A New Synthetic Route to Polyaza-crown Macrocycles Through the Per(*N*-formyl)polyaza-crowns

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Seven new per(*N*-formyl)polyaza-crown macrocycles **1-7** containing 14 to 21 ring members have been synthesized in yields of over 40% *via* the cyclization reaction of the appropriate per(*N*-formyl)polyamine **11-13** with the appropriate ditosylate, dibromide or diiodide. Three of the per(*N*-formyl) macrocycles **5-7** were hydrolyzed under acidic conditions to give the unsubstituted polyaza macrocycles **8-10** in yields of over 77%.

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Introduction.

Aza-crown macrocycles are important chelating agents for metal and organic cations, anions, and neutral molecules [1,2]. In general, aza-crowns with secondary amine units in the ring are not easy to prepare because of the need for nitrogen atom protecting groups [3]. There are, however, a few methods to prepare macrocycles containing secondary amines which do not require nitrogen protecting groups [4]. The most prevalent method to prepare the aza-crowns involves the reaction of a bistosylamide with an alkyl ditosylate [3,5]. The *N*-tosyl group both activates the nitrogen and acts as a protecting group. Ring closure using the bistosylamide reactant has been carried out at high temperature giving yields of 50-75%, although new studies show that reactions at 50° or lower give the best results [6-9]. Nearly quantitative yields of per-*N*-tosylated [17]N_4 and [21]N_5 macrocycles were produced at the lower temperature from ditosylate esters which are more reactive than the dibromides.

The tosyl groups are not easy to remove from the *N*-tosylated aza-crowns. In general, drastic conditions, such as treatment with concentrated sulfuric acid, sodium and alcohol or reduction with lithium aluminum hydride, are required. These conditions often produce ring decomposition products, especially when oxygen atoms are present in the ring, and give low yields of the desired aza-crowns. New groups are needed to protect and activate primary amines for the ring closure step and which can be removed easily after cyclization.

Many substituent groups have been used to protect and activate primary amines for the ring closure step to form aza macrocycles. The trifluoroacetyl group was easily removed from the product diaza macrocycles, but the ring closure reaction using the bis(*N*-trifluoroacetyl) starting material gave yields of only 5-20% [10,11]. The ethoxycarbonyl group (in the form of a urethane) has been used to protect and activate diamines [12-15]. In general, cyclization yields using a bisurethane were only 30-35%. No aza-crowns containing more than two nitrogen atoms have been prepared by this process. Saccharin also has been used to prepare aza-crown compounds. After a two-step process with the appropriate dihalide, the saccharin-containing diaza-crown is obtained in a moderate yield. The saccharin protecting groups can be removed in mild 20% hydrochloric acid [16]. The diethylphosphoryl group is another nitrogen protecting group that has been used in aza-crown synthesis [17,18]. Simple acetyl protecting groups have been used in these reactions to a limited degree [19,20]. BOC nitrogen protection, used in peptide synthesis, also has been tried for aza-crown formation with some success [21]. Each of the above protecting/activating groups has been used to prepare the secondary amine-containing polyaza-crowns with some success. However, with exception to tosyl and diethylphosphoryl, none of these protecting/activating groups are being used for the synthesis of aza-crowns.

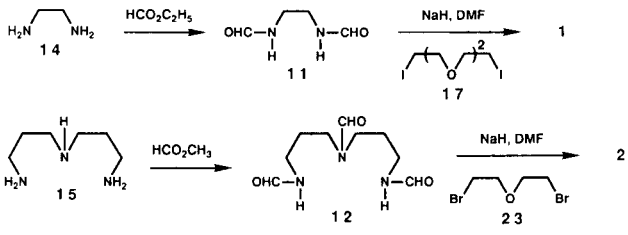
We now report the use of the formyl group to protect and activate primary amines for ring closure reactions to form per(*N*-formyl)polyaza-crown macrocycles. The formyl group is easy to introduce in quantitative yields using methyl or ethyl formate. The Ritter reaction also allows the preparation of *N*-formyl derivatives of diamines from available diols [22,23]. The formyl group is strongly electronegative and has little or no steric requirements so it is ideal to use to form secondary amines. Indeed, *N*-formyl derivatives of primary amines have been used to prepare open chain secondary amines [24,25]. The *N*-formyl group can be removed in a variety of conditions such as using concentrated hydrochloric acid [24], in 10% aqueous sulfuric acid [25], using hydrazine [26], using hydrogen/Pd-C [27], 15% aqueous hydrogen peroxide [28] or in aqueous sodium hydroxide [29].

Results and Discussion.

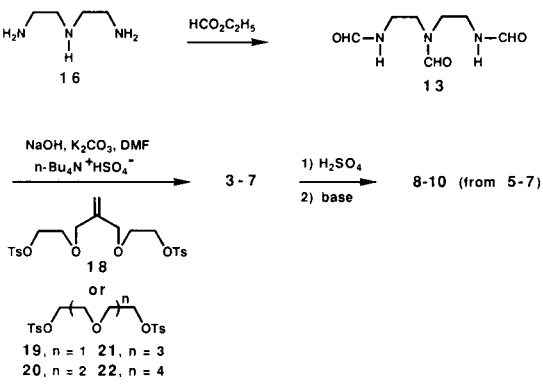
Seven new per(*N*-formyl)polyaza-crown macrocycles **1-7** (Figure 1) were prepared by treating the appropriate per-(*N*-formyl)polyamine with the appropriate dibromide, diiodide or ditosylate (see Schemes I and II). The starting *N*-formylamines **11-13** were prepared in high yields by treating the relevant polyamines **14-16** with methyl or ethyl formate in the absence of a solvent. Compound **11**, reported previously [24,30,31], was purified by recrystallization

from ethanol. Starting materials **12** and **13** were oils and required silica gel chromatography for purification.

Scheme I. Preparation of Per(N-formyl)polyaza Macrocycles 1 and 2



Scheme II. Preparation of Per(N-formyl)polyaza Macrocycles 3-7 and Some of Their Hydrolysis Products



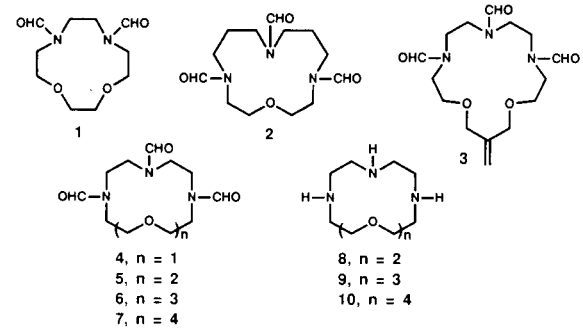
Starting *N*-formylamines **11** and **12** were treated with diiodide **17** and dibromide **23** to form per(*N*-formyl)diaza-12-crown-4 (**1**) and per(*N*-formyl)triaza-14-crown-4 (**2**), respectively. These reactions were carried out in DMF using sodium hydride as the base to give low yields of the products (Scheme I). Cyclization yields were greatly improved by using tetra-*n*-butylammonium hydrogen sulfate as a catalyst. Per(*N*-formyl)triamine **13** was treated with ditosylate esters **18-22** to form per(*N*-formyl)triaza-16-crown-5 (**3**), -12-crown-4 (**4**), -15-crown-5 (**5**), -18-crown-6 (**6**) and -21-crown-7 (**7**) (Scheme II). These reactions were carried out in DMF in the presence of sodium hydroxide, potassium carbonate and tetra-*n*-butylammonium hydrogen sulfate to give yields of 40-56% of the macrocyclic products. Benzene has been used as the solvents to prepare linear *N*-formyl compounds [25]. Our starting materials were not soluable in benzene or toluene. The product per(*N*-formyl)triaza-crown macrocycles were purified by silica gel chromatography.

Per(*N*-formyl)triaza-crown macrocycles **5-7** were converted to the corresponding unsubstituted triaza-crowns (see Scheme II). The *N*-formyl groups were removed using 10% aqueous sulfuric acid. Macrocycles **8-10** were isolated in over 77% yields. Compounds **8** and **9** are known compounds [32-34], but **10** is a new triaza-crown.

The structures of all new per(*N*-formyl)polyaza-crown macrocycles **1-7** and triaza-21-crown-7 (**10**) were consistent with their ^{1}H nmr spectra, mass spectra and elemental analyses. The structure of **10** was also consistent with its ^{13}C nmr spectrum. An ir band at 3050 cm^{-1} found in the ir spectra of **1-7** can be attributed to the amide linkage (N-C(O)-H $\rightleftharpoons$ N=C(O$^-$)-H).

This cyclization method appears to be appropriate for the preparation of polyaza-crowns containing unsubstituted amine nitrogen atoms. The method provides the per(*N*-formyl)polyaza-crowns in good yields especially when using the available ditosylate esters. The per(*N*-formyl)-polyaza-crowns can be easily deformylated to form the polyaza-crown macrocycles.

Figure 1. Per(N-formyl)polyaza-crown Macrocycles and Unsubstituted Polyaza-crown Ethers



EXPERIMENTAL

Infrared (ir) spectra were obtained on a Perkin-Elmer FT 1600 Spectrometer. Nuclear magnetic resonance (^{1}H and ^{13}C nmr) spectra were obtained on a Varian Gemini 200 Spectrometer in deuteriochloroform. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Molecular weights were determined by the electron impact method on a Finnegan 8430 High Resolution Mass Spectrometer. Starting diamine **14**, triamines **15** and **16**, dibromide **23** and diiodide **17** were purchased from Aldrich and other chemical companies. Per(*N*-formyl)polyamines **11-13** were prepared as reported [31] except for improved isolation procedures as reported below. Ditosylates **18** [35] and **19-22** [36] were prepared from the corresponding oligoethylene glycols and *p*-toluenesulfonyl chloride according to the reported procedure.

1,5,9-Triformyl-1,5,9-triazanonane (**12**) (Scheme I).

1,5,9-Triazanonane (**15**) (13.1 g, 0.1 mole) was refluxed in 80 g of methyl formate for 24 hours. Excess of methyl formate was evaporated and the residue was purified by flash chromatography on silica gel using ethanol then methanol as eluents to give a yield of 78% of **12** (lit yield was 100% when purified by distillation) [31]; ^{1}H nmr: (δ) 1.8 (m, 4 H), 3.3 (m, 8 H), 6.9 (b, 1 H), 7.0 (b, 1 H), 8.0 (m, 3 H). This material was used without further purification to give **2**.

1,4,7-Triformyl-1,4,7-triazaheptane (**13**) (Scheme II).

1,4,7-Triazaheptane (**16**) (10.3 g, 0.1 mole) was refluxed in 50 ml of ethyl formate for 24 hours. Excess of ethyl formate was evaporated and the residue was purified by flash chromatography on silica gel using ethanol then methanol as eluents to give a 68% yield of **13** (lit yield was not reported) [37]; ^{1}H nmr: (δ) 3.4 (m, 8 H), 6.8 (b, 1 H), 7.0 (b, 1 H), 8.0 (m, 3 H). This material was used without further purification to form **3-7**.

7,10-Diformyl-1,4-dioxa-7,10-diazacyclododecane (**1**) (Scheme I).

A mixture of sodium hydride (0.4 g), 110 ml of DMF and 0.84 g (7 mmoles) of **11** was stirred for 1 hour at 60° under an atmosphere of argon. Diiodide **17** (2.8 g, 7.5 mmoles) in 30 ml of DMF was added during 10 minutes. The resulting mixture was stirred for 10 hours at 70°. After cooling, the solvent was evaporated, the residue was dissolved in 10 ml of water and extracted two times with chloroform. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified first on a neutral alumina column using toluene/ethanol:13/1 and then on silica gel using toluene/ethanol:5/1 as eluents to give 0.35 g (22%) of **1**; ^{1}H nmr: (δ) 3.5 (m, 16 H), 8.0 (d, 2 H).

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.17; H, 7.83; mol wt, 230.26. Found: C, 51.93; H, 7.59; mol wt, 231.

4,8,12-Triformyl-1-oxa-4,8,12-triazacyclotetradecane (**2**) (Scheme I).

Macrocycle **2** was prepared as above from 0.66 g (5 mmoles) of **12**, 1.25 g (5.4 mmoles) of **23** and 0.3 g of sodium hydride to give 19% of **2**; ^{1}H nmr: (δ) 1.9 (m, 4 H), 3.4 (m, 16 H), 8.1 (m, 3 H).

Anal. Calcd. for $C_{13}H_{23}N_3O_4 \cdot 0.1H_2O$: C, 54.37; H, 8.10; mol wt 285.34. Found: C, 54.16; H, 8.01; mol wt, 285.

General Procedure for the Preparation of 1,4,7-Triformyl-1,4,7-triaza-crown Macrocycles **3-7** (Scheme II).

A mixture of 1.9 g (0.01 mole) of **13**, 2.0 g of finely powdered sodium hydroxide, 8.0 g of powdered anhydrous potassium carbonate, 0.5 g (1.4 mmoles) of tetra-*n*-butylammonium hydrogen sulfate, and 120 ml of DMF was stirred for 1 hour at 50-60°. The appropriate ditosylate, **18-22**, (0.011 mole) in 50 ml of DMF was added dropwise over a period of 1 hour at 70-80°. Stirring was continued for 36 hours at 70-80°. The solvent was evaporated under reduced pressure. The residue was dissolved in 50 ml of water and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and evaporated. The residue was purified by chromatography on neutral alumina using toluene/ethanol: 30/1 and 5/1 as eluents, and then on silica gel using toluene/ethanol: 15/1 and 5/1 as eluents. After evaporation of the solvent, the purified product was dissolved in toluene (in dichloromethane for **4**), filtered to remove inorganic materials and evaporated. Product yields and spectral properties are listed below.

15-Methylenyl-4,7,10-triformyl-1,13-dioxa-4,7,10-triazacyclohexadecane (**3**).

Macrocycle **3** was isolated as a colorless oil in a yield of 40%; ^{1}H nmr: (δ) 3.4-3.6 (m, 16 H), 3.9-4.0 (m, 4 H), 5.2 (d, 2 H), 8.0-8.2 (m, 3 H); ir: 3053, 2865, 1678, 1650, 1427, 1106 cm^{-1}.

Anal. Calcd. for $C_{15}H_{25}N_3O_5$: C, 55.03; H, 7.69; mol wt, 327.38. Found: C, 55.04; H, 7.86; mol wt, 327.

4,7,10-Triformyl-1-oxa-4,7,10-triazacyclododecane (**4**).

Macrocycle **4** was isolated as white crystals in a yield of 26%, mp 163-165°; ^{1}H nmr: (δ) 3.3-3.8 (m, 16 H), 8.0 (s, 1 H), 8.1 (s, 1H), 8.2 (s, 1 H); ir: 3054, 2871, 1674, 1667, 1651, 1434, 1119 cm^{-1}.

Anal. Calcd. for $C_{11}H_{19}N_3O_4$: C, 51.35; H, 7.44; mol wt, 257.29. Found: C, 51.50; H, 7.60; mol wt, 257.

7,10,13-Triformyl-1,4-dioxa-7,10,13-triazacyclopentadecane (**5**).

Macrocycle **5** was isolated as a colorless oil in a yield of 45%; ^{1}H nmr: (δ) 3.4-3.7 (m, 20 H), 8.1 (s, 2 H), 8.2 (s, 1 H); ir: 3054, 2870, 1681, 1673, 1651, 1434, 1087 cm^{-1}.

Anal. Calcd. for $C_{13}H_{23}N_3O_5$: C, 51.81; H, 7.69; mol wt, 301.34. Found: C, 51.84; H, 7.56; mol wt, 301.

10,13,16-Triformyl-1,4,7-trioxa-10,13,16-triazacyclooctadecane (**6**).

Macrocycle **6** was isolated as a colorless oil in a yield of 56%; ^{1}H nmr: (δ) 3.3-3.7 (m, 24 H), 8.0-8.2 (m, 3 H); ir: 3053, 2872, 1682, 1673, 1651, 1428, 1100 cm^{-1}.

Anal. Calcd. for $C_{15}H_{27}N_3O_6$: C, 52.16; H, 7.88; mol wt, 345.39. Found: C, 51.98; H, 7.88; mol wt, 345.

13,16,19-Triformyl-1,4,7,10-tetraoxa-13,16,19-triazacyclohenicosane (**7**).

Macrocycle **7** was isolated as a colorless oil in a yield of 48%; ^{1}H nmr: (δ) 3.3-3.7 (m, 28 H), 8.0-8.1 (m, 3 H); ir: 3053, 2868, 1680, 1428, 1114 cm^{-1}.

Anal. Calcd. for $C_{17}H_{31}N_3O_7$: C, 52.43; H, 8.02; mol wt, 389.44. Found: C, 52.48; H, 8.04; mol wt, 389.

Preparation of 1,4-Dioxa-7,10,13-triazacyclopentadecane (**8**).

A mixture of 1.5 g (5.0 mmoles) of macrocycle **5** and 75 ml of 10% aqueous sulfuric acid was heated under reflux with stirring for 8 hours. The homogeneous solution was cooled to room temperature and treated with 50% aqueous sodium hydroxide to *p*H = 5-7. The solution was treated with concentrated ammonium hydroxide solution to *p*H = 12 and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and evaporated. The residue was purified by chromatography on silica gel using methanol/30% aqueous ammonium hydroxide: 30/1, 20/1 and 5/1 as eluents. After evaporation of the solvent, the purified product was dissolved in toluene, filtered to remove inorganic materials and evaporated to give 0.85 g (79%) of **8** as a pale yellow oil which solidified at room temperature; ^{1}H nmr: (δ) 2.3 (s, 3 H, disappeared in deuterium oxide), 2.5-2.6 (m, 4 H), 2.7-2.8 (m, 8 H), 3.5-3.6 (m, 8 H); ^{13}C nmr: (δ) 70.47, 70.39, 49.58, 49.42, 48.36; ir: 3310, 2876, 1455, 1347, 1125 cm^{-1}; ms: m/z 217 (M^+); CI, m/z 218 ($M^+ + 1$). Our spectral data are similar to that reported [32-34].

Preparation of 1,4,7-Trioxa-10,13,16-triazacyclooctadecane (**9**).

Macrocycle **9** was prepared as above for **8** from 0.52 g (1.5 mmoles) of **6** and 40 ml of 10% aqueous sulfuric acid. Purification by chromatography on silica gel using methanol/30% aqueous ammonium hydroxide: 30/1, 20/1 and 10/1 as eluents gave 0.30 g (77%) of **9** as a colorless oil which solidified at room temperature to give white needles; ^{1}H nmr: (δ) 1.9 (s, 3 H, disappeared in deuterium oxide), 2.5-2.7 (m, 12 H), 3.4-3.6 (m, 12 H); ^{13}C nmr: (δ) 70.86, 70.77, 70.71, 49.84, 49.66, 49.39; ir: 3324, 2873, 1452, 1348, 1123 cm^{-1}; ms: m/z 261 (M^+); CI, m/z 262 ($M^+ + 1$). Our spectral data are similar to that reported [33].

Preparation of 1,4,7,10-Tetraoxa-13,16,19-triazacyclohenicosane (**10**).

Macrocycle **10** was prepared as above for **8** from 1.17 g (3.0 mmoles) of **7** and 60 ml of 10% aqueous sulfuric acid. Purification by chromatography on silica gel using methanol/30% aqueous ammonium hydroxide: 30/1 and 10/1 as eluents gave 0.71 g (77%) of **10** as a pale yellow oil; ^{1}H nmr: (δ) 2.6-2.8 (m, 12 H), 2.9 (s, 3 H, disappeared in deuterium oxide), 3.5-3.6 (m, 16 H); ^{13}C nmr: (δ) 71.27, 71.07, 70.73, 49.47, 49.25, 49.14; ir: 3314, 2872, 1454, 1349, 1116 cm^{-1}.

Anal. Calcd. for $C_{14}H_{31}N_3O_4$: C, 55.05; H, 10.23; mol wt, 305.41. Found: C, 54.93; H, 10.37; mol wt, 305; CI, 306 ($M^+ + 1$).

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