123. Synthesis and Protonation Features of 24-, 27- and 32-membered Macrocyclic Polyamines

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Summary

Three macrocyclic polyamines [24]ane-N_6 **1**, [32]ane-N_8 **2** and [27]ane-N_6O_3 **3** of ring size 24, 32 and 27, respectively, have been synthesized. They contain either trimethylenediamine of ethylenediamine units. The acyclic analog **4**, as the reference compound, was also prepared. Compounds **1–3** are macrocyclic analogs of natural polyamines and are potential ligands for metal cations as well as, when protonated, for anions. The protonation constants of compounds **1–4** have been determined. They are high enough for compounds **1–4** to be fully protonated in a pH-range close to neutrality, as required for binding of anions of weak acids. The effect of structural features on the protonation constants are briefly discussed in relation to the design of macrocyclic polyamine ligands.

Introduction. – Polyaza macrocycles have been the first macrocyclic ligands extensively studied, apart from the polypyrrole-type macrocycles. Numerous reports describe their binding properties towards many metal cations; most of the earlier work concerns the tetraaza 14-membered ring system (for reviews see [1–5]).

In recent years, it was found that various acyclic, macrocyclic and macropolycyclic polyammonium or polyguanidinium species can form stable and selective complexes with various inorganic and organic anions [6–16]. Thus, the development of an *anion coordination chemistry*, the design of anion receptor and carrier molecules [7] [17], could be envisaged and pursued.

The investigation of new polyaza-macrocycles has therefore become doubly interesting, for their complexation properties towards metal cations on one hand, and for their anion-binding features in their protonated states on the other hand.

We are pursuing such studies on macrocyclic as well as macropolycyclic polyamines and we describe here the synthesis of three macrocycles, [24]ane-N_6 **1**, [32]ane-N_8 **2**, [27]ane-N_6O_3 **3**, and of the acyclic analog **4**. Large rings containing several trimethylenediamine units have been obtained by the 'Zip' reaction [20]. Their protonation features have been studied and compared to those of the macro-

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cycles [24]-N_6O_2 **5** [18] and [18]-N_6 **6** [19]. The anion-binding properties of the protonated forms of compounds **1**, **2** and **3** have been reported earlier [11].

Design of the polyaza-macrocycles. – In order to efficiently bind either cations or anions, the macrocyclic polyamines should fulfill certain structural requirements. Metal cations are best bound by ethylenediamine and trimethylenediamine units.

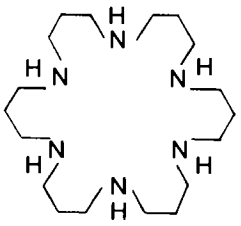
Because of the dominant role played in most cases by electrostatic charge-charge interactions, strongest binding of anions occurs usually with the fully protonated form of the polyamine. On the other hand, most organic anions (especially carboxylates of biological relevance) correspond to weak acids and thus are protonated below a pH of about 4. Thus, the structure of the macrocycles should be chosen so as to realize a compromise between the pH-values required for full protonation of the ligand and the need to remain in a pH-range where the anion to be bound may exist. Highest charge density in the ligand is achieved by accumulation of ammonium sites, but this will also lower the pH for full protonation. Thus, the structural elements of the macrocycles must allow accumulation of positive charge while keeping the corresponding pH above a given value.

Thus, the lowest pK_a of ethylenediamine is 7.28 [21], whereas it is 8.88 [21] for trimethylenediamine. The difference in pK_a-values for full protonation is even larger for 'diethylenetriamine' (= 3-azapentane-1,5-diamine) (4.25) [22a] and for 'di-1,3-propanetriamine' (= 4-azaheptane-1,7-diamine) (7.72) [22b].

For the naturally occurring acyclic polyamines, putrescine, cadaverine, spermidine and spermine, the pK_a-values of full protonation are rather high, because the charges are separated by three or more C-atoms: $\log K_2 = 9.63$ for putrescine $H_2N(CH_2)_4NH_2$ [21], $\log K_3 = 8.34$ for spermidine $H_2N(CH_2)_3NH(CH_2)_4NH_2$ [23a] and $\log K_4 = 7.96$ for spermine $H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$ [23b] (see *Equations 1* and *2* for definition of K_n). These polyammonium ions display moderate binding of biologically important anions [24]. Cyclic polyamines based only on ethylenediamine units are fully protonated only at low pH, generally below 2 as in [12]-N_4 [25] and in [15]-N_5 [26] macrocycles. In fact, such compounds have been found to bind anions in partially protonated LH_3^{3+}- [14] [16] or LH_4^{4+}- [15] forms.

These considerations on potential binding ability towards both metal cations and anions led to the choice of the macrocycles **1**–**3** as first synthetic targets. Compounds **1** and **2** are based on the trimethylenediamine group for reasons given above. The design of macrocycle **3** takes into account the higher charge density of ethylenediammonium group but tries to avoid low pK_a-values for full protonation by spreading the three N–C–C–N units around the macrocycles and separating them by five atoms. The presence of an O-atom in position 3 with respect to an N-atom may be expected to lower the pK_a-values compared to a CH_2-group, as found for instance in $HOCH_2CH_2NH_2$ (9.74) and $CH_3OCH_2CH_2NH_2$ (9.45) with respect to $CH_3CH_2CH_2NH_2$ (10.92) [27]. On the other hand the $CH_2CH_2OCH_2CH_2$-rearrangement is conformationally more adaptable for encircling a bound anion, and furthermore may gain some structure-holding ability from electrostatic $N-H^+ \ldots O$ interactions.

The polyamine **4** may be considered as an open-chain reference compound for comparison with the corresponding macrocycle **1**.



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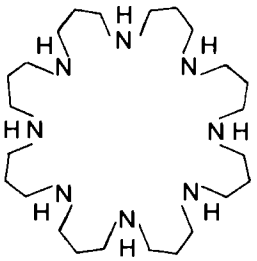

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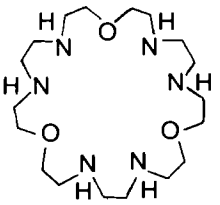

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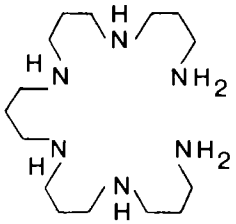

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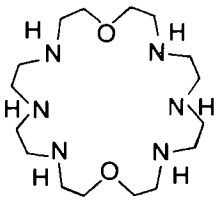

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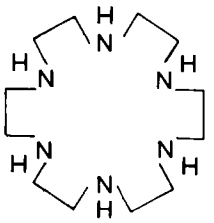


6

As far as the pH for full protonation is concerned, linear polyamines should have higher $\log K_n$ values than the cyclic analogs where the concentration of positive charges is higher; this effect is indeed observed in macrocycles containing spermine- or spermidine-type units [28] but should decrease as the ring becomes larger (see below).

Synthesis of the macrocycles *1–3*. – For the macrocyclic polyamines **1–3**, the key step, the cyclization, was achieved by the condensation of the disodium salt of an α,ω-ditosylamide with an α,ω-ditosylate (or dimesylate or dibromide) in dimethylformamide (DMF) following the methods described for the synthesis of a diaza-cyclodecadiene [29] and of polyheteromacrocycles [30].

Macrocycle [24]ane-N_6 **1** *(Scheme 1).* The tritosyl derivative **7** of 4-azaheptane-1,7-diamine, which was easily obtained in high yield, was the common starting material for the two linear parts used in the cyclization step. Treatment of **7** with 3-chloro-1-propanol in DMF in presence of excess solid K_2CO_3 gave the diol **8** which was converted into the di(mesyloxy) derivative **9**. The latter was condensed with the second cyclization partner, the disodium salt **10** of **7**, at 110° in DMF, yielding the hexatosyl macrocycle **11** in 50% yield.

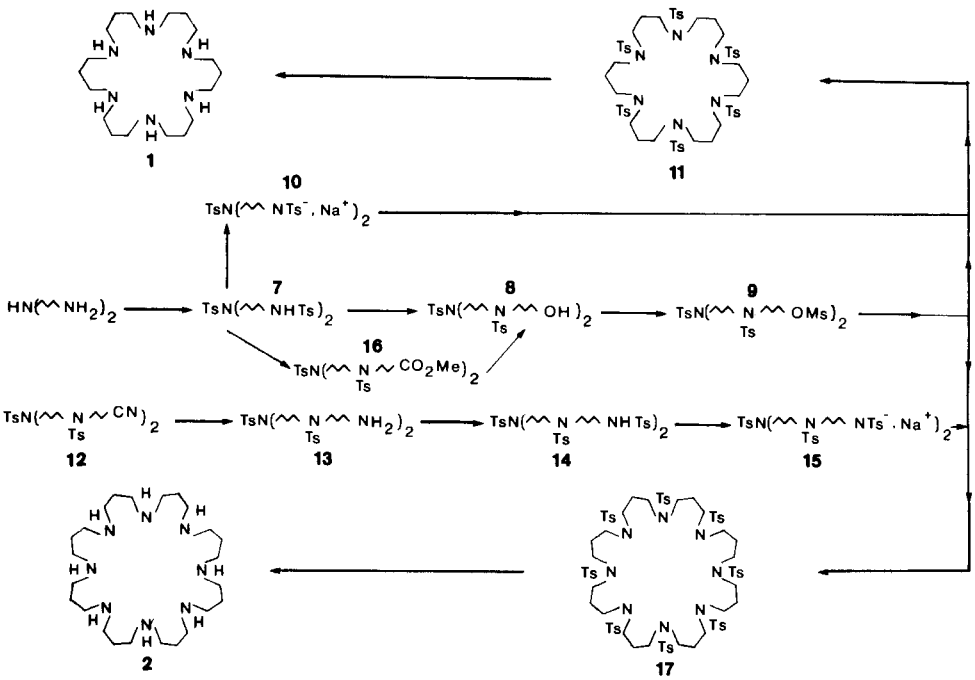
The tosyl groups of **11** were removed by treatment with 30% HBr in AcOH in presence of a large excess of phenol [29] [31] [32] giving **1** · 6 HBr in 92% yield.

This method gave higher yields than the treatment with conc. H_2SO_4 at 100° for an extended period of time [25a] [30].

The free macrocyclic hexaamine **1** was obtained by passing **1** · 6 HBr over a *Dowex 1×8* resin in its basic form. It should be stored under N_2 or kept as its hexaammonium salt; the same holds for the macrocycles **2** and **3**.

Macrocycle [32]ane-N_8 **2** *(Scheme 1).* Reaction of compound **7** with acrylonitrile in DMF in the presence of K_2CO_3, gave the dinitrile **12**. Reduction of **12** with B_2H_6 [33] led to the diamine **13**, which was converted into the pentatosyl derivative **14**. The di(mesyloxy) derivative **9** may be obtained either as described above or *via* the dimethyl ester **16** prepared either by *Michael* addition of methylacrylate to **7** or by methanolysis of the dinitrile **12**. Cyclization of the disodium salt **15** with **9** by the same method as used for macrocycle **1**, gave the octatosyl macrocycle **17** in 35% yield. Detosylation of **17** with HBr/AcOH/phenol as described above gave **2** · 6 HBr (80% yield), which may be converted into another salt by anion exchange column or into the parent macrocyclic octaamine **2** by passing over a *Dowex 1×8* resin in its basic form.

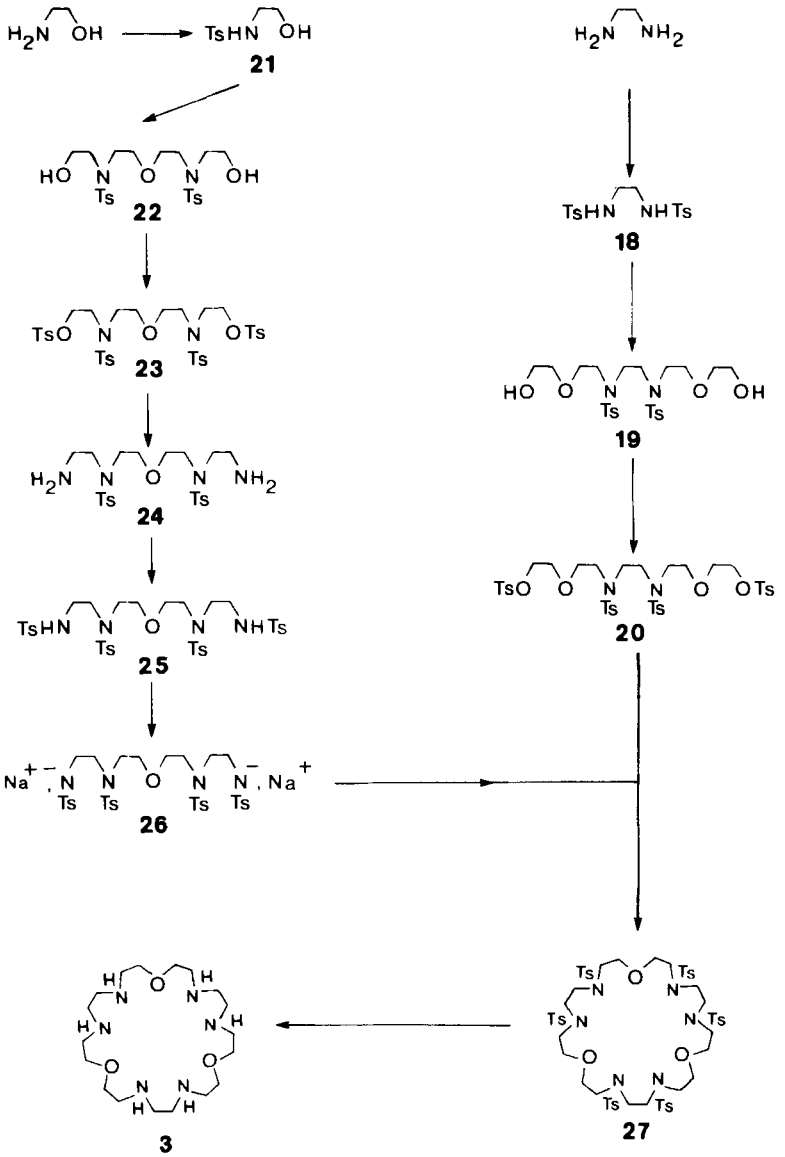
Scheme 1. *Reaction sequence for the synthesis of the macrocyclic polyamines* **1** *and* **2**



Macrocycle [27]ane-N_6O_3 **3** *(Scheme 2).* The ditosyl derivative **18** of ethylenediamine [34] treated with 2-(2-chloroethoxy)ethanol in DMF in presence of excess K_2CO_3 gave the diol **19**, which was converted into the tetratosyl derivative **20**, one of the cyclization partners. Treatment of the *N*-tosyl derivative **21** of ethanolamine

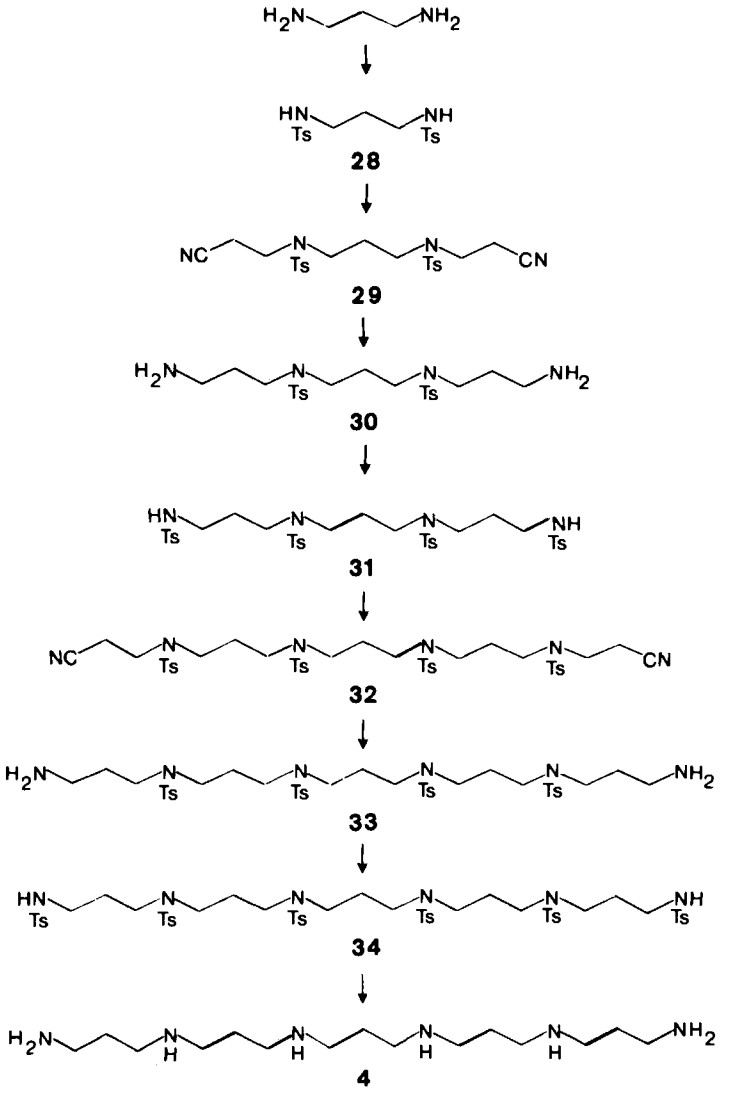
[35] with bis(2-chloroethyl) ether afforded the diol **22** which was converted into the diamine **24** *via* the sequence of *Gabriel* reactions [36] [37]. The disodium salt **26** of the tetratosyl derivative **25** of **24** was condensed with **20** under conditions similar to those employed for the other macrocycles giving the hexatosyl macrocycle **27** in 65% yield. After deprotection with HBr/AcOH/Phenol, the cristalline **3** · 6 HBr was obtained.

Scheme 2. *Reaction sequence for the synthesis of macrocyclic polyamine* **3**



Linear hexaamine **4** *(Scheme 3).* The linear hexaamine **4** was prepared as the acyclic analog of the macrocyclic hexaamine [24]ane-N_6 (**1**). Symmetric elongation of trimethylenediamine by tosylation, *Michael* condensation with acrylonitrile and reduction with B_2H_6 gave **30** which, subjected to the same sequence of reactions, afforded compound **33**. The latter was purified *via* the hexatosyl derivative **34** which, by detosylation with HBr/AcOH/phenol, yielded **4** · 6 HBr. As in the case of the macrocycles **1**–**3**, the free amine **4** may be obtained by passing the salt over a basic *Dowex 1* × *8* resin. Other reactions of chain elongation by $(CH_2CH_2CH_2NH)$-units have been reported recently [20] [38].

Scheme 3. *Reaction sequence for the synthesis of the linear hexaamine* **4**



Protonation features of the macrocyclic polyamines **1–3** *and of the linear hexaamine* **4**. The protonation constants $\log K_n$ ($= pK_a$-values) corresponding to the equilibria of the polyamines L = **1–4** (*Equations 1* and *2*) are listed in the *Table*.

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

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

These results lead to the distribution curves of the various species represented in *Figure 1*. The $\log K_n$ data for macrocycles **5** and **6** [19] are also given in the *Table* for comparison purposes.

It may first be noted that the lowest $\log K_n$ values of the macrocyclic polyamines **1–3** are close to 6–7, so that they are fully protonated at pH-values close to neutrality. Furthermore, since the polyammonium forms of **1–3** are anion receptors capable of binding a variety of anions [11], the $\log K_n$ values found depend on the anion, being higher the stronger the complex formed. The present data were obtained using 0.1 M sodium *p*-toluenesulfonate (TsNa) as supporting electrolyte, so as to minimize anion binding; indeed, lower pK_a-values were obtained with this anion than with chloride, indicating that the latter is bound to some extent; as also detected by ^{35}Cl-NMR. [39].

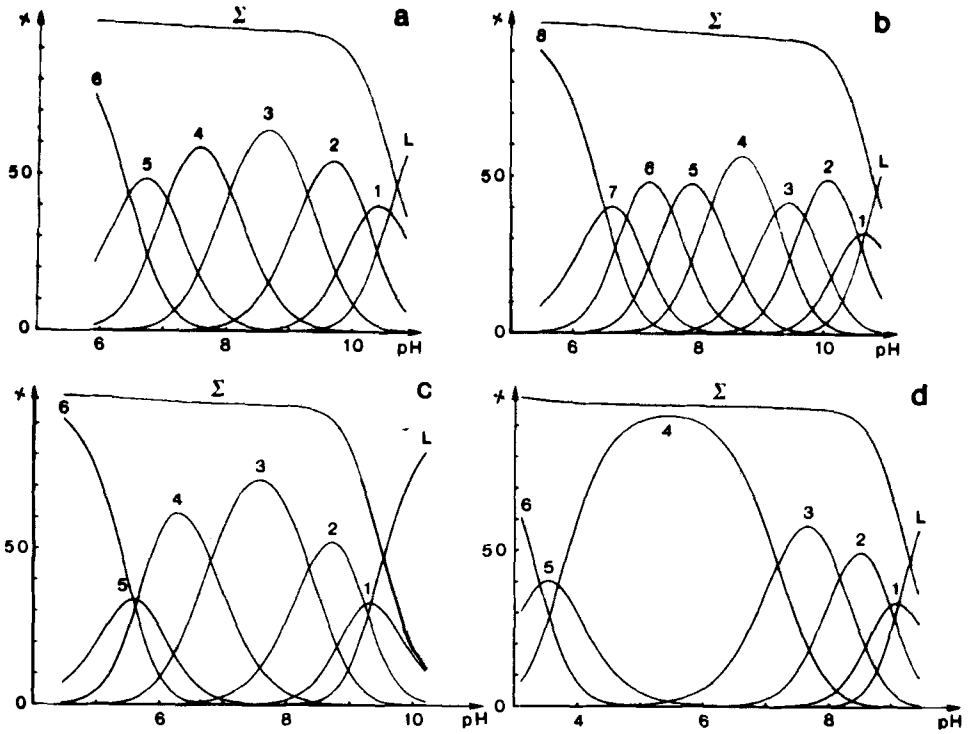


Fig. 1. *Distribution curves of the unprotonated and protonated forms of the macrocyclic polyamines as a function of pH:* a) **1**; b) **2**; c) **3**; d) **5** (L: unprotonated species; the figures 1–6 *or 1–8 refer to the successive protonated species bearing 1–6 or 1–8 protons;* Σ: summation over all the protonated species)

Table. *Protonation equilibrium constants* $\log K_n$ *(=*pK_n*) of the macrocyclic polyamines* **1**, **2**, **3**, **5** *and* **6** *and of the linear polyamine* **4**[a])

n	**1**	**2**	**3**	**4**	**5**	**6**[b])
1	10.50	10.65	9.35	10.10	9.15	10.20
2	10.20	10.55	9.25	10.10	9.00	9.25
3	9.25	9.70	8.35	9.30	8.20	8.75
4	8.00	9.20	6.80	8.70	7.20	4.10
5	7.05	8.20	5.65	7.70	3.70	~2
6	6.40	7.55	5.55	7.00	3.40	~1
7		6.85				
8		6.50				

[a]) In water, ionic strength = 0.1 M (TsNa); at 25°; see *Equations 1* and *2* for definition of K_n.
[b]) From [19].

The nature of the species formed by successive protonation of macrocycles **1**–**3** is not directly indicated by the $\log K_n$ data. However, in a first approximation one may consider that the successive introduction of protons leads to the species presenting *maximum dispersion of positively charged ammonium sites.* Accordingly, the predominant LH_4^{4+}-species of the hexaamine macrocycles **1**, **3**, **5** and **6** are probably those given in *Figure 2;* it shows also the LH_4^{4+}-, LH_5^{5+}- and LH_6^{6+}-forms of the macrocyclic octaamine **2** which are probably the preferred ones[2]).

Instructive comparisons can be made between the $\log K_n$ values of the macrocycles **1**, **3**, **5** and **6** (*Table* and *Fig. 3*).

We may discuss these values by considering the macrocycles **1**, **3**, **5** as formally derived from macrocycle **6**: *a)* Macrocycle **5** is derived by a *symmetrical separation*

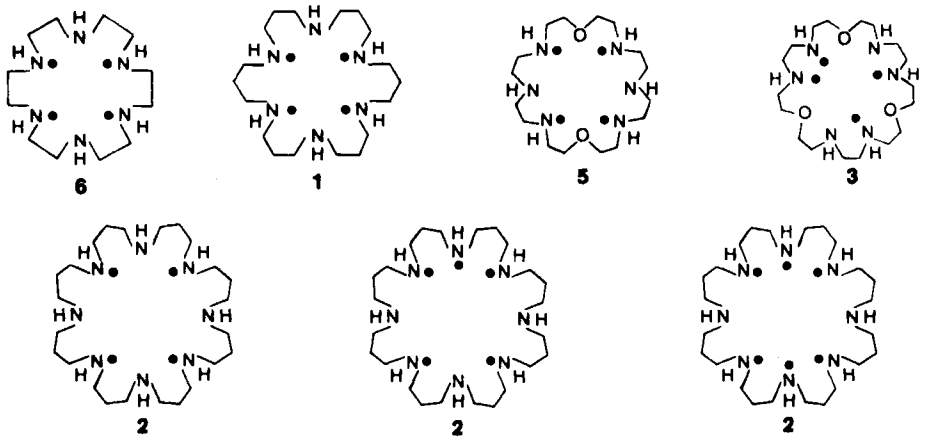


Fig. 2. *Probable proton distribution in tetraprotonated forms of macrocyclic polyamines* **1**, **2**, **3**, **5** *and* **6**, *and in the penta- and hexaprotonated forms of* **2** (The dots indicate the site of protonation)

[2]) Partially protonated forms of symmetrical polyamines, like some of those shown in *Figure 2*, may present interesting prototropic features involving correlated internal proton-transfer processes between protonated and unprotonated N-sites. Such phenomena would deserve further investigation.

of **6** *into two subunits* each with three N-atoms. This results in a pairwise grouping of the successive protonation constants, reflecting that the two parts of the molecule behave almost independently. It also brings $\log K_6$ of **5** to a value of 3.4, much higher than the corresponding pK_a of **6** (≈ 1).

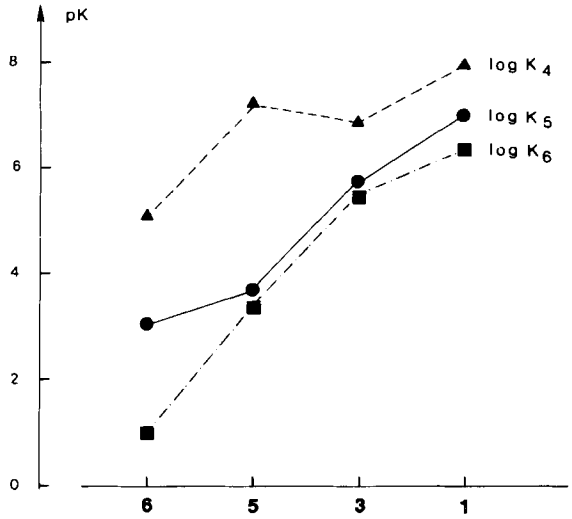


Fig. 3. *Graphical comparison of the three last protonation constants* $\log K_4$, $\log K_5$ *and* $\log K_6$ *of the macrocyclic hexaamines* **1**, **3**, **5** *and* **6**

b) Macrocycle **3** is obtained by a *symmetrical separation of* **6** *into three subunits* each of ethylenediamine-type. The titration curve shows mainly two domains: the domain of monoprotonation of the almost independent ethylenediamine units ($\log K_1$, $\log K_2$, $\log K_3$) and the domain of second protonation ($\log K_4$, $\log K_5$, $\log K_6$). This spacing operation raises the $\log K_n$ of the full protonation to a value of 5.55.

c) Macrocycle **1** is derived by a *symmetrical spacing*, insertion of one additional ethylene group between two N-atoms (converting the ethylene group to a trimethylene unit). It results in very large changes in the $\log K_n$'s; $\log K_6$ of macrocycle **1** is increased by almost 7 units with respect to macrocycle **6**.

Such structural modifications may also be performed on other systems and provide a means of controlling the protonation constants of macrocyclic polyamines. Furthermore more highly connected ligands, macro*poly*cyclic polyamines may allow a higher spatial accumulation of positive sites, while nevertheless keeping the sites well-separated along the intramolecular bonding framework; thus, the $\log K_n$ value for hexaprotonation of a macrobicyclic hexaamine (bis-tren)is about 6 [8] [40].

Comparing macrocycle **1** to its open-chain analog **4**, one notes that the lowest protonation constant, $\log K_6$, is only slightly higher (by about 0.6 unit) for the linear polyamine **4** than for the cyclic one **1**; this is far less than what was found in the case of spermine, and of a cyclic spermine [28] described earlier. Macrocycle **1** has thus both a rather high value for full protonation ($\log K_6 = 6.40$) and quite high

charge-density resulting from the symmetrical distribution of the six positive charges around the macrocycle. The same holds of course for **2**.

Finally, the *geometry* of the protonated macrocycles, and especially of the fully protonated species, should play an important role in their anion-binding properties. The electrostatic repulsion between the charged sites is expected to lead to maximum separation between them; furthermore the trimethylenediamine unit probably takes up the *anti, anti*-conformation which may result in elongated shapes for the macrocycles. The crystal structures of two **1**–6 H^+ salts have been determined and will be described elsewhere [41]. As mentioned in the *Introduction*, macrocyclic polyamines are of interest, as ligands for both metal cations and, when protonated, for anions. Those described here have indeed been shown to display such properties; for example they form stable and selective complexes with a variety of anions [11] and the macrocycle **3** is able to assemble three Cu(II)-cations into a bridged trinuclear cluster [42]. These and other binding features of macrocycles **1**–**3** as well as **5** will be reported later.

Experimental Part

General. Melting points (m.p.) are uncorrected. ^{1}H-NMR. spectra were recorded on a *Varian A 60* and ^{13}C-NMR. on a *Varian XL 100* spectrometer. Chemical shifts δ are given in ppm with tetramethylsilane (TMS) as the standard; *s* = singulet; *d* = doublet; *t* = triplet; *qa* = quadruplet; *m* = multiplet; br. = broad. Mass spectra (MS.) were performed by the *'Laboratoire de Spectrométrie de Masse Moderne'*, Strasbourg. Due to the high molecular weight the FDOR. method was used [43] [44]. Microanalysis were performed by the 'Service Central de Microanalyse du CNRS'.

For the pH-metric measurements a *Metrohm 636* titrimeter was used. The cell was thermostated at 25°±0.1°, the solution stirred and all measurements performed under N_2-atmosphere. The $\log K_n$ values of the compounds were determined by titration with 0.1N NaOH of a solution containing typically 10^{-3} M of the polyammonium salt in the presence of TsNa (0.1M).

Data from all titrations were analyzed by the computer program *SCO 76* [45].

N,N',4-Tri(p-toluenesulfonyl)-4-azaheptanediamine (**7**). A 5 l aq. solution of 3,3'-diaminodipropylamine (100 g, 0.76 mol) and K_2CO_3 (250 g, 1.74 mol) was stirred vigorously at 60°. Tosyl chloride (580 g, 3.0 mol) was added in batches over a period of 3 h. Stirring was continued at 60° for 3 more h before the reaction mixture was allowed to cool overnight. After filtration the residue was dissolved in 2 l CH_2Cl_2; this solution was washed once with 1.5 l 1N HCl, twice with H_2O and then dried over $MgSO_4$. The major part of the CH_2Cl_2 was evaporated, MeOH was added and crystallization of **7** (428 g) rapidly occurred (95% yield), m.p. 119–120°. – ^{1}H-NMR. ($CDCl_3$): 1.75 (br., 4 H, 2 CH_2–CH_2–CH_2); 2.40 (*s*, 9 H, 3 CH_3); 3.05 (br. 8 H, 4 CH_2–N); 5.80 (br., 2 H, 2 NH); 7.37, 7.76, 7.88 (*m*, 12 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.2, 143.9, 137.5, 136.2, 130.3, 127.6 (arom. C); 47.1 (CH_2–NTs–CH_2); 40.7 (HNTs–CH_2), 29.5 (CH_2–CH_2–CH_2); 22.0 (CH_3).

$C_{27}H_{35}N_3O_6S_3$ (593.7) Calc. C 54.55 H 5.94 N 7.17% Found C 54.61 H 5.94 N 7.07%

Note: Disodium salt **10**, which will be described later, is made *in situ* just before use and was not isolated.

4,8,12-Tri(p-toluenesulfonyl)-4,8,12-triazapentadecane-1,15-diol (**8**). Compound **8** was prepared by two methods *(Scheme 1). Method 1.* To a mixture of **7** (40 g, 0.067 mol) and K_2CO_3 (50 g, 0.35 mol) in 200 ml DMF, heated at 100° and stirred, a solution of 3-chloro-1-propanol (20 g, 0.21 mol) in 40 ml DMF was added dropwise over a period of 1 h. Stirring was continued at 110° for 20 h. After cooling, the mixture was filtered, the solid was washed with CH_2Cl_2 and the org. solutions evaporated to dryness. The crude material was dissolved in CH_2Cl_2, washed with H_2O and dried over $MgSO_4$. The pure compound **8** (20 g, 42%) was obtained as an oil after chromatography on alumina and elution with CH_2Cl_2 containing 1% MeOH. – ^{1}H-NMR. ($CDCl_3$): 1.83 (br., 8 H, 4 CH_2–CH_2–CH_2);

2.44 (*s*, 9 H, 3 CH_3); 3.16 (br., 12 H, 6 CH_2–N); (br. *s*, 2 H, 2 OH); 3.70 (*t*, 4 H, 2 CH_2–OH); 7.38, 7.76 (*m*, 12 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.1, 136.4, 130.4, 127.7 (arom. C); 59.7 (CH_2–OH); 47.7, 47.6, 46.7 (CH_2–N); 32.3, 29.3 (CH_2–CH_2–CH_2); 22.0 (CH_3).

Method 2. $LiAlH_4$ (17 g, 0.44 mol) was added to 300 ml dry THF and the mixture stirred and cooled in an ice bath. A solution of dimethylester **16** (47.4 g, 0.062 mol) in 200 ml THF was added dropwise over a period of 45 min. The mixture was allowed to come to r.t. and stirring was continued overnight. While the solution was cooled in an ice bath, 50 ml of H_2O was added cautiously over about 45 min. The mixture was partitioned between 1 l of 1N H_2SO_4 and 500 ml CH_2Cl_2. The aq. layer was extracted with further portions of CH_2Cl_2 (2×200 ml) and the org. layers were combined, washed with 100 ml sat. NaCl-solution and dried over $MgSO_4$. The CH_2Cl_2-solution was passed through a bed of *Celite* and 10 g silica gel and evaporated to dryness. Traces of 1,4-butanediol were removed by dissolving the product in CH_2Cl_2 and precipitating it as an oil by addition of 600 ml Et_2O. The solvents were decanted and the residue pumped dry to give 31.2 g (71%) of **17** as a pale yellow viscous oil. – ^{1}H-NMR. ($CDCl_3$): 1.80 (br., 8 H, 4 CH_2–CH_2–CH_2); 2.41 (*s*, 9 H, 3 CH_3); 3.15 (br., 12 H, CH_2–N); 3.6 (br. *s*, 2 H, 2 OH); 3.68 (*t*, 4 H, 2 CH_2OH); 7.36, 7.76 (*m*, 12 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.1, 136.4, 130.4, 127.7 (arom. C); 59.7 (CH_2–OH), 47.7, 47.6, 46.7 (CH_2–N); 32.3, 29.3 (CH_2–CH_2–CH_2); 22.0 (CH_3).

1,15-Di(methanesulfonyloxy)-4,8,12-tri(p-*toluenesulfonyl*)-*4,8,12-triazapentadecane* (**9**). A solution of **8** (19.88 g, 0.028 mol) in 400 ml dry CH_2Cl_2 was placed in a 1 l flask, cooled down to −18° and Et_3N (16 g, 0.175 mol) was added. To the stirred solution, a solution of methanesulfonyl chloride (8.08 g, 0.056 mol) in 20 ml dry CH_2Cl_2 was added dropwise over a period of 30 min. Stirring was continued for 90 min and then the reaction was allowed to warm up to r.t. for 10 min. The mixture was washed with 200 ml of 2N H_2SO_4, then with sat. NaCl-solution, dried over $MgSO_4$ and evaporated to dryness, giving compound **9** (97%) which was used without further purification for the following step; it did not crystallize. – ^{1}H-NMR. ($CDCl_3$): 1.95 (br., 8 H, 4 CH_2–CH_2–CH_2); 2.41 (*s*, 9 H, 3 CH_3 (Ts)); 3.02 (*s*, 6 H, 3 CH_3 (Ms)); 3.13 (br., 12 H, 6 CH_2–N); 4.31 (*t*, 4 H, 2 CH_2–OMs); 7.31, 7.71 (*m*, 12 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.3, 144.2, 136.3, 136.2, 130.6, 127.8 (arom. C); 68.2 (CH_2–OMs); 47.6, 47.4, 46.2 (CH_2–N); 37.8 (CH_3Ms); 29.4, 29.2 (CH_2–CH_2–CH_2); 22.0 (CH_3 (Ts)).

1,5,9,13,17,21-Hexa(p-*toluenesulfonyl*)-*1,5,9,13,17,21-hexaazacyclotetraeicosane* (**11**). The tritosyl compound **7** (6.86 g, 0.0115 mol), 150 ml DMF and NaH (1.86 g, 0.04 mol) suspended in oil were introduced into a 500 ml flask. This mixture was stirred for 30 min and then filtered rapidly to remove the excess of unreacted NaH. The clear solution containing compound **10** was transferred to a 500 ml two-necked flask and heated to 110°. A solution of **9** (10 g, 0.0115 mol) in 120 ml DMF was added through an addition funnel over a period of 1 h. Heating was continued for 2 more h and then the solution was stirred at r.t. overnight. After removing the DMF, the crude material was dissolved in 300 ml CH_2Cl_2 and washed with 150 ml 1N HCl. The aq. layer was extracted twice with 150 ml CH_2Cl_2. The org. layers were dried over $MgSO_4$. The CH_2Cl_2-solution was concentrated and passed through an aluminium column; **11** (7.3 g, 50% yield) was obtained by using CH_2Cl_2 containing 1% MeOH as eluent and was crystallized from CH_2Cl_2/abs. EtOH, m.p. 197–198°. – ^{1}H-NMR. ($CDCl_3$): 2.05 (br., 12 H, CH_2–CH_2–CH_2); 2.42 (br., 18 H, 6 CH_3); 3.16 (br., 24 H, 12 CH_2–N); 7.30, 7.68 (*m*, 24 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.0, 136.6, 130.5, 127.8 (arom. C); 48.5 (CH_2–N); 30.5 (CH_2–CH_2–CH_2); 22.2 (CH_3). – MS.: 1266 (M^+), 1112 (M^+ – Ts).

$C_{60}H_{78}N_6O_{12}S_6$ (1267.6) Calc. C 56.84 H 6.20 N 6.63% Found C 56.70 H 6.31 N 6.58%

1,5,9,13,17,21-Hexaazacyclotetraeicosane (**1**). The hexatosyl macrocycle **11** (2 g, 0.0016 mol), phenol (2.85 g, 0.030 mol) and 50 ml of a 33% solution of HBr in AcOH were heated to 80° for 14 h under a well-ventilated hood. After cooling, AcOH was removed under vacuum. The residue was dissolved in 75 ml H_2O and the solution was extracted with CH_2Cl_2 (3×50 ml). After removing the H_2O on the rotatory evaporator, the residue did not crystallize; it was redissolved in the minimum amount of and passed over a basic exchange column *(Dowex 1×8)*. The eluate was treated with HCl, and evaporated to dryness. The residue was dissolved in the minimum amount of H_2O and abs. EtOH was added until the solution became cloudy. Crystallization of **1**·6 HCl (92% yield) occurred after a while, m.p. >250°. – ^{1}H-NMR. (D_2O): 2.2 (br., 12 H, CH_2–CH_2–CH_2); 3.36 (*t*, 24 H, 12 CH_2–N). – ^{13}C-NMR. (D_2O): 45.60 (CH_2–N); 23.5 (CH_2–CH_2–CH_2).

$C_{18}H_{78}Cl_6N_6 \cdot H_2O$ (579.3) Calc. C 37.22 H 8.69 N 14.50% Found C 37.22 H 8.70 N 14.53%

*3,7,13-Tri(*p*-toluenesulfonyl)-3,7,11-triazapentadecanedinitril* (**12**). Tritosyl compound **7** (113.7 g, 0.192 mol), K_2CO_3 (50 g, 0.35 mol) and 250 ml DMF were stirred at r.t. while acrylonitrile (24.2 g, 0.46 mol) was added dropwise over a period of 2 h. The mixture was stirred for 4 more h and then allowed to partition between 1 l CH_2Cl_2 and 1 l H_2O. The org. layer was dried over $MgSO_4$ and filtrated through alumina (300 g) and was well-washed with CH_2Cl_2. Evaporation of the CH_2Cl_2 left a yellow oil which was crystallized from a warm EtOH/AcOEt (total volume 700 ml) giving fine white needles of **12** (104.7 g, 78% yield), m.p. 98°. – ^{1}H-NMR. ($CDCl_3$): 1.95 (br., 4 H, $CH_2-CH_2-CH_2$); 2.41 (*s*, 9 H, 3 CH_3); 2.77 (br. *t*, 4 H, CH_2-CN); 3.2 (br., 12 H, 6 CH_2-N); 7.38, 7.78 (*m*, 12 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.7, 144.2, 136.3, 135.6, 130.6, 127.8 (arom. C); 118.4 (CN); 48.3, 47.5, 45.7 (CH_2-N); 29.3 ($CH_2-CH_2-CH_2$); 22.0 (CH_3); 19.5 (CH_2-CN).

$C_{33}H_{41}N_5O_6S_3$ (699.9) Calc. C 56.63 H 5.91 N 10.01% Found C 56.50 H 5.92 N 9.93%

*4,8,12-Tri(*p*-toluenesulfonyl)-4,8,12-triazapentadecane-1,15-diamine* (**13**). The dinitrile **12** (5 g, 0.007 mol) was refluxed overnight in a 0.9 M solution of B_2H_6 in THF (50 ml), under N_2. After cooling to r.t., 10 ml of H_2O in THF was added cautiously. The solvent was evaporated, 100 ml of 6 N HCl were added and the solution was refluxed for 2 h. It was then evaporated to dryness, and the residue was allowed to partition between aq. NaOH and CH_2Cl_2. The CH_2Cl_2-solution was dried over $MgSO_4$ and evaporated to leave **13** as a pale yellow oil which solidified to a glass upon standing for several days. Without further purification the product was transformed into its tosyl derivative **14**.

*N,N',4,8,12-Penta(*p*-toluenesulfonyl)-4,8,12-triazapentadecanediamine* (**14**). The crude diamine **13** (27.07 g, 0.038 mol) was dissolved in 300 ml THF containing 50 ml Et_3N (36.3 g, 0.36 mol). TsCl (16.2 g, 0.085 mol) was added to this stirred solution over a period of 5 min. The mixture was stirred overnight and the THF was evaporated. The semi-solid residue was partitioned between CH_2Cl_2 (300 ml) and 2 N H_2SO_4 (200 ml). The org. layer was separated and the aq. layer extracted again with 100 ml of CH_2Cl_2. The combined org. layers were washed with sat. NaCl-solution and dried over $MgSO_4$. Evaporation gave a solid which was recrystallized from hot AcOEt/EtOH 1:4 affording 31.6 g (80%) of **14** as a white powder, m.p. 142°. – ^{1}H-NMR. ($CDCl_3$): 1.85 (br., 8 H, $CH_2-CH_2-CH_2$); 2.41 (*s*, 15 H, 5 CH_3); 3.1 (br. *m*, 16 H, 8 CH_2-N); 5.5 (br., 2 H, 2 NH); 7.37, 7.76, 7.85 (*m*, 20 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.2, 143.9, 137.6, 136.5, 136.3, 130.5, 130.4, 127.8, 127.7 (arom. C); 48.1, 47.6, 47.3 (CH_2-N); 40.9 (CH_2-NHTs); 29.9, 29.6 ($CH_2-CH_2-CH_2$); 22.0 (CH_3).

$C_{47}H_{61}N_5O_{10}S_5$ (1016.3) Calc. C 55.54 H 6.05 N 6.89% Found C 55.52 H 5.98 N 7.01%

The disodium salt **15** was prepared *in situ* just before cyclization.

*Dimethyl 4,8,12-tri(*p*-toluenesulfonyl)-4,8,12-triazapentadecane-1,15-dioate* (**16**). A mixture of **7** (200 g, 0.34 mol), methyl acrylate (191.2 g, 2.22 mol), K_2CO_3 (100 g, 0.69 mol) and 200 ml DMF was stirred magnetically and heated to 80° under a reflux condenser overnight. After cooling the mixture was allowed to partition between 1 l H_2O and 1 l $CHCl_3$ and the aq. layer extracted with a further 200 ml $CHCl_3$. The combined $CHCl_3$-layers were dried and evaporated. The resulting dark brown oil was filtered through alumina (MeOH/$CHCl_3$ as solvent) and treated with charcoal. The product **16** obtained was pure according to its NMR. spectrum and used without further purification. – ^{1}H-NMR. ($CDCl_3$): 1.85 (br., 4 H, 2 $CH_2-CH_2-CH_2$); 2.41 (*s*, 9 H, 3 CH_3(Ts)); 2.5–3.6 (*m*, 16 H, 2 $CH_2-COOCH_3$ and 6 CH_2-N); 3.70 (*s*, 6 H, CH_3 (ester)); 7.34, 7.74 (*m*, 12 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 172.2 ($COOCH_3$); 144.1, 136.5, 130.3, 127.7 (arom. C); 52.2 (CH_3 (ester)); 47.6, 47.3, 45.1 (CH_2-N); 34.7 ($CH_2-C=O$); 28.9 ($CH_2-CH_2-CH_2$); 21.9 (CH_3 (Ts)).

*1,5,9,13,17,21,25,29-Octa(*p*-toluenesulfonyl)-1,5,9,13,17,21,25,29-octaazacyclodotriacontane* (**17**). Compound **14** (9.0 g, 0.0104 mol) was stirred with a 50% suspension in oil of NaH (2 g, 0.042 mol) in 100 ml DMF. After 2 h the excess of NaH was removed by filtration and the filtrate compound containing **15** was stirred and heated to 110°. A solution of **9** (10.6 g, 0.0104 mol) in 30 ml DMF was added dropwise in 5 min to the solution of the dianion. Heating was continued for 3 h and then the solvent was removed by evaporation. The residue was partitioned between 400 ml CH_2Cl_2, 300 ml sat. NaCl-solution and 100 ml 2 N H_2SO_4. The phases were separated after filtration through a bed of *Celite* and the org. layer was washed with 50 ml sat. NaCl-solution, dried over $MgSO_4$ and evaporated to dryness. Chromatography on the residue on 500 g silica gel eluted with CH_2Cl_2 containing 0–1% MeOH, afforded pure **17** (6 g, 35%) as a colorless glass which was crystallized from CH_2Cl_2/EtOH, m.p. 185°. – ^{1}H-NMR. ($CDCl_3$): 1.90 (br., 16 H, 8 $CH_2-CH_2-CH_2$); 2.41 (*s*, 24 H,

8 CH_3); 3.14 (br., 32 H, 16 CH_2–N); 7.29, 7.68 (*m*, 32 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.0, 136.6, 130.5, 127.8 (arom. C); 47.6 (CH_2–N); 29.5 (CH_2–CH_2–CH_2); 22.1 (CH_3). – MS.: 1688 (M^+), 1533 (M^+ – Ts).

$C_{80}H_{104}N_8O_{16}S_8$ (1690.1) Calc. C 56.85 H 6.20 N 6.63% Found C 56.70 H 6.26 N 6.70%

1,5,9,13,17,21,25,29-Octaazacyclodotriacontane (**2**). The octatosyl macrocycle **17** (1.9 g, 0.011 mol), phenol (3 g, 0.03 mol) and 60 ml of 48% HBr in AcOH were stirred and heated at 80° under reflux for 14 h. After evaporation under vacuum, the residue was heated with 200 ml Et_2O. The pale brown solid obtained was isolated by filtration and washed well with acetone and CH_2Cl_2. Crude 2 · **8** HBr was dissolved in 20 ml H_2O, filtered and passed over a column of *Dowex 1×8* resin in the basic form. The aq. solution of the free base was acidified to pH = 3 with 2N HCl and H_2O removed by evaporation. The residue was crystallized from hot aq. EtOH giving **2** · 8 HCl (0.6 g, 80%) as white needles, m.p. >250°. – ^{1}H-NMR. (D_2O): 2.20 (br., 16 H, 8 CH_2–CH_2–CH_2); 3.30 (*t*, 32 H, 16 CH_2N). – ^{13}C-NMR. (D_2O): 45.9 (CH_2–N); 23.8 (CH_2–CH_2–CH_2).

$C_{24}H_{64}Cl_8N_8$ (748.4) Calc. C 38.5 H 8.62 N 15.09% Found C 38.42 H 8.78 N 15.09%

By a similar procedure **2** · 8 $HClO_4$ can be obtained (recrystallized from EtOH), decomp. 190°.

$C_{24}H_{64}Cl_8N_8O_{32}$ (1260.4) Calc. C 22.87 H 5.12 N 8.89% Found C 22.81 H 5.02 N 8.92%

*3,12-Dioxa-6,9-diaza-6,9-di(*p*-toluenesulfonyl)tetradecane-1,14-diol* (**19**). In a 500 ml flask a mixture of **18** (7.4 g, 0.02 mol), K_2CO_3 (13.8 g, 0.1 mol), 50 ml DMF and 2-(2-chloroethoxy)ethanol (10 g, 0.04 mol) was heated at 60° for 24 h. Then DMF was removed by evaporation under vacuum and the residue was allowed to partition between 100 ml CH_2Cl_2 and 100 ml H_2O. The org. layer was washed with H_2O (3× 100 ml), dried over Na_2SO_4, concentrated to about one third of its volume and toluene was added. The diol **19** (8.8 g, 80%) crystallized, m.p. 92°. – ^{1}H-NMR. ($CDCl_3$): 2.43 (*s*, 6 H, 2 CH_3); 3.07 (*s*, 2 H, 2 OH); 3.52 (br. *m*, 20 H, 6 CH_2O, 4 CH_2N); 7.57 (*m*, 8 H, arom. H).

$C_{24}H_{36}N_2O_8S_2$ (544,6) Calc. C 52.92 H 6.66 N 5.14% Found C 52.85 H 6.68 N 5.07%

*6,9-Di(*p*-toluenesulfonyl)-1,14-di(*p*-toluenesulfonyloxy)-6,9-diazatetradecane* (**20**). TsCl (20 g, 0.105 mol) in 60 ml dry pyridine was placed in a 500 ml flask, cooled in an ice bath and a solution of the diol **19** (26 g, 0.048 mol) in 40 ml pyridine was added over a period of 1 h under stirring. The mixture was kept in a refrigerator at 0° overnight, then poured into crushed ice and, after stirring for a few min, the solid residue was filtered, washed with cold H_2O and allowed to partition between 100 ml CH_2Cl_2 and 100 ml 1N HCl. The org. layer was washed three times with H_2O and then dried over Na_2SO_4 and concentrated. Filtration of this solution over 100 g silica gel eluted with CH_2Cl_2 afforded **20** (35 g, 85%) which was crystallized from a CH_2Cl_2/toluene mixture, m.p. 100–101°. – ^{1}H-NMR. ($CDCl_3$): 2.42 (*s*, 12 H, 6 CH_3); 3.35 (*s* + *t*, 8 H, 4 CH_2–N); 3.57 (br. *t*, 8 H, 2 OCH_2–CH_2 OTs); 4.1 (br. *t*, 4 H, 2 OCH_2–CH_2–N); 7.57 (*m*, 16 H, arom. H).

$C_{38}H_{48}N_2O_{12}S_4$ (853.0) Calc. C 53.52 H 5.63 N 3.29% Found C 53.58 H 5.33 N 3.64%

*2-(*p*-Toluenesulfonylamino)ethanol* (**21**). Preparation as described by *Slotta & Behnisch* [35] (60% yield), m.p. 56° (lit.: 56°). – ^{1}H-NMR. ($CDCl_3$): 2.40 (*s*, 3 H, CH_3); 3.67 (*t*, 2 H, CH_2O); 5.97 (*s*, 1 H, HN–TS); 7.58 (*m*, 4 H, arom. H).

*3,9-Di(*p*-toluenesulfonyl)-6-oxa-3,9-diazaundecane-1,11-diol* (**22**). The compound **21** (43 g, 0.2 mol), bis(2-chloroethyl) ether (14.3 g, 0.1 mol) and K_2CO_3 (55.2 g, 0.4 mol) in 100 ml of DMF were heated at 70° for 24 h. DMF was removed by evaporation under vacuum. The crude residue was extracted several times with $CHCl_3$. The concentrated org. layer was passed through 150 g silica gel column and **22** (33 g, 65%) was eluted with $CHCl_3$ and crystallized from a CH_2Cl_2/toluene, m.p. 94°. – ^{1}H-NMR. ($CDCl_3$): 2.42 (*s*, 6 H, 2 CH_3); 3.33 (br., 8 H, 4 CH_2–N); 3.72 (br., 8 H, 4 CH_2O); 7.55 (*m*, 8 H, arom. H).

$C_{22}H_{32}N_2O_7S_2$ (500.6) Calc. C 52.78 H 6.44 N 5.60% Found C 52.90 H 6.37 N 5.76%

*3,9-Di(*p*-toluenesulfonyl)-1,11-di(*p*-toluenesulfonyloxy)-6-oxa-3,9-diazaundecane* (**23**). Diol **22** (22 g, 0.044 mol) in 40 ml dry pyridine was added slowly over a period of 1 h to a solution of TsCl (22 g, 0.155 mol) in dry pyridine (60 ml) stirred magnetically and cooled to 0° with an ice-water bath. The mixture was kept cool overnight and then poured into crushed ice, filtered and washed with H_2O.

The oily residue was dissolved in CH_2Cl_2 and the solution washed with a 5% solution of HCl and three times with water. The org. layer was dried over Na_2SO_4 and evaporated giving **23** (33 g, 93%) as a viscous oil. – ^{1}H-NMR. ($CDCl_3$): 2.42 (br. *s*, 12 H, 4 CH_3); 3.42 (br. *m*, 8 H, 4 CH_2–N); 4.17 (*t*, 8 H, CH_2O); 7.53 (*m*, 16 H, arom. H).

*3,9-Di(*p*-toluenesulfonyl)-6-oxa-3,9-diazaundecane-1,11-diamine* (**24**). Freshly prepared potassium phthalimide [46] (17.5 g, 0.095 mol) was suspended in 100 ml DMF, in a 500 ml flask, protected by a drying tube ($CaCl_2$). The stirred mixture was heated to 100° and a solution of **23** (35 g, 0.043 mol) in 100 ml DMF was added over a period of 1 h. Heating was continued for 4 h and then the reaction was allowed to stand at r.t. overnight. The mixture was poured over crushed ice and after stirring the entire mixture was filtered and washed with H_2O. The residue was dissolved in 200 ml $CHCl_3$, washed three times with H_2O and evaporated to dryness. The residue was passed through a 100 g silica gel column, the compound was eluted with CH_2Cl_2/toluene 1:1. After evaporation of the solvents the diphthalimido derivative was crystallized from $CHCl_3$/EtOH (70% yield), m.p. 156°. – ^{1}H-NMR. ($CDCl_3$): 2.30 (*s*, 6 H, 2 CH_3); 3.58 (br., 12 H, 6 CH_2–N); 3.8 (br., 4 H, 2 CH_2–O); 7.42 (*m*, 8 H, arom. H (Ts)); 7.73 (br., 8 H, arom. H (phthalimide)).

The diphthalimido compound described above (23 g, 0.03 mol) was suspended in 120 ml abs. EtOH and hydrazine (3.3 ml, 0.068 mol) was added. A condenser was adapted to the 500 ml flask and the mixture was refluxed for 12 h. After the mixture cooled, 6N HCl was added to bring the pH to 1. The mixture was refluxed for 1 h. After cooling the mixture was filtered and the eluate evaporated to dryness. An aq. solution of NaOH (40 g in 250 ml) was added to the residue; this solution was extracted with $CHCl_3$ (3 × 100 ml). The org. layer was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness giving **24** (14.5 g, 96%) as a viscous oil. – ^{1}H-NMR. ($CDCl_3$): 1.4 (*s*, 4 H, 2 H_2N); 2.43 (*s*, 6 H, 2 CH_3); 2.85 (*t*, 4 H, 2 H_2N–CH_2); 3.17, 3.26 (*t*+*t*, 8 H, 2 N–CH_2–CH_2–O); 3.62 (*t*, 4 H, H_2N–CH_2–CH_2–N); 7.57 (*m*, 8 H, arom. H).

*N,N',3,9-Tetra(*p*-toluenesulfonyl)-6-oxa-3,9-diazaundecane-1,11-diamine* (**25**). To a well-stirred solution containing **24** (14.5 g, 0.029 mol), 60 ml H_2O, 60 ml Et_2O and NaOH (3.2 g, 0.080 mol), TsCl (15.3 g, 0.080 mol) was added over a period of 30 min. Stirring was continued for 12 h. The mixture was filtered and the viscous residue dissolved in 100 ml CH_2Cl_2. The org. solution was washed three times with H_2O and dried over Na_2SO_4 and evaporated. Chromatography of the residue on 200 g silica gel eluted with CH_2Cl_2 gave compound **25** (12.8 g, 57%) as a viscous oil. – ^{1}H-NMR. ($CDCl_3$): 2.4 (*s*, 12 H, 4 CH_3); 3.2 (br., 12 H, 3 N–CH_2–CH_2–O); 3.6 (br., 4 H, 2 CH_2–NH–Ts); 5.8 (br., 2 H, 2 HN–Ts); 7.47 (*m*, 16 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 143.9, 143.4, 136.9, 135.1, 129.8, 127.3, 127.2 (arom. C); 70.2 (CH_2O); 50.1 (CH_2N); 43.0 (CH_2–N); 21.4 (CH_3).

$C_{36}H_{46}N_4O_9S_4$ (807.0) Calc. C 53.58 H 5.74 N 6.94% Found C 53.60 H 5.86 N 7.11%

*4,7,13,16,22,25-Hexa(*p*-toluenesulfonyl)-1,10,19-trioxa-4,7,13,16,22-hexaazacycloheptaeicosane* (**27**). A solution of sodium (0.5 g, 0.0217 mol) in 50 ml of abs. EtOH under Ar, was added to **25** (8.1 g, 0.01 mol) in suspension in 50 ml abs. EtOH and the mixture was heated and stirred magnetically at 60° for 30 min. Evaporation to dryness afforded **26** as a solid residue.

Dry DMF (160 ml) was added to this dry disodium salt. An addition funnel and a condenser were fitted to the flask and the solution was heated to 100° under Ar. The tetratosylated product **20** (8.54 g, 0.01 mol) dissolved in 80 ml DMF was added in 90 min. Heating was maintained for 1 h. After the solution cooled to r.t., a mixture of 200 ml H_2O and 200 g ice was added; a precipitate appeared rapidly which was filtered and washed with H_2O. The solid residue was dissolved in 100 ml CH_2Cl_2; the solution was washed three times with H_2O and dried over Na_2SO_4. The solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2/toluene 1:1 and passed through a silica gel (200 g) column. Elution with CH_2Cl_2/toluene 1:1 to 3:1 gave after evaporation compound **27** as a viscous oil which crystallized with difficulty from toluene/heptane, m.p. 126–127°. – ^{1}H-NMR. ($CDCl_3$): 2.4 (*s*, 18 H, 6 CH_3); 3.4 (br., 36 H, 12 CH_2); 7.52 (*m*, 24 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 143.4, 136.1, 129.8, 127.2 (arom. C); 69.5 (CH_2O); 49.0 (CH_2N); 21.4 (CH_3). – MS.: 1314 (M^+), 1160 (M^+ – Ts).

$C_{60}H_{78}N_6O_{15}S_6$ (1315.6) Calc. C 54.77 H 5.98 N 6.39% Found C 54.74 H 5.96 N 6.34%

1,10,19-Trioxa-4,7,13,16,22,25-hexaazacycloheptaeicosane (**3**). The hexatosylated macrocycle **27** (2 g, 0.0015 mol), phenol (3 g, 0.032 mol) and 40 ml of a 33% solution of HBr in AcOH were heated at 80° for 14 h. After the solution was cooled, the acids were removed under vacuum; 75 ml toluene

was added and evaporated to remove the rest of AcOH. The residue was allowed to partition between 100 ml CH_2Cl_2 and 50 ml H_2O. The aq. layer was washed three times with CH_2Cl_2 and finally concentrated to 5 ml; abs. EtOH was then added until the mixture became cloudy (about 50 ml EtOH); 1.2 g (90%) of **3** · 6 HBr crystallized, m.p. 240°. – ^{1}H-NMR. (D_2O): 3.25 (*t*, 12 H, 6 O–CH_2–CH_2–N); 3.45 (*s*, 12 H, 3 HN–CH_2–CH_2–NH); 3.70 (*t*, 12 H, 6 O–CH_2). – ^{13}C-NMR. (D_2O): 68.0 (O–CH_2–CH_2–N); 50.4 (O–CH_2–CH_2N); 46.1 (N–CH_2–CH_2–N).

$C_{18}H_{48}Br_6N_6O_3$ (876.0) Calc. C 24.68 H 5.52 N 9.59% Found C 24.26 H 5. 3 N 9.68%

The hexabromide was dissolved in 20 ml H_2O and passed over *Dowex 1 × 8* resin in the basic form. The aq. solution of the free amine was acidified to pH 3 with 2 N HCl and H_2O removed by evaporation. The residue was crystallized with difficulty in MeOH/conc. HCl/EtOH/2-propanol 60:2: ≈ 20: ≈ 20 giving **3** · 6 HCl.

$C_{18}H_{48}Cl_6N_6O_3 \cdot H_2O$ (627.3) Calc. C 34.46 H 8.03 N 13.40% Found C 34.31 H 7.43 N 13.31%

*1,3-Di(*p*-toluenesulfonyl)-1,3-propandiamine* (**28**). TsCl (128.6 g, 0.67 mol) was added over a period of 15 min to a 1.2 l aq. solution of 1,3-propanediamine (20 g, 0.27 mol) and NaOH (32 g, 0.8 mol) and the mixture was stirred vigorously at 70°. Stirring was continued at 70° for 4 h before the mixture was allowed to cool overnight. After filtration the residue was washed with H_2O, dissolved in 500 ml CH_2Cl_2 and dried over $MgSO_4$. The major part of CH_2Cl_2 was evaporated. MeOH was added to this solution and 83.6 g (81%) of **28** crystallized, m.p. 144–148°. – ^{1}H-NMR. ((D$_6$)DMSO): 1.68 (br., 2 H, CH_2–CH_2–CH_2); 2.45 (*s*, 6 H, 2 CH_3); 2.90 (*m*, 4 H, 2 CH_2–N); 7.0 (*m*, 2 H, 2 NH); 7.35, 7.85 (*m*, 8 H, arom. H). – ^{13}C-NMR. ((D$_6$)DMSO): 143.4, 138.4, 130.5, 127.3 (arom. C); 40.5 (CH_2–N); 30.2 (CH_2–CH_2–CH_2); 21.8 (CH_3).

$C_{17}H_{22}N_2O_4S_2$ (382.5) Calc. C 53.38 H 5.79 N 7.32% Found C 53.07 H 5.50 N 7.80%

*4,8-Di(*p*-toluenesulfonyl)-4,8-diazaundecanedinitrile* (**29**). Ditosyl compound **28** (5 g, 0.013 mol), K_2CO_3 (5.42 g, 0.039 mol) and 50 ml DMF were stirred at r.t. while acrylonitrile (3.45 ml, 0.052 mol) in 15 ml DMF was added dropwise over a period of 10 min. The mixture was stirred for 10 h and then allowed to partition between 50 ml CH_2Cl_2 and 50 ml H_2O. The org. layer was dried over $MgSO_4$ and filtered through a bed of alumina (20 g). Evaporation of the CH_2Cl_2 left a yellow oil which was crystallized from warm MeOH giving 4.8 g (75%) of **29**, m.p. 129°. – ^{1}H-NMR. ($CDCl_3$): 1.9 (br., 2 H, CH_2–CH_2–CH_2); 2.45 (*s*, 6 H, 2 CH_3); 2.78 (*m*, 4 H, 2 CH_2CN); 3.35 (*m*, 4 H, 2 CH_2NTs); 7.45, 7.85 (*m*, 8 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.3, 135.0, 130.2, 127.4 (arom. C); 118.0 (CN); 47.9, 45.4 (CH_2–N); 28.8 (CH_2–CH_2–CH_2); 21.5 (CH_3); 19.1 (CH_2CN).

$C_{23}H_{28}N_4O_4S_2$ (488.6) Calc. C 56.53 H 5.77 N 11.46% Found C 56.44 H 5.74 N 11.43%

*4,8-Di(*p*-toluenesulfonyl)-4,8-diazaundecane-1,11-diamine* (**30**). The dinitrile **29** (10 g, 0.02 mol) was refluxed overnight in a 1 M solution of B_2H_6 in 150 ml of THF, under N_2. After cooling to r.t., 50 ml of H_2O in THF (1:1) was added cautiously to the solution. The solvent was evaporated, 6 N HCl (100 ml) was added and the solution was refluxed for 4 h. After evaporation to dryness, the residue was allowed to partition between 2 N NaOH (200 ml) and CH_2Cl_2 (200 ml). The org. layer was separated and the aq. layer extracted again with 100 ml of CH_2Cl_2. The combined org. layers were dried over $MgSO_4$ and evaporated to leave **30** compound as a pale yellow oil. (This compound must be stored under N_2; it was converted into **31** without further purification). – ^{1}H-NMR. ($CDCl_3$): 1.75 (br., 6 H, 3 CH_2–CH_2–CH_2); 2.45 (*s*, 6 H, 2 CH_3); 2.75 (br., 4 H, CH_2–NTs); 3.15 (br., 12 H, 6 CH_2–NH_2); 7.35, 7.80 (*m*, 8 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 143.5, 136.1, 129.9, 127.2 (arom. C); 48.8 (CH_2–NTs); 38.8 (CH_2–NH_2); 29.1, 28.9 (CH_2–CH_2–CH_2); 21.5 (CH_3).

*N,N′,4,8-Tetra(*p*-toluenesulfonyl)-4,8-diazaundecane-1,11-diamine* (**31**). The crude diamine **30** (8.73 g, 0.0175 mol) obtained in the previous step was dissolved in 100 ml THF containing 28.5 ml Et_3N and TsCl (9 g, 0.047 mol) was added under stirring over a period of 10 min. The mixture was stirred overnight and then the THF was evaporated. The semi-solid residue was partitioned between CH_2Cl_2 (300 ml) and 2 N H_2SO_4 (200 ml). The org. layer was separated, washed with 100 ml of sat. NaCl-solution and dried over $MgSO_4$. Evaporation gave a solid which was recrystallized from CH_2Cl_2/Et_2O giving 10.2 g (72%) of **31** as a white powder, m.p. 130–131°. – ^{1}H-NMR. ($CDCl_3$): 1.80 (br., 6 H, 3 CH_2–CH_2–CH_2); 2.41 (*s*, 12 H, 4 CH_3); 3.10 (br., 12 H, 6 CH_2–NTs); 5.40 (br., 2 H, 2 NHTs); 7.3, 7.6, 7.8 (*m*, 16 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 143.7, 143.5, 137.2, 136.0, 130.0, 129.9, 127.3, 127.2 (arom. C); 47.4, 46.6, 40.4 (CH_2–NTs); 29.5, 28.8 (CH_2–CH_2–CH_2); 21.6 (CH_3).

$C_{43}H_{54}N_6O_8S_4$ (911.1) Calc. C 56.68 H 5.97 N 9.22% Found C 56.67 H 5.97 N 9.30%

*4,8,12,16-Tetra(*p*-toluenesulfonyl)-4,8,12,16-tetraazaundecanedinitrile* (**32**). Compound **31** (13.7 g, 0.017 mol), K_2Co_3 (16.46 g, 0.119 mol) and 150 ml DMF were stirred at r.t. while acrylonitrile (3.5 ml, 0.053 mol) in 15 ml DMF was added dropwise over a period of 10 min. The mixture was stirred for 30 h and then evaporated to dryness. The residue partitioned between 300 ml CH_2Cl_2 and 200 ml H_2O. The org. layer was separated, washed with 200 ml 2N HCl, then with 100 ml sat. NaCl-solution and dried over $MgSO_4$. Evaporation of CH_2Cl_2 left an orange oil. Compound **32** (9.0 g, 58%) was obtained as a glass after chromatography on alumina (300 g) eluted with CH_2Cl_2 containing 1% MeOH. – ^{1}H-NMR. ($CDCl_3$): 1.95 (br., 6 H, 3 CH_2–CH_2–CH_2); 2.41 (*s*, 12 H, 4 CH_3); 2.75 (*t*, 4 H, 2 CH_2–CN); 3.2 (br., 16 H, CH_2–NTs); 7.35, 7.75 (*m*, 16 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 144.2, 143.6, 135.9, 135.3, 130.1, 129.9, 127.3, 127.2 (arom. C), 117.9 (CN), 47.9, 47.1, 47.0, 45.2 (CH_2–NTs); 29.0, 28.8 (CH_2–CH_2–CH_2); 21.5 (CH_3); 19.0 (CH_2–CN).

$C_{43}H_{54}N_6O_8S_4$ (911.1) Calc. C 56.68 H 5.97 N 9.22% Found C 56.67 H 5.97 N 9.30%

*4,8,12,16-Tetra(*p*-toluenesulfonyl)-4,8,12,16-tetraazanonadecane-1,19-diamine* (**33**). The dinitrile **32** (6.86 g, 0.0075 mol) was refluxed for 16 h in a 1.1M solution of B_2H_6 in THF (100 ml), under N_2. After cooling the mixture in an ice bath, 50 ml of H_2O in THF (1:1) was added cautiously. The solvent was evaporated, 6N HCl (200 ml) was added and the solution was refluxed for 5 h. The solution was evaporated to dryness and the residue was allowed to partition between 2N NaOH (200 ml) and CH_2Cl_2 (200 ml). The org. layer was separated and the aq. layer extracted again with 200 ml of CH_2Cl_2. The combined org. layers were dried over $MgSO_4$ and evaporated to leave **33** as a pale yellow glass. (This compound must be stored under N_2; it was transformed into its tosyl derivative **34** without further purification). – ^{1}H-NMR. ($CDCl_3$): 1.35 (br., 4 H, 2 NH_2); 1.75 (br., 10 H, 5 CH_2–CH_2–CH_2); 2.40 (*s*, 12 H, 4 CH_3); 2.65 (br., 4 H, CH_2–NH_2); 3.20 (br., 16 H, 8 CH_2–NTs); 7.35, 7.75 (*m*, 16 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 143.5, 143.4, 136.1, 135.9, 129.9, 129.8, 127.2 (arom. C); 46.9, 46.7 (CH_2–NTs); 39.1 (CH_2–NH_2); 32.3, 28.7 (CH_2–CH_2–CH_2); 21.5 (CH_3).

*N,N′,4,8,12,16-Hexa(*p*-toluenesulfonyl)-4,8,12,16-tetraazanonadecane-1,19-diamine* (**34**). The crude diamine **33** (6.24 g, 0.0068 mol) was dissolved in 100 ml THF containing 6 ml Et_3N and TsCl (6 g, 0.047 mol) was added under stirring over a period of 10 min. The mixture was stirred for 40 h and then the THF was evaporated. The yellow residue was partitioned between CH_2Cl_2 (200 ml) and 2N HCl (200 ml). The org. layer was evaporated, washed with H_2O (200 ml), sat. NaCl-solution (200 ml) and dried over $MgSO_4$. Evaporation gave a glass which was purified by chromatography on alumina (300 g), eluting with CH_2Cl_2 containing 1% MeOH to give 7.7 g (92%) of **34** as a glass. – ^{1}H-NMR. ($CDCl_3$): 1.83 (br., 10 H, 5 CH_2–CH_2–CH_2); 2.40 (*s*, 18 H, 6 CH_3); 3.15 (br., 20 H, 10 CH_2–NTs); 5.65 (br., 2 H, 2 CH_2NTs*H*); 7.35, 7.70, 7.75, 7.85 (*m*, 24 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 143.6, 135.8, 129.9, 129.7, 127.2, 127.1 (arom. C); 47.4, 47.2, 46.7 (CH_2–NTs); 40.4 (CH_2–NHTs); 29.4, 29.0 (CH_2–CH_2–CH_2); 21.5 (CH_3).

$C_{57}H_{74}N_6O_{12}S_6$ (1227.5) Calc. C 55.76 H 6.07 N 6.84% Found C 55.15 H 6.15 N 7.08%

4,8,12,16-Tetraazanonadecane-1,19-diamine (**4**). The hexatosyl compound **34** (4 g, 0.0032 mol), phenol (3.2 g, 0.03 mol) and 200 ml of a 33% solution of HBr in AcOH were heated at 90° for 23 h under a well-ventilated hood. After cooling the purple precipitate was isolated by filtration and washed thoroughly with Et_2O. The crude hexahydrobromide was dissolved in 50 ml H_2O and passed over *Dowex 1×8* resin in the basic form. The aq. solution of the free base was acidified to pH 3 with conc. HCl and H_2O removed by evaporation. The residue was precipitated from hot aq. EtOH giving 1.56 g (92%) of **4**·6 HCl as white powder, m.p. > 250°. – ^{1}H-NMR. (D_2O): 2.25 (br., 10 H, 5 CH_2–CH_2–CH_2); 3.25 (*m*, 20 H, 10 CH_2N). – ^{13}C-NMR. (D_2O): 46.1 (CH_2–NH_2^+); 38.1 (CH_2–NH_3); 25.1, 23.9 (CH_2–CH_2–CH_2).

$C_{15}H_{44}Cl_6N_6$ (521.2) Calc. C 34.56 H 8.50 N 16.12% Found C 34.60 H 8.67 N 15.99%

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