassium hydroxide in 300 ml of dry THF at 0° under argon. Tosyl chloride (36.1 g, 0.19 mole) in 180 ml of dry THF was added dropwise to the above stirred mixture. The resulting mixture was stirred at 0° for 5 hours and at room temperature for 7 hours and the solvent was evaporated under reduced pressure. The residue was stirred thoroughly in a mixture of 200 g of ice, 200 ml of water and 1000 ml of methylene chloride. The organic phase was dried over anhydrous magnesium sulfate and the solvent was evporated under reduced pressure to give 46.7 g (99%) of crude product. The crude product was recrystallized by dissolving it in 47 ml of hot methylene chloride and adding 470 ml of hot methanol. This hot solution was allowed to stand at room temperature for 2 hours and in the refrigerator overnight. The crystals were filtered and dried in a vacuum desiccator to give 41.1 g (87%) of white crystals, mp 90-91% (lit value [10], 89-91°). All physical properties for **13** were as reported [10].

General Procedure for the Preparation of Macrocyclic Compounds **1-4**.

3,5-Bis(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4,-triazole (**7**) (2.50 g, 10 mmoles) and 10 mmoles of the appropriate diamine, **8-11** was added to 450-600 ml of acetonitrile containing 15 g of anhydrous sodium carbonate and the mixture was stirred for 16 hours at room temperature and then under reflux for 24 hours. The mixture was cooled, filtered and the filtrate was evaporated. The residue was dissolved in a small amount of pure dichloromethane and filtered. The filtrate was evaporated and the residue was chromatographed on alumina using toluene/ethanol 100/1 or 50/1 as eluants. The THP-blocking group was removed from the crude product by stirring in about 50 ml of 15% methanolic hydrogen chloride for several hours at 25°. The methanol was evaporated and the residue was neutralized with saturated aqueous sodium bicarbonate solution. The product was extracted with three 100 ml portions of chloroform. The organic layer was dried over anhydrous magnesium sulfate. The mixture was filtered, evaporated to give **1-4** as oils. Some of the products were further purified by alumina chromatography using toluene/ethanol as eluants. Product yields and spectral properties are as follows.

Compound **1** (62%) was prepared from **7** and **8**; ^{1}H nmr: δ 2.65 (t, 4 H), 2.8 (b, 1 H), 3.6 (m, 16 H), 3.8 (s, 4 H), 7.2 (m, 10 H); M^+/e 465.

Anal. Calcd. for $C_{26}H_{35}N_5O_3$: C, 67.07; H, 7.57. Found: C, 67.25; H, 7.70.

Compound **2** (42%) was prepared from **7** and **9**; ^{1}H nmr: δ 1.7 (m, 5 H), 2.7 (t, 4 H), 3.7 (m, 20 H), 7.3 (m, 10 H); M^+/e 493.

Anal. Calcd. for $C_{28}H_{39}N_5O_3$: C, 68.12; H, 7.96. Found: C, 68.32; H, 8.02.

Compound **3** (53%) was prepared from **7** and **10**; ^{1}H nmr: δ 1.0 (t, 6 H), 2.6 (m, 12 H), 3.4 (m, 9 H), 3.6 (s, 2 H), 3.8 (m, 4 H), 7.2 (m, 5 H); M^+/e 430.

Anal. Calcd. for $C_{23}H_{38}N_6O_2$: C, 64.16; H, 8.89. Found: C, 63.98; H, 8.73.

Compound **4** (36%) was prepared from **7** and **11**; ^{1}H nmr: δ 0.85 (t, 6 H), 1.05 (t, 6 H), 3.55 (m, 20 H), 3.7 (b, 1 H), 3.8 (s, 4 H); M^+/e 351.

Anal. Calcd. for $C_{18}H_{37}N_7 \cdot 0.25\ H_2O$: C, 60.72; H, 10.61. Found: C, 60.73; H, 10.56.

Preparation of Bistriazole-Containing Macrocycle **5**.

Compound **7** (1.25 g, 5 mmoles) and (1.2 g, 5 mmoles) of *N,N'*-dibenzyl-1,2-ethylenediamine **12** was added to the 150 ml of acetonitrile containing 10 g of anhydrous sodium carbonate. The mixture was stirred under reflux for 48 hours, filtered and the solvent was evaporated. The residue was purified on alumina chromatography using toluene/ethanol 100/1 as eluant. The THP-blocking group was removed as above. The product was purified using a short alumina column by mixing the crude product with alumina and placing the coated alumina on top of the column. The column was eluted using gradient solutions of chloroform and ethanol. Compound **5** was crystallized from a DMF and methanol mixture to give a 22% yield, mp 260°; ^{1}H nmr (DMSO): δ 2.5 (s, 8 H), 3.6 (m, 16 H), 7.3 (s, 20 H), the proton peaks could be masked by the DMSO peaks; M^+/e 666.

Anal. Calcd. for $C_{40}H_{46}N_{10} \cdot 1.5\ H_2O$: C, 69.24; H, 7.12. Found: C, 69.36; H, 7.15.

Preparation of Bispyridono-Containing Macrocycle **6**.

Trans-1,2-cyclohexanediol (2.6 g, 22 mmoles) in 150 ml of THF was added dropwise to a suspension of 1.9 g (62 mmoles) of sodium hydride (80% suspension in mineral oil) in 40 ml of dry THF at room temperature under argon. The mixture was stirred at room temperature for 20 minutes and at reflux temperature for 3 hours. The mixture was cooled to 0° and 12.0 g (22 mmoles)

of solid **13** was added. The mixture was stirred at 0° for 5 minutes and at reflux temperature for 24 hours. The solvent was removed under reduced pressure and the residue was thoroughly stirred in a mixture 100 g of ice, 60 ml of water and 600 ml of methylene chloride. The organic phase was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude product was stirred in a mixture of 72 ml of glacial acetic acid and 8 ml of water at 90° for 3 hours and then overnight at room temperature. The solvent was removed fully under reduced pressure and the residue was mixed with 500 ml of methylene chloride and 150 ml of water. Part of the residue did not dissolve and this was filtered. The *p*H of the mixture was adjusted to 8 by adding triethylamine. The mixture was shaken and the *p*H readjusted until it remained at *p*H 8. The organic phase was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give 2.19 g of crude product. This material was chromatographed on silica gel (ethanol/methylene chloride 1/5 and then 1/3) and the solid was recrystallized from 1,2-dichloroethane-toluene to give 0.45 g (8%) of **6**, mp 148-150°; ir (potassium bromide): 3250, 3080, 3060, 3030, 1635, 1110 cm^{-1}; ^1H nmr: δ 1.0-1.32 (m, 8H), 1.59-1.91 (m, 4 H and broad s, 4 H disappeared in deuterium oxide), 2.1-2.3 (m, 4 H), 3.1-3.3 (m, 4 H), 4.38 (d, 4 H, J = 20 Hz), 4.58 (d, 4 H, J = 20 Hz), 6.20 (s, 4 H), 10.5 (b, 2 H, disappeared in deuterium oxide); $(M+1)^+/e$ 471.

Anal. Calcd. for $C_{26}H_{34}N_2O_6 \cdot 2H_2O$: C, 61.64; H, 7.56. Found: C, 61.43; H, 7.71.

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