Synthesis of New Dibenzo Nitrogen-Oxygen Donor Macrocycles Containing Two Amide Groups

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Four new nitrogen-oxygen, dibenzo macrocyclic ligands containing two amide groups have been prepared by combining a dibenzo-containing diamidodialdehyde with an appropriate diamine followed by reduction of the intermediate bis Schiff-base. The starting dibenzo-containing diamidodialdehyde was prepared by treating 2 equivalents of salicylaldehyde with a bis(α-chloroamide).

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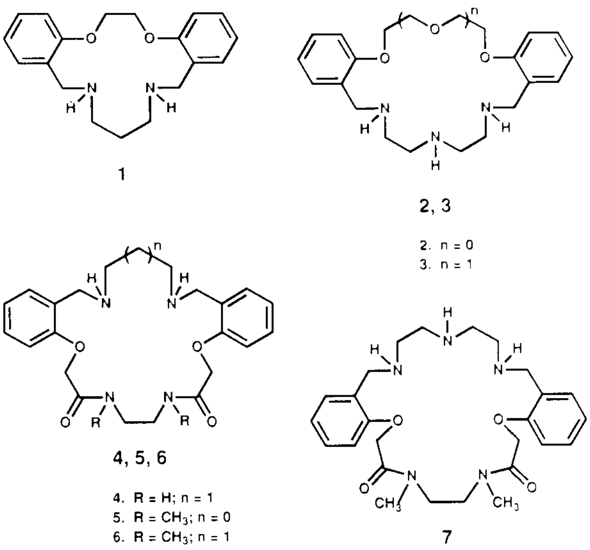
Introduction.

Mixed donor macrocycles have received much attention as receptors for a range of metal ions and other cations [1,2]. It has been clearly documented that the coordination properties of such ligands often span those of the well studied crown polyether and polyaza categories of macrocycle and particular attention has been given to rings such as **1-3** in studies of metal ion discrimination [3,4].

Benzoaza-crown ethers incorporating saturated aliphatic chains were first reported in the early 1970's [5-7]. The phenol group is much more reactive than an alcohol so that strategies other than those used for the aliphatic aza-crown ethers are available for the synthesis of benzoaza-crowns.

The use of Schiff-base condensation in the cyclization step (either in the presence or absence of a metal template), followed by reduction of the resultant imine functions has frequently provided a facile route to the aza-crowns [8,9]. However, in the case of the template procedure, the choice of the correct template metal ion is not straightforward, nor is the prediction of certain ring contraction reactions that sometimes occurs [9-12]. On the other hand, provided the initial condensation does not result in the formation of polymeric products, non-template reactions followed by direct reduction of the imine-containing product usually yields the corresponding cyclic amine. Such a procedure is used in the present study to obtain new mixed-donor macrocycles **4-7** which also contain two amide groups. Similar dibenzo-macrocycles contain 19 to 23 ring members and extend the range of mixed donor diamide and tetraamide benzo-macrocylces reported previously [13].

Figure 1. Dibenzo Nitrogen-Oxygen Donor Macrocycles



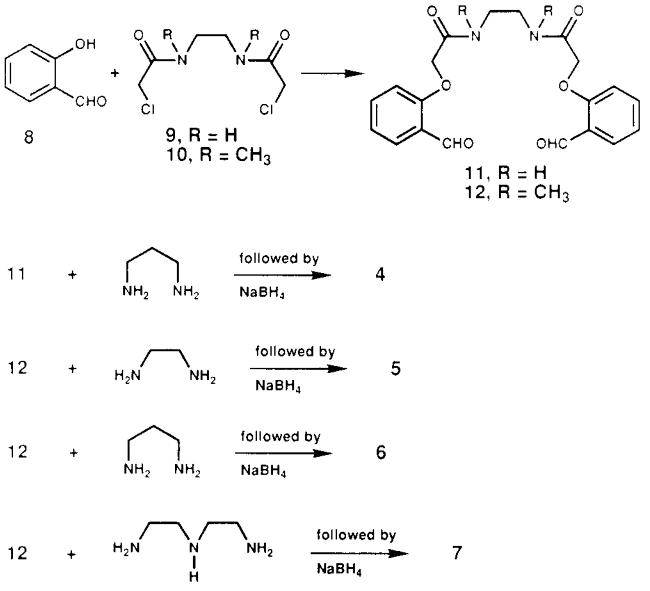
There have been recent developments in the use of particular macrocyclic amides for metal ion discrimination. For example, diamide-containing macrocycles have been reported with selectivities for lithium which are superior to that reported for 14-crown-4 [14,15]. In a second study, a 14-membered ligand ring containing two amide and two sulfur donor groups was shown to be selective for Pd(II) and Pt(II) over Co(II), Ni(II) and Cu(II) [16]. Lariat crown ether ligands containing amide groups in their side chains exhibit remarkable selectivity for calcium over sodium [17]. The metal complexing abilities of other cyclic species containing amide linkages have also been widely investigated. For example, a number of synthetic cyclopeptides have been reported to be potassium or calcium ionophores [18] and they form complexes with transition metal ions [19].

The present study reports new amide-containing macrocycles which might exhibit interesting metal-ion complexing behavior related to that discussed above.

Results and Discussion.

The preparation of macrocycles **4** and **7** from the bis(α-chloroamides) **9** and **10** is illustrated in Scheme 1. The latter precursors were synthesized previously for use in "crab-like" cyclization reactions [20]. In the present study the amides **9** and **10** were each reacted with two molecules of salicylaldehyde under basic conditions in DMF or *t*-butyl alcohol. Previously, related reactions of particular (α-chloroamides) with phenol derivatives have been reported to yield new linear-multidentate ionophores of the ether-amide type [21]. The excess of salicylaldehyde used in the preparation of **11** and **12** was present in order to "consume" excess *t*-butoxide. Amides tend to decompose under both basic and acidic conditions. In fact, α-haloacetamides are more readily cleaved by acid or base than by nucleophiles [22]. In spite of this, it was found more advantageous to use potassium *t*-butoxide rather than sodium carbonate in the reaction; the use of the latter resulted in significantly poorer yields.

Scheme I. Preparation of Macrocycles 4-7



In the synthesis of species such as **1-3**, the corresponding precursor dialdehydes were condensed with 1,3-diaminopropane or diethylenetriamine in hot methanol. The corresponding Schiff base derivatives were not isolated but instead reduction was carried out *in situ* by slow addition of sodium borohydride to the reaction solution. A similar non-template, direct-reduction procedure was employed in the present study to prepare **4-7** from dialdehydes **11** and **12**. It was not necessary to carry out the ring closure step under high dilution conditions.

It needs to be pointed out that attempts to use linear polyamines in Schiff base condensation reactions sometimes result in a non-terminal (secondary) amine reacting in concert with one primary amine and the aldehyde to yield a 1,3-diazapentane or a 1,3-diazacyclohexane derivative [23,24]. Nevertheless, it has been shown that the reduction of such products leads to the generation of the desired linear amine backbone incorporating only secondary amines (as occurs in **3**) [25]. Such internal 1,3-diazapentanes could be formed as an intermediate in the synthesis of **7**, however, it would also be reduced under the experimental conditions to give macrocycle **7**.

EXPERIMENTAL

Infrared (ir) spectra were obtained on a Perkin-Elmer FT 1600 spectrometer. The nuclear magnetic resonance spectra were obtained on a Varian Gemini 200 or Bruker AM300 spectrometer.

Elemental analyses were performed by the Canadian Microanalytical Service Ltd. Parent ions were determined by the electron impact method on a Finnegan 8430 high resolution mass spectrometer or by positive ion FAB mass spectrometry using a Jeol JMS-DX300 spectrometer. The starting bis(α-chloroamides) **9, 10** were prepared as reported previously [21,26].

Preparation of Precursor Bis(amidoaldehyde) **11** (Scheme I).

Potassium *t*-butoxide (4.5 g, 0.04 mole) was added to a solution of salicylaldehyde (5.36 g, 0.044 mole) in 200 ml of DMF. The solution was then stirred and heated at 60°. After one hour, **9** (4.26 g, 0.02 mole) in 50 ml of DMF was added to the above solution and the mixture was stirred and heated at 80° overnight. As the solution cooled, solid formed and was redissolved by the addition of a minimum amount of methanol. This solution was then poured into stirred ice water containing a few drops of hydrochloric acid. The product which precipitated was removed by filtration and dried in a vacuum oven at 40-50°. It was recrystallized from acetonitrile to give 5.5 g (72%) of **11**, mp 188-189°; ^{1}H nmr: δ 3.64 (d, CH_2NHC(O)), 4.58 (s, CH_2OAr), 6.90-7.73 (Ar), 8.05 (b, NH), 10.11 (s, CHO); ir: ~1650, 3400 cm^{-1}; fab ms: m/z 384 (M$^+$), 385 (M$^+$ + 1); tlc on silica plates (Merck) using a chloroform/ethanol mixture (20:1) confirmed the purity of the product.

Anal. Calcd. for $C_{20}H_{20}N_2O_6 \cdot 0.1H_2O$: C, 62.20; H, 5.27. Found: C, 62.03; H, 5.27.

Preparation of Precursor Bis(amidoaldehyde) **12** (Scheme I).

To a solution of salicylaldehyde (10.8 g, 0.088 mole) in 400 ml of *t*-butyl alcohol at 30-35° was added potassium *t*-butoxide (9 g, 0.08 mole). The solution was stirred of 10 minutes and then **10** (9.64 g, 0.04 mole) was added. This solution was stirred and heated at reflux temperature overnight after which the solvent was evaporated. The residue was dissolved in chloroform and this solution was washed with a cold solution of 0.2% aqueous hydrochloric acid several times. The chloroform layer was dried over anhydrous magnesium sulfate and the chloroform was removed. The product was recrystallized from water and then from toluene and dried in a vacuum oven at 105° to give 8 g (48%) of **12**, mp 152°; ^{1}H nmr: [27] δ 3.07 (s, NCH$_3$), 3.63 (s, CH_2NHC(O)), 4.74 (s, CH_2OAr), 6.88-7.89 (Ar), 10.55 (s, CHO); ir: ~1650, 3440 cm^{-1}; fab ms: m/z 412 (M$^+$), 413 (M$^+$ + 1). In the presence of water, the compound appeared to form a hydrate (mp ~120°) and hence it was stored in a vacuum over drying agent.

Anal. Calcd. for $C_{22}H_{24}O_6N_2$: C, 64.06; H, 5.86; N, 6.79. Found: C, 64.12; H, 5.80; N, 6.76.

Preparation of Macrocycle **4**.

1,3-Diaminopropane (0.04 g, 0.54 mmole) in 30 ml of methanol was added dropwise to a hot stirred solution of 0.2 g (0.52 mmole) of dialdehyde **11** in 150 ml of methanol. The solution was stirred and heated for 15 minutes and then allowed to cool to room temperature. Sodium borohydride (0.5 g) was added slowly to this stirred solution. (Note: it appears important that the reduction is preformed near room temperature.) The solution was evaporated to a small volume under reduced pressure. Excess water was added to the solution, the *p*H was adjusted to 12 with sodium hydroxide, and the macrocycle was then extracted 3 times by chloroform. The chloroform extracts were combined and the product was extracted with 3*M* aqueous hydrochloric acid. The acid phase was then neutralized with 10% aqueous sodium hydroxide, adjusted to *p*H 12, and the product was again extracted 3 times by chloroform. The chloroform extracts were combined, dried over anhydrous sodium sulfate, and evaporated to dryness to give 0.09 g (41%) of **4** as an oil; ^1H nmr (deuteriochloroform): δ 1.73 (quin, $CC\mathit{H}_2C$), 1.80 (br, $CH_2N\mathit{H}CH_2$), 2.77 (t, $CH_2NHC\mathit{H}_2$), 3.36 (s, $C(O)NHC\mathit{H}_2$), 3.76 (d, $ArC\mathit{H}_2$), 4.49 (s, $OC\mathit{H}_2$), 6.85-7.31 (Ar), 8.66 (br, $N\mathit{H}C(O)$); ^{13}C nmr (deuteriochloroform): δ 29.28 ($CH_2\mathit{C}H_2CH_2$), 38.59 ($CH_2N\mathit{C}H_2$), 48.20, 50.49 [($C(O)NH\mathit{C}H_2$) ($Ar\mathit{C}H_2$)], 62.01 (OCH_2), 112.02, 121.45, 127.34, 129.34, 131.02, 156.03 (Ar), 169.05 (C(O)); fab ms: m/z 484 (M^+ + 1).

Anal. Calcd. for $C_{23}H_{30}N_4O_4 \cdot 0.7H_2O$: C, 62.90; H, 7.20; N, 12.65. Found: C, 63.03; H, 6.98; N, 12.76.

Preparation of Macrocycle **5**.

Dialdehyde **12** (3.0 g, 7.28 mmoles) was dissolved in 150 ml of warm methanol and, to this stirred solution, was added 0.44 g (7.33 mmoles) of 1,2-diaminoethane in 15 ml of methanol. The solution was warmed and stirred for a further 15 minutes. Sodium hydroxide (2.0 g) was added in small portions to the cooled (room temperature) and stirred solution. The solution was reduced to a small volume. Excess water was added, the *p*H was adjusted to 12 with sodium borohydride, and the macrocycle was extracted 3 times with chloroform. The product was purified using the acid extraction procedure described for the preparation of macrocycle **4** to give 1.78 g (47%) of **5** as a solid; ^1H nmr (deuteriochloroform): [27] δ 2.33 (s, NH), 2.74 (s, $NHC\mathit{H}_2CH_2$), 3.00 (s, NCH_3), 3.64 (s, $N(CH_3)C\mathit{H}_2$), 3.77 (s, $ArCH_2$), 4.57 (s, OCH_2), 6.88-7.27 (Ar); ^{13}C nmr (deuteriochloroform): [27] δ 34.39 ($N\mathit{C}H_3$), 44.66 ($\mathit{C}H_2CH_2$), 47.18, 48.55 [($Ar\mathit{C}H_2$) ($N(CH_3)\mathit{C}H_2$)], 66.48 ($O\mathit{C}H_2$), 110.70, 122.68, 122.86, 130.03, 155.5 (Ar) 167.72 ($\mathit{C}(O)$); fab ms: m/z 441 (M^+ + 1).

Anal. Calcd. for $C_{24}H_{32}N_4O_4 \cdot 4.5H_2O$: C, 55.26; N, 10.74. Found: C, 55.19; N, 10.49.

Preparation of Macrocycle **6**.

Dialdehyde **12** (3.0 g, 7.28 mmoles) was dissolved in 200 ml of hot methanol and 0.5 g (6.75 mmoles) of 1,3-diaminopropane in 40 ml of methanol was added dropwise. The solution was heated and stirred for 15 minutes and then allowed to cool to room temperature. Sodium borohydride (2.0 g) was added slowly to the stirred solution. The solution was then evaporated to a small volume and excess water was added. The solution was adjusted to *p*H 12 with sodium hydroxide and then extracted 3 times with chloroform. The chloroform extracts were combined and extracted with 3*M* aqueous hydrochloric acid as in the preparation of **4**. The acid phase was separated, neutralized with 10% aqueous sodium hydroxide to a *p*H of 12. The product was once again extracted 3 times into chloroform and the combined chloroform extracts were dried over anhydrous sodium sulfate. The solvent was then removed to give a 1.41 g (36%) of **6** as an oil; ^1H nmr (deuteriochloroform): [27] δ 1.78 (quin, $CH_2C\mathit{H}_2CH_2$), 1.85 (br, $CH_2N\mathit{H}CH_2$), 2.78 (t, $C\mathit{H}_2CH_2C\mathit{H}_2$), 3.00 (s, NCH_3), 3.68 (s, $N(CH_3)C\mathit{H}_2$), 3.76 (s, $ArC\mathit{H}_2$), 4.40 (s, OCH_2), 6.76-7.21 (Ar); fab ms: m/z 455 (M^+ + 1).

Treatment of the oil in a minimum amount of hot ethanol with concentrated hydrochloric acid (added dropwise) resulted in crystallization of the product as its white hydrochloride salt as the solution cooled.

Anal. Calcd. for $C_{25}H_{34}N_4O_4 \cdot 2HCl$: C, 56.93; H, 6.88; N, 10.62. Found: C, 57.02; H, 7.24; N, 10.63.

Preparation of Macrocycle **7**.

To a stirred solution of 3.0 g (7.78 mmoles) of dialdehyde **12** in 200 ml of hot methanol was added dropwise 0.75 g (6.87 mmoles) of diethylenetriamine in 40 ml of methanol. Stirring was continued for 15 minutes after which the solution was allowed to cool to room temperature. Sodium borohydride (2.0 g) was added in small portions. The volume of the solution was then reduced under reduced pressure. Excess water was added to the mixture, the *p*H was adjusted to 12, and the macrocyclic product was extracted 2 times into chloroform. The chloroform extracts were combined and dried over anhydrous sodium sulfate. The chloroform was then removed to give 1.71 g (41%) of **7** as an oil which solidied on standing; ^1H nmr (deuteriochloroform): [27] δ 2.04 (s, NH), 2.76 (s, $NHC\mathit{H}_2C\mathit{H}_2N$), 3.07 (s, NCH_3), 3.66 (s, $N(CH_3)C\mathit{H}_2$), 3.78 (s, $ArCH_2$), 4.52 (s, OCH_2), 6.80-7.27 (Ar); ^{13}C nmr (deuteriochloroform): [27] δ 34.30 ($N\mathit{C}H_3$), 44.01, 48.40 ($N\mathit{C}H_2\mathit{C}H_2N$), 48.56, 49.19 [($N(CH_3)\mathit{C}H_2$) ($Ar\mathit{C}H_2$)], 66.73 ($O\mathit{C}H_2$), 111.46, 121.20, 128.00, 128.95, 130.54, 158.094, (Ar), 168.47 ($\mathit{C}(O)$); fab ms: m/z 484 (M^+ + 1).

Anal. Calcd. for $C_{26}H_{37}N_5O_4 \cdot 4.5H_2O$: C, 55.30; N, 12.40. Found: C, 55.03; N, 12.18.

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[27] The spectrum of this *N*-methyl compound also contained small additional peaks near the main peaks. These appear to arise from the presence of conformational isomers in solution. In the case of the precursor dialdehyde **12**, further evidence for this was obtained by rerunning the proton spectrum in DMSO-d_6 at 60°; under these conditions broadening and partial coalition of peaks from each set occurred.