Macrobicyclic Aminoethers with Twelve-membered Rings

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A one-pot reaction between alkane-1,2-diamines and triethyleneglycol ditosylate, or similar compounds having tosylamine functions instead of ether functions, gives without high dilution good yields of bicyclic compounds consisting of two twelve-membered rings with the alkane-diamine unit in common.
The simplest representatives, 4,7,13,16-tetraoxa-1,10-diaza-bicyclo[8.8.2] eicosane and its 19-substituted derivatives, show strong cation complexation with a high selectivity for Na^+ over Li^+ and K^+. Dynamic NMR spectroscopy shows that conformational processes, including amine inversion, are fast when the ethylene bridge is unsubstituted but become hindered when a methyl substituent is present.

On the basis of the structural parameters of the well-established complexing conformation of 1,4,7,10-tetraoxacyclododecane (12-crown-4)[1,2] it was anticipated that perfect cubic coordination around cations the size of Na^+ and Ca^{2+} would be achieved by ligand structures consisting of several twelve-membered rings bridged or condensed together.[3] Trivalent amino nitrogen must then be used at bridgehead positions instead of bivalent ether oxygen. The fully closed quinquecyclic cage structure will therefore no longer be an ether, but an octaamine as shown schematically in Fig. 1a.

We have already briefly reported multistep syntheses of two partially closed ligands of this topology, a tricyclic tetraaminotetraether[4] (Fig. 1b) and a bicyclic diaminohexaether[5] (Fig. 1c). Both show strong complexation and high selectivity for Na^+ among the alkali cations. However, since it turned out that the coordination number chosen by Na^+ with a related unicyclic ligand[6] (Fig. 1d) was only seven (one arm rejected and no anion contact), the much simpler bicyclic ligand shown in Fig. 1e seemed a more promising candidate for ion-pair complexation in connection with extraction processes. The same basic topology would be imposed by the fusion of two twelve-membered rings, but the ligand provides only six ligating atoms, leaving the last coordination site on Na^+ for contact with the anion.

Synthetic approach

An obvious synthesis of 1,4-dioxa-7,10-diazacyclododecane *2* (Fig. 2) would be to cyclize the tosyl-protected ethane-1,2-diamine with triethyleneglycol ditosylate, and in fact the tosyl-protected 12-ring *1* can be easily obtained.[7,8] However, the removal of the tosyl groups with $LiAlH_4$ was an exceedingly slow reaction, and in attempts to hydrolyse off the groups in water/sulfuric acid, ether cleavage occurred.[8]

In view of our previous experience[4,5] in using unprotected amines in acetonitrile containing suspended Na_2CO_3, the direct reaction of ethane-1,2-diamine with triethyleneglycol ditosylate was attempted. Although the reactants were used in a 1:1 ratio, the main product was somewhat surprisingly already the desired bicyclic compound *3*, isolated as a complex with sodium tosylate, from which the free ligand was obtained by pyrolysis in vacuum. Only a small amount of the isomeric bicyclic 9-ring compound *5* was isolated, and the monocyclic intermediates *2* and *4* could

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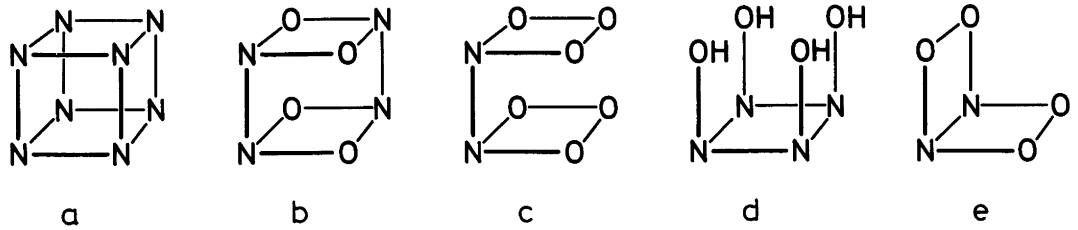

Fig. 1. Schematic structures of ligands with 12-membered rings. The $-CH_2CH_2-$ units joining heteroatoms are drawn as straight lines.

not be detected. The yield of *3* was improved by using the reactants in the correct ratio 1:2. The main byproduct was shown to be polymeric, and the yield could be improved somewhat by increased dilution, that is, the slow synchronized addition of separate solutions of the two components to a moderate volume of refluxing acetonitrile. At very high dilution, however, the reaction becomes so slow that reactants accumulate and the whole effort is illusory. It was more important to destroy all traces of unreacted tosylate with strong base in order to avoid quaternization during work-up (concentration, distillation). Quaternized amine functions have a catalytic effect leading to loss by ring opening and polymerization.

The bicyclic compound *3* was also obtained from 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane *6* by transannular bridging using ethyleneglycol ditosylate.

Synthesis of related compounds

For certain applications simple organic ligands like *3* are too hydrophilic and have to be made more lipophilic. This can easily be accomplished by replacing ethane-1,2-diamine with other 1,2-diamines. Thus, the cyclization reaction works equally well with propane-1,2-diamine to yield the 19-methyl derivative *7*, and with 3-phenylpropane-1,2-diamine to give the 19-benzyl derivative *8*. With this larger substituent the second step is slower than the first, as shown by GLC analysis of the reaction mixture as a function of time.

Modifications were also made in the other component in order to prepare intermediates re-

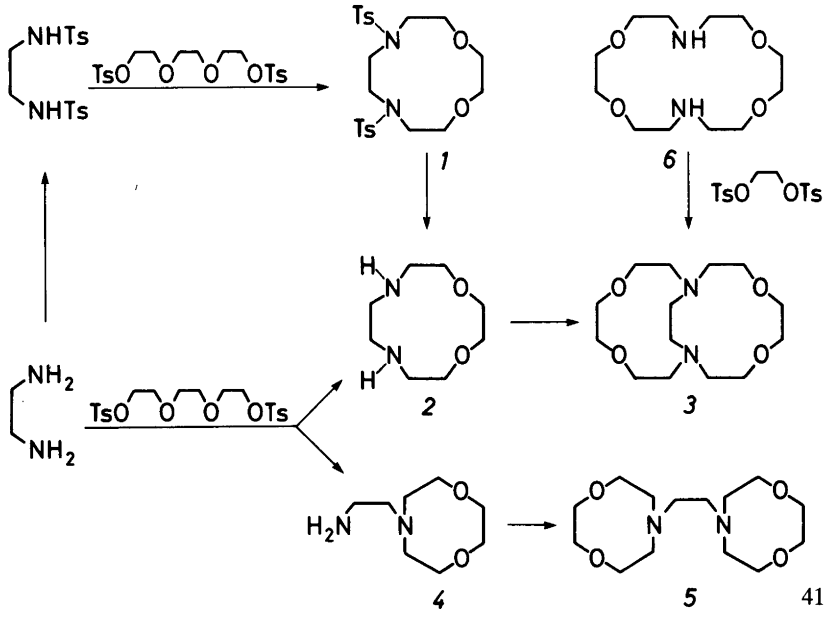

Fig. 2. Synthesis of ligands from ethane-1,2-diamine.

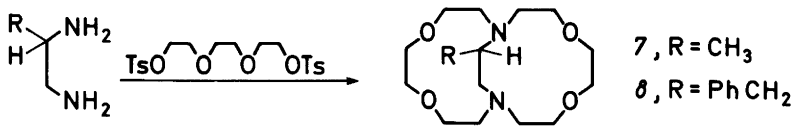

Fig. 3. Synthesis of lipophilic aminoethers.

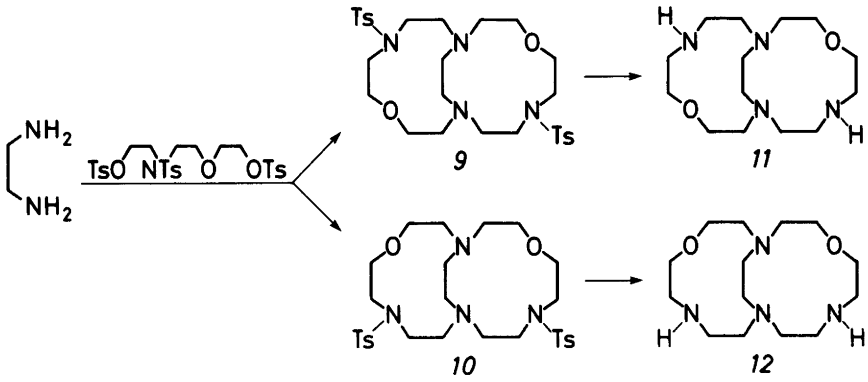

Fig. 4. Synthesis of potential ligand intermediates.

quired for the synthesis of further tri- and quatercyclic ligands related to those in Fig. 1. Thus, the reaction between ethane-1,2-diamine and tritosylated *N*-hydroxyethyl-(2-hydroxyethyloxy)ethaneamine (Fig. 4) gave a mixture of the two isomeric bicyclic compounds *9* and *10* as shown by ^{13}C NMR spectroscopy. One of these could be obtained crystalline. Only the X-ray structure[9] could reveal that this isomer had the most symmetric structure *9*. Detosylation of the crude mixture of *9* and *10* was effected by HBr/CH_3COOH to give an impure mixture of the two bicyclic tetraaminodiethers *11* and *12*. These could not be separated and purified, but detosylation of the crystalline isomer *9* led in good yield to the pure tetraaminodiether *11*.

The reaction between ethane-1,2-diamine and tetratosylated 1,2-bis(2-hydroxyethyl)ethane-1,2-diamine (Fig. 5) led to the expected bicyclic 12-ring compound *14*. The corresponding hexaamine *15* was obtained by hydrolysis in sulfuric acid, which presented no problems since the compound contains no ether oxygen. Using a larger excess of ethane-1,2-diamine, both isomeric monocyclic compounds *13* and *16* were obtained in preparative yields. The 12-ring isomer *13* was finally reacted with triethyleneglycol ditosylate and afforded the bicyclic aminoether *17*.

Complexation properties

Complex formation with alkali cations was studied primarily with the simplest representative, the unsubstituted tetraoxadiazabicyclo-[8.8.2]eicosane *3*, but the complexation behaviour was quite analogous with the 19-methyl derivative *7*. Some results have already been briefly reported[10] and will be discussed later in more detail and in a broader context. Only some salient results are summarized here.

The stoichiometry was determined by titration with solid LiSCN, NaSCN or KSCN in CD_3OD, D_2O, or mixtures thereof, monitored by ^{13}C NMR spectroscopy, and was always 1:1. The complexation constants were determined by pH-metric titrations, first of the ligand alone and then in the presence of each salt,[11] using H_2O or CH_3OH/H_2O (9:1) as solvent. The activation barriers of decomplexation were determined by DNMR spectroscopy on 1:1 mixtures of complexed and free ligand in CD_3OD, D_2O and CD_3OD/D_2O (9:1), but a comprehensive set of

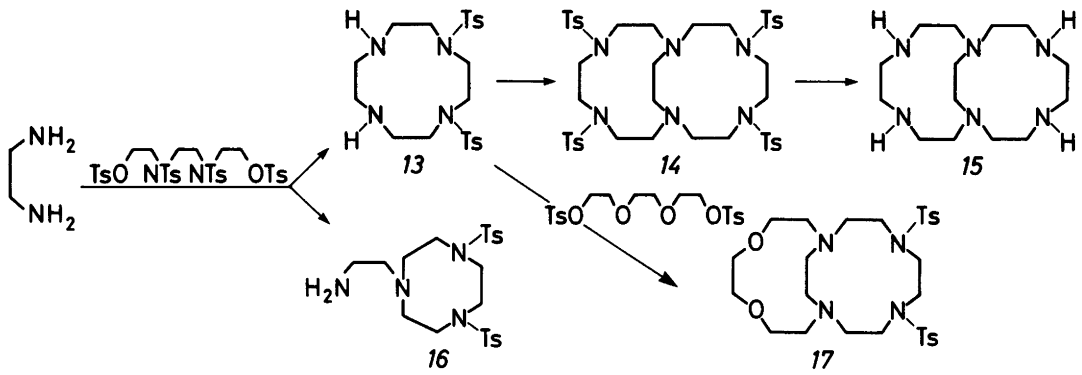

Fig. 5. Synthesis of macrocyclic polyamines.

data could for practical reasons be obtained only with the latter solvent mixture. These data are given in Table 1 together with activation barriers for complex formation calculated from it.

It is noteworthy that the sequence of complexation free energies is not the same as the sequence of decomplexation activation energies, as might have been anticipated[12] if the rates of complexation were the same and diffusion-controlled. The calculated activation barriers to complex formation show the sequence $Li^+ > Na^+ > K^+$ which possibly reflects the decreasing energy of solvation in methanol/water. All three values are substantially larger than the values 4–5 kcal/mol commonly cited for diffusion-controlled processes.[12] This was rather unexpected for the relatively open structure of this bicyclic ligand *3*.

On the other hand the high selectivity observed for Na^+ in complexation was as expected. Since the ^{13}C chemical shifts are quite different for the three complexes, and all very much upfield from those of the free ligand, the complexation selectivity can be nicely confirmed and directly demonstrated in the following competition experiments: The free ligand (1 mol) is dissolved in CD_3OD and the ^{13}C NMR lines recorded. On addition of KSCN (1 mol) these lines are completely replaced by the lines of the K^+ complex. Further addition of LiSCN (1 mol) gives line positions intermediate between those for the pure K^+ and Li^+ complexes from which a ratio K^+ complex/Li^+ complex $\approx$ 2:1 can be calculated. When finally NaSCN (1 mol) is added, these lines are replaced completely by those for the pure Na^+ complex. Since at the temperature used (35 °C) exchange of ligand with the Na^+ complex is slow, any other complex would have been seen as separate lines.

Table 1. Complexation free energies and activation barriers to dissociation and formation for complexes of ligand *3* with alkali salts in methanol/water (9:1).

	LiSCN	NaSCN	KSCN
K^a	$2.4 \cdot 10^3$	$1.1 \cdot 10^6$	$5.9 \cdot 10^3$
$-\Delta G°$/kcal mol^{-1}	4.7	8.3	5.2
T_c for ^{13}C (°C)	8	70, 77	−23
$\Delta\nu$/Hz	366	213, 348	380
$\Delta G^{\ddagger}_{diss.}$/kcal mol^{-1}	12.7	16.0, 16.0	11.6
Calcd. $\Delta G^{\ddagger}_{form.}$/kcal mol^{-1}	8.0	7.7	6.4

[a]Determined by pH-metric titration.

Conformational properties

The NMR spectra of the simplest bicyclic ligands *3* and *7* showed unexpected dissimilarities, especially with respect to temperature variation. This suggested that their conformational dynamics were quite different, although there is no reason to expect that the basic conformation of the methyl-substituted ligand *7* should be different from that of the unsubstituted ligand *3*. For the latter all details are known from crystal structures determined on both the free ligand and its alkali complexes.[10]

Ligand *3* was designed to fit Na^+, which implies that its predicted conformation in the Na^+ complex was that shown in Fig. 6a.[3] Both rings should take the familiar [3333] conformation and be joined together in such a way that the helicity of the *gauche* bonds within both rings are all of the same sign. The X-ray structure[10] proved to be exactly this, with SCN^- as expected occupying the seventh coordination site on Na^+. Perhaps surprisingly, the crystal structures of the weaker alkali complexes also revealed[10] the same type of conformation, only adjusted by slight rotation about certain bonds to either narrow the cleft to fit the smaller Li^+ cation (whereby the anion contact is lost) or widen the cleft to fit the larger K^+ cation. The free ligand (Fig. 6b) has both rings in the [39] conformation, whereby the cleft becomes filled by two CH_2 groups, but the bridging ethanediamine unit remains essentially unchanged with both nitrogen lone pairs pointing in ("in,in"). It seems likely that it is this perfect juncture of two 12-membered rings that explains the rapid cyclization of the second ring after the first ring has been formed. A chain linked to one nitrogen becomes directed towards the other nitrogen. The general topology and opening-closing behaviour of this type of ligand has led us to propose[10] the generic name *diptychand* (di-ptychos = hinged double tablet).

Dynamic NMR studies shed some light on the conformational interconversion processes of the macrobicyclic compounds *3* and *7*. All the spectral details will be given in a separate paper, and only the main conclusions are summarized here. The free ligand *3* in CD_3OD has at room temperature a ^1H spectrum corresponding to the constitutional symmetry, including fast geminal CH_2 exchange, nitrogen inversion and exchange of non-equivalent ring-atom positions (Fig. 6). To accomplish this, the steps expected to be most critical in a multistep interconversion scheme are the rotation about the bridge CC bond and inversion about the two nitrogen atoms. These are shown in Fig. 7 (R=H), and the scheme implies that the process goes through the "out,out" conformer having the bridge CC bond in *anti*. This by the way is exactly the conformation chosen by the tosylated aza-derivative *9* in the crystal.[9] It is assumed that all the accompanying bond rotations that are required to follow step by step elsewhere in both rings until the inverted conforma-

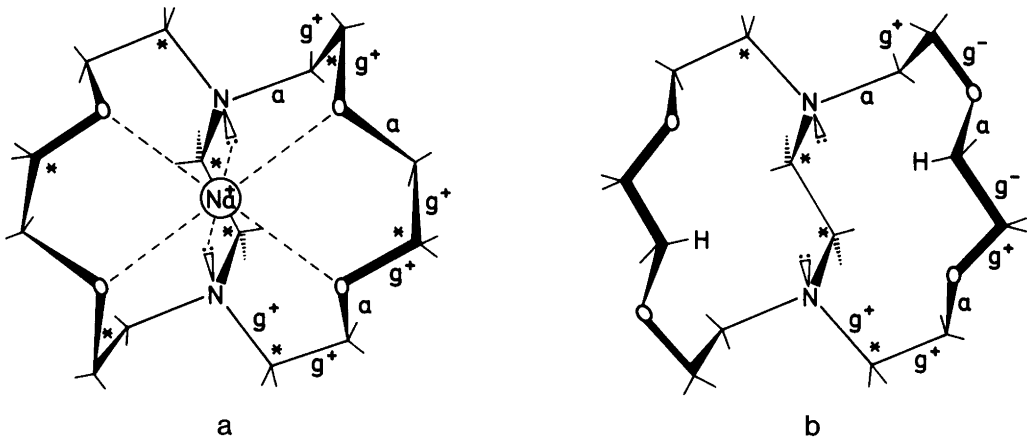

Fig. 6. The crystal structure of ligand *3* in a) its NaSCN complex and b) in the uncomplexed state.[10] The asterisks indicate "corner atoms".[1,2]

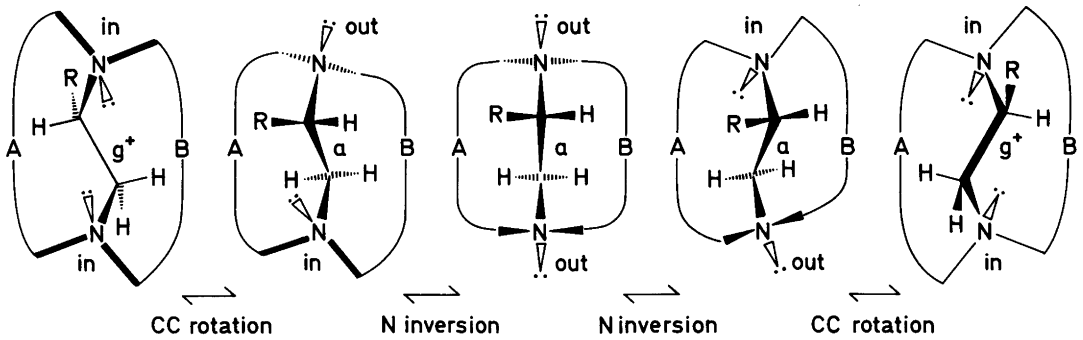

Fig. 7. Critical interconversion steps to effect geminal site exchange when R = H or to make the interaction between the R-substituent and the ring chains A and B equivalent when R ≠ H.

tion is obtained, are of much lower energy. On cooling, each of the $>NCH_2CH_2O-$ triplets broadens and then splits into two broad bands, but the $>NCH_2CH_2N<$ line remains a singlet. This means that the higher-energy process in Fig. 7, leading to geminal exchange, has become slow (T_C −58 °C, $\Delta G^{\ddagger}$ 10.5 kcal/mol), whereas the lower-energy processes, such as the passing of all CC bonds through *syn*-eclipsing to produce the enantiomeric conformation, remain fast down to −90 °C, $\Delta G^{\ddagger} \leqslant 8$ kcal/mol.

The ^{1}H NMR spectrum of the NaSCN complex of *3* in CD_3OD already shows for the $>NCH_2CH_2O-$ system different shifts for geminal protons at room temperature and is unchanged at least to 60 °C (two resolved multiplets for NCH_2 and two for OCH_2). This proves the expected necessity of decomplexation to effect geminal exchange, since the coalescence temperature for ligand exchange was also higher than 60 °C. On cooling there is a broadening of all lines and further splitting into a very complicated spectrum (T_C −30 °C). The interpretation is clearly that the process of passing all CC bonds through *syn*-eclipsing has become slow and the rings have become frozen in their enantiomeric conformations, one of which is shown in Fig. 6a. This process is seen more clearly in the ^{13}C spectrum (T_C −45 °C, $\Delta G^{\ddagger}$ 10.8 kcal/mol). The corresponding values were also determined for the Li^+ and K^+ complexes and are shown in Table 2. The interesting conclusion to be drawn is that the lower-energy process (CC eclipsing to give the mirror image) is still quite easy in the undissociated complex, whereas the higher-energy process (geminal exchange) is higher in the complexes by an amount corresponding to the complexation energy (ΔG°), hence requires complete dissociation to the free ligand in order to occur.

The ^{1}H NMR spectrum of the free 19-methyl

Table 2. Conformational barriers for ligand *3* and its complexes with alkali salts in methanol.

	3	*3*·LiSCN	*3*·NaSCN	*3*·KSCN
Geminal exchange				
T_C for ^{1}H/°C	−58	23	>>55	42
$\Delta G^{\ddagger}$/kcal mol^{-1}	10.5	14.7	>>16	15.7
Ring atom exchange				
T_C for ^{1}H/°C	<−90	~−80	~−30	~−25
T_C for ^{13}C/°C	<−90	−83	−45	−36
$\Delta G^{\ddagger}$/kcal mol^{-1}	< 8	8.6	10.8	11.0

substituted ligand 7 was extremely complicated in CD_3OD, and all lines retained their sharpness even up to 112 °C in DMSO. The lower constitutional symmetry and the inherent impossibility of geminal site exchange is not sufficient to explain the spectral complexity.

The situation was more clearly defined by ^{13}C NMR spectroscopy. Altogether 15 lines (1 CH_3, 1 CH, 5 CH_2N and 8 CH_2O) were present, which means that all carbons are non-equivalent. This is only possible if the critical interconversion process shown in Fig. 7 is hindered. Thus, the same process which can only be observed as the exchange of geminal sites when R = H, rings A and B being already equivalent, should when R = CH_3 have made the nonequivalent rings A and B equivalent if it were fast. The expected number of ^{13}C lines should then reduce to 9 (1 CH_3, 1 CH, 3 CH_2N, 4 CH_2O), but even heating to 112 °C in DMSO showed no evidence of beginning coalescence.

The critical step in the interconversion (Fig. 7) must be the turning of the CHR group through the ring so that the "in,in" conformer (right) can transform to the "out,out" conformer, but not further to the other "in,in" conformer (left). Actually, the benzyl-derivative *8* shows two coalescing sets of ^{13}C lines at room temperature, which can best be interpreted as population, also the "out,out" together with the "in,in" conformer. They interconvert over a barrier of about 15 kcal/mol, considerably higher than the barrier to geminal exchange in the unsubstituted *3*.

The low-energy conformational barriers, eclipsing of the CC-bonds, should not be much influenced by substitution, but as the rings would thereby be changed from g^+ into the enantiomeric conformation g^-, which is only compatible sterically with the *S*-configuration, and not with the *R*-configuration as drawn, this will not become populated.

Experimental

1,4-Dioxa-7,10-diazacyclododecane 2. A vigorously stirred mixture of 7,10-ditosyl-1,4-dioxa-7,10-diazacyclododecane *1*[7,8] (0.82 g, 1.7 mmol) and $LiAlH_4$ (0.78 g, 20.4 mmol) in dry THF (75 ml) was refluxed for 48 h. The excess of $LiAlH_4$ was destroyed by dropwise addition of water. The solids were removed by filtering and washed with ethyl acetate (150 ml). The combined solutions were evaporated and the residue taken up in $CHCl_3$ (25 ml). After addition of an excess of concentrated HCl, the solution was again made basic (pH ~ 14) with NaOH, and a precipitate was filtered off. The two phases of the filtrate were separated, the aqueous phase extracted with $CHCl_3$ (2×25 ml), and the combined $CHCl_3$ solutions concentrated. Chromatography on alumina gave with $CHCl_3$ first the unreacted ditosyl compound, then with ethanol *the cyclic aminoether 2* (30 mg, 10 %) as an oil. ^1H NMR ($CDCl_3$) δ 2.90 (4H, *m*, NCH_2CH_2O), 3.00 (4H, *s*, NCH_2CH_2N), 3.65 (4H, *m*, NCH_2CH_2O), 3.65 (4H, *s*, CH_2O), 4.65 (2H, *s*, NH).

The reaction between ethane-1,2-diamine and triethyleneglycol ditosylate. To a vigorously stirred suspension of dry, finely powdered Na_2CO_3 (10 g) in refluxing acetonitrile (100 ml) was dropped over 48 h synchronously *one* solution of ethane-1,2-diamine (1.20 g, 20 mmol) in acetonitrile (100 ml) and *another* solution of triethyleneglycol ditosylate[13] (18.32 g, 40 mmol) in acetonitrile (100 ml). After further stirring and refluxing for 4 days, the solid salts were removed by centrifugation and washed with acetonitrile (2×100 ml), and the combined solvents evaporated in a Rotavapor. The residue was taken up in $CHCl_3$ (50 ml) and water (5 ml), and the aqueous phase further extracted with $CHCl_3$ (3×50 ml). After evaporation of $CHCl_3$, the residue was refluxed with $NaOCH_3/CH_3OH$ to destroy any unreacted tosyl functions, and the methanol was evaporated. The residue was taken up in water (50 ml) and the aqueous solution repeatedly extracted with small portions (10 ml) of $CHCl_3$ until the gas chromatogram of the aqueous phase showed only the presence of the 12-ring isomer *4,7,13,16-tetraoxa-1,10-diazabicyclo[8.8.2]eicosane 3* (as complex), the $CHCl_3$ extracts containing mainly the 9-ring isomer *1,2-bis(4,7-dioxa-1-azacyclononyl)ethane 5*. The aqueous phase was then concentrated, and further extractions with larger portions (4×50 ml) of $CHCl_3$ yielded the sodium tosylate complex of the 12-ring ligand *3*, which on pyrolysis in Kugelrohr at 200 °C/0.01 mmHg gave *the free ligand 3* (2.35 g, 41 %), m.p. 61–65 °C, MS (CI, isobutane) 289 (*M*+1). ^1H NMR (CD_3OD) δ 2.68 (8H, *t*, NCH_2CH_2O), 2.93 (4H, *s*, NCH_2CH_2N), 3.64 (8H, *s*, OCH_2CH_2O), 3.70 (8H, *t*, NCH_2CH_2O); in $CDCl_3$: δ 2.60, 2.75, 3.65, 3.70. ^{13}C NMR (CD_3OD) δ 52.8

(NCH_2CH_2N), 57.6 (NCH_2CH_2O), 71.6, 71.7 (CH_2O).
Monohydrochloride of 3: ^{13}C NMR (CD_3OD) δ 54.2, 56.3, 68.2, 71.5.
LiSCN complex of *3*: m.p. 64–66 °C, ^{13}C NMR (CD_3OD) δ 51.7, 52.7, 66.3, 67.8.
NaSCN complex of *3*: m.p. 250–253 °C, ^{13}C NMR (CD_3OD) δ 49.7, 52.5, 65.1, 67.1.
KSCN complex of *3*: m.p. 212–213 °C, ^{13}C NMR (CD_3OD) δ 49.9, 54.0, 65.6, 67.0.

The $CHCl_3$ extract containing mainly the 9-ring isomer *5* was evaporated and the residue taken up in water (15 ml) and NaCl (0.3 g) added. Extraction with small portions (5 ml) of $CHCl_3$ yielded after evaporation an oil which was distilled in Kugelrohr at 180 °C/0.01 mmHg. The distillate was the pure *ligand 5* (0.20 g, 4 %), MS (CI, isobutane) 289 (*M*+1, 40), 144 (*M*/2, 100). ^1H NMR ($CDCl_3$) δ 2.78 (4H, *s*, NCH_2CH_2N), 2.88 (8H, *t*, NCH_2CH_2O), 3.75 (8H, *t*, NCH_2CH_2O), 3.75 (8H, *s*, CH_2O). Addition of solid $LiClO_4$ (mol. ratio 1:1) gave only slight downfield displacements: δ 2.88, 2.88, 3.78, 3.85.

The ligand *3* was also prepared from 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane *6* (= "Cryptofix 22") (5.25 g, 20 mmol) and ethyleneglycol ditosylate[13] (7.41 g, 20 mmol) by synchronized addition over 32 h of two separate acetonitrile solutions to a stirred suspension of Na_2CO_3 in refluxing acetonitrile. After further refluxing for 7 days, the mixture was worked up as above. Pyrolysis gave *the free ligand 3* (3.62 g, 63 %), m.p. 60–65 °C.

19-methyl-4,7,13,16-tetraoxa-1,10-diazabicyclo-[8.8.2]eicosane 7. The reaction was carried out as for compound 3 but with propane-1,2-diamine instead of ethane-1,2-diamine. Isolation and pyrolysis in the same way yielded the free ligand *7*, m.p. 90 °C, MS (CI, isobutane) 303 (*M*+1). ^{13}C NMR (CD_3OD) δ 10.6 (CH_3), 48.7, 52.1, 53.1, 55.6, 57.2 (CH_2N), 59.5 (CHN), 67.8, 68.0, 69.2, 69.4, 69.6, 70.7, 72.5, 72.6 (CH_2O).

19-Benzyl-4,7,13,16-tetraoxa-1,10-diazabicyclo-[8.8.2]eicosane 8. To a stirred refluxing suspension of finely powdered Cs_2CO_3 (2 g) in acetonitrile (100 ml) was first added 3-phenyl-propane-1,2-diamine[14] (334 mg, 2.2 mmol), and then was added dropwise a solution of triethyleneglycol ditosylate[13] (2.7 g, 7.0 mmol) in acetonitrile (70 ml). The mixture was refluxed for 48 h when GLC analysis showed that the diamine had been consumed. The solvents were evaporated in a Rotavapor and the residue dissolved in water (25 ml) and extracted with $CHCl_3$ (100 ml). After evaporation of the solvent, the residue was taken up in water and passed through an ion exchange column IRA 400 loaded with NaCl. The water eluate was concentrated and the NaCl complex of ligand *8* extracted with $CHCl_3$. Double distillation in a Kugelrohr at 250 °C/0.001 mbar yielded *the free ligand 8* as a yellowish oil (395 mg, 47 %), MS (CI, isobutane) 379 (*M*+1). ^1H NMR ($CDCl_3$) δ 2.3–3.1 (CH_2Ph + CH_2N), 3.3–4.1 (CH_2O), 7.2–7.4 (Ph). ^{13}C NMR ($CDCl_3$) at 55 °C: δ 33.3 (bz CH_2), 49.8, 53.5, 56.3, 56.6, 57.0 (CH_2N), 61.6 (CHN), 68.3, 69.2, 69.9, 70.1 (x2), 71.3, 72.8, 73.0 (CH_2O), 125.9, 128.4, 129.5, 140.3 (ar C). Splitting into two sets of lines occurred on cooling.

The reaction between ethane-1,2-diamine and tritosylated N-hydroxyethyl-(2-hydroxyethyloxy) ethaneamine. To a suspension of Na_2CO_3 (10 g) in refluxing acetonitrile (50 ml) was added dropwise and in parallel over 48 h one solution of ethane-1,2-diamine (1.67 g, 25 mmol) in acetonitrile (125 ml) and another solution of tritosylated *N*-hydroxyethyl-(2-hydroxyethyloxy)ethaneamine[15] (31 g, 50 mmol) in acetonitrile (125 ml). The mixture was further refluxed for 24 h, then cooled and filtered, and the solvent evaporated in a Rotavapor. The residue was partitioned between water and $CHCl_3$, and the organic phase dried and concentrated, and then chromatographed on silicagel. Ethyl acetate eluted unreacted tritosylate, whereafter methanol saturated with NaCl eluted the bicyclic product. After concentration the residue was taken up in $CHCl_3$. Evaporation yielded a mixture of the two ditosylated dioxatetraazabicyclo[8,8,2]eicosanes *9* and *10* as an oil (7.92 g, 11.8 mmol, 47 %), MS (CI, isobutane) 595 (*M*+1). ^{13}C NMR spectroscopy showed two sets of lines, but only one of the isomers crystallized partly from acetonitrile, m.p. 188 °C. ^{13}C NMR ($CDCl_3$): δ 21.5 (ar CH_3), 48.6 (x2), 49.5 (CH_2N), 53.6, 55.4 (CH_2NS), 70.3, 72.1 (CH_2O), 127.2, 129.7, 136.1, 143.1 (ar C). The X-ray structure[9] showed that this was the isomer *9*: *7,16-ditosyl-4,13-dioxa-1,7,10,16-tetraazabicyclo[8.8.2]eicosane.*

A mixture of *9* (0.78 mmol), phenol (3 g) and glacial acetic acid saturated with HBr (25 ml) was

stirred for 2 days at 80 °C. The solution was concentrated and diluted with water (25 ml). By-products were removed by extraction with CH_2Cl_2, and the aqueous phase evaporated to dryness. Recrystallization from ethanol gave the tetrahydrobromide of diptychand *11* (335 mg = 71 %). ^{1}H NMR (D_2O/CH_3CN): δ = 3.0–3,5 (CH_2N), 3.55–3.9 (CH_2O). The free diptychand was isolated by dissolution of the tetrahydrobromide in concentrated KOH and extraction with $CHCl_3$. Sublimation in vacuum gave colourless hygroscopic crystals of *4,13-dioxa-1,7,10,16-tetraazabicyclo[8.8.2]eicosane,* m.p. 75–77 °C. MS (CI, isobutane): 287 (*M*+1), ^{13}C NMR ($CDCl_3$): δ 47.3, 49.1 (CH_2NH), 52.5 (x2), 55.3 (CH_2N), 67.3, 69.1 (CH_2O). Detosylation of the crude oily mixture of *9* and *10* gave an impure mixture of *11* and *12*. This proved unstable in GLC analysis, and extensive destruction took place on attempts to purify it by sublimation.

The reaction between ethane-1,2-diamine and tetratosylated N,N'-bis(2-hydroxyethyl)-ethane-1,2-diamine.

a) *With large excess of ethane-1,2-diamine.*

To a refluxing solution of ethane-1,2-diamine (2.75 g, 46.0 mmol) in acetonitrile (300 ml) containing dispersed sodium tosylate (1.78 g, 9.2 mmol) and Na_2CO_3 (4 g), was dropped a solution of tetratosylated *N,N'*-bis(2-hydroxyethyl)-ethane-1,2-diamine[16] (7 g, 9.2 mmol) in acetonitrile (200 ml) over a period of 20 h. After further refluxing for 3 days, the solids were removed by centrifugation and the solvents evaporated in a Rotavapor. Crystallization of the residue from methanol gave *1,4-di-tosyl-1,4,7,10-tetraazacyclododecane 13* (0.61 g, 14 %), and column chromatography on alumina of the evaporated mother liquor ($CHCl_3$/methanol 1:1) a second crop (1.15 g, 26 %); total yield 40 %. M.p. 190–192 °C; MS (CI, isobutane) 481 (*M*+1). Found: C 54.9; H 6.7; N 11.4. Calc. for $C_{22}H_{32}N_4O_4S_2$: C 55.0; H 6.7; N 11.7. ^{1}H NMR ($CDCl_3$) δ 1.5 (2H, *s,* NH), 2.5 (6H, *s,* ar CH_3), 2.7 (4H, *s,* CH_2N), 2.8–3.1 (4H, *m,* CH_2N), 3.1–3.4 (4H, *m,* CH_2 NTS), 3.6 (4H, *s,* CH_2 NTS), 7.3–7.9 (8H, *q,* ar CH). ^{13}C NMR ($CDCl_3$) δ 21.5 (ar CH_3), 47.0, 48.1 (CNH), 50.5 (CNTs), 127.6, 129.8, 134.4, 143.6 (ar C).

In a similar run, but using a smaller excess of ethanediamine (28 mmol), there was also isolated by column chromatography the sesquihydrochloride of *1-(2-aminoethyl)-4,7-ditosyl-1,4,7-triazacyclononane 16* (15 %). MS (CI, isobutane) 481 (*M*+1). Found: C 49.0; H 6.4; Cl 9.7. Calc. for $C_{22}H_{32}N_4O_4S_2$. 1.5 HCl: C 49.3; H 6.5; Cl 9.9. Dissolution in aq. KOH and extraction with $CHCl_3$ afforded *the free amine 16* as an oil. MS (CI, isobutane) 481 (*M*+1). ^{1}H NMR ($CDCl_3$) δ 2.4 (6H, *s,* ar CH_3), 2.6–2.9 (6H, *m,* $CH_2CH_2NH_2$), 2.9–3.0 (4H, *m,* CH_2 N ring), 3.2–3.3 (4H, *m,* CH_2NTs), 3.4 (4H, *s,* CH_2 NTs), 7.3–7.7 (8H, *q,* ar CH). ^{13}C NMR ($CDCl_3$) δ 22.3 (ar CH_3), 39.8 (CNH_2), 52.4, 53,4, 55.9 (6 CN ring), 60.0 (CN side chain), 127.4, 130.0, 135.4, 143.8 (ar C).

The main product in this run is also the 12-ring compound *13,* with some of the bicyclic compound *14* (see below).

b) *With the stoichiometric ratio.*

To a refluxing suspension of Na_2CO_3 (21 g) in acetonitrile (50 ml) were dropped in parallel over two days one solution of ethane-1,2-diamine (0.275 g, 4.57 mmol) in acetonitrile (150 ml) and another solution of tetratosylated N,N'-bis(2-hydroxyethyl)-ethane-1,2-diamine (6.987 g, 9.13 mmol) in acetonitrile (150 ml). After further refluxing for one day, the solids were removed by centrifugation and the solvents evaporated in a Rotavapor. Column chromatography on alumina (toluene/$CHCl_3$ 1:3) yielded *4,7,13,16-tetratosyl-1,4,7,10,13,16-hexaazabicyclo[8.8.2]eicosane 14* (2.54 g, 62 %), m.p. 263–265 °C. ^{1}H NMR ($CDCl_3$) δ 2.4 (12H, *s,* ar CH_3), 2.7 (4H, *s,* CH_2N), 2.9 (8H, *m,* CH_2N), 3.2 (8H, *m,* CH_2NTs), 3.5 (8H, *s,* CH_2NTs), 7.3–7.7 (16H, *q,* ar CH). ^{13}C NMR ($CDCl_3$) δ 21.5 (ar CH_3), 51.5, 52.7 (4 CNTs), 55.3, 55.7 (3 CNTs), 127.2, 129.8, 135.5, 143.3 (ar C).

1,4,7,10,13,16-Hexaaza-bicyclo[8.8.2]eicosane 15.

The tetratosyl derivative *14* (0.94 g, 1.0 mmol) was stirred in 96 % H_2SO_4 (2 ml) at 100 °C for 48 h. 6N HCl (aq) in 96 % ethanol was added, and the hydrochloride crystallized in the refrigerator. After recrystallization from 6N HCl (aq) the m.p. was 240–250° (0.35 g). This hydrochloride was dissolved in water (8 ml) and solid KOH (1 g) was added. Extraction with $CHCl_3$ (4×75 ml) gave after evaporation and drying the free *hexaamine 15* (0.15 g, 53 %), partially crystalline in the

refrigerator. MS (CI, isobutane) 285 (M+1). ^{1}H NMR ($CDCl_3$) δ 2.6–2.7 (CH_2), NH broad. ^{13}C NMR ($CDCl_3$) δ 46.5, 46.7, 53.3 (ring), 56.0 (bridge).

13,16-Ditosyl-4,7-dioxa-1,10,13,16-tetraaza-bicyclo[8.8.2]-eicosane 17.
To a refluxing suspension of sodium tosylate (1.5 g, 7.7 mmol) and Na_2CO_3 (8 g) in acetonitrile (25 ml) were dropped in parallel over 4 days one solution of 1,4-ditosyl-1,4,7,10-tetraazacyclododecane *13* (0.227 g, 0.47 mmol) in acetonitrile (10 ml) and another solution of triethyleneglycol ditosylate[13] (0.217 g, 0.47 mmol) in acetonitrile (10 ml). After further refluxing for one day, the solids were filtered off and washed with $CHCl_3$. The combined organic phases were concentrated and left in the refrigerator. Some precipitated sodium tosylate was filtered off and the solvent evaporated to leave the *bicyclic compound 17* (0.20 g, 71 %). MS (CI, isobutane) 595 (M+1). ^{1}H NMR ($CDCl_3$) δ 2.5 (6H, *s*, ar CH_3), 2.5–2.9 (12H, *m*, CH_2N), 3.2–4.8 (8H + 8H, *m*, CH_2NTs + CH_2O), 7.2–7.8 (8H, *q*, ar CH). ^{13}C NMR ($CDCl_3$) δ 21.5 (ar CH_3), 48.4, 49.9, 52.1 (CN), 55.9, 57.6 (CNTs), 69.7, 71.5 (CO), 127.3, 129.5, 137.3, 142.9 (ar C).

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