Bi- and Tricyclic Twelve-ring Azacrowns by Stepwise Annelation

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Starting from unprotected 1,4,7,10-tetraazacyclododecane, a second ring can be annelated in a direct reaction with triethyleneglycol ditosylate. The main bicyclic product with the bridge between N1 and N4 (12-membered ring), is accompanied by an isomer (10 %) presumed to have the bridge between N1 and N7 (15-membered ring). There is no further reaction when Na_2CO_3 (in acetonitrile) is used as the base. With Cs_2CO_3 a tricyclic product, bridged exclusively between N1 and N4 and between N7 and N10, is formed. In its complex with NaI only two of the rings are used, as shown by ^{13}C NMR.
Analogous bicyclic products were obtained from 1-oxa-4,7,10-triazacyclododecane.

The conformational properties of 12-membered "crowns" are such that when they are ethylene-bridged or condensed together, the heteroatoms become perfectly oriented for cubic octacoordination to cations the size of Na^+ or Ca^{++}.[1-6] Among our synthetic goals in this context is the tricyclic tetraoxatetraaza compound *6*. One obvious route was to annelate one ring after the other onto the central 12-azacrown-4 system properly protected in the first step to secure the correct ring size (Fig. 1, *1* → *2* → *4* → *6*), and we have recently reported the synthesis of the ditosylated azacrown *1* and its further conversion to the bicyclic compound *2*.[6] Since the removal of the protecting tosyl groups proved in most cases quite difficult,[6] we decided to try the direct preparation of the bicyclic compound *4* from the unprotected azacrown *3*.

We now report that the reaction between equimolar quantities of the tetraazacrown *3*[7] and triethyleneglycol ditosylate in refluxing acetonitrile containing suspended Na_2CO_3 gave a mixture of the two bicyclic compounds *4* and *5* in good yield. The desired 1,4-annelated isomer *4* predominated over the 1,7-annelated isomer *5* by a factor of 10, as compared with the statistical factor 2. There was no indication of further reaction to the tricyclic compounds *6* or *7*. This is clearly due to the formation of a strong complex with sodium tosylate formed in the reaction, since it was shown in a separate experiment that ligand *4* and $NaBF_4$ in a molar ratio of 2:1 gives in $CDCl_3$ at room temperature a slow exchange ^{13}C NMR spectrum with separate signals for complexed and free ligand. When Na_2CO_3 was replaced by K_2CO_3 or Cs_2CO_3, the reaction mixture contained additional products as well as some unreacted azacrown *3*. The complexation of ligand *4* is in these cases much weaker, as reflected in the small difference of the ^{13}C NMR shifts between the reaction mixture and the isolated ligand.

The best yield of the tricyclic ligand *6*, was obtained with Cs_2CO_3 as the suspended base and the correct 1:2 ratio of azacrown *3* to triethyleneglycol ditosylate. The ligand was isolated as its 1:1 complex with NaI, and then converted to its NaOH complex on an ion exchange column before pyrolysis to liberate ligand *6*. Again, the strong complexation with Na^+ was demonstrated by the appearance of separate ^{13}C NMR signals for free and complexed ligand in a 2:1 mixture of ligand *6* and $NaBF_4$ in $CDCl_3$ at room temperature. When Cs_2CO_3 was replaced by K_2CO_3, the reaction was much slower and incomplete even

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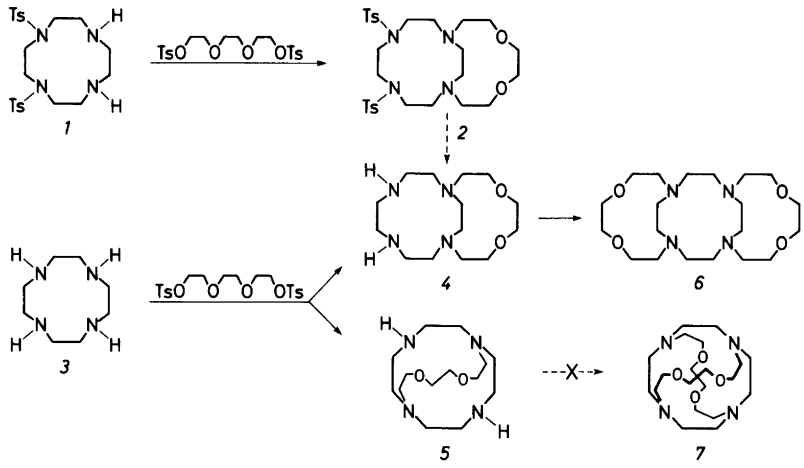

Fig. 1. Bi- and tricyclic ligands from 12-tetraazacrown-4.

after 6 days. Thus, complexation of K^+ with the intermediate *4*, although weak, still retards its further reaction. On the other hand, the product *6* gives a strong K^+ complex, with ^{13}C shifts just as much displaced upfield from those of the free ligand as observed for the Na^+ complex.

The analogous reaction (Fig. 2) between the triazacrown *8*[7] and triethyleneglycol ditosylate in the presence of Na_2CO_3 also gave a mixture of two isomers, the bicyclic compounds *9* and *10*. The 1,4-annelated isomer was again quite predominant but only by a factor of 5.

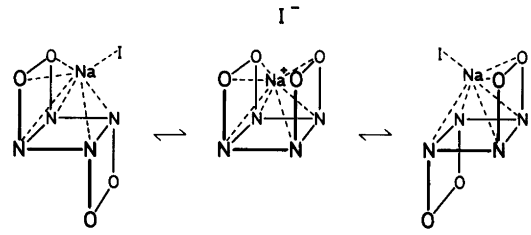

Fig. 3. Proposed internal interconversion path for the unsymmetric heptacoordinate *6*·NaI complex via an intermediate symmetric octacoordinate complex. The $-CH_2CH_2-$ units between heteroatoms are represented by straight lines.

Optimum coordination number for sodium

The cation complexation properties of the ligands reported here have not yet been studied systematically. Only one striking phenomenon observed in the ^{13}C NMR spectrum of the NaI complex of the tricyclic ligand *6* deserves comment. As this ligand was designed originally[1] to provide cubic octacoordination for Na^+ *etc.*, it was expected that the two outer rings would be equivalent in the complex so as to give five sharp signals of equal intensity in the ^{13}C NMR spectrum, conformational site-exchange processes of the CC-eclipsing type[6] being fast at room temperature. However, the two low-field signals (OCH_2) were very broad at room temperature, and this could only result from coalescence of two pairs of signals, since they sharpened rapidly on heating to ~50 °C.

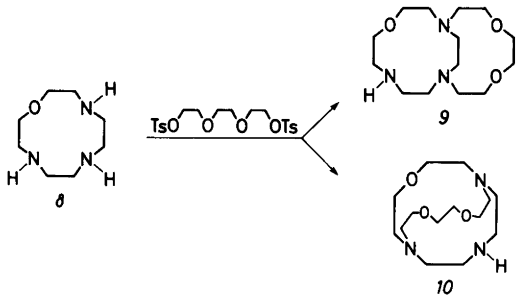

Fig. 2. Bicyclic ligands from 12-triazacrown-4.

The natural interpretation is that the eight ligating atoms of ligand *6* are incompletely utilized by Na^+ so that at any time the two ether oxygens

of one of the terminal rings are rejected (Fig. 3). In a relatively slow process the two outer rings exchange roles, and at sufficiently high temperature a ^{13}C spectrum representing the averaged symmetry is observed.

The conclusion is that octacoordination is excessive for Na+, although in fact observed when there is a "take it or leave it" situation, such as in the sandwich complex with 12-crown-4,[8] or when two 12-azacrowns are connected by a single bridge[2] or by two bridges in diametric positions.[3] Heptacoordination is in fact clearly preferred for Na^+ in its complex with tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane,[4] since one sidearm is rejected, and in its complex with 4,7,13,16-tetraoxa-1,10-diazabicyclo[8.8.2]dodecane,[5] since the anion maintains direct contact with the cation.

On this basis we propose for the present complex the unsymmetric heptacoordinate structure with anion contact (Fig. 3). A symmetric octacoordinate structure with separated anion is assumed for the (unpopulated) intermediate in the exchange process.

The topological properties of tricyclic ligands like *6* lead us to propose the generic name "triptychand" (tri-ptychos = hinged triple tablet) in analogy with our earlier proposal[5,6] of "diptychand" for related bicyclic ligands like *4*.

Experimental

The reaction between 1,4,7,10-tetraazacyclododecane and triethyleneglycol ditosylate

(a) With molar ratio 1:1.

To a refluxing solution of 1,4,7,10-tetraazacyclododecane[4] *3* (0.50 g, 2.9 mmol) in acetonitrile (80 ml) containing suspended Na_2CO_3 (5 g) and Na tosylate (0.56 g, 2.9 mmol) was dropped over 48 h a solution of triethyleneglycol ditosylate[9] (1.33 g, 2.9 mmol) in acetonitrile (20 ml). The mixture was further stirred and refluxed for 24 h. After cooling, the solids were removed by centrifugation and washed with $CHCl_3$. The solvents were evaporated and the residue taken up in acetonitrile. Crystallization gave the *Na tosylate complex of 4,7-dioxa-1,10,13,16-tetraazabicyclo-[8.8.2]eicosane 4* (0.44 g, 32%), m.p. 192–200 °C. ^1H NMR ($CDCl_3$): δ 1.7 (2H, br.s, NH), 2.3 (3H, s, $arCH_3$), 2.4–3.0 (20H, m, NCH_2), 3.4–3.9 (8H, m, OCH_2), 7.1–7.8 (4H, q, arH). ^{13}C NMR ($CDCl_3$): δ 21.3 ($arCH_3$), 43.0, 45.3 ($NHCH_2$), 49.3, 51.9, 52.3 (NCH_2), 64.3, 66.3 (OCH_2), 126.2, 128.2 (arCH), 138.5, 144.4 (arC).

Pyrolysis of the complex in a Kugelrohr apparatus at 180 °C/3 · 10^{-4} mmHg gave the *free ligand 4* (99%), m.p. <20 °C, a single GLC peak, MS (CI, isobutane): 287 (M+1). ^1H NMR ($CDCl_3$): δ 2.5–3.0 (20H, m, NCH_2), 3.5–3.8 (8H, m, OCH_2), NH broad. ^{13}C NMR ($CDCl_3$): δ 45.1, 47.4 ($NHCH_2$), 51.4, 52.5, 54.8 (NCH_2), 69.0, 72.2 (OCH_2).

The mother liquor after crystallization was distilled in a Kugelrohr at 180–250 °C/3 · 10^{-4} mmHg and afforded an additional crop of *4* (0.35 g, 37%), thus increasing the total yield to 69%. However, this product showed by GLC a second peak attributed to a ligand with the isomeric structure *4,7-dioxa-1,10,13,18-tetraazabicyclo-[8,5,5]eicosane 5*. GLC of the crude reaction mixture showed that *4* and *5* are formed in the ratio 10:1, expected statistically 2:1.

When Na_2CO_3 is replaced by K_2CO_3 or Cs_2CO_3 the reaction mixture contains additional products, as shown by ^{13}C NMR. In the case of Cs_2CO_3 about 25% of the tetraamine *3* has not reacted, suggesting that in this case the product *4* undergoes further reaction with the ditosylate. The crude product from the Cs_2CO_3 reaction shows ^{13}C shifts for ligand *4* corresponding to the uncomplexed state, and the product from the K_2CO_3 reaction shows the ^{13}C shifts only slightly upfield as compared with the strong upfield shift of the Na_2CO_3 reaction product. A 1:1 mixture of complexed and free ligand shows slow exchange in $CDCl_3$ at room temperature.

(b) With molar ratio 1:2.

To a suspension of Cs_2CO_3 (7.5 g) in refluxing acetonitrile (150 ml) was added in parallel over 8 h one solution of 1,4,7,10-tetraazacyclododecane *3* (0.25 g, 1.45 mmol) in acetonitrile (50 ml) and another solution of triethyleneglycol ditosylate (1.33 g, 2.9 mmol) in acetonitrile (50 ml). After further stirring and refluxing for 66 h, the solids were filtered off and washed with $CHCl_3$. The combined organic phases were concentrated and left in the refrigerator for 24 h. Precipitated Cs-tosylate was filtered off and the solvents evaporated. The residue was dissolved in water (15 ml) together with NaI (0.60 g, 4.0 mmol) and the aqueous solution extracted with $CHCl_3$ (4×100

ml). After drying with molecular sieve (4Å), filtering, and evaporation, a residue of the slightly impure *NaI complex of 7,10,19,22-tetraoxa-1,4,13,16-tetraazatricyclo[14.8.2.2^{4,13}]octacosane* *6* was left (0.59 g, 74 %). ^{1}H NMR ($CDCl_3$): δ 2.3–3.0 (24H, m, NCH_2), 3.5–3.9 (16H, m, OCH_2). ^{13}C NMR ($CDCl_3$, ~50 °C): δ 49.4, 50.2, 51.9 (NCH_2), 64.3, 65.9 (OCH_2); at room temperarure the two low-field signals are broadened.

The NaI complex was transformed to the NaOH complex on a strongly basic anion-exchange column (Amberlite IRA-400). The NaOH complex (0.113 g) was pyrolysed in a Kugelrohr at 200–250 °C/3 · 10^{-4} mmHg to give the free ligand *6* (0.062 g, 58 %), m.p. 125–129 °C, MS (CI, isobutane): 401 (M+1). ^{13}C NMR ($CDCl_3$): δ 55.4, 56.0, 56.5 (NCH_2), 70.6, 71.3 (OCH_2). A 1:1 mixture of ligand *6* and its $NaBF_4$ complex in $CDCl_3$ gave a slow exchange spectrum at room temperature.

When Cs_2CO_3 was replaced by K_2CO_3, the reaction was much slower, and even after 6 days about 20 % of the triethyleneglycol ditosylate could be recovered by extraction. This corresponds to 60 % conversion in the second step. The ligand *6* must be present in the reaction mixture entirely as a K tosylate complex, as the ^{13}C shifts are exactly the same as for the Na^+ complex.

The reaction between 1-oxa-4,7,10-triazacyclododecane and triethyleneglycol ditosylate. To a refluxing solution of 1-oxa-4,7,10-triazacyclododecane[4] *8* (0.30 g, 1.73 mmol) in acetonitrile (50 ml) containing suspended Na_2CO_3 (5 g) and Na tosylate (0.34 g, 1.73 mmol) was dropped over 48 h a solution of triethyleneglycol ditosylate[9] (0.79 g, 1.73 mmol) in acetonitrile (20 ml). The mixture was further stirred and refluxed for 24 h. The solids were removed by centrifugation and washed with $CHCl_3$. After evaporation of the solvents, the residue was pyrolysed in a Kugelrohr at 180 °C/3 · 10^{-4} mmHg to yield an inseparable mixture of ligands *9* and *10* (0.27 g, 54 %), MS (CI, isobutane): 228 (M+1). GLC showed two peaks in the ratio 5:1, and the major isomer has the structure *4,7,13-trioxa-1,10,16-triazabicyclo-[8.8.2]eicosane* *9*. ^{1}H NMR ($CDCl_3$): δ 2.5–3.0 (16H, m, NCH_2), 3.5–4.0 (12H, m, OCH_2), NH broad. ^{13}C NMR ($CDCl_3$): δ 46.6, 48.3 ($NHCH_2$), 51.7, 53.6, 54.1, 55.2, 55.8, 57.0 (NCH_2), 67.3, 69.1, 69.2, 71.0, 71.3, 72.4 (OCH_2).

The minor isomer is assigned the structure *4,7,13-trioxa-1,10,18-triazabicyclo[8.5.5]eicosane* *10*.

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References

1. Dale, J. *Oslo Symposium 1982, Ion Exchange and Solvent Extraction,* Soc. Chem. Ind. London (1982).
2. Calverley, M. J. and Dale, J. *Chem. Commun.* (1981) 684.
3. Calverley, M. J. and Dale, J. *Chem. Commun.* (1981) 1084.
4. Buøen, S., Dale, J., Groth, P. and Krane, J. *Chem. Commun.* (1982) 1172.
5. Alfheim, T., Dale, J., Groth, P. and Krautwurst, K. D. *Chem. Commun.* (1984) 1502.
6. Alfheim, T., Buøen, S., Dale, J. and Krautwurst, K. D. *Acta Chem. Scand. In press.* (B 2432).
7. Buøen, S., Dale, J. and Krane, J. *Acta Chem. Scand. B 38* (1984) 773.
8. Krane, J., Amble, E., Dale, J. and Daasvatn, K. *Acta Chem. Scand. B 34* (1980) 255.
9. Dale, J. and Kristiansen, P.O. *Acta Chem. Scand. 26* (1972) 1471.

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