61. Anion Coreceptor Molecules. Linear Molecular Recognition in the Selective Binding of Dicarboxylate Substrates by Ditopic Polyammonium Macrocycles

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Three macrocyclic hexaamines **1**, **2**, and **4** and the acyclic tetraamine **5** and hexaamine **6** have been synthesized. The hexaamines **1**, **2**, and **4** are ditopic coreceptor molecules containing two triamine subunits which may bind anionic substrates when protonated. The stability constants of the complexes between the protonated forms of the macrocyclic polyamines and terminal dicarboxylates $^{-}O_2C-(CH_2)_m-CO_2^{-}$ as well as amino-acid and dipeptide dicarboxylates have been determined by pH-metric measurements. Around neutral pH, **1** and **2** give mainly complexes of the fully protonated species $\mathbf{1}\cdot 6H^+$ and $\mathbf{2}\cdot 6H^+$, whereas **4** yields predominantly complexes of $\mathbf{4}\cdot 5H^+$ and $\mathbf{4}\cdot 4H^+$. The stability sequences of the complexes formed indicate preferential binding of the dianionic substrates whose length is compatible with the separation of the triammonium binding subunits in the protonated receptor molecules **1**, **2**, and **4**. This selectivity pattern corresponds to a process of *linear molecular recognition* based on ditopic binding between the two ammonium subunits of the coreceptor and the terminal carboxylates of the substrate of complementary length. The complexes of the acyclic ligands **5** and **6** are much weaker and much less selective, indicating a marked macrocyclic effect on both stability and selectivity of binding, *i.e.* on recognition.

Introduction. – The incorporation of two or more binding subunits into a macropolycyclic structure yields coreceptor molecules in which the subunits may cooperate for the multiple binding of a polyfunctional substrate or for the simultaneous complexation of two or more substrates. Such coreceptors add a new dimension to the chemistry of molecular receptors [1]. Thus, cylindrical macropolycycles form selective cryptates of $^{+}H_3N-(CH_2)_n-NH_3^{+}$ cations, bound by each terminal NH_3^{+} group to a macrocyclic subunit, with a stability and selectivity depending on the complementarity between the length of the substrate and the cavity size of the receptor [1–3].

In a similar fashion, strong and selective binding of a dianionic molecule requires the design of a ditopic molecular coreceptor possessing two binding subunits arranged in such a way that they cooperate for substrate binding by interacting with the anionic groups of the target species. The binding subunits themselves must contain a suitable array of interaction sites capable of forming intermolecular bonds to the anionic sites of the substrate.

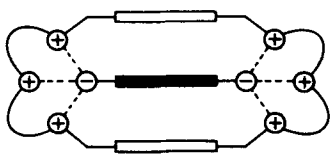
Macrocyclic [4–8] and macropolycyclic [9–14] polyammonium molecules have been shown to complex strongly and selectively a variety of inorganic and organic anions, thus laying the bases for the developing field of anion-coordination chemistry [1] [10] [13] [15] [16]. The anion-complexation units of these receptor molecules consist of several positively charged binding sites arranged around a cavity defined by the macropolycyclic architecture.

[1]) U.A. N° 422 of the *C.N.R.S.*

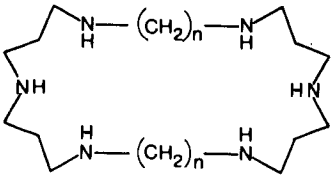
We have incorporated such polyfunctional binding features in the design of ditopic coreceptors for dianionic substrates. We describe here the synthesis of ditopic macrocyclic polyamines and their binding properties towards terminal dicarboxylate substrates ($^{-}O_2C-R-CO_2^{-}$[2]).

Design of the Polyaza-macrocycles. – In order to achieve the binding of terminal dicarboxylates, the receptor must present two binding subunits located at the poles of the structure and held by the molecular framework. Since electrostatic charge-charge interactions play a dominant role in binding of anions, polyammonium cations should be suitable complexing agents; strongest binding occurs usually with the fully protonated form of the polyamine.

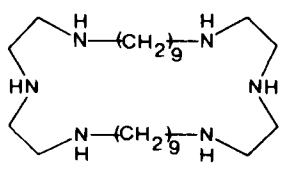
Because most organic anions, especially polycarboxylates, correspond with weak acids and thus are protonated below a pH of *ca.* 4, the receptor molecule should be designed so as to fulfill a compromise between the pH values required for full protonation of the polyamine receptor and the need to remain in a pH range where the substrate to be bound may exist as dicarboxylate. In order to accumulate the highest charge density in each binding subunit of the ligand, the number of ammonium binding sites may be increased, but this will also lower the pH for full protonation. Thus, in the design of a suitable ditopic coreceptor, the following parameters must be taken into account: the number of ammonium binding sites forming the binding subunits; the distance separating the ammonium sites from each other within a binding subunit, and the distance separating the two binding subunits. Structure **A** gives a schematic representation of the binding of a terminal dianionic substrate to a ditopic coreceptor containing two triammonium subunits located at the poles of the molecule.



A



1 $n = 7$, 32[N_6]
2 $n = 10$, 38[N_6]
4 $n = 3$, 24[N_6]



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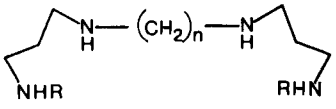


5 $n = 10$, R = H
6 $n = 10$, R = $(CH_2)_3$-NH_2
22 Hexa(*p*-toluenesulfonamide) of **6**

[2]) Preliminary report, see [7].

'Diethylenetriamine' (= dien = 3-azapentane-1,5-diamine) and 'di(trimethylene)-triamine' (= dpen = 4-azaheptane-1,7-diamine) are attractive binding subunits, since their lowest pK_a values are 4.25 [17] and 7.72 [18], respectively. For the naturally occurring acyclic polyamines putrescine, cadaverine, spermidine, and spermine, the pK_a values for full protonation are rather high (> 7.5) [19]. These polyammonium cations display weak binding of biologically relevant anions [20]. On the other hand, unprotonated diethylenetriamine and di(trimethylene)triamine groups bind transition metal ions so that macrocycles containing two such units should also be able to form dinuclear cation complexes which may have interesting structures and properties [21].

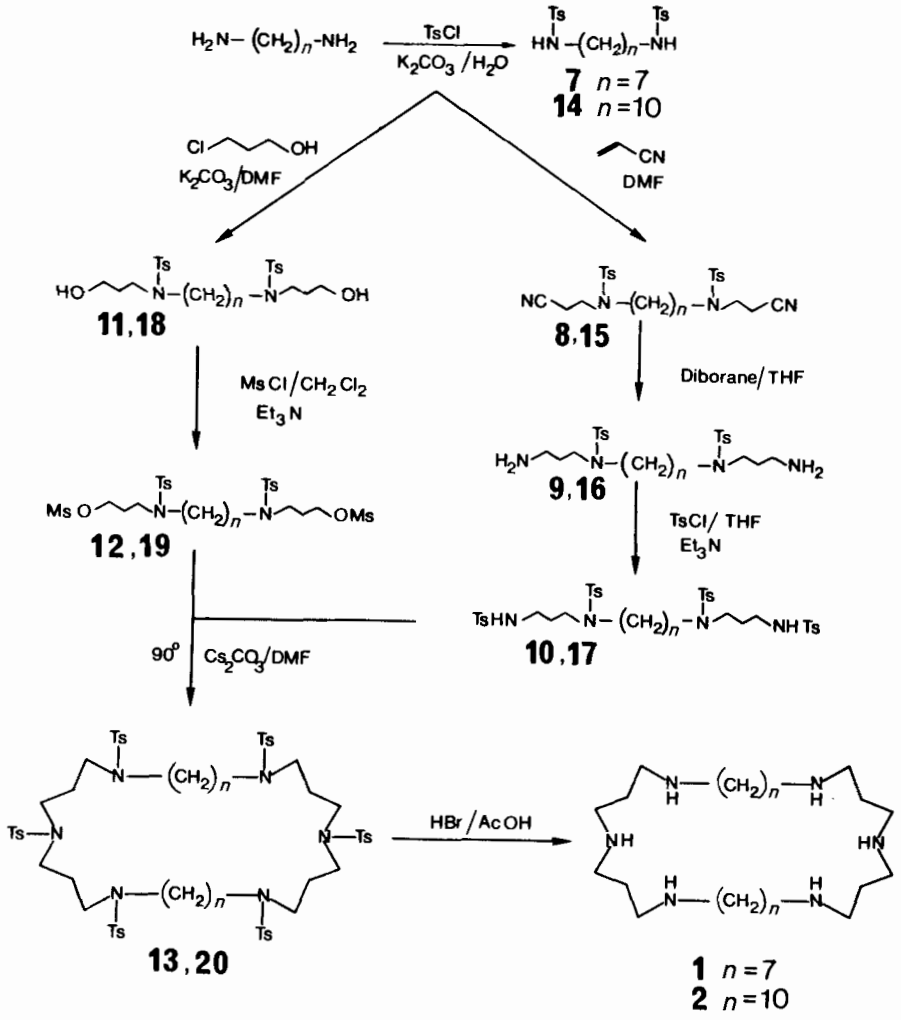
These considerations on potential binding ability towards both metal cations and anions led to the choice of the macrocycles **1–3**. Compounds **1** and **2** are 32- and 38-membered macrocyclic polyamines containing two 'di(trimethylene)triamine' groups as subunits separated by linear chains of 7 or 10 methylene groups. They may also be considered to incorporate two fragments reminiscent of the natural acyclic polyamines cited above which play an important biological role [22]. The 32-membered macrocyclic polyamine **3** is based on 'diethylenetriamine' groups as the binding units separated by 9 methylene groups. The polyamines **5** and **6** may be considered as open-chain reference compounds for comparison with the corresponding macrocycle **2**.

Synthesis of the Macrocycles 1–3 and the Linear Polyamines 5 and 6. – For the macrocyclic polyamines **1–3**, the key step, the cyclisation, was achieved by condensation of an α,ω-di(*p*-toluenesulfonamide) with an α,ω-ditosylate in dimethylformamide (DMF) in the presence of caesium carbonate (Cs_2CO_3) following the methods described for the synthesis of diazacyclodecadiene [23] and of polyhetero macrocycles [24].

Macrocycles 32 ⟨N_6-3$_2$.7.3$_2$.7-Coronand-6⟩ [32]ane-$N_6(C_7)$ **1** *and 38 ⟨N_6-3$_2$.10.3$_2$.10-Caronand-6⟩ [38]ane-$N_6(C_{10})$* **2** (see *Scheme 1*). The synthesis of **1** and **2** follows a reaction sequence similar to that used earlier for the related macrocycle **4** [4] [25]. The ditosyl derivatives **7** and **14** were obtained in high yield by the tosylation of the corresponding diamines. These two compounds were common starting materials for the two chains used in the cyclization steps. Treatment of **7** and **14** with acrylonitrile in DMF in the presence of K_2CO_3 gave the dinitriles **8** and **15**, respectively. Reduction of **8** and **15** with B_2H_6 [26] led to the diamines **9** and **16**, which were converted into their tetratosyl derivatives **10** and **17**, respectively. On the other hand, treatment of **7** and **14** with 3-chloro-1-propanol in DMF in the presence of excess solid K_2CO_3 gave the diols **11** and **18**, which were converted into the di(mesyloxy) derivatives **12** and **19** [27], respectively. Condensation of **12** and **19** with the second cyclization partner **10** and **17**, respectively, at 90° in DMF in the presence of Cs_2CO_3 [28] led to the hexatosyl macrocycles **13** and **20**, respectively, which were purified carefully. Removal of the tosyl groups was achieved by treatment with 33% HBr/AcOH/phenol at 80° [23] [29] yielding **1** · 6 HBr or **2** · 6 HBr. This method gave higher yields than the treatment with conc. H_2SO_4 at 100° for an extended period of time [24] [30]. The free macrocyclic hexaamines **1** and **2** were obtained by passing **1** · 6 HBr or **2** · 6 HBr over a *Dowex 1 × 8* resin in its basic form; they should be stored under N_2 or kept as their hexaammonium salts.

The linear tetraamine **5** was obtained from **17** by removal of the tosyl groups as described above. The linear hexaamine **6** was prepared by condensation of the disodium salt of *N,N'*,4-tri(*p*-tolylsulfonyl)-4-azaheptanediamine, prepared as described earlier

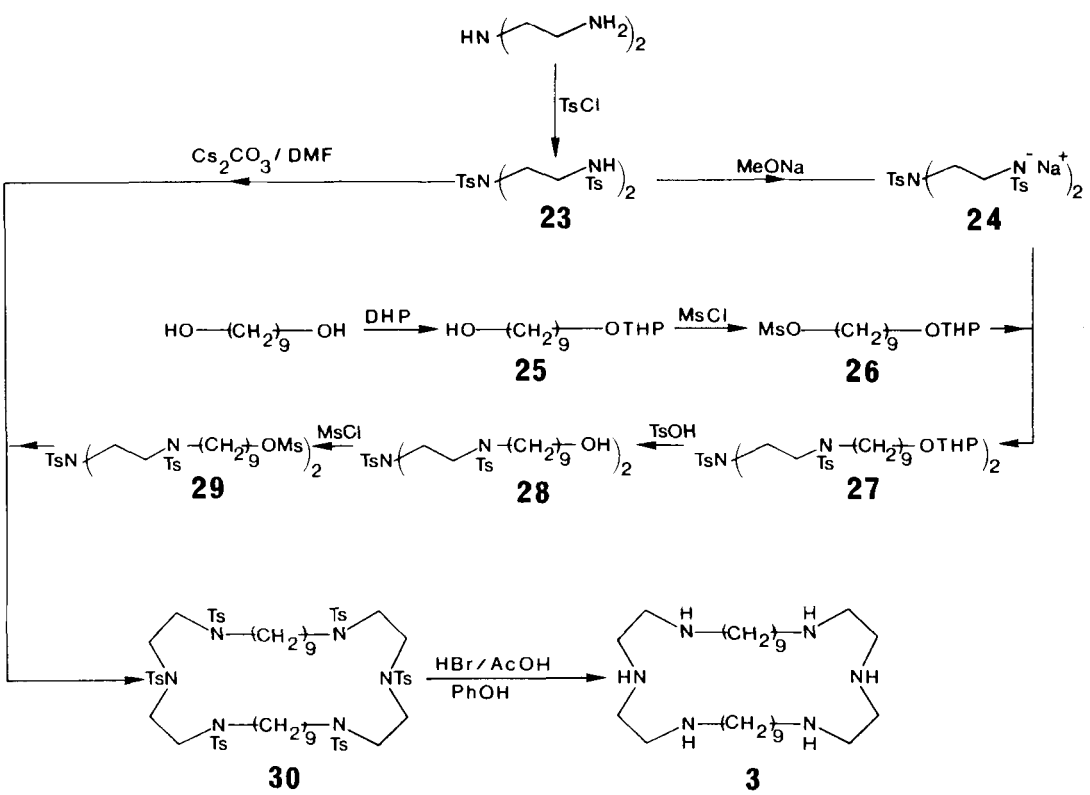
Scheme 1



[25], with 1,10-di(methanesulfonyloxy)decane (**21**), yielding the linear hexatosyl derivative **22** which gave **6** after deprotection as described above.

Macrocycle [32]ane-N_6(C_9) **3** (see *Scheme 2*). The synthesis of **3** follows a reaction sequence similar to that used earlier for the synthesis of smaller macrocyclic hexaamines [31]. The monoprotection of 1,9-nonanediol was achieved by treatment with dihydropyran [32] yielding **25** which was converted into the mesyloxy derivative **26**. Condensation of the latter with the disodium salt **24**, prepared as described earlier [33], gave **27** which was refluxed in EtOH/H_2O in the presence of *p*-toluenesulfonic acid [34] yielding the diol **28**. The latter was converted into the di(mesyloxy) derivative **29**. The cyclisation step was performed by condensation of **29** with the tritosyl derivative **23** in DMF in the presence of Cs_2CO_3 yielding the hexatosyl macrocycle **30**. Deprotection of the latter was performed as described above and afforded the hexaamine **3**.

Scheme 2



Results. – *Protonation Features of the Macrocyclic Polyamines* **1–4** *and of the Linear Tetraamine* **5** *and Hexaamine* **6**. The protonation constants log K_n (= pK_a values) corresponding to the equilibria of the polyamines L = **1–6** (*Eqn. 1* and *2*) are listed in *Table 1*. They lead to the distribution curves of the various species represented in *Fig. 1* in the case of L = **1** and **3**.

$$H_{n-1}L^{(n-1)+} + H^+ \rightleftharpoons H_nL^{n+} \tag{1}$$

$$K_n = \frac{[H_nL^{n+}]}{[H_{n-1}L^{(n-1)+}][H^+]} \tag{2}$$

It may first be noted that in the case of macrocyclic polyamines **1** and **2**, the lowest log K_n values are close to 7, so that they are fully protonated at pH values close to neutrality. The lowest log K_n value for the compound **3** is around 3.5; thus, at pH *ca.* 7, the most abundant species in solution is the tetraprotonated form $\mathbf{3}\cdot 4H^+$ *(Fig. 1)*. This clearly shows the importance of the choice of the binding subunits. Furthermore, since the polyammonium forms of **1–6** are anion receptors, the log K_n values found depend on the anion, being higher the stronger the interaction with the anion present in the supporting electrolyte. The latter was chosen so as to minimize such effects of the medium. However, it is clear that in view of this, the pK_a values determined (as well as the stability constants,

Table 1. *Protonation Equilibrium Constants log* K_n *(* $= pK_a$*) of the Macrocyclic Polyamines* **1–4** *and of the Linear Polyamines* **5** *and* **6**[a])

n	**1**	**2**	**3**	**4**	**5**	**6**
1	10.70 (10.85)	> 10.25 (> 10.50)[b])	> 9.70[b])	10.45 (10.50)	10.75	10.80
2	10.70 (10.60)	> 10.25 (> 10.50)[b])	> 9.65[b])	10.35 (10.20)	10.70	10.75
3	9.85 (9.80)	10.10 (10.15)	9.60	9.05 (9.25)	9.30	9.95
4	9.60 (9.05)	9.60 (9.45)	9.25	7.90 (8.00)	8.75	9.60
5	7.90 (7.40)	7.95 (7.65)	4.15	7.15 (7.05)	–	8.05
6	7.30 (6.65)	7.30 (6.95)	3.55	6.60 (6.40)	–	7.45

[a]) In H_2O, at 25°, see *Eqn. 1* and *2* for definition of K_n; supporting electrolyte 0.1M or 0.01M (values in parentheses) Me_4NCl; see also [7] for **1** and **2** and [4] [25] for **4**.

[b]) The pK_1 and pK_2 values cannot be determined since these compounds are not soluble in H_2O in their unprotonated form.

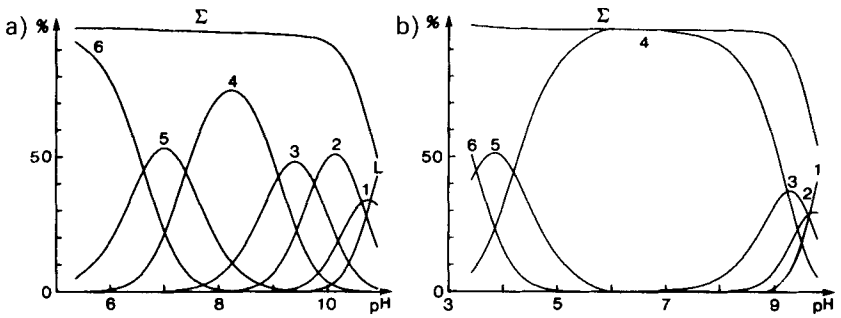


Fig. 1. *Distribution curves of the unprotonated and protonated forms of the macrocyclic polyamines as a function of pH;* a) *compound* **1**, b) *compound* **3**. L: unprotonated species; the numbers 1–6 refer to the successive protonated species bearing 1–6 protons; Σ: summation over all the protonated species. In the case of **3**, the unprotonated macrocycle L precipitates and is not represented; Σ does not contain LH^+.

see below) hold specifically for the medium used here. Although complexation of chloride is probably weak, it nevertheless affects the data so that the protonation constants determined in its presence are apparent values. The fact that the three lowest log K_n values of the free ligands **1–2** are appreciably more basic in 0.1M than in 0.01M Me_4NCl, whereas the three highest ones are almost unaffected, is indication of weak chloride binding, as also seen by ^{35}Cl-NMR studies of the chloride resonance [35]. The log K_n values for compound **4** in 0.1M sodium *p*-toluenesulfonate (TsONa) also show the same effect [25]. The pK_a values of the anionic substrates have also been determined under the same conditions for use in the stability-constant computations.

Complexation Features of the Macrocylic and Linear Polyamines **1–6**. The stability constants $\log K_s^n$ corresponding to the equilibria of the polyammonium ions H_nL^{n+} (L = **1–6**) with various dicarboxylate anions A^{m-} (*Eqn.3* and *4*) have been determined by pH-metric titration (see *Exper. Part*); they are listed in *Table 2*. Those for **4** are taken from earlier work [4].

$$L + nH^+ + A^{m-} \rightleftharpoons (H_nLA)^{(n-m)+} \tag{3}$$

$$K_s^n = \frac{[(H_nLA)^{(n-m)+}]}{[H^+]^n[L][A^{m-}]} \tag{4}$$

Table 2. *Stability Constant log* K_s *(±0.2), for Dicarboxylate-Anion Binding by the Polyammonium Receptor Molecules* **1–6** *in Aqueous Solution*[a])

Dicarboxylate anions (m)[b])	n[c])	Macrocyclic and linear polyamines				
		1	**2**	**3**	**4**	**6**[d])
Oxalate[b]) (0)	6	(3.20)	(6.30)		(3.80)	
	5	(2.50)	(4.70)		(3.20)	
	4	(1.90)	(2.85)		(2.60)	
Malonate[b]) (1)	6	(2.75) 3.80	(3.80) 4.05		(3.30)	
	5	(2.05) 2.90	(2.65) 3.05		(2.60)	
	4	(1.35) 1.50	(2.20) 1.95		(2.45)	
Succinate[b]) (2)	6	(3.40) 4.30	(3.0) 3.15		(2.40)	
	5	(2.85) 3.30	(2.35) 2.40	(3.65)	(2.05)	
	4	(2.45) 2.55	(2.20) < 1.2	(1.20)	(1.80)	
Glutarate[b]) (3)	6	(3.40) 4.40	(2.90) 3.30	(6.10)	(2.35)	(1.95)
	5	(2.90) 3.40	(2.45) 2.55	(5.50)	(2.30)	(1.65)
	4[d])	(2.50) 2.80	(2.40) 1.55	(2.95)	(2.20)	
Adipate[b]) (4)	6	(2.30) 3.20	(2.95) 3.20	(4.50)	(2.35)	(2.05)
	5	(1.90) 2.65	(2.50) 2.55	(3.80)	(2.30)	(1.80)
	4[d])	(1.65) 1.75	(2.40) 1.45	(1.54)	(2.20)	
Pimelate (5)	6	(2.25) 3.10	(3.40) 4.40			(2.25)
	5	(1.85) 2.40	(2.85) 3.55	(3.10)		(2.0)
	4	(1.85) 1.60	(2.70) 2.75	(1.10)	(2.00)	
Suberate[b]) (6)	6		(3.45) 4.25			
	5		(3.00) 3.45			
	4		(2.65) 2.65			
Azelate[b]) (7)	6	–	(3.20) 3.60	–	–	–
	5	–	(2.85) 3.15	–	–	–
	4	–	(2.55) 2.50	–	–	–
Sebacate[b]) (8)	6	–	(3.05) 3.50	–	–	–
	5	–	(2.90) 3.15	–	–	–
	4	–	(2.65) 2.40	–	–	–
Maleate[b]) (2)	6	4.30	–	–	(3.70)	–
	5	3.30	–	–	(2.95)	–
	4	2.30	–	–	(2.70)	–
Fumarate[b]) (2)	6	4.10	–	–	(2.20)	–
	5	3.25	–	–	(1.90)	–
	4	2.50	–	–	(1.75)	–
N-Acetyl-L-aspartate[b]) (2)	6	4.10	3.35	–	–	–
	5	3.10	2.60	–	–	–
	4	2.30	< 2	–	–	–
N-Acetyl-L-glutamate[b]) (3)	6	4.15	3.25	–	–	–
	5	3.10	2.60	–	–	–
	4	2.30	< 2	–	–	–
N-Acetyl-L-(1-glutamyl)-glycinate[b]) (6)	6	3.15	4.30	–	–	–
	5	2.40	3.50	–	–	–
	4	< 2	2.40	–	–	–

[a]) The log K_s values are determined in the presence of either 0.01M or 0.1M (values in parentheses) Me_4NCl.
[b]) Chain length in $^-O_2C-(CH_2)_m-CO_2^-$ or number of atoms separating the two terminal carboxylate groups.
[c]) Number of protons involved in complexes of the type (receptor, anion, nH^+).
[d]) For compound **5** with glutarate and adipate, log K_s = (1.60) and (1.80), respectively.

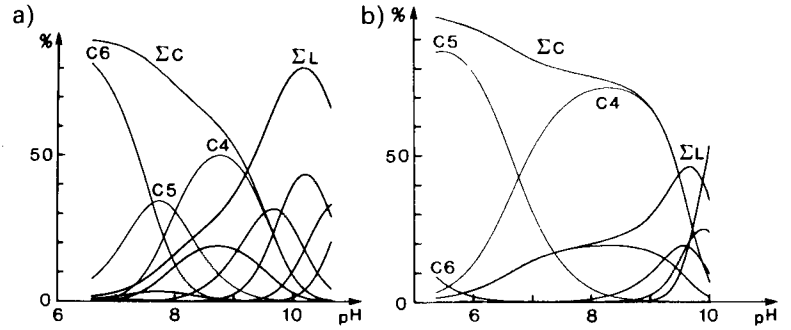


Fig. 2. *Distribution curves for the species present in the medium as a function of pH in two cases;* a) *macrocyclic polyamine* **1**, *and* b) *macrocyclic polyamine* **3** *in presence of glutarate* $^{-}O_2C-(CH_2)_3-CO_2^{-}$. C4, C5, C6: complexes (L, A^{2-}, nH^{+}) with $n = 4,5,6$. Σ C: summation over all complexes. Σ L: summation over all uncomplexed ligand species (except unprotonated and monoprotonated for **3**).

The results lead to the distribution curves of the various species present in solution; two examples are shown in *Fig. 2*. *Fig. 3–5* (see below) give graphical representations of the stability constants in comparative series of complexes in order to provide a clearer visualization of the selectivity sequences observed.

The polyamines **1–6** were used as their hydrochloride salts. The supporting electrolyte was 0.1M or 0.01M Me_4NCl. In the latter case, the ionic strength is only approximately constant over the titration, so the absolute K_s^n values are less reliable than the relative ones. As mentioned above, weak complexation of chloride competes to some extent with the anion studied; consequently the stability constants determined are apparent constants, the real values for a given anion being even higher than those listed in *Table 2*. The $\log K_s^n$ values are appreciably higher in 0.01M than in 0.1M Me_4NCl; this may be due both to the known marked decrease in binding constant when the ionic strength increases and to chloride competition.

The stoichiometry of the complexes was assumed to be 1:1 in the data-analysis procedure. However, the presence of a certain amount of higher-order complexes cannot be excluded. This holds especially for the smaller substrates (oxalate, malonate) for which simultaneous binding of a single molecule to the two binding subunits of the receptor is geometrically unfeasible, unless there is a marked deformation of the macrocycle; the high stability constants calculated for oxalate and malonate, assuming 1:1 stoichiometry, probably result from the presence of 2:1 dianion/hexacation complexes (see *Table 2*).

Discussion. – The synthetic procedures developed here provide a general route to ditopic macrocyclic polyamines containing two chelating subunits separated by structural units of given geometrical features.

The distribution of protonated species, as illustrated in *Fig. 1*, substantiates the choice of 'di(trimethylene)triamine' subunits in order to obtain receptor molecules which are fully protonated around neutral pH, as it is the case for **1** and **2**. Comparison with **4** [4] [25] also shows that increasing the separation of the subunits markedly increases the pK_a's for full protonation, as expected. On the other hand, **3** which contains two 'diethylenetriamine' subunits is only tetraprotonated in the same pH domain. This has important consequences for the nature, stability, and distribution of the complexes formed.

As a result, only **1** and **2** are expected to yield preferentially the most stable complexes, which are those of the hexaprotonated forms. This is clearly seen in *Fig. 2* which compares complexation of glutarate by **1** and by **3**. Thus, the binding properties of **1** and **2** around neutral pH are mainly those of $\mathbf{1}\cdot 6H^+$ and of $\mathbf{2}\cdot 6H^+$ forming the $(L\cdot 6H^+,A^{2-})$ complexes. On the other hand, the analogous complexes of **3** have very low abundance, the species formed being of the type $(\mathbf{3}\cdot 5H^+,A^{2-})$ and $(\mathbf{3}\cdot 4H^+,A^{2-})$.

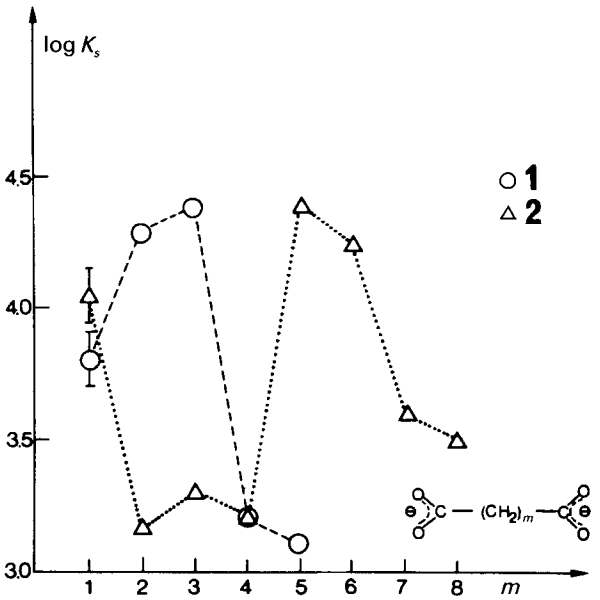


Fig. 3. *Graphical representation of the stability constants log* K_s *of the complexes formed by the polyammonium macrocycles* $\mathbf{1}\cdot 6H^+$ (○) *and* $\mathbf{2}\cdot 6H^+$ (△) *with the dicarboxylates* $^-O_2C-(CH_2)_m-CO_2^-$ *as a function of chain length* m. See also *Table 2* and text.

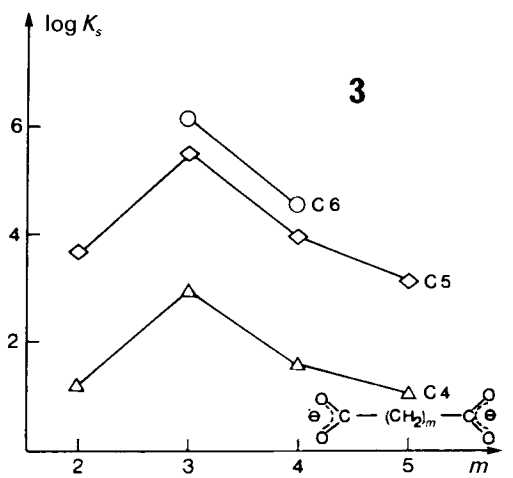


Fig. 4. *Graphical representation of the stability constants log* K_s *of the complexes formed by the polyammonium macrocycle* **3** *with the dicarboxylates* $^-O_2C-(CH_2)_m-CO_2^-$ *as a function of chain length* m. C4, C5 and C6 correspond to the $(\mathbf{3},A^{2-},nH^+)$ species with n = 4,5, and 6. See also *Table 2*.

The polyammonium macrocycles **1–4** are efficient *anion-receptor molecules* forming strong complexes with dicarboxylate anions in aqueous solution *(Table 2)*. The most stable species are those of the hexaprotonated forms $L \cdot 6H^+$ which exert the largest electrostatic interactions. The stability decreases markedly for the ligands of lower protonation state.

The *complexation selectivity* presents a marked structural dependence. Each receptor **1–3** shows a selectivity peak among the homologous $^-O_2C-(CH_2)_m-CO_2^-$ substrates (*Fig. 3* and *4*). Furthermore, the selectivity peak shifts from $m = 2$ and 3 to $m = 5$ and 6 on going from **1** to **2**, which corresponds to the same increase in length (by three CH_2 groups) both for the most strongly bound dicarboxylates and for the $(CH_2)_n$ bridges separating the two binding subunits in **1** ($n = 7$) and in **2** ($n = 10$). The smaller receptor **4** ($n = 3$) binds best the shorter dicarboxylates. There is, thus, a close correspondence between binding-site separation and substrate length. The low selectivity between the two neighbouring substrates $m = 2$ and 3 for **1** and $m = 5$ and 6 for **2** *(Fig. 3)* may result from the opposite effects of stronger electrostatic forces in the shorter substrate ($m = 2$ or 5) and better structural fit of the longer one ($m = 3$ or 6), as well as from unsufficient rigidity of the present receptors. On the other hand, a definite selectivity peak is found for the binding of glutarate by protonated **3** *(Fig. 4)*. This may be due to the higher structural localisation of the ammonium sites when the subunits are of the dien rather of the dpen type; the same factor may explain the strong binding shown by **3** as compared to **1** and **2** in the same protonation state.

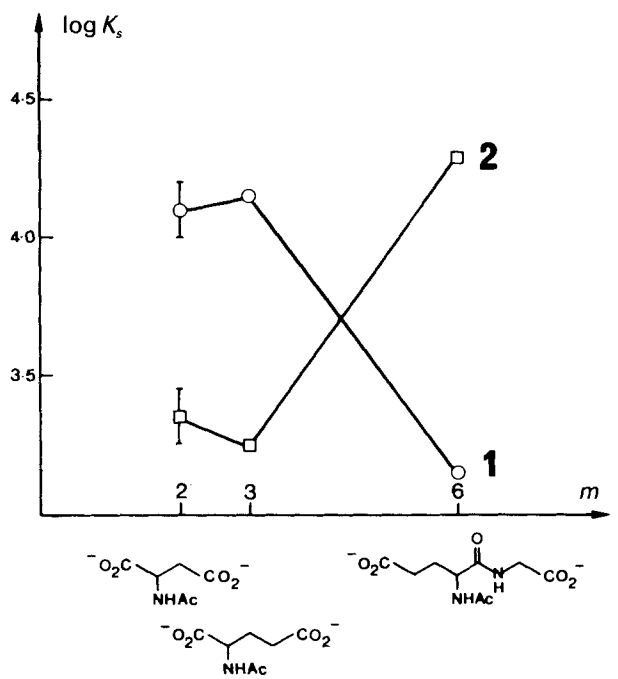


Fig. 5. *Graphical representation of the stability constants log* K_s *of the complexes formed by the polyammonium macrocycles* $1 \cdot 6H^+$ (○) *and* $2 \cdot 6H^+$ (□) *with amino-acid and depeptide dicarboxylates as a function of the number of atoms* m *separating the two* $-CO_2^-$ *groups.* See also *Table 2.*

Selective binding of *biological dicarboxylate substrates* also occurs following the same lines. Thus, **1** binds preferentially *N*-acetyl-L-aspartate and *N*-acetyl-L-glutamate with respect to the dipeptide *N*-acetyl-L-(1-glutamyl)glycinate, whereas the reverse holds for **2**, in line with the chain length of these substrates *(Fig. 5)*.

Comparison of the complexation ability of compounds **2** and **6** demonstrates a pronounced *macrocyclic effect*. The linear hexaamine **6** forms much less stable complexes than its macrocyclic analogue **2** and shows almost no selectivity peak *(Table 2)*.

Both the stability and the selectivity of the complexes formed by the macrocycles **1–3** display the operation of special *structural features*. The high stabilities observed for the optimal coreceptor-dicarboxylate pairs result from the incorporation of two binding subunits in the macrocycle and from double (ditopic) carboxylate-group/triammonium-site binding; this is indicated by the low stabilities found for the single-site interactions of butyrate with $\mathbf{2}\cdot 6H^+$ and of pimelate or butyrate with the subunit reference triammonium cation $^+H_3N-(CH_2)_3-NH_2^+-(CH_2)_3-NH_3^+$ (log $K_s^n < 2.0$).

The peak selectivity observed as a function of chain length reveals a dominant structural factor in dicarboxylate binding. Electrostatic charge-charge interactions which favor binding of anions of high charge density were usually found to dominate both the strength and the selectivity of complexation between highly charged partners [4] [6]. However, an effect of ring-size was observed earlier for ligands of type **4** [4]. The present chain-length selection describes a *linear molecular recognition* process analogous to that found for diammonium substrates [1–3]. It may be attributed to *structural complementarity* between the dianionic substrate and the ditopic coreceptor molecules $\mathbf{1}\cdot n\,H^+$, $\mathbf{2}\cdot n\,H^+$, and $\mathbf{3}\cdot n\,H^+$ in which the two binding subunits cooperate for substrate binding. The terminal anionic groups of the dicarboxylate would each interact with a di- or triammonium unit of the coreceptor, the polymethylene-chain stretching between the polymethylene bridges of the macrocycle, in more or less extended conformations (see also structure **A**). Highest stability of the complex should correspond to the best fit between substrate length and site separation in the coreceptor; substrates that are either too short or too long form less stable complexes. Linkage of the binding subunits by more rigid bridges than polymethylene chains may be expected to increase the complexation selectivity, *i.e.* to improve the recognition of molecular length operated on the dianionic substrates.

Conclusion. – The present results on the binding of terminal dicarboxylate anions, together with those obtained earlier for the binding of diammonium cations of different chain lengths by macrotricyclic receptor molecules, demonstrate that it is possible to design coreceptor molecules for the selective ditopic binding of difunctional molecular substrates [1–3]. Higher stabilities and selectivities may be achievable by incorporating more rigid structural unit and by designing amphiphilic anion receptors of speleand type [1]. Extension to polytopic receptors may follow similar lines and lead to more elaborate molecular recognition *via* polyfunctional binding. Furthermore, subunit cooperation in coreceptor molecules containing suitable structural elements may allow to perform cocatalysis and cotransport processes [1] [36] [37].

Experimental Part

1. *General.* M.p.: uncorrected. pH-Metric measurements: *Metrohm-636* titrimeter; the cell was thermostated at 25° ± 0.1°, the soln. stirred, and all measurements were performed under N_2. The $\log K_n$ values of the compounds were determined by titration with 0.1N NaOH of a soln. containing typically 10^{-3}M of the polyammonium salt in the presence of Me_4NCl (0.1M or 0.01M). The $\log K_s$ values of the complexes were determined by titration with 0.1N NaOH of a soln. containing 10^{-3}M of the HCl salt of the desired polyamine and 5×10^{-3}M of the desired dianions in the presence of Me_4NCl (0.1M or 0.01M). Data analysis for all titration results was performed following the same procedures as previously for the determination of protonation constants [25] and stability constants [13] [38] using the computer program *SCO 76* [39]. ^{1}H-NMR: *Varian-A-60, Varian-EM-360A* or *Bruker-SY-200* spectrometer. ^{13}C-NMR: *Varian-XL-100* or *Bruker-SY-200* spectrometer. Chemical shifts δ are given in ppm with tetramethylsilane as internal standard. MS and microanalyses were performed by the 'Service de Spectrométrie de Masse' and by the 'Service de Microanalyse', resp., Institut de Chimie, Strasbourg.

2. *Protected Diamines* **7** *and* **14**. The diamine, K_2CO_3, and H_2O were heated to 80°. To the vigorously stirred soln., TsCl was added in batches within *ca.* 30 min. Stirring was continued at 80° for 24 h. Then the mixture was allowed to cool to r.t. After filtration, the white solid was washed with H_2O and the desired compound crystallized from hot EtOH.

*1,7-Bis(*p*-tolylsulfonyl)-1,7-heptanediamine* (= *N,N'*-(heptane-1,7-diyl)bis(*p*-toluenesulfonamide); **7**). From 1,7-heptanediamine (10 g, 0.076 mol), K_2CO_3 (52 g), H_2O (1 l), and TsCl (30.74 g, 0.16 mol). Yield 32.66 g (97%), m.p. 144–145°. ^{1}H-NMR ($CDCl_3$): 1.22 (br., 10 H, $CH_2CH_2CH_2$); 2.42 (*s*, 2 CH_3); 2.85 (br., 2 CH_2N); 5.12 (br., 1 NH); 7.28, 7.78 (2*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 143.4, 137.4, 129.8, 127.2 (arom. C); 43.2 (CH_2N); 29.3, 28.4, 26.2 ($CH_2CH_2CH_2$); 21.6 (CH_3). Anal. calc. for $C_{21}H_{30}N_2O_4S_2$ (438.58): C 57.50, H 6.89, N 6.38; found: C 57.64, H 6.98, N 6.39.

*1,10-Bis(*p*-tolylsulfonyl)-1,10-decanediamine* (= *N,N'*-(decane-1,10-diyl)bis(*p*-toluenesulfonamide); **14**). From 1,10-decanediamine (25 g, 0.145 mol), K_2CO_3 (100 g), H_2O (1.5 l), and TsCl (55.32 g, 0.288 mol). Yield 66.2 g (95%), m.p. 127–128°. ^{1}H-NMR ($CDCl_3$): 1.15 (br., 16 H, $CH_2CH_2CH_2$); 2.35 (*s*, 2 CH_3); 2.90 (*m*, 2 CH_2N); 5.10 (br., 2 NH); 7.18, 7.69 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 143.1, 137.0, 129.5, 127.0 (arom. C); 43.0 (CH_2N); 29.2, 28.9, 28.7, 26.2 ($CH_2CH_2CH_2$); 21.3 (CH_3). Anal. calc. for $C_{24}H_{36}N_2O_4S_2$ (480.66): C 59.96, H 7.54, N 5.82; found: C 59.84, H 7.47, N 5.99.

3. *Dinitriles* **8** *and* **15**. To a mixture of compounds **7** or **14**, K_2CO_3, and DMF, a soln. of acrylonitrile in DMF was added dropwise at r.t. Stirring was continued for 15 h. After evaporation to dryness, the residue was taken up in CH_2Cl_2 and washed with H_2O and brine. The org. layer was dried over $MgSO_4$ and evaporated. The pure compounds **8** and **15** were obtained by crystallization from hot EtOH.

*4,12-Bis(*p*-tolylsulfonyl)-4,12-diazapentadecane-1,15-dinitrile* (= *N,N'*-bis(2-cyanoethyl)-*N,N'*-(heptane-1,7-diyl)bis(*p*-toluenesulfonamide); **8**). From **7** (27.19 g, 0.062 mol), K_2CO_3 (60 g), DMF (300 ml), acrylonitrile (10 ml, 0.15 mol), and DMF (20 ml). Yield 21.61 g (64%), m.p. 98–99°. ^{1}H-NMR ($CDCl_3$): 1.30 (br., 10 H, $CH_2CH_2CH_2$); 2.43 (*s*, 2 CH_3); 2.69 (*m*, 2 CH_2CN); 3.20 (*m*, 8 H, CH_2N); 7.30, 7.80 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 144.1, 135.9, 130.1, 127.3 (arom. C); 119.8 (CN); 49.6, 44.5 (CH_2N); 28.5, 26.4 ($CH_2CH_2CH_2$); 21.6 (CH_3); 19.1 (CH_2CN). Anal. calc. for $C_{27}H_{36}N_4O_4S_2$ (544.64): C 59.53, H 6.66, N 10.29; found: C 59.68, H 6.67, N 10.26.

*4,15-Bis(*p*-tolylsulfonyl)-4,15-diazaoctadecane-1,18-dinitrile* (= *N,N'*-bis(2-cyanoethyl)-*N,N'*-(decane-1,10-diyl)bis(*p*-toluenesulfonamide); **15**). From **14** (30 g, 0.062 mol), K_2CO_3 (60 g), DMF (300 ml), acrylonitrile (10 ml, 0.15 mol), and DMF (20 ml). Yield 29.67 g (81%), m.p. 127–128°. ^{1}H-NMR ($CDCl_3$): 1.28 (br., 16 H, $CH_2CH_2CH_2$); 2.45 (*s*, 2 CH_3); 2.75 (*m*, 8 H, CH_2N); 3.28 (*m*, 2 CH_2CN); 7.30, 7.70 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 144.0, 136.0, 130.1, 127.4 (arom. C); 117.7 (CN); 49.3, 44.4 (CH_2N); 29.3, 29.1, 28.7, 26.6 ($CH_2CH_2CH_2$); 21.6 (CH_3); 19.0 (CH_2CN). Anal. calc. for $C_{30}H_{42}N_4O_4S_2$ (586.78): C 61.40, H 7.21, N 9.54; found: C 61.44, H 7.16, N 9.59.

4. *Diamines* **9** *and* **16**. Under Ar, **8** (10 g, 18 mmol) or **15** (10 g, 17 mmol) in 80 ml of THF were cooled and stirred in an ice bath. To this, 1M B_2H_6 in 150 ml of THF was added and the mixture refluxed overnight. Then, it was allowed to cool to r.t., and stirring was continued for another 6 h. The mixture was cooled in an ice bath, and 15 ml of H_2O were added cautiously. The solvant was evaporated; 6N HCl (300 ml) was added and the soln. refluxed overnight. After evaporation, the residue was partitioned between 1N NaOH (400 ml) and CH_2Cl_2 (300 ml). The org. layer was separated and the aq. layer extracted again with CH_2Cl_2 (2 × 100 ml). The combined org. layers were dried over $MgSO_4$ and evaporated to leave **9** (10 g) and **16** (10 g), resp., as a pale yellow oil. These compounds must be stored under N_2 and were converted to **10** or **17** without further purification.

*4,12-Bis(*p*-tolylsulfonyl)-4,12-diazapentadecane-1,15-diamine* (= *N,N'*-bis(3-aminopropyl-*N,N'*-(heptane-1,7-diyl)bis(*p*-toluenesulfonamide); **9**). ^{1}H-NMR ($CDCl_3$): 1.29 (br., 10 H, $CH_2CH_2CH_2$); 1.57 (br., 8 H,

$CH_2CH_2NH_2$); 2.43 (*s*, 2 CH_3); 2.72 (*m*, 2 CH_2NH_2); 3.13 (*m*, 8 H, CH_2NTs); 7.29, 7.80 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 143.3, 137.1, 129.9, 127.3 (arom. C); 48.6, 46.1 (CH_2NTs); 39.3 (CH_2NH_2); 32.5, 28.7, 26.7 ($CH_2CH_2CH_2$); 21.6 (CH_3). Anal. calc. for $C_{27}H_{44}N_4O_4S_2$ (552.77): C 58.66, H 8.02, N 10.29; found: C 57.28, H 8.22, N 9.77.

4,15-Bis(p-*tolylsulfonyl)-4,15-diazaoctadecane-1,18-diamine* (= *N,N'*-bis(3-aminopropyl)-*N,N'*-(decane-1,10-diyl)bis(*p*-toluenesulfonamide); **16**). ^{1}H-NMR ($CDCl_3$): 1.25 (br., 16 H, $CH_2CH_2CH_2$); 1.68 (br., 8 H, $CH_2CH_2NH_2$); 2.40 (*s*, 2 CH_3); 2.72 (*m*, 2 CH_2NH_2); 3.15 (*m*, 8 H, CH_2NTs); 7.30, 7.70 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 143.2, 137.1, 129.8, 127.3 (arom. C); 48.6, 46.0 (CH_2NTs); 39.2 (CH_2NH_2); 32.4, 29.5, 29.3, 28.8, 26.9 ($CH_2CH_2CH_2$); 21.6 (CH_3). Anal. calc. for $C_{30}H_{50}N_4O_4S_2$ (594.85): C 60.57, H 8.47, N 9.42; found: C 58.91, H 8.58, N 9.54.

5. *Tetratoluenesulfonamides* **10** *and* **17**. To a stirred mixture of **9** or **16**, Et_3N, and THF, TsCl was added at r.t. and stirring continued for 12–16 h. After evaporation, the yellow residue was taken up in CH_2Cl_2, washed with 1N HCl or 1N NaOH, H_2O or sat. NaCl soln., and dried over $MgSO_4$. Evaporation gave a colored residue which was purified by chromatography on alumina with CH_2Cl_2/0 to 1% MeOH.

N,N'-*4,12-Tetrakis(* p-*tolylsulfonyl)-4,12-diazapentadecane-1,15-diamine* (= *N,N'*-[4,12-bis(*p*-tolylsulfonyl)-4,12-diazapentadecan-1,15-diyl]bis(*p*-toluenesulfonamide); **10**). From **9** (5 g, 9 mmol), Et_3N (10 ml), THF (100 ml), and TsCl (3.6 g, 18 mmol); CH_2Cl_2 (300 ml), 1N HCl (250 ml), and H_2O (200 ml). Yield 6 g (85%). ^{1}H-NMR ($CDCl_3$): 1.21 (br., 10 H, $CH_2CH_2CH_2$); 1.75 (br., 2 CH_2CH_2NHTs); 2.40 (*s*, 4 CH_3); 3.05 (br., 12 H, CH_2N); 5.60 (br., 2 NH); 7.29, 7.65, 7.80 (*m*, 16 arom. H). ^{13}C-NMR ($CDCl_3$): 143.5, 143.4, 137.2, 136.4, 129.9, 127.3 (arom. C); 48.9, 45.7, 40.2 (CH_2N); 29.1, 28.3, 26.3 ($CH_2CH_2CH_2$); 21.5 (CH_3). Anal. calc. for $C_{42}H_{58}N_4O_8S_4 \cdot 1$ MeOH (907.19): C 56.47, H 6.77, N 6.27; found: C 56.15, H 6.60, N 6.44.

N,N',*4,15-Tetrakis(* p-*tolylsulfonyl)-4,15-diazaoctadecane-1,18-diamine* (= *N,N'*-[4,15-bis(*p*-tolylsulfonyl)-4,15-diazaoctadecan-1,18-diyl]bis(*p*-toluenesulfonamide); **17**). From **16** (10 g, 16.8 mmol), Et_3N (9.3 ml), THF (120 ml), and TsCl (8 g, 40 mmol); CH_2Cl_2 (300 ml), 1N HCl (300 ml), sat. NaCl (300 ml), 1N NaOH (300 ml), and H_2O (200 ml). Yield 12.75 g (84%). ^{1}H-NMR ($CDCl_3$): 1.19 (br., 16 H, $CH_2CH_2CH_2$); 1.65 (*m*, 2 CH_2CH_2NHTs); 2.35 (*s*, 4 CH_3); 3.05 (*m*, 12 H, CH_2N); 5.60 (br., 2 NH); 7.25, 7.65, 7.78 (*m*, 16 arom. H). ^{13}C-NMR ($CDCl_3$): 143.5, 137.3, 136.5, 130.0, 127.3 (arom. C); 49.0, 45.8, 40.5 (CH_2N); 29.2, 26.8 ($CH_2CH_2CH_2$); 21.6 (CH_3). Anal. calc. for $C_{44}H_{62}N_4O_8S_4$ (903.20): C 58.50, H 6.92, N 6.20; found: C 58.54, H 7.03, N 6.38.

6. *Diols* **11** *and* **18**. Compounds **7** or **14**, K_2CO_3, and DMF were stirred and heated to 80°. To this, a soln. of 3-chloro-1-propanol in DMF was added dropwise. Stirring at 80° was continued for 24 to 36 h. After evaporation, the residue was taken up in CH_2Cl_2, washed with H_2O, 1N NaOH, sat. NaCl soln., and dried over $MgSO_4$. Evaporation gave a colored oil which was purified by chromatography on alumina with CH_2Cl_2/2.5 to 4% MeOH.

4,12-Bis(p-*tolylsulfonyl)-4,12-diazapentadecane-1,15-diol* (= *N,N'*-bis(3-hydroxypropyl)-*N,N'*-(heptane-1,7-diyl)bis(*p*-toluenesulfonamide); **11**). From **7** (10 g, 0.023 mol), K_2CO_3 (15.75 g), DMF (150 ml), and 3-chloro-1-propanol (10.77 g, 0.11 mol) in DMF (30 mol); CH_2Cl_2 (400 ml), H_2O (500 ml), 1N NaOH (150 ml), and sat. NaCl soln. (150 ml). Yield 8.6 g (88%). ^{1}H-NMR ($CDCl_3$): 1.25 (br., 10 H, $CH_2CH_2CH_2$); 1.75 (*m*, 2 CH_2CH_2OH); 2.35 (*s*, 2 CH_3); 3.10 (*m*, 10 H, CH_2N, OH); 3.70 (br., 2 CH_2OH); 7.30, 7.80 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 143.5, 136.8, 129.9, 127.2 (arom. C); 59.3 (CH_2OH); 48.9, 45.5 (CH_2N); 31.8, 28.7, 26.6 ($CH_2CH_2CH_2$); 21.6 (CH_3). Anal. calc. for $C_{27}H_{42}N_2O_6S_2$ (554.74): C 58.45, H 7.63, N 5.05; found: C 58.56, H 7.64, N 5.18.

4,15-Bis(p-*tolylsulfonyl)4,15-diazaoctadecane-1,18-diol* (*N,N'*-bis(3-hydroxypropyl)-*N,N'*-(decane-1,10-diyl)bis(*p*-toluenesulfonamide); **18**). From **14** (10 g, 0.02 mol) K_2CO_3 (14.38 g), DMF (130 ml), and 3-chloro-1-propanol (9.84 g, 0.1 mol) in DMF (30 ml); CH_2Cl_2 (400 ml), H_2O (500 ml), and sat. NaCl soln. (100 ml). M.p. 84–86°, yield 9.0 g (73%). ^{1}H-NMR ($CDCl_3$): 1.20 (br., 16 H, $CH_2CH_2CH_2$); 1.75 (*m*, 2 CH_2CH_2OH); 2.35 (*s*, 2 CH_3); 3.32 (*m*, 14 H, CH_2N, CH_2OH, OH); 7.25, 7.69 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 143.4, 136.9, 130.0, 127.3 (arom. C); 59.4 (CH_2OH); 48.9, 45.5 (CH_2N); 31.8, 29.2, 28.8, 26.8 ($CH_2CH_2CH_2$); 21.6 (CH_3). Anal. calc. for $C_{30}H_{48}N_2O_6S_2$ (568.82): C 60.37, H 8.10, N 4.69; found: C 60.25, H 8.19, N 4.70.

7. *Dimesylates* **12** *and* **19**. Compound **11** or **18**, Et_3N, and dry CH_2Cl_2 were stirred and cooled in an ice bath. To this was added MsCl. Stirring was continued for 30–90 min before the soln. was allowed to warm to r.t., and it was stirred for another 3–4 h. The mixture was washed with 1N HCl, 1N NaOH, and dried over $MgSO_4$. Evaporation gave an orange liquid which was used for the next step without further purification.

4,12-Bis(p-*tolylsulfonyl)-4,12-diazapentadecane-1,15-diyl Bis(methanesulfonate)* (**12**). From **11** (4.09 g, 7.3 mmol), Et_3N (5 ml), CH_2Cl_2 (120 ml), and MsCl (1.42 ml, 18.4 mmol); 1N HCl (2 × 50 ml) and 1N NaOH (50 ml). Yield 4.70 g (90%). ^{1}H-NMR ($CDCl_3$): 1.29 (br., 10 H, $CH_2CH_2CH_2$); 2.0 (*m*, 2 CH_2CH_2OMs); 2.41 (*s*, 2 $CH_3C_6H_4$); 3.08 (*s*, 2 CH_3SO_2); 3.15 (*m*, 8 H, CH_2N); 4.30 (*m*, 2 CH_2OMs); 7.30, 7.70 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 143.7, 136.6, 130.1, 127.4 (arom. C); 68.1 (CH_2OMs); 49.2, 45.2 (CH_2N); 37.3 (CH_3SO_2); 29.0, 28.6, 26.6

($CH_2CH_2CH_2$); 21.6 (CH_3). Anal. calc. for $C_{29}H_{46}N_2O_{10}S_4 \cdot \frac{1}{2}\ CH_2Cl_2$ (753.37): C 47.02, H 6.28, N 3.71; found: C 47.34, H 6.60, N 3.85.

4,15-Bis(p-*tolylsulfonyl)-4,15-diazaoctadecane-1,18-diyl Bis(methanesulfonate)* (**19**). From **18** (5.5 g, 92 mmol), Et_3N (5 ml), CH_2Cl_2 (170 ml), and MsCl (1.8 ml, 23.3 mmol); 1N HCl (2 × 50 ml). Yield 6.59 g (95%). ^{1}H-NMR ($CDCl_3$): 1.25 (br., 16 H, $CH_2CH_2CH_2$); 2.0 (*m*, 2 CH_2CH_2OMs); 2.40 (*s*, 2 $CH_3C_6H_4$); 3.03 (*s*, 2 CH_3SO_2); 3.19 (*m*, 8 H, CH_2N); 4.29 (*m*, 2 CH_2OMs); 7.30, 7.70 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 143.6, 136.6, 130.0, 127.3 (arom. C); 67.9 (CH_2OMs); 49.2, 45.0 (CH_2N); 37.3 (CH_3SO_2); 29.4, 29.2, 28.7, 26.8 ($CH_2CH_2CH_2$); 21.6 ($CH_3C_6H_4$). Anal. calc. for $C_{32}H_{52}N_2O_{10}S_4 \cdot \frac{1}{2}\ CH_2Cl_2$ (752.99): C 51.12, H 6.99, N 3.67; found: C 50.29, H 7.33, N 4.02.

8. *Protected Macrocycles* **13** *and* **20**. *1,5,9,17,21,25-Hexakis(* p-*tolylsulfonyl)-1,5,9,17,21,25-hexaazacyclodotriacontane* (**13**). A mixture of **10** (2.71 g, 3.1 mmol), Cs_2CO_3 (5.12 g), and DMF (100 ml) was stirred and heated to 100°. To this, a soln. of **12** (2.23 g, 3.1 mmol) in DMF (30 ml) was added dropwise within 15 min. Stirring at 100° was continued for 24 h. After evaporation, the yellow residue was taken up in CH_2Cl_2 (120 ml), washed with 1N NaOH (100 ml), 1N H_2SO_4 (2 × 100 ml), sat. NaCl soln. (100 ml), and dried over $MgSO_4$. Evaporation gave 6 g of mixture. Pure **13** (1.08 g, 25%) was obtained as a glass after chromatography on alumina (150 g) with CH_2Cl_2/0.5% MeOH, then on silica gel (100 g) with CH_2Cl_2/0 to 4% MeOH, and finally by gel permeation (HPLC, *Prepak, Waters*). ^{1}H-NMR ($CDCl_3$): 1.30 (br., 20 H, $CH_2CH_2CH_2$); 1.90 (br., 8 H, $NCH_2CH_2CH_2N$); 2.40 (*s*, 6 CH_3); 3.10 (br., 24 H, CH_2N); 7.30, 7.70 (*m*, 24 arom. H). ^{13}C-NMR ($CDCl_3$): 143.5, 143.3, 137.3, 136.8, 129.8, 127.3 (arom. C); 49.2, 47.4, 46.7 (CH_2N); 29.3, 29.0, 26.6 ($CH_2CH_2CH_2$); 21.5 (CH_3). MS: 1378 (M^+), 1223 (M^+ – Ts), 1068 (M^+ – 2Ts), 913 (M^+ – 3Ts), 758 (M^+ – 4Ts), 603 (M^+ – 5Ts). Anal. calc. for $C_{68}H_{94}N_6O_{12}S_6$ (1379.83): C 59.18, H 6.86, N 6.09; found: C 59.08, H 6.99, N 6.02.

1,5,9,20,24,28-Hexakis(p-*tolylsulfonyl)-1,5,9,20,24,28-hexaazacyclooctatriacontane* (**20**). A mixture of **17** (8.14 g, 9 mmol), Cs_2CO_3 (17.59 g), and DMF (120 ml) was stirred and heated to 90°. To this, a soln. of **19** (6.50 g, 9 mmol) in DMF (30 ml) was added dropwise within 10 min. Stirring at 90° was continued for 48 h. After evaporation, the colored residue was taken up in CH_2Cl_2 (250 ml), washing with 1N NaOH (200 ml) produced an emulsion which was broken by addition of sat. NaCl soln. (100 ml). The org. layer was dried over $MgSO_4$. Evaporation gave 12.96 g of a mixture. Pure **20** (2.39 g, 25%) was obtained as a glass after chromatography on alumina (500 g) with CH_2Cl_2/0.5% MeOH, then on silica gel (200 g) with CH_2Cl_2/2% MeOH, and finally by gel permeation (HPLC, *Prepak, Waters*). ^{1}H-NMR ($CDCl_3$): 1.27 (br., 32 H, $CH_2CH_2CH_2$); 1.85 (br., 8 H, $NCH_2CH_2CH_2N$); 2.42 (*s*, 6 CH_3); 3.13 (br., 24 H, CH_2N); 7.30, 7.70 (*m*, 24 arom. H). ^{13}C-NMR ($CDCl_3$): 143.4, 136.6, 129.9, 127.3 (arom. C); 49.1, 47.4, 46.5 (CH_2N); 29.5, 29.3, 26.8 ($CH_2CH_2CH_2$); 21.6 (CH_3). MS: 1462 (M^+), 1307 (M^+ – Ts), 1152 (M^+ – 2Ts), 997 (M^+ – 3Ts). Anal. calc. for $C_{74}H_{10}N_6O_{12}S_6$ (1463.99): C 60.70, H 7.29, N 5.74; found: C 60.58, H 7.32, N 5.84.

9. *Deprotection of Macrocycles* **13** *and* **20**. Compound **13** or **20**, phenol, and a 33% soln. of HBr in AcOH (60 ml) were refluxed for 16–18 h under a well ventilated hood. Evaporation gave **1**·6 HBr or **2**·6 HBr which was suspended in Et_2O (50 ml), filtered, and washed with Et_2O (150 ml). The crude hexahydrobromides were dissolved in H_2O (15–25 ml) and passed over *Dowex 1 × 8* (basic form). Amine **2** is insoluble in H_2O; it was, therefore, eluted with H_2O/EtOH 1:1. The soln. containing **1** and **2** were acidified to pH 2 with conc. HCl and the solvent removed by evaporation. The residue was precipitated from aq. EtOH giving **1**·6 HCl or **2**·6 HCl.

1,5,9,17,21,25-Hexaazacyclodotriacontane (**1**). From **13** (1.11 g, 0.8 mmol) and phenol (2.5 g). Yield 0.48 g (92%), m.p. > 260°. ^{1}H-NMR (D_2O): 1.29 (br., 12 H, $CH_2CH_2CH_2$); 1.59 (br., 8 H, CH_2CH_2N); 2.02 (br., 8 H, $NCH_2CH_2CH_2N$); 3.06 (*m*, 24 H, CH_2N). ^{13}C-NMR (D_2O): 48.8, 45.9, 45.5 (CH_2N); 28.4, 26.3, 26.2, 23.6 ($CH_2CH_2CH_2$). Anal. calc. for $C_{24}H_{64}Cl_6N_6$ (673.51): C 45.15, H 9.62, N 12.15; found: C 45.07, H 9.58, N 12.22.

1,5,9,20,24,28-Hexaazacyclooctatriacontane (**2**). From **20** (1.30 g, 0.88 mmol) and phenol (2.5 g). Yield 0.62 g (93%), m.p. > 260°. ^{1}H-NMR (D_2O): 1.38 (br., 24 H, $CH_2CH_2CH_2$); 1.74 (br., 8 H, CH_2CH_2N); 2.17 (br., 8 H, $NCH_2CH_2CH_2N$); 3.22 (br., 24 H, CH_2N). ^{13}C-NMR (D_2O): 49.1, 46.0, 45.6 (CH_2N); 29.2, 29.0, 26.7, 26.6, 23.9 ($CH_2CH_2CH_2$). Anal. calc. for $C_{32}H_{76}Cl_6N_6$ (757.67): C 50.72, H 10.11, N 11.09; found: C 50.56, H 10.22, N 11.02.

10. *4,15-Diazaoctadecane-1,18-diamine* (**5**). Under a well ventilated hood, **17** (2.40 g, 2.65 mmol), phenol (2.3 g), and a 33% soln. of HBr in AcOH (150 ml) were refluxed for 16 h. The soln. was allowed to cool and the solid decanted, filtered, washed with Et_2O (2 × 50 ml), dissolved in H_2O (30 ml), and passed over *Dowex 1 × 8* (basic form). The soln. containing **5** was acidified with conc. HCl to pH 2 and the solvent evaporated. The residue was precipitated from aq. EtOH giving **5**·4 HCl (1.1 g, 95%), m.p. > 260°. ^{1}H-NMR (D_2O): 1.41 (br., 12 H, $CH_2CH_2CH_2$); 1.77 (br., 2 $CH_2CH_2NH_2^+$–); 2.12 (br., 2 $NCH_2CH_2CH_2N$); 3.28 (br., 12 H, CH_2N). ^{13}C-NMR (D_2O): 49.4, 45.9 ($CH_2NH_2^+$–); 38.15 ($CH_2NH_3^+$); 29.9, 29.7, 27.2, 27.0, 25.2 ($CH_2CH_2CH_2$). Anal. calc. for $C_{16}H_{42}Cl_4N_4 \cdot 2\ H_2O$ (466.34): C 41.20, H 9.51, N 12.01; found: C 41.28, H 9,47, N 12.16.

11. *Decane-1,10-diyl Bis(methanesulfonate)* (**21**). At r.t., 1,10-decanediol (11.7 g, 0.067 mol), Et_3N (47 ml), dry CH_2Cl_2 (200 ml), and dry THF (50 ml) were stirred. To this, MsCl (16 ml) in dry CH_2Cl_2 (130 ml) was added dropwise within 1 h. Stirring at r.t. was continued for 15 h. After filtration, the soln. was washed with 10% HCl (150 ml), sat. $NaHCO_3$ soln. (200 ml), and H_2O (200 ml), dried over $MgSO_4$, and evaporated. Pure **21** (20.62 g, 93%) was obtained by crystallization from CH_2Cl_2/hexane, m.p. 74–76°. ^{1}H-NMR ($CDCl_3$): 1.40 (br., 12 H, $CH_2CH_2CH_2$); 1.72 (br., 2 CH_2CH_2OMs); 3.10 (*s*, 2 CH_3); 4.25 (*m*, 2 CH_2OMs). ^{13}C-NMR ($CDCl_3$): 69.8 (CH_2OMs); 37.6 (CH_3); 29.4 (CH_2CH_2OMs); 29.3, 29.1, 25.6 ($CH_2CH_2CH_2$). Anal. calc. for $C_{12}H_{26}O_6S_2$ (330.45): C 43.61, H 7.93; found: C 43.67, H 7.93.

12. N,N′,*4,8,19,23-Hexakis*(p-*tolylsulfonyl*)-*4,8,19,23-tetraazahexaicosane-1,26-diamine* (= *N,N′*-[4,8,19,23-tetrakis(*p*-tolylsulfonyl)-4,8,19,23-tetraazahexaicosan-1,26-diyl]bis(*p*-toluenesulfonamide); **22**). Na (1.74 g) and dry MeOH (100 ml) were stirred at r.t. under Ar until dissolution. To this, 17.96 g of *N,N′*,4-tris(*p*-tolylsulfonyl)-4-azaheptanediamine (17.96 g) prepared as described in [25] was added and the mixture refluxed for 1 h. After evaporation, the disodium salt was dissolved in DMF (100 ml), stirred, and heated to 90°. To this, a soln. of compound **21** (2 g) in DMF (100 ml) was added within 14 h. Stirring at 90° was continued for 10 h. After filtration, the solvent was removed, and the yellow residue was taken up in CH_2Cl_2 (100 ml), washed with 1N NaOH (100 ml), H_2O (100 ml), and sat. NaCl soln. (100 ml), and dried over $MgSO_4$. Pure **22** (0.53 g, 6%) was obtained after chromatography on alumina with CH_2Cl_2. ^{1}H-NMR ($CDCl_3$): 1.25 (br., 12 H, $CH_2CH_2CH_2$); 1.75 (br., 12 H, CH_2CH_2N); 2.40 (*s*, 6 CH_3); 3.10 (br., 20 H, CH_2N); 5.30 (br., 2 NH); 7.25, 7.68, 7.80 (*m*, 24 arom. H). ^{13}C-NMR ($CDCl_3$): 143.3, 143.2, 129.8, 127.1 (arom. C); 49.0, 47.3, 46.4, 46.2, 40.0 (CH_2N); 29.3, 29.2, 29.1, 28.8, 28.6, 26.7 ($CH_2CH_2CH_2$); 21.5 (CH_3). Anal. calc. for $C_{64}H_{88}N_6O_{12}S_6$ (1325.74): C 57.97, H 6.69, N 6.34; found: C 56.63, H 7.25, N 6.05.

13. *4,8,19,23-Tetraazahexaicosane-1,26-diamine* (**6**). Under a well ventilated hood, **22** (0.52 g), phenol (1.50 g), and a 33% soln. of HBr in AcOH (100 ml) were refluxed for 16 h. The soln. was allowed to cool to r.t. and the solid decanted, filtered, washed with Et_2O (2 × 50 ml), dissolved in H_2O (20 ml), and passed over *Dowex 1* × *8* (basic form). The soln. containing **6** was acidified to pH 2 with conc. HCl and the solvent evaporated. The residue was precipitated from aq. EtOH giving **6**·6 HCl (0.22 g, 93%), m.p. > 260°. ^{1}H-NMR (D_2O): 1.37 (br., 12 H, $CH_2CH_2CH_2$); 1.74 (br., 2 $CH_2CH_2NH_3^+$); 2.06 (br., 8 H, $CH_2CH_2NH_3^+$–); 3.09 (*m*, 20 H, CH_2N). ^{13}C-NMR (D_2O): 49.5, 46.3, 45.8 (CH_2N); 30.0, 29.8, 27.3, 27.1, 25.3, 24.2 ($CH_2CH_2CH_2$). Anal. calc. for $C_{22}H_{58}Cl_6N_6 \cdot 2$ EtOH (711.56): C 43.88, H 9.91; found: C 44.24, H 9.90.

14. N,N′,*3-Tris*(p-*tolylsulfonyl*)-*3-azapentanediamine* (= *N,N′*-[3-(*p*-tolylsulfonyl)-3-azapentane-1,5-diyl]-bis(*p*-toluenesulfonamide); **23**) was prepared by following the procedure described in [33].

15. *Bissodium Salt* **24** *of* **23**. Na (1.42 g) and dry MeOH (200 ml) were stirred at r.t. under Ar until dissolution. To this, **23** (16.43 g, 0.029 mol) was added and the mixture refluxed for 4 h. After evaporation, the white solid (17.53 g) was dried under vacuum for 12 h.

16. *9-[(2*H*-Tetrahydropyran-2-yl)oxy]nonan-1-ol* (**25**). Nonane-1,9-diol (60 g, 0.37 mol), conc. HCl (10 drops), and THF (20 ml) were stirred at r.t. To this, a soln. of 2 *H*-dihydropyran (10.5 g, 0.12 mol) in THF (60 ml) was added dropwise and stirring continued for 7 h. After evaporation, the residue was taken up in toluene (300 ml) and heated to 60° until homogeneous. The unreacted diol crystallized from soln. upon cooling to 4°. The solid was filtered, washed with toluene, and the combined filtrates were washed with H_2O (200 ml), dried over $MgSO_4$, and evaporated. Pure **25** (34 g) was obtained as an oil, after chromatography on silica gel with AcOEt/hexane 4:6. ^{1}H-NMR ($CDCl_3$): 1.50 (br., 20 H, $CH_2CH_2CH_2$); 3.60 (*m*, 7 H, CH_2OH, OH); 4.60 (br., OCHO). ^{13}C-NMR ($CDCl_3$): 98.7 (OCHO); 67.5, 62.4, 62.1 (CH_2O); 32.6, 30.6 (CH_2CH_2O); 29.3, 26.1, 25.4, 19.5 ($CH_2CH_2CH_2$). Anal. calc. for $C_{14}H_{28}O_3$ (224.36): C 68.80, H 11.54; found: C 68.12, H 10.97.

17. *9-[(2*H*-Tetrahydropyran-2-yl)oxy]nonyl Methanesulfonate* (**26**). A mixture of **25** (5.86 g, 0.024 mol), Et_3N (5 ml), and dry CH_2Cl_2 (60 ml) was stirred and cooled to −18°. To this, a soln. of MsCl (2.04 ml) in dry CH_2Cl_2 (20 ml) was added dropwise within 20 min. The mixture was allowed to warm to r.t. and stirring continued for 2 h. The soln. was washed with ice-water (50 ml), cold 1N HCl (50 ml), sat. $NaHCO_3$ soln. (50 ml), sat. NaCl soln. (50 ml), and dried over $MgSO_4$. Evaporation left **26** (98%) as an oil which was used without further purification for the following step. ^{1}H-NMR ($CDCl_3$): 1.50 (br., 20 H, $CH_2CH_2CH_2$); 3.05 (*s*, CH_3); 3.60 (*m*, 2 CH_2O); 4.25 (*t*, CH_2OMs). ^{13}C-NMR ($CDCl_3$): 98.7 (OCHO); 70.1, 67.4, 62.1 (CH_2O); 37.1 (CH_3); 30.7, 29.6, 29.2, 28.9, 26.1, 25.4, 25.2, 19.5 ($CH_2CH_2CH_2$).

18. *10,13,16-Tris*(p-*tolylsulfonyl*)-*1,25-bis[(2*H*-tetrahydropyran-2-yl)oxy]-10,13,16-triazapentaicosane* (**27**). Under Ar, **24** (17.53 g, 28.7 mmol) and dry DMF (300 ml) were stirred and heated to 95°. To this, a soln. of **26**

(18.35 g, 56.9 mmol) in dry DMF (150 ml) was added dropwise within 20 min. Stirring was continued at 95° for 6 h. After evaporation, the residue was taken up in CH_2Cl_2 (300 ml), washed with H_2O (300 ml), and dried over $MgSO_4$. Evaporation gave 25 g of a yellow liquid which was purified by chromatography on alumina (400 g) with CH_2Cl_2/0.5–1% MeOH: 22 g (72%) of **27**. ^{1}H-NMR ($CDCl_3$): 1.50 (br., 40 H, $CH_2CH_2CH_2$); 2.45 (*s*, 3 CH_3); 3.30 (*m*, 20 H, CH_2O, CH_2N); 4.55 (br., 2 OCHO); 7.30, 7.80 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.5, 136.0, 130.1, 129.9, 127.5 (arom. C); 67.8 (OCHO); 62.5 (CH_2O); 50.2, 49.9, 48.1 (CH_2N); 31.0, 29.9, 29.7, 29.6, 29.4, 28.8, 26.8, 26.4, 25.7 ($CH_2CH_2CH_2$); 21.5 (CH_3); 19.9 ($CH_2CH_2CH_2$). Anal. calc. for $C_{53}H_{83}N_3O_{10}S_3$ (1018.39): C 62.50, H 8.21, N 4.12; found: C 62.44, H 8.45, N 4.43.

19. *10,13,16-Tris(* p-*tolylsulfonyl)-10,13,16-triazapentaicosane-1,25-diol* (**28**). For 8 h, **27** (20.64 g, 20.2 mmol) and TsOH (3.85 g) were refluxed in H_2O/EtOH 5:95 (250 ml). The mixture was allowed to cool to r.t. and stirring continued for another 12 h. After evaporation, the residue was taken up in CH_2Cl_2 (300 ml) and washed with H_2O (200 ml). The aq. layer was further extracted with CH_2Cl_2 (2 × 100 ml). The org. layers were combined, dried over $MgSO_4$, and evaporated: 18 g of a mixture. Pure **28** (12 g, 70%) was obtained after chromatography on alumina (500 g) with CH_2Cl_2/3–5% MeOH and recrystallized from CH_2Cl_2/EtOH, m.p. 74–77°. ^{1}H-NMR ($CDCl_3$): 1.30 (br., 28 H, $CH_2CH_2CH_2$); 2.55 (*s*, 11 H, CH_3, OH); 3.45 (*m*, 16 H, CH_2N, CH_2OH); 7.30, 7.80 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.5, 136.0, 130.0, 129.9, 127.3 (arom. C); 63.2 (CH_2OH); 50.2, 49.9, 48.2 (CH_2N); 32.9, 29.5, 29.4, 29.2, 28.8, 26.7, 25.8 ($CH_2CH_2CH_2$); 21.6 (CH_3). Anal. calc. for $C_{43}H_{67}N_3O_6S_3$ (850.16): C 60.74, H 7.94, N 4.94; found: C 60.45, H 8.00, N 4.98.

20. *10,13,16-Tris(* p-*tolylsulfonyl)-10,13,16-triazapentaicosane-1,25-diyl Bis(methanesulfonate)* (**29**). At −18°, **28** (10.88 g, 12.8 mmol) and Et_3N (9 ml) were stirred in dry CH_2Cl_2 (150 ml). To this, a soln. of MsCl (2.2 ml) in dry CH_2Cl_2 (50 ml) was added dropwise. The mixture was allowed to warm to r.t., and stirring was continued for 18 h. The colored soln. was washed with ice-water (100 ml), cold 1N HCl (100 ml), sat. $NaHCO_3$ soln. (100 ml), and sat. NaCl soln. (100 ml), and dried over $MgSO_4$. Evaporation gave **29** (12.6 g) as an oil which was used without further purification for the following step. ^{1}H-NMR ($CDCl_3$): 1.30 (br., 28 H, $CH_2CH_2CH_2$); 2.45 (*s*, 3 $CH_3C_6H_4$); 3.2 (*m*, *s*, 18 H, CH_2N, CH_3SO_2); 4.22 (*t*, 2 CH_2OMs); 7.30, 7.80 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.6, 136.0, 130.1, 130.0, 127.5 (arom. C); 70.3 (CH_2OMs); 50.2, 50.0, 48.2 (CH_2N); 37.6 (CH_3SO_2); 29.4, 29.3, 29.2, 29.0, 28.7, 26.7, 25.5 ($CH_2CH_2CH_2$); 21.7 ($CH_3C_6H_4$). Anal. calc. for $C_{45}H_{71}N_3O_{12}S_5$ (1006.34): C 53.70, H 7.11, N 4.17; found: C 53.79, H 7.19, N 4.03.

21. *1,4,7,17,20,23-Hexakis(* p-*tolylsulfonyl)-1,4,7,17,20,23-hexaazacyclodotriacontane* (**30**). A mixture of **29** (7.02 g, 12.4 mmol), Cs_2CO_3 (24.24 g), and DMF (600 ml) was stirred and heated to 90°. To this, a soln. of **23** (12.50 g, 12.4 mmol) in DMF (250 ml) was added dropwise within 1 h. Stirring at 90° was continued for 71 h. The mixture was allowed to cool to r.t. and the solid removed by filtration. After evaporation, the residue was taken up in $CHCl_3$ (400 ml), washed with 1N NaOH (200 ml), sat. NaCl soln. (200 ml), and dried over $MgSO_4$. Evaporation gave 20 g of mixture which was purified by chromatography on alumina (300 g) with $CHCl_3$. Pure **30** (8.18 g, 47%) was obtained by recrystallization from CH_2Cl_2/EtOH, m.p. 150–152°. ^{1}H-NMR ($CDCl_3$): 1.3 (br., 28 H, $CH_2CH_2CH_2$); 2.45 (*s*, 6 CH_3); 3.2 (br., 24 H, CH_2N); 7.30, 7.80 (*m*, 24 arom. H). ^{13}C-NMR ($CDCl_3$): 143.5, 136.2, 135.7, 130.1, 127.6 (arom. C); 50.4, 50.2, 48.5 (CH_2N); 29.1, 28.8, 26.6 ($CH_2CH_2CH_2$); 21.7 (CH_3). MS: 1379 (M^+), 1223 ($M^+ - Ts$), 1068 ($M^+ - 2Ts$), 913 ($M^+ - 3Ts$), 758 ($M^+ - 4Ts$). Anal. calc. for $C_{68}H_{94}N_6O_{12}S_6$ (1379.83): C 58.96, H 7.07, N 5.89; found: C 58.63, H 6.77, N 5.96.

22. *1,4,7,17,20,23-Hexaazacyclodotriacontane* (**3**). A mixture of **30** (3.43 g, 2.48 mmol), phenol (3.2 g), and a 33% soln. of HBr in AcOH (200 ml) was refluxed for 46 h. The mixture was allowed to cool to r.t. and the solid decanted, filtered, washed with Et_2O (3 × 100 ml), and dissolved in H_2O and passed over *Dowex 1* × *8* (basic form). Since **3** is insoluble in H_2O, the resin was eluted with H_2O/MeOH 3:1. The soln. containing **3** was acidified with conc. HCl to pH 3, and after evaporation, **3**·6 HCl (1.50 g, 90%) was recrystallized from H_2O/MeOH/EtOH, m.p. > 260°. ^{1}H-NMR (D_2O): 1.40 (br., 20 H, $CH_2CH_2CH_2$); 3.20 (*m*, 8 H, CH_2CH_2N); 3.55 (br., 24 H, CH_2N). ^{13}C-NMR (D_2O): 49.6, 45.0, 44.3 (CH_2N); 29.0, 26.5 ($CH_2CH_2CH_2$). Anal. calc. for $C_{26}H_{64}Cl_6N_6$ (673.53): C 46.25, H 9.57, N 12.47; found: C 46.24, H 9.57, N 12.36.

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