

Twelve-ring Azacrowns with 2-Alkoxyethyl Side-Arms

Solfrid Buøen and Johannes Dale*

Kjemisk Institutt, Universitetet i Oslo, 0315 Oslo 3, Norway

Buøen, Solfrid and Dale, Johannes. 1986, Twelve-ring Azacrowns with 2-Alkoxyethyl Side-Arms. – Acta Chem. Scand. B 40: 278–282.

The hydrophilic azacrown ligand 1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane can be easily tetramethylated and tetraethylated. Complexation with sodium salts remains strong for both derivatives in chloroform, but extraction with water removes NaI from its complex with the tetraethylated ligand. Pyrolysis of complexes of the tetramethylated ligand liberates the ligand if pure, but results in degradation to 1,4-bis(2-methoxyethyl)piperazine if traces of alkylation reagent are present. The methylated derivative is also obtained by cyclooligomerization of *N*-(2-methoxyethyl)aziridine, which is however difficult to prepare. The direct reaction between ethyleneglycol ditosylate and 2-methoxyethaneamine (1:1) gives mainly the piperazine, but with excess of amine a series of acyclic oligoamines are obtained. Attempts to prepare 12-azacrowns by reacting the triamine with tosylated diethanolamine or diethylene glycol led instead to six-ring compounds.

The macrocyclic ligand *1*, obtained^{1,2} by hydroxyethylation of the parent “azacrown” 1,4,7,10-tetraazacyclododecane, is a selective complexing agent for sodium among the alkali cations.¹ It is however too hydrophilic for applications in salt extraction or in ion-selective electrodes. We now report various approaches to make this type of ligand more lipophilic.

Alkylation of hydroxyethylated azacrowns

Using iodomethane in THF, and NaH as the base, the tetramethoxy compound *2* was obtained in quantitative yield. An excess of reagents was needed, since the tetrahydroxy compound *1* is only available as a very stable monohydrate¹ which survives even sublimation in vacuum. Increased lipophilicity was in fact achieved, as ligand *2*, although soluble in water, could be extracted from water with chloroform as the NaI complex. This was converted to the NaCl complex, from which the free ligand was obtained by pyrolysis. However, the procedure was successful only if the complex was first treated with alkoxide to remove traces of unreacted io-

domethane and/or quaternized ligand. If pyrolysed directly, one obtains only 1,4-bis(2-methoxyethyl)piperazine, identified by synthesis from piperazine and 2-methoxyethyl iodide. The degradation probably takes place as shown in Fig. 2 through ring opening by iodide anion of a quaternized twelve-ring molecule. Recyclization in two steps produces two six-ring molecules, one of which is quaternized. The next catalytic cycle is then initiated by methyl transfer to a new twelve-ring molecule.

The tetraethoxy derivative *3* could be prepared in a similar manner using iodoethane, and both the complex and the free ligand are very little soluble in water. The complexation of Na⁺ remains strong, at least in CHCl₃, as evidenced by a slow-exchange ¹³C NMR spectrum at room temperature for a mixture of the free and complexed ligand. On the other hand, NaI can be extracted with water from a CHCl₃ solution of this complex, the ligand remaining in the organic phase. Clearly, the ethyl groups are already too large and interfere sufficiently with the complexation that solvation of the salt in water becomes favoured.

Using 1-iodobutane, the tetrabutoxy derivative *4* was formed only very slowly and could not be

*To whom correspondence should be addressed.

TWELVE-RING AZACROWNS

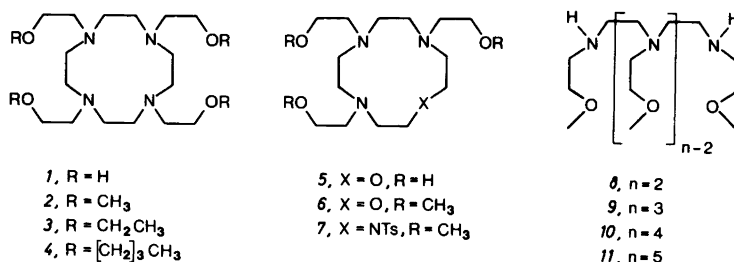


Fig. 1. Cyclic and acyclic polyamines with ligating side arms.

Fig. 2. Mechanism for catalytic degradation of azacrowns.

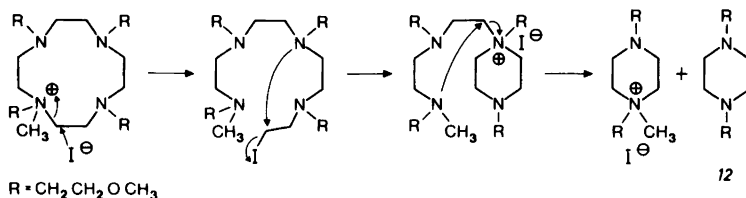
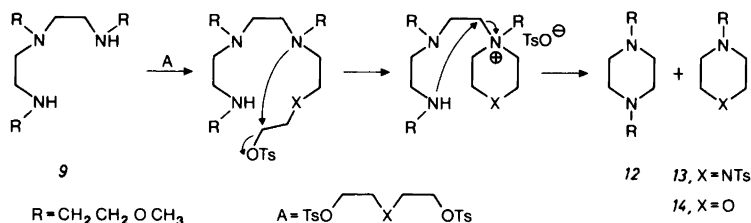


Fig. 3. Mechanism for piperazine formation in azacrown synthesis.



isolated from its mixture with starting material and intermediates.

Also the closely related ligand **5**² was methylated, to give **6**, using iodomethane/NaH under the same conditions as for the methylation of **1**, but the reaction was very much slower. This is remarkable, and the explanation may be that all three side arms, methylated or not, are needed for the optimum heptacoordination around Na⁺,¹ and no fourth uncoordinated side arm is therefore available all the time to undergo reaction, as was the case with ligand **1**.

Alternative syntheses of alkoxyethylated azacrowns

The synthesis of the parent azacrowns being already lengthy,³ the additional hydroxyethylation and alkylation steps make the total synthesis impractical. A more direct route is the acid catalysed cyclooligomerization of *N*-(2-hydroxyethyl)-aziridine⁴ or *N*-(2-methoxyethyl)aziridine, and it has been claimed⁴ that the dominant product from the former is the tetramer.

The methylation of *N*-(2-hydroxyethyl)aziridine, obtained in low yield by hydroxyethylation of aziridine with ethylene oxide,⁵ was carried out with dimethyl sulfate in ether using NaH as the base. The yield here is also low (25%), and this may again be due to the problem that during work-up traces of unreacted methylating reagent are present. Quaternization is expected to initiate uncontrolled polymerization. In the alternative reaction between 2-methoxyethyl iodide and aziridine, some *N*-(2-methoxyethyl)aziridine was formed, as seen by GC/MS, but could not be isolated. The cyclooligomerization of *N*-(2-methoxyethyl)aziridine with *p*-toluenesulfonic acid was incomplete even after 2 h at 120°C. The piperazine **12** was formed in 5% and higher-boiling products in 20%, with the desired tetramer **2** dominating.

Of greater interest was the reaction between 1,2-dichloro-, dibromo- or bis(tosyloxy)ethane and 2-methoxy-ethaneamine, which was expected to give directly *N*-(2-methoxyethyl)aziridine.⁷ No aziridine could be identified in the product. Instead, some acyclic and cyclic poly-

amines were formed directly, among the latter the desired compound 2.

Thus, using equimolar quantities of ethylene-glycol ditosylate and 2-methoxyethaneamine in refluxing acetonitrile containing suspended alkali carbonate, the main product after distillation/pyrolysis (43%) was, not unexpectedly, the piperazine 12, but also the twelve-ring 2 (3%) was present, together with the acyclic triamine 9 (0.6%) and tetramine 10 (1.3%) and homologues (8%). To suppress six-ring formation, an excess (100%) of 2-methoxyethaneamine was tried, and now the yield of six-ring dropped to 22% and of twelve-ring to 0%, but the acyclic polyamines 8, 9, 10, and 11 were formed in yields of 19%, 35%, 10%, and 4% respectively.

Having now a simple preparative method for the acyclic triamine 9, an attempt was finally made to cyclize this with tritosylated diethanolamine to obtain the twelve-ring ligand 7, and with diethyleneglycol ditosylate to obtain the twelve-ring ligand 6. In both cases, the two possible six-ring compounds, 12 + 13 or 12 + 14, were formed instead. They were identified before distillation and cannot therefore be secondary degradation products from initially formed twelve-rings. The competing cyclization to a six-ring must thus be so much preferred over twelve-ring formation that it occurs whenever possible, even if this implies quaternization of a tertiary amine instead of alkylation of a secondary amine. The likely intermediates are shown in Fig. 3.

Experimental

1,4,7,10-Tetrakis(2-methoxyethyl)-1,4,7,10-tetraazacyclododecane 2. To a solution of 1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane monohydrate I^2 (2.72 g, 7.43 mmol) in dry THF (200 ml) was added NaH (1.43 g, 60 mmol) and the mixture stirred at room temp. for 2–3 h. A solution of iodomethane (6.33 g, 45 mmol) in THF (100 ml) was then added dropwise over 20 h, and stirring continued for 4 days. The excess of NaH was destroyed by addition of methanol, and the solvents evaporated. The residue was taken up in water (30 ml), and the solution extracted with CHCl_3 (4 × 400 ml). After drying over molecular sieve (4Å), the solvent was evaporated to leave the *NaI complex of ligand 2* (4.00 g, 97%), giving a single GC peak on a SP 2100 capillary column. $^1\text{H NMR}$ (CDCl_3) δ 2.6

(16H, s, CH_2N ring), 2.5–2.8 (8H, t, CH_2N side arm), 3.4 (12H, s, CH_2O), 3.5–3.8 (8H, t, CH_2O). $^{13}\text{C NMR}$ (CDCl_3) δ 49.3 (CH_2 ring), 52.4 (CH_2N side arm), 59.2 (CH_3O), 68.9 (CH_2O). The complex was then warmed with $\text{CH}_3\text{ONa}/\text{CH}_3\text{OH}$ to destroy any traces of quaternary amines and/or iodomethane, then passed through a Dowex-1 (Cl^-) column. Evaporation yielded the NaCl complex of ligand 2 which was pyrolysed in a Kugelrohr apparatus at 200°C/ $3 \cdot 10^{-4}$ mmHg. From 0.65 g of complex was obtained 0.49 g of *free ligand 2* (86%), giving the same single GC peak on a SP 2100 capillary column. MS (CI, isobutane) 405 ($M+1$). $^{13}\text{C NMR}$ (CDCl_3) δ 52.9 (CH_2N ring), 55.2 (CH_2N side arm), 58.8 (CH_3O), 71.2 (CH_2O). Direct pyrolysis of the crude NaI-complex of ligand 2 gave also a single, but different product, MS (CI, isobutane) 203 ($M+1$). $^{13}\text{C NMR}$ (CDCl_3) δ 52.2 (CH_2N ring), 56.6 (CH_2N arm), 57.3 (CH_3O), 69.0 (CH_2O). It was identified as 1,4-bis-(2-methoxyethyl) piperazine 12 by synthesis from piperazine and 2-methoxyethyl iodide.

1,4,7,10-Tetrakis(2-ethoxyethyl)-1,4,7,10-tetraazacyclododecane 3. To a solution of 1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane monohydrate I^2 (0.25 g, 0.68 mmol) in dry THF (20 ml) was added NaH (0.14 g, 6.0 mmol) and the mixture refluxed for 1 h. Iodoethane (0.64 g, 4.1 mmol) in THF (10 ml) was added dropwise over 5–6 h and refluxing continued for 20 h. After destruction of excess NaH with methanol and evaporation, the residue proved to be very insoluble in water, and was therefore taken up in CHCl_3 (3 × 80 ml). The solution was dried over molecular sieve (4Å) and evaporated. Dissolution in a small volume of CHCl_3 left a residue (44 mg) which was filtered off. Evaporation gave the slightly impure *NaI complex of ligand 3* (0.29 g, 70%), MS (CI, isobutane) 461 ($M+1$). $^{13}\text{C NMR}$ (CDCl_3) δ 14.6 (CH_3), 49.8 (CH_2N ring), 53.1 (CH_2N side arm), 65.8, 66.5 (CH_2O). This impure complex was dissolved in CHCl_3 (10 ml) and the solution extracted with water (2 × 80 ml), dried and evaporated. The residue was the pure *free ligand 3*, showing just one GC peak on a SP 2100 capillary column. $^1\text{H NMR}$ (CDCl_3) δ 1.1–1.5 (12H, m, CH_3), 2.5–2.9 (24H, m, CH_2N), 3.4–3.8 (16H, m, CH_2O). $^{13}\text{C NMR}$ (CDCl_3) δ 15.2 (CH_3), 53.1 (CH_2N ring), 55.4 (CH_2N side arm), 66.3, 69.1 (CH_2O).

A solution of ligand 3 and NaSCN (molar ratio 2:1) gave a ^{13}C spectrum at room temperature which was a superposition of the ligand and its sodium complex.

In an attempt to similarly prepare the tetrabutylated ligand 4 from 1 and 1-iodobutane at room temperature a product was obtained which in MS (CI, isobutane) showed the presence of both 1 and 4, as well as all intermediates.

4,7,10-Tris(2-methoxyethyl)-1-oxa-4,7,10-triazacyclododecane 6. The methylation of 4,7,10-tris(2-hydroxyethyl)-1-oxa-4,7,10-triazacyclododecane 5^2 was carried out under the same conditions as described for ligand 1. The isolated product turned out by GC/MS to consist of a mixture of mono-, di-, and tri-methylated compounds, not further investigated.

N-(2-methoxyethyl)aziridine. To a solution of *N*-(2-hydroxyethyl)aziridine 5 (2.00 g, 23 mmol) in diethyl ether (15 ml) was added NaH (0.83 g, 34 mmol). Dimethyl sulfate (1.45 g, 11.5 mmol) in diethyl ether (5 ml) was added dropwise over 4–5 h at room temperature and the mixture stirred for another 20 h. The excess of NaH was destroyed with methanol, and most of the solvents removed by distillation at 760 mm Hg. Water (10 ml) was added, and the aqueous solution extracted with diethyl ether (4×20 ml). The dried ether solution was distilled and gave a fraction, b.p. 54–80°C, containing mainly *N*-(2-methoxyethyl)aziridine (20–25%). ^1H NMR (CCl_4) δ 1.0–1.1 (2H, *m*, CH_2 ring), 1.5–1.6 (2H, *m*, CH_2 ring), 2.1–2.4 (2H, *t*, CH_2N arm), 3.3 (3H, *s*, CH_3O), 3.3–3.6 (2H, *t*, CH_2O).

In a reaction between aziridine and 2-methoxyethyl iodide in methanol, using K_2CO_3 as the base, the methoxyethylated product was identified by GC/MS, but could not be isolated by distillation.

Cyclooligomerization of N-(2-methoxyethyl)aziridine. A solution of the aziridine (0.24 g, 2.4 mmol) and *p*-toluenesulfonic acid monohydrate (0.02 g, 0.1 mmol) in 96% ethanol (4 ml) was heated in a sealed tube at 120°C for 2 h and left for further 15 h at room temperature. The mixture was made alkaline with $\text{CH}_3\text{OK}/\text{CH}_3\text{OH}$ and distilled in a Kugelrohr. A first fraction contained unreacted starting material and the dimer

12 (~5%), a second fraction (0.047 g) contained mainly the tetramer 2 (~20%).

The reaction between 2-methoxyethaneamine and ethyleneglycol ditosylate

a) *With the stoichiometric ratio*

To a stirred solution of 2-methoxyethaneamine (4.13 g, 55 mmol) in refluxing acetonitrile (200 ml) containing suspended Na_2CO_3 (16 g) was added dropwise over 12 h a solution of ethyleneglycol ditosylate (18.52 g, 50 mmol) in acetonitrile (300 ml). The mixture was further stirred and refluxed for 48 h. Solids were then removed by centrifugation, and the solvents evaporated. The residue was taken up in water (30 ml) and the aqueous solution extracted with CHCl_3 (5×100 ml). After drying over molecular sieve (4Å), the solvent was evaporated. The oily residue was heated with $\text{CH}_3\text{ONa}/\text{CH}_3\text{OH}$ before pyrolysis in a Kugelrohr at 0.01 mmHg. The first fraction, 100–150°C (2.09 g), was mainly six-ring 12 by GC, the second fraction, 150–200°C (0.73 g), contained six-ring 12 and twelve-ring 2 as well as acyclic triamine 9 and tetramine 10 and higher boiling products, and a residue (0.11 g) did not distil at 250°C (for spectral data see under b). The total yields were: 43% of 12, 3.1% of 2, 0.6% of 9, 1.3% of 10 and ~8% of higher boiling products.

b) *With twofold excess of 2-methoxyethaneamine*

To a stirred solution of 2-methoxyethaneamine (22.5 g, 300 mmol) in refluxing acetonitrile (150 ml) containing now suspended Li_2CO_3 (25 g) was added dropwise over 20 h a solution of ethyleneglycol ditosylate (55.5 g, 150 mmol) in acetonitrile (350 ml). The mixture was further stirred and refluxed for 14 days. Undissolved Li_2CO_3 and precipitated Li-tosylate was filtered from the warm solution. On standing in the refrigerator, a mixed salt $\text{CH}_3\text{OCH}_2\text{CH}_2\text{NH}_3^+ \cdot \text{Li}^+ \cdot 2\text{TsO}$ crystallized (20 g, 50 mmol). The filtered solution was evaporated, the residue was taken up in water (50 ml), and the pH adjusted to 13 with LiOH(s) . Extraction of the aqueous phase with CHCl_3 (3×500 ml) gave after drying and evaporation of CHCl_3 an oil (19.5 g), which was shown by GC/MS to contain six-ring 12 as the only cyclic product (22%) and mainly acyclic amines (19% of 8, 35% of 9, 10% of 10 and 4% of 11). Dis-

tillation of the oil at $5 \cdot 10^{-4}$ mmHg gave a first fraction, 55–106 °C (6.88 g), consisting mainly of cyclic and acyclic diamines **8** and **12**, a second fraction, 106–124 °C (7.25 g), of acyclic triamine **9**, and a third fraction, 152–155 °C (1.95 g), of acyclic tetramine **10**. Analytical data for the acyclic amines are as follows:

2,11-Dioxa-5,8-diazadodecane 8: MS (CI, isobutane) 177 (*M*+1), ^{13}C NMR (CDCl_3) σ 48.1, 48.2 (CH_2NH), 57.3 (CH_3O), 70.7 (CH_2O).

8-(2-Methoxyethyl)2,14-dioxa-5,8,11-triazapentadecane 9: MS (CI, isobutane) 278 (*M*+1), ^{13}C NMR (CDCl_3) δ 46.8(2), 48.4(2) (CH_2NH), 53.0(1), 53.0(2) (CH_2N), 57.7(3) (CH_3O), 70.3(1), 71.2(2) (CH_2O).

Reactions of 8-(2-methoxyethyl)-2,14-dioxa-5,8,11-triazapentadecane **9**

a) With tritosylated diethanolamine

Tritosylated diethanolamine was not prepared as described in the literature,⁸ but by direct tosylation of diethanolamine with tosyl chloride in $\text{CHCl}_3/\text{pyridine}$,⁹ m.p. 69–70 °C.

To a refluxing suspension of Na_2CO_3 (16 g) in acetonitrile (300 ml) were dropped in parallel one solution of the acyclic triamine **9** (1.03 g, 3.7 mmol) in acetonitrile (50 ml) and another solution of tritosylated diethanolamine (2.10 g, 3.7 mmol) in acetonitrile (50 ml). Refluxing was continued for 7 days. After the usual work-up, an oil remained which by ^{13}C NMR was a 1:1 mixture of the two six-ring compounds **12** and **13**. Distillation of the oil in Kugelrohr gave **1,4-bis(2-methoxyethyl)piperazine 12** (0.60 g, 81%), identified as above. The residue was chromatographed on alumina. Elution with toluene/ CHCl_3 (1:1) gave **1-(2-methoxyethyl)-4-tosylpiperazine 13** (0.95 g, 86%), MS (CI, isobutane) 299 (*M*+1), ^1H NMR (CDCl_3) δ 2.4 (3H, *s*, ar CH_3), 2.4–2.7 (6H, *m*, CH_2N), 3.0–3.3 (4H, *t*, CH_2NTs), 3.3 (3H, *s*, CH_3O), 3.3–3.6 (4H, *t*, CH_2O). ^{13}C NMR (CDCl_3) δ 21.4 (ar CH_3), 45.9 (CH_2NTs), 52.5

(CH_2N ring), 57.4 (CH_2N arm), 58.9 (CH_3O), 69.8 (CH_2O), 127.9, 129.6, 132.3, 143.7 (arC).

b) With diethyleneglycol ditosylate⁶

The reaction was carried out as described in a). The product was shown by GC/MS and ^{13}C NMR to be a 1:1 mixture of the two six-ring compounds **12** and **14**. The data for the **1,4-bis(2-methoxyethyl)piperazine 12** are given above. The other compound is ***N*-(2-methoxyethyl)morpholine 14**, MS (CI, isobutane) 146 (*M*+1). ^{13}C NMR (CDCl_3) δ 54.1 (CH_2N ring), 57.8 (CH_2N arm), 58.5 (CH_3O), 66.6 (CH_2O ring), 70.3 (CH_2O arm).

Acknowledgement. We thank the Norges Teknisk-Naturvitenskapelige Forskningsråd for financial support.

References

- Buøen, S., Dale, J., Groth, P. and Krane, J. *Chem. Commun.* (1982) 1172.
- Buøen, S., Dale, J. and Krane, J. *Acta Chem. Scand. B38* (1984) 773.
- Richman, J. E. and Atkins, T. H. *J. Am. Chem. Soc.* **96** (1974) 2268.
- Ham, G. E. in *Polymeric Amines and Ammonium Salts*, ed. Goethals, E. J., Pergamon Press, New York, (1980) p. 1.
- Funke, A. and Benoit, G. *Bull. Soc. Chim. France* **20** (1953) 1021.
- Dale, J. and Kristiansen, P. O. *Acta Chem. Scand.* **26** (1972) 1471.
- Miller, G. R., Ham, G. E., Cobb, J. E. and Jensen, F. R. *U.S. Pat.* **3, 336, 294** (1967).
- Peacock, D. H. and Dutta, U. C. *J. Chem. Soc.* (1934) 1303.
- Amble, E. Thesis, University of Oslo (1979).

Received August 30, 1985.