Preparation of Macrocyclic Di- and Tetraamides Containing Unsubstituted Macroring Nitrogen Atoms, Tertiary Amine Sidearms and/or Piperazine Subcyclic Units

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Seven new macrocyclic di- and tetramides have been prepared by the cyclization reaction of various polyamines or, in one case, a dimercaptan with a bis(α-chloroamide) or diethyl malonate. Three of the resulting macrocyclic diamides were reduced with borane to form the corresponding polyaza-crown analogs. Macrocycles prepared include two tetraaza-12-crown-4, two tetraaza-13-crown-4, two tetraaza-14-crown-4, one dithiadiaza-14-crown-4, one tetraaza-15-crown-4 with a piperazine subcyclic group, one dibenzotetraaza-24-crown-8 and one octaaza-30-crown-8 with two piperazine subcyclic groups.

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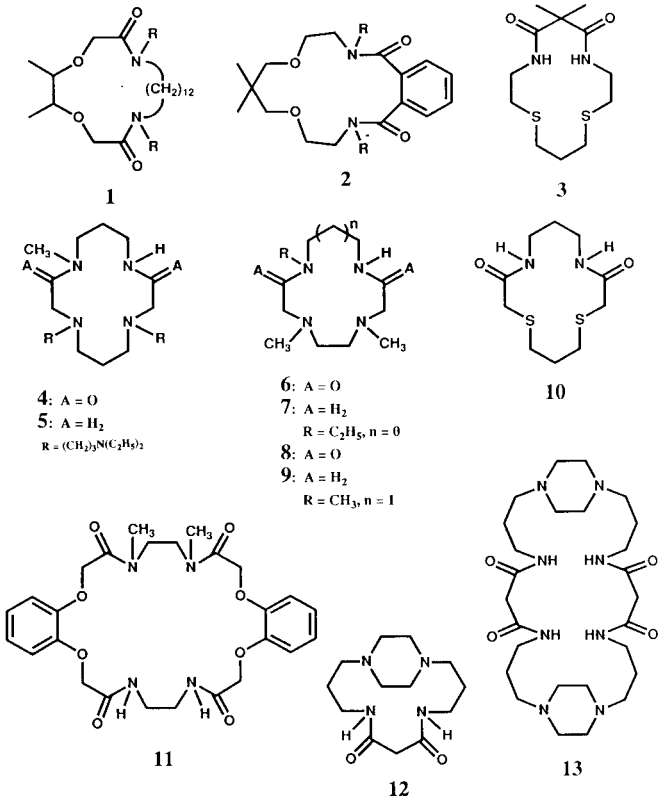
Introduction.

Macrocyclic ligands with amide units in the macroring are of interest because they often complex with metal ions where the metal ion has replaced the amide proton. The macrocyclic amides (lactams) have been prepared by many researchers and have been used as starting materials for the preparation of polyaza- and peraza-crowns [1-8]. These lactams also complex selectively with certain metal ions without a need for reorganization. Macrocyclic diamides of 4,4,5,5-tetramethyl-3,6-dioxaoctanedioic acid (**1** for example, see Figure 1) when incorporated into membranes show a remarkable selectivity for lithium ions [9]. A fifteen-membered cyclic diamide **2** has shown remarkable selectivity for lithium over potassium, calcium and magnesium ions--even better selectivity than that shown by certain 14-crown-4 ligands [10]. A 14-crown-4 diamide containing two sulfur atoms **3** exhibited high selectivity for Pt(II) and Pd(II) over Cu(II), Ni(II) and Co(II) ions [11]. The reduced form of **3** does not have this selectivity. The similar macrocyclic diamide with two oxygen atoms substituted for the sulfur atoms formed a complex with Pt(II) ions and was proposed for use to selectively extract Pt(II) ions from aqueous mixtures of ions [12]. The tetraaza analog (the reduced dioxo form of **3**) failed to complex with these metal ions [13]. Similar macrocyclic dioxadiamides act as carriers for the membrane transport of Cu(II) ions [14]. Macrocyclic tetraamides, such as certain cyclic peptides, have also been studied as complexing agents for Fe(IV) ions [15] and other metal ions [16,17].

Because of these interesting complexing properties, it is important to have good high yield syntheses for these macrocyclic diamides. Up to now, only a few methods have been used to prepare these ligands. Some of the methods include the use of starting materials such as the malonates [6] and other esters [19], diacid dichlorides under high dilution conditions [1,8,18] and bis(α-chloroamides) [2-4]. These materials, when reacted with various diamines, form macrocyclic diamides from 1:1 cyclization reactions or macrocyclic tetraamides by 2:2 cyclization reactions.

Figure 1. Macrocyclic Compounds



We now report the synthesis of seven new macrocyclic di- and tetraamides and the reduced forms of three of them. A "crab-like" bis(α-chloroamide) was reacted with a bisamide-containing diphenol for the first preparation of a crown compound by the reaction of the "crab-like" bis-(α-chloroamide) starting material with a dihydroxy compound. This paper describes the synthesis of these new ligands along with their physical properties. Metal ion complexation by some of these new materials will be re-

ported when the work is completed.

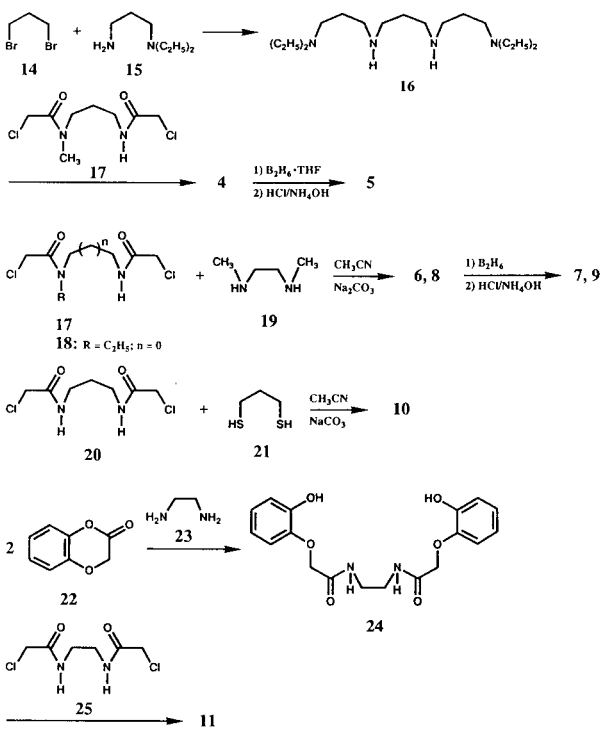
Results and Discussion.

The "crab-like" cyclization reactions to form macrocyclic diamides shown in Scheme 1 do not need complicated starting materials or unusual techniques. The starting diamines or polyamines are usually commercially available. Only tetraamine **16** needed to be prepareed. The "crab-like" bis(α-chloroamides) are likewise very easy to prepare in high yields [2-4]. In this case, a suitable diamine is reacted with chloroacetyl chloride using potassium carbonate as the base.

The cyclization reactions were performed in refluxing acetonitrile using sodium carbonate as the base. High dilution conditions were not necessary for these reactions. The yields of the cyclization products were about 40-50%. The reaction can be carried out at room temperature over a longer period of time but the yields were usually lower. High dilution conditions using syringe pumps to add the two reactants sometimes gave 10-15% higher yields [4].

Macrocycle **4** was obtained from the reaction of "crab-like" bis(α-chloroamide) **17** and tetraamine **16** which was prepared from 1,3-dibromopropane and *N,N*-diethyl-1,3-propanediamine (Scheme 1). Macrocyclic diamide **4** was reduced by borane to give bis[3-(*N,N*-diethylamino)propyl]-substituted tetraaza-14-crown-4. Macrocycles **6** and **8** were prepared in 56% and 48% yields, repectively, from "crab-like" bischloroamides **17** and **18** and *N,N'*-dimethylethylenediamine (**19**). Reduction of **6** and **8** gave the tetraaza-crowns **7** and **9** in 47% and 38% yields, respectively.

Scheme 1. Preparation of Compounds 4-11



Dithiacyclam **10** was prepared from bischloroamide **20** and 1,3-propanedithiol (**21**) using two different reaction processes. The first process used cesium carbonate as the base in DMF. The second condition used sodium carbonate as the base in acetonitrile. Product yields were about the same but separation of products was easier by the second method. In this second case, about 10% of the 28-membered tetraamide resulting from a 2:2 cyclocondensation was also isolated. This tetraamide material was not purified but analyzed by mass spectrometry.

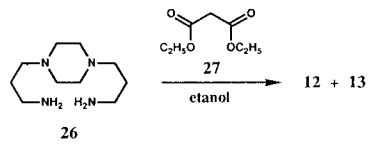
Macrocycle **10** has two proton-ionizable N-H groups so that it can form neutral complexes with the divalent cations. This is an area of complexation that has received some attention [13]. These ligands with one or two proton-ionizable N-H functions can readily be prepared using the "crab-like" bis(α-chloroamide) starting materials because the amide nitrogen atom is not reactive as a nucleophile in these reactions. Compound **3** is a similar compound prepared from diethyl dimethylmalonate and the appropriate dithiadiamine [12]. It will be interesting to see the effect of carbonyl placement on the complexation properties of **3** *versus* **10**.

The reaction of "crab-like" bischloroamide **25** with bisphenol **24** in DMF using less than an equivalent amount of *t*-butoxide base resulted in the formation of **11** in a 46% yield. This is the first example of forming a macrocyclic diamide from a bis(α-chloroamide) and a dihydroxy-containing starting material. The α-chloroamides are decomposed in strong base. α-Haloacetamides are more easily cleaved by acid or base (0.01 *M* potassium hydroxide) than unsubstituted amides using "assisted removal" reagents that contain two nucleophiles [20]. Thus, it is likely that aliphatic diols, which require the use of a strong base for deprotonation, cannot be used with the "crab-like" starting materials to make macrocyclic diamides. In spite of this, ligand **11** was prepared using potassium *t*-butoxide. It is interesting to note that sodium methoxide was used in this type of reaction for the preparation of linear polyamides [21]. Starting bisphenol **24** was prepared as reported [22,23].

In contrast to the "crab-like" method to prepare macrocyclic diamides where cyclization yields of 40-80% are observed, the preparation of macrocyclic diamides using diesters usually gives only moderate product yields [24]. Macrocycles **12** and **13** were prepared in a combined yield of only 9% by reacting diethyl malonate with 1,4-bis(3-aminopropyl)piperazine (**26**) using high dilution conditions. The products were separated from linear polyamide by-products by chromatography on both alumina and silica gel. Macrocycles **12** and **13** could not be separated but were proved by their respective mass spectral analyses.

The structures proposed for the new macrocycles are consistent with data obtained from their ir, ^{1}H nmr, and ms spectra and combustion analyses. The ir spectrum for **5** and **7** gave two bands attributable to the N-H functions. Stetter and Meyer also reported two N-H bands in the ir spectra for similar tetraaza macrocycles and they suggested that strong hydrogen bonding caused the single N-H bond to separate into two bands [25].

Scheme 2. Preparation of Compounds 12 and 13



EXPERIMENTAL

Infrared (ir) spectra were obtained on a Perkin-Elmer FT 1600 spectrometer. The proton nuclear magnetic resonance (^{1}H nmr) spectra were obtained on a Varian Gemini 200 spectrometer using deuteriochloroform. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Molecular weights were determined by the electron impact method on a Finnegan 8430 High Resolution Mass Spectrometer. Starting diamines, polyamines and hydroxyamines were purchased when available (Aldrich, Alfa and Phaltz and Bauer Chemical Companies).

The starting bis(α-chloroamides) and other materials **17** [2], **18** [26], **22** [23], **24** [22] and **25** [27], were prepared as reported. Compound **20** was prepared by a similar procedure as that used to prepare **17** and **18**, mp 124° (lit value 125° [28]). Tetraamine **16** was prepared as follows. 1,3-Dibromopropane (**14**) (10.05 g, 0.05 mole) in 100 ml of toluene was slowly added to a mixture of 65 g (0.55 mole) of *N,N*-diethyl-1,3-propanediamine and 10 g of sodium carbonate in 250 ml of toluene at 80°. The mixture was stirred at reflux temperature for 48 hours using a Dean-Stark trap to remove water. The mixture was cooled, filtered and the solvent was removed under reduced pressure. The residue was distilled to give 6 g (52%) of **16**, bp 125-128°/0.25 mm; ^{1}H nmr: δ 0.90 (t, 12 H), 1.25 (b, 2 H), 1.55 (m, 6 H), 2.50 (m, 20 H). This material was used without further purification to prepare macrocycle **4**.

General Procedure for the Preparation of Macrocyclic Diamides **4**, **6**, and **8**.

A mixture of 0.01 mole each of the bis(α-chloroamide) **17** or **18**, diamine **16** or **19** and 20 g of anhydrous sodium carbonate was stirred in 250 ml of refluxing acetonitrile for 24-36 hours. The mixture was cooled, filtered and the solvent was evaporated under reduced pressure. The residue was chromatographed in a short silica gel column using successively isopropyl alcohol, ethanol and then methanol as eluants. Alternatively, the residue was mixed with methylene chloride, filtered, evaporated and the residue was chromatographed as above. The product was evaporated under reduced pressure for a long period of time to remove all traces of solvent. The product yields and physical properties are as follows.

Macrocycle **4** (48%) was isolated as an oil; ^{1}H nmr: δ 1.00 (t, 12 H), 1.65 (m, 8 H), 2.45 (m, 20 H), 2.90 (s, 3 H), 3.05 (s, 2 H), 3.20 (s, 2 H), 3.30 (m, 2 H), 3.50 (t, 2 H), 7.85 (b, 1 H); M$^+$/e 468. Macrocycle **5**, a derivative of **4** gave a satisfactory elemental analysis.

Macrocycle **6** (56%) was isolated as an oil; ^{1}H nmr: δ 1.05 (t, 3 H), 2.3 (s, 3 H), 2.4 (s, 3 H), 2.5 (s, 4 H), 3.0-3.6 (m, 10 H), 9.10 (b, 1 H); ir (neat): 3280, 2980, 1650 cm^{-1}; M$^+$/e 256. Macrocycle **7**, a derivative of **6**, gave a satisfactory elemental analysis.

Macrocycle **8** (48%) was isolated as an oil; ^{1}H nmr: δ 1.80 (m, 2 H), 2.25 (s, 3 H), 2.35 (s, 3 H), 2.45 (m, 4 H), 2.85 (s, 3 H), 3.00 (s, 2 H), 3.20 (s, 4 H), 3.45 (m, 2 H), 8.70 (b, 1 H); ir (neat): 3300, 3000, 1650 cm^{-1}; M$^+$/e 256, 257. Macrocycle **9**, a derivative of **8**, gave a satisfactory elemental analysis.

Preparation of Macrocyclic Dithiadiamide **10**.

A mixture of 2.16 g (0.02 mole) of **21** and 15 g of anhydrous sodium carbonate was stirred and refluxed in 500 ml of acetonitrile for 10 minutes. Bis(α-chloroamide) **20** (4.54 g, 0.02 mole) in 150 ml of acetonitrile was added to the above cold solution and the resulting mixture was stirred under reflux for 48 hours. The mixture was filtered, evaporated under reduced pressure to about 150 ml and then placed in the refrigerator for 16 hours. The resulting solid was filtered and suspended in methylene chloride/methanol 10/1. A few grams of silica gel was added and the solvent was evaporated under reduced pressure. The silica gel-residue was placed on the top of a silica gel column and eluted with methylene chloride/methanol 15/1 then 10/1 to give 1.65 g (31%) of **10**, mp 186°; ^{1}H nmr: δ 1.85 (m, 4 H), 2.70 (m, 4 H), 3.20 (s, 4 H), 3.45 (m, 4 H), 7.05 (b, 2 H); M$^+$/e 262.

Anal. Calcd. for $C_{10}H_{18}N_2S_2O_2$: C, 45.77; H, 6.91; N, 10.68. Found: C, 46.00; H, 7.09; N, 10.58.

General Procedure for the Preparation of Peraza-Crowns **5**, **7** and **9**.

Macrocycle **4**, **6** or **8** (0.01 mole) was added to 200 ml of 1 *M* diborane in THF at room temperature. The mixture was refluxed for 24 hours. After cooling, 20 ml of water was carefully dripped into the solution to decompose the excess diborane. The solvent was evaporated under reduced pressure to dryness and about 100 ml of 18% aqueous hydrochloric acid was added. The mixture was stirred overnight at room temperature and then at 80-100° for 15 minutes. The mixture was then evaporated under reduced pressure and 30 ml of water was added to the residue. This mixture was filtered and ammonium hydroxide was added to the filtrate to the solution basic (*p*H higher than 12). The solution was extracted several times with 100 ml portions of methylene chloride. The combined methylene chloride extracts were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was chromatographed on 200-400 mesh silica gel on a short column using methanol/ammonium hydroxide as eluant. After evaporation of the solvents, the purified product was dissolved in toluene or methylene chloride, filtered to remove any inorganic material and evaporated. Product yields and spectral properties are as follows.

Macrocycle **5** (34%) was isolated as an oil; ^{1}H nmr: δ 1.00 (t, 12 H), 1.60 (m, 8 H), 2.10 (s, 3 H), 2.50 (m, 33 H); ir (neat): 3304, 3298, 3000, 2800, 1470 cm^{-1}; M$^+$/e 440.

Anal. Calcd. for $C_{25}H_{56}N_6$: C, 68.12; H, 12.81; N, 19.07. Found: C, 67.88; H, 12.60; N, 18.83.

Macrocycle **7** (47%) was isolated as an oil; ^{1}H nmr: δ 0.95 (t, 3 H), 2.20 (s, 3 H), 2.28 (s, 3 H), 2.40 (m, 18 H), 3.00 (b, 1 H); ir (neat): 3310, 3285, 3000, 2780, 1460 cm^{-1}; M$^+$/e 228.

Anal. Calcd. for $C_{12}H_{28}N_4$: C, 63.11; H, 12.36. Found: C, 63.10; H, 12.18.

Macrocycle **9** (38%) was isolated as an oil; ^{1}H nmr: δ 1.60 (m, 2 H), 2.15 (two s, 6 H), 2.25 (s, 3 H), 2.3-2.8 (m, 17 H); ir (neat): 3280, 2960, 2800, 1450 cm^{-1}; M$^+$/e 228.

Anal. Calcd. for $C_{12}H_{28}N_4$: C, 63.11; H, 12.36. Found: C, 63.00; H, 12.15.

Preparation of Macrocyclic Tetraamide **11**.

A mixture of 3.6 g (10.7 mmoles) of **24** and 2.4 g (21 mmoles) of potassium *t*-butoxide was stirred in 180 ml of DMF at 50-70° under Argon for 30 minutes. A solution of 2.56 g (10.7 mmoles) of **25** in 70 ml of DMF was slowly added to the above stirred mixture at 40-50°. The resulting mixture was stirred under Argon at 140-145° for 10 hours. The solid was filtered and the filtrate was evaporated under reduced pressure. The residue was added to a 200 ml of water-200 ml of chloroform mixture. The mixture was acidified to *p*H 4-6 with concentrated hydrochloric acid. The organic layer was separated. The aqueous layer was extracted with 200 ml of chloroform. The combined chloroform layers were dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from chloroform/methanol 2/1 to give 2.6 g (46%) of **11** as white needles, mp 214-215°; ^{1}H nmr: δ 3.05 (s, 6 H), 3.56 (d, 4 H), 3.62 (s, 4 H), 4.39-4.60 (m, 8 H), 6.80-6.93 (m, 8 H), 7.95 (b, 2 H); M$^+$/e 528.

Anal. Calcd. for $C_{26}H_{32}N_4O_8$: C, 59.08; H, 6.10. Found: C, 58.88; H, 6.08.

Preparation of Piperazine-Containing Macrocyclic Di- and Tetraamides **12** and **13**.

Diethyl malonate (3.2 g, 0.02 mole) in 60 ml of ethanol and 4.0 g (0.02 mole) of **26** in 60 ml of ethanol were each added simultaneously *via* syringe pumps to 250 ml of stirred and refluxed ethanol over a period of 3 days. The solvent was evaporated and the residue was chromatographed on alumina using chloroform/ethanol 20/1 as eluant. The crude product was then chromatographed on silica gel using methanol/ammonium hydroxide 50/1 as eluant to give 0.48 g (9%) of a mixture of **12** and **13**, mp 250-252°; ^{1}H nmr: δ 1.7 (m, 12 H, 4 H disappeared after shaking with deuterium oxide), 2.5 (m, 24 H), 3.2 (s, 4 H), 3.35 (m, 8 H); ir (potassium bromide): 3297, 3082, 2939, 2876, 2813, 1645, 1540, 1438, 1310, 1273, 1159, 1109, 1013, 698, 616; M$^+$/e 536, 268; M$^+$/e (chemical ionization, isobutane) 537, 269.

Anal. Calcd. for $C_{13}H_{24}N_4O_2$ and $C_{26}H_{48}N_8O_4$: C, 58.18; H, 9.01. Found: C, 57.98; H, 8.97.

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