Synthesis of Macrocyclic Polyethers Possessing the Piperazine Subunit

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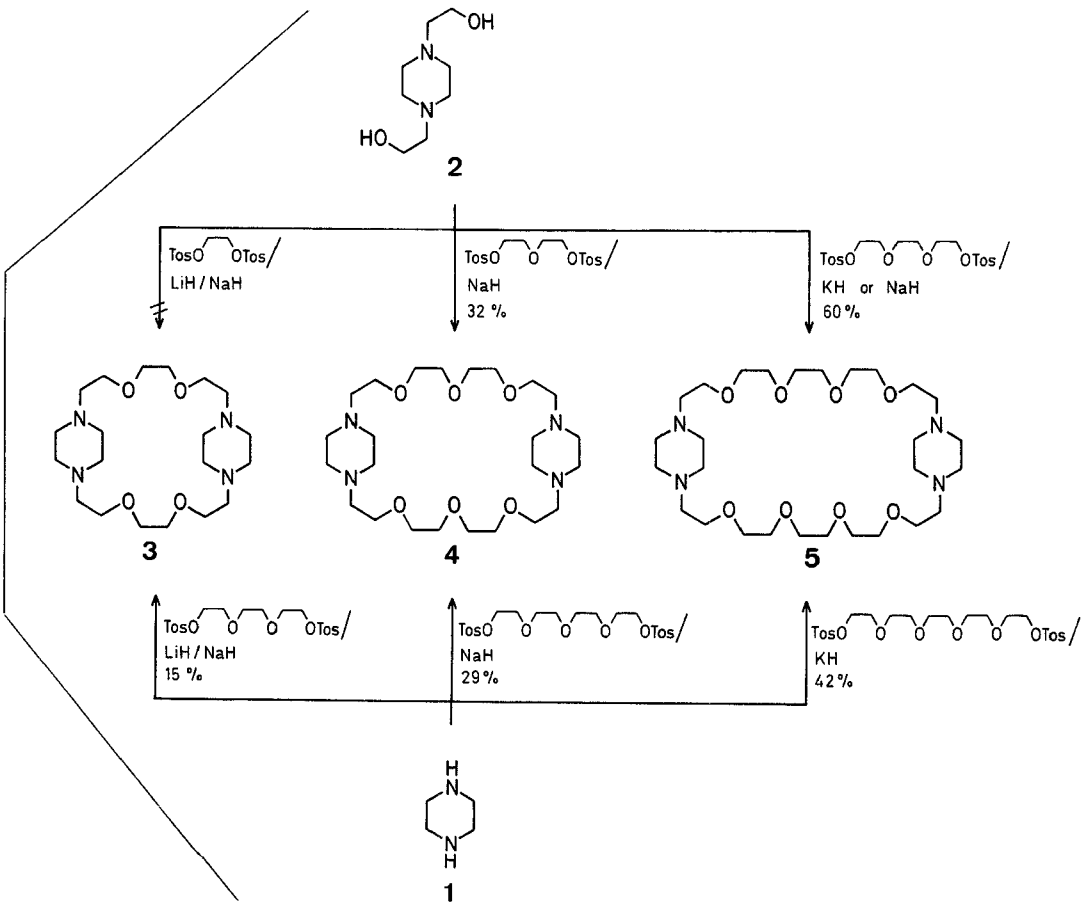
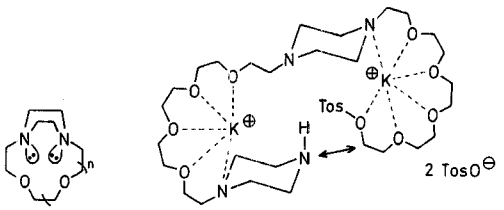
During the past decade, a large number of synthetic macrocyclic compounds have been prepared and investigated[1,2]. These crown ethers and other related molecules have been shown to possess very interesting and unusual ion binding properties[3,4,5]. A number of donor atoms (mainly nitrogen and sulfur) have been incorporated into crown ethers. The mixed ligands have the ability to bind alkali as well as alkaline earth and transition metal ions. The synthesis of azacrown compounds has been reviewed recently[6]. We report here the preparation of azacrowns incorporating the piperazine subunit.

We used piperazine **(1)** or *N,N'*-bis[2-hydroxyethyl]piperazine **(2)** as starting materials in the preparation of azacrowns. Compounds **3, 4,** and **5** were obtained in good yield by double condensation between piperazine **1** and the appropriate polyethylene glycol ditosylate in the presence of an alkali metal hydride. Azacrowns **4** and **5** were also obtained by double condensation between *N,N'*-bis[2-hydroxyethyl]-piperazine **(2)** and the appropriate polyethylene glycol ditosylate in the presence of an alkali metal hydride. The crown **3** was not obtained by this type of condensation, ethylene glycol ditosylate was found to be unreactive under the reaction conditions. No trace of monomeric crowns possessing only one piperazine unit has been isolated from the reaction mixtures.



Studies of molecular models indicate that cyclic compounds of this type must be in the boat conformation as illustrated by **6** and there would be a very unfavourable interaction between the lone pairs on the nitrogen atoms.

The good yields in the ring closure reactions to give 24-, 30-, or 36-membered macrocycles could be explained by some kind of template effect[7,8,9]. Due to the large size of the rings, we suggest the operation of a double template effect as expressed by formula **7**.



6 **7**

Several complexes having two potassium or sodium ions attached to one cyclic polyether, at adjacent binding sites, have been reported[10,11]. Studies on the ion binding properties of crown ethers described here are in progress and results will be published elsewhere.

The mono- to pentaethylene glycol ditosylates were prepared according to well-known procedures[12,13]. Piperazine (**1**) and *N,N'*-bis[2-hydroxyethyl]piperazine (**2**) are commercially available (Aldrich Co.). All piperazine derivatives are light-sensitive and should be stored in the dark.

1,10,13,22-Tetraaza-4,7,16,18-tetraoxatricyclo[20.2.2^{10,13,1,22}]octacosane (3):

The mixture of piperazine (**1**; 603 mg, 7.00 mmol), lithium hydride (117 mg, 14.3 mmol), sodium hydride (353 mg, 14.7 mmol), and anhydrous tetrahydrofuran (350 ml) is stirred under nitrogen at 60°C for 2 h. Triethylene glycol ditosylate (3.28 g, 7.35 mmol) in dry tetrahydrofuran (100 ml) is added over 1 h and the mixture is stirred under reflux for five days. The solvent is evaporated to a volume of 50 ml, the precipitated salts are filtered off, and evaporation is resumed until complete removal of the solvent. The crude product is purified by flash column chromatography (neutral alumina, 40 g, Woelm N32-63, activity I). The eluent is dichloromethane (200 ml), then ethyl acetate/methanol (20/1; 200 ml) under a 10 psi pressure. The compound **3** is an hygroscopic oil; yield: 210 mg (15%).

$C_{20}H_{40}N_4O_4$	calc.	C 59.96	H 10.06	N 13.99
(400.4)	found	60.21	10.15	13.67

M.S.: $m/e = 400$ (M^+).

I.R. (CCl_4): $\nu = 2935, 2875, 2810, 1452, 1347, 1324, 1304, 1114, 1012$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.50$–2.93 (m, 24H, CH_2—N); 3.62–3.94 ppm (m, 16H, CH_2—O).

1,13,16,28-Tetraaza-4,7,10,19,22,25-hexaoxatricyclo[26.2.2^{13,16,1,28}]tetratriacontane (4):

Method A: The mixture of *N,N'*-bis[2-hydroxyethyl]piperazine (**2**; 870 mg, 5.00 mmol), sodium hydride (511 mg, 21.3 mmol), and anhydrous tetrahydrofuran (350 ml) is stirred under nitrogen at 60°C for 1 h. Diethylene glycol ditosylate (2.13 g, 5.14 mmol) in dry tetrahydrofuran (100 ml) is added over 1 h and the mixture is stirred under reflux for four days. The solvent is evaporated to a volume of 50 ml, the precipitated salts are filtered off, and evaporation is resumed until complete removal of the solvent. The crude product is purified by flash column chromatography (neutral alumina, 40 g, Woelm N32-63, activity I). The eluent is ethyl acetate/dichloromethane (1/1; 250 ml) then ethyl acetate/methanol (100/1) (200 ml) under a 10 psi pressure. The compound **4** is an hygroscopic oil; yield: 390 mg (32%).

Method B: Same procedure as above but the diol **2** is replaced by piperazine (**1**; 603 mg, 7.00 mmol) and tetraethylene glycol ditosylate (3.62 g, 7.20 mmol) is used instead of triethylene glycol ditosylate; yield: 504 mg (29%).

$C_{24}H_{48}N_4O_6$	calc.	C 58.99	H 9.90	N 11.47
(488.6)	found	59.13	9.98	11.32

M.S.: $m/e = 488$ (M^+).

I.R. (CCl_4): $\nu = 2935, 2865, 2805, 1454, 1349, 1305, 1276, 1190, 1120, 1012$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.52$–2.91 (m, 24H, CH_2—N); 3.66–3.94 ppm (m, 24H, CH_2—O).

1,16,19,34-Tetraaza-4,7,10,13,22,25,28,31-octaoxatricyclo[32.2.2^{16,19,1,34}]tetracontane (5):

Method A: The mixture of *N,N'*-bis[2-hydroxyethyl]piperazine (**2**; 870 mg, 5.00 mmol), potassium hydride (50% in oil, 800 mg, 20.0 mmol), and anhydrous tetrahydrofuran (350 ml) is stirred under nitrogen at 60°C for 1 h. Triethylene glycol ditosylate (2.52 g, 5.50 mmol) in dry tetrahydrofuran (150 ml) is added over 1 h and the mixture is stirred under reflux for six days. The solvent is evaporated to a volume of 50 ml, the precipitated salts are filtered off, and evaporation is resumed until complete removal of the solvent. The crude product is purified by flash column chromatography (neutral alumina, 40 g, Woelm N32-63, activity I). The eluent is dichloromethane (250 ml), then ethyl acetate/methanol (10/1; 250 ml) under a 10 psi pressure. The compound **5** is an hygroscopic oil; yield: 858 mg (60%).

Method B: Same procedure as above but potassium hydride is replaced by sodium hydride (480 mg, 2.00 mmol); yield: 801 mg (56%).

Method C: Same procedure as in Method A but the reagents are the following: piperazine (**1**; 1.21 g, 14.0 mmol), potassium hydride (1.18 g, 24.4 mmol), and pentaethylene glycol ditosylate (8.03 g, 14.7 mmol); yield: 1.69 g (42%).

$C_{28}H_{56}N_4O_8$	calc.	C 58.30	H 9.78	N 9.71
(576.8)	found	58.42	9.86	9.58

M.S.: $m/e = 576$ (M^+).

I.R. (CCl_4): $\nu = 2930, 2865, 2800, 1452, 1348, 1320, 1302, 1245, 1114, 1010, 906$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.55$–2.93 (m, 24H, CH_2—N); 3.67–3.95 ppm (m, 32H, CH_2—O).

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[1] G. W. Gokel, S. H. Korzeniowski, *Macrocyclic Polyether Synthesis*, Springer Verlag, Berlin, 1982.
[2] S. T. Jolley, J. S. Bradshaw, R. M. Izatt, *J. Heterocycl. Chem.* **19**, 3 (1982).
[3] M. Dobler, *Ionophores and their Structures*, John Wiley & Sons, New York, 1981.
[4] G. A. Melson, *Coordination Chemistry of Macrocyclic Compounds*, Plenum, New York, 1979.
[5] R. M. Izatt, J. J. Christensen, Eds., *Synthetic Multidentate Macrocyclic Compounds*, Academic Press, New York, 1978.
[6] G. W. Gokel, D. M. Dishong, R. A. Schultz, V. J. Gatto, *Synthesis* **1982**, 997.
[7] R. N. Greene, *Tetrahedron Lett.* **1972**, 1793.
[8] G. R. Newkome, T. Kawato, W. H. Benton, *J. Org. Chem.* **45**, 626 (1980).
[9] B. R. Bowsher, A. J. Rest, *J. Chem. Soc. Dalton Trans.* **1981**, 1157.
[10] D. L. Hughes, *J. Chem. Soc. Dalton Trans.* **1975**, 2374.
[11] M. Mercer, M. R. Truter, *J. Chem. Soc. Dalton Trans.* **1973**, 2469.
[12] M. Newcomb, S. S. Moore, D. J. Cram, *J. Am. Chem. Soc.* **99**, 6405 (1977).
[13] C. G. Krespan, *J. Org. Chem.* **39**, 2351 (1974).