54. Synthesis of Selectively Substituted Lipocyclopolyamines

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Dedicated to the memory of Professor *Claude Benezra* and Doctor *Rossana Fraginals-Rendon*

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A general synthetic strategy for the preparation of polyazamacrocycles containing long aliphatic chains is reported. These compounds are 22- or 24-membered hexaazamacrocycles incorporating two diethylenetriamine subunits ($H_2NCH_2CH_2NHCH_2CH_2NH_2$) linked together either by two $CH_2CH_2OCH_2CH_2$ (see **4–6**), two tetramethylene (see **7**), or two pentamethylene (see **8**) fragments. Whereas for compound **4**, one of the centrally located amine functionalities of the triamine subunit bears a hexadecyl chain, for compound **5**, two of such chains are centrally attached to both subunits. In macrocycles **6–8**, all six amino functionalities bear hexadecyl chains. Compounds **4–8** are potential candidates for the construction of selective chemical sensors such as specific electrodes for adenosine mono-, di-, and tri-phosphate. They may also be used for nucleoside polyphosphates extraction and/or transport.

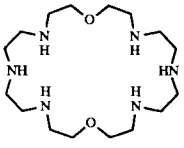
Introduction. – The emergence of anion coordination chemistry, the coordination of negatively charged species by either natural or synthetic receptor molecules [1–6], invites us to investigate chemical devices for analytical purposes. In order to be useful, analytical tools such as specific electrodes must possess the following characteristics: short response delay, measurable response in low-concentration domain, high specificity and accuracy [7]. For a given substrate, these requirements may be achieved using chemical sensors containing specific receptor molecules. Thus, this type of sensors is based on molecular recognition processes.

Among various anions present in biological systems, nucleoside polyphosphates play important roles in almost all living organisms. They participate in a variety of biological processes as chemical energy sources. It may be quite useful to have in hand chemical devices allowing measurements of their concentrations in real time. It was shown that protonated macrocyclic polyamines bind strongly and selectively nucleoside polyphosphates such as adenosine mono-, di-, and tri-phosphate (AMP, ADP, and ATP, resp.) [4] [8–13].

Potentiometric liquid-membrane sensors incorporating a pentaazamacrocycle bearing one hexadecyl chain for nucleotides [14] and dicarboxylates [15] were reported. In view of these results, an improvement in specificity for nucleotides might be achieved by suitable design of the receptor part of the sensor, involving the structure, the number of potential binding sites, as well as the degree of protonation of the macrocyclic polyamine used, so as to optimize these features for nucleoside-polyphosphate recognition. Using appropriate receptor molecules displaying higher recognition should lead to more efficient and more selective sensors.

Design of Receptors. – Among the various polyamines investigated for their ability to bind nucleoside polyphosphates, the hexaazamacrocycle **1** was found to bind most strongly in aqueous solution AMP, ADP, and ATP with a rather high selectivity, induced mainly by electrostatic interactions [4] [8] [9]. Whereas the association constants in aqueous solution ranged from 10^4 to 10^{11} depending on the protonation degree of both the receptor and the substrates, a selectivity factor of *ca.* 100 between ADP and ATP in favour of the latter was obtained for the tetraprotonated form of **1**.

Macrocycle **1**, covalently linked to a polymer such as polystyrene through a ten-atom-long spacer, was shown to maintain its ability to bind nucleoside polyphosphates with the



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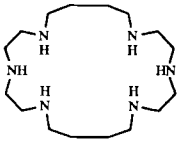

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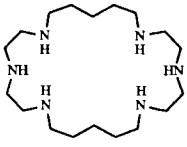

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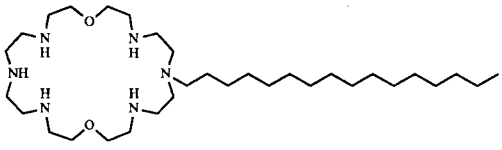

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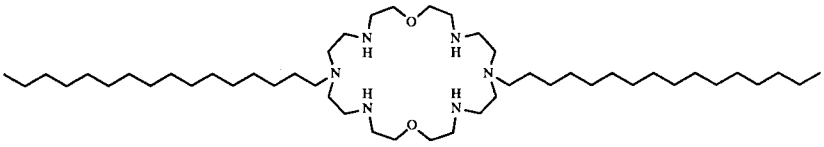

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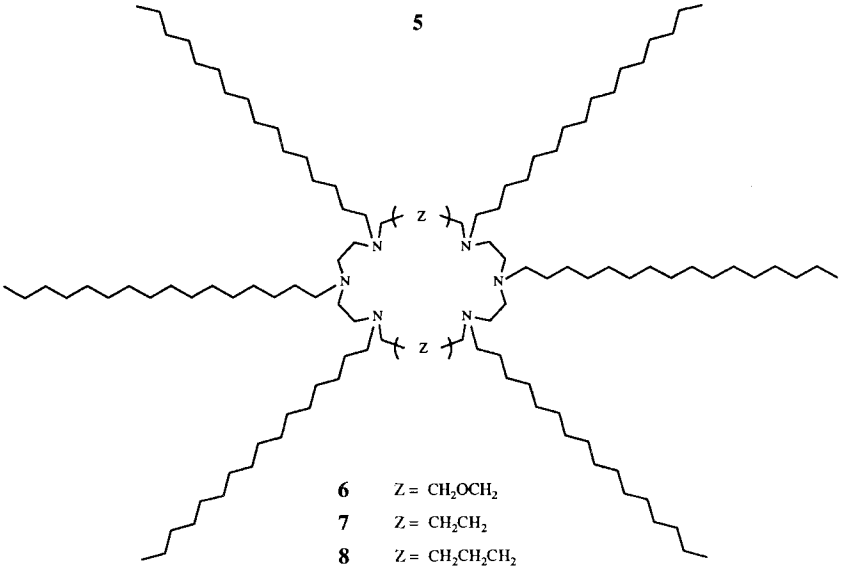


6 Z = CH_2OCH_2

7 Z = CH_2CH_2

8 Z = $CH_2CH_2CH_2$

same selectivity between ADP and ATP as the parent compound **1** [16]. It was previously reported that an analogue of **1** bearing an acridine moiety as side chain was also able to bind strongly ATP and ADP with appreciable selectivity between them [11]. Furthermore, both **1** [8] [9] and its acridine-substituted analogue [10] [11] were shown to form 1:1 complexes with ATP and ADP.

In **1**, because of the distances separating the amine functionalities in the two diethylenetriamine subunits, a gap of 3.5 pK_a units between pK_{a4} and pK_{a5} was experimentally measured [17]. Consequently, the tetraprotonated form of **1**($\mathbf{1} \cdot 4\ H^+$), was found to be the predominant species in a large pH interval, in particular near physiological pH [4] [17].

Since the hexaazamacrocycles **1–3** containing diethylenetriamine subunits were shown to fulfil the above mentioned characteristics, these compounds were chosen as potential candidates for the construction of specific electrodes for ATP. To be immobilized on the surface of a membrane, the receptor molecules **1–3** were functionalized with lipophilic anchoring groups such as hexadecyl chains, yielding lipomacrocycles **4–8**. Compounds **4–8** are close analogues of **1**; thus, one may reasonably expect the same type of behaviour in terms of binding, stoichiometry, and protonation degree as for **1**. *E.g.* at physiological pH, binding one ATP^{4-} molecule to the tetraprotonated form of **4–8** should release four Cl^- ions, thus leading to overall neutral complexes, whereas complexation of ADP^{3-} and AMP^{2-} by these receptors under the same conditions should yield complexes bearing overall one and two positive charges, respectively. Hence, one would anticipate a good selectivity between ATP, ADP, and AMP.

The chemical part of the sensor that we are currently building is composed of a receptor molecule (**4–8**) bearing 1, 2, or 6 hexadecyl chains immobilized on the surface of a PTFE membrane using a dipping technique [14]. We now report the synthesis of these five new hexaazamacrocycles **4–8**. Their physical properties will be reported elsewhere.

Syntheses. – Functionalization of hexaazamacrocyclic compounds such as **1** may be performed either by introduction of the alkyl chains after cyclization or at an early stage of the synthesis using the precursors. Whereas modification at all N-atoms in presynthetized macrocyclic polyamines such as **1–3** is rather straightforward, the synthesis of selectively functionalized macrocyclic polyamines such as **4** and **5** is rather tedious. Nevertheless, the preparation of selectively protected macrocyclic compounds possessing either one (*e.g.* **A**) or two (*e.g.* **B**) centrally located unprotected amino groups was reported [18], but this route is rather long and requires a series of delicate protection-deprotection steps. The introduction of the alkyl chains into the precursors prior to cyclization seems to be a more flexible and general strategy.

In a first attempt to prepare **4**, the cyclization following the *Richman* and *Atkins* method [19] was applied to the hexadecyl-substituted bis(toluenesulfonamide) **9** and the dimesylate **10**. Unfortunately, although the desired macrocyclic compound (see below, **14**) was formed, its yield was less than 5%. Since this poor yield could be due to the presence of the tertiary-amine moiety in **9**, its hexadecyl chain was replaced by a palmitoyl chain (see **11**), which has the advantage of functionalizing and protecting the centrally located amine moiety simultaneously and of avoiding later tedious protection-deprotection steps. This strategy was successfully applied in the following syntheses.

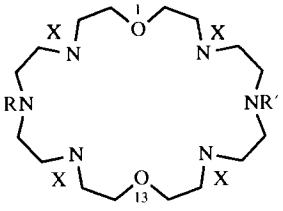
The common precursor for the synthesis of **4** and **5** from an α,ω-bis(toluenesulfonamide) and an α,ω-dimesylate was the palmitoyl-substituted bis(toluenesulfonamide) **11**,

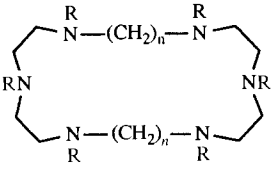
$RN(CH_2CH_2NHX)_2$

9 R = $CH_3(CH_2)_{15}$, X = Ts
11 R = $CH_3(CH_2)_{14}CO$, X = Ts
12 R = H, X = Ts

$R'N(CH_2CH_2N(X)CH_2CH_2OCH_2CH_2OR'')_2$

10 R′ = Ts, R″ = Ms, X = Ts
15 R′ = $CH_3(CH_2)_{14}CO$, R″ = Ms, X = Ts
16 R′ = $CH_3(CH_2)_{14}CO$, R″ = H, X = Ts





A R = H, R′ = X = Ts
B R = R′ = H, X = Ts
13 R = $CH_3(CH_2)_{14}CO$, R′ = X = Ts
14 R = $CH_3(CH_2)_{15}$, R′ = X = Ts
4 R = $CH_3(CH_2)_{15}$, R′ = X = H

17 R = R′ = $CH_3(CH_2)_{14}CO$, X = Ts
18 R = R′ = $CH_3(CH_2)_{15}$, X = Ts
5 R = R′ = $CH_3(CH_2)_{15}$, X = H

19 R = R′ = X = $CH_3(CH_2)_{14}CO$
6 R = R′ = X = $CH_3(CH_2)_{15}$

20 *n* = 4, R = $CH_3(CH_2)_{14}CO$
7 *n* = 4, R = $CH_3(CH_2)_{15}$

21 *n* = 5, R = $CH_3(CH_2)_{14}CO$
8 *n* = 5, R = $CH_3(CH_2)_{15}$

obtained from palmitoyl chloride and the known **12** [18] [20]. Reaction of **11** (1 equiv.) with dimesylate **10** [21] (1 equiv.) in dimethylformamide (DMF) at 90° in the presence of Cs_2CO_3 gave **13** in 49% yield. This yield was not improved by running the reaction in the presence of K_2CO_3 or by preforming the sodium salt of **11** (treatment with NaOMe). Attempts to reduce all amide functions of **13** by treatment with $LiAlH_4$ in dry tetrahydrofuran (THF) gave a rather complicated mixture. Thus, **13** was first reduced by B_2H_6 in dry THF to the hexadecyl-substituted macrocycle **14** (73% yield) and subsequently deprotected by treatment with HBr/AcOH in the presence of phenol [22] leading to the desired **4** (90%). The latter was stored as its hydrochloride salt.

For the synthesis of **5**, the palmitoyl-substituted dimesylate **15** was needed. It was obtained from **11** and monochloroethylene glycol [21] in the presence of K_2CO_3 *via* diol **16** (see *Exper. Part*). Macrocyclization of **11** (1 equiv.) and dimesylate **15** (1 equiv.) in DMF at 90° in the presence of Cs_2CO_3 as described above gave **17** (14%). Again, the use of K_2CO_3 or of the sodium salt of **11** did not improve the conversion. Reduction and deprotection of **17** as described above for **13** yielded the macrocycle **5** *via* **18** in excellent yield.

Compounds **6–8** were prepared in good yields from the presynthesized macrocycles **1** [21] and **2** and **3** [20] [23] with palmitoyl chloride in dry THF in the presence of Et_3N (→ **19–21**), followed by diborane reduction. As **4** and **5**, compounds **6–8** were stored as their hydrochloride salts.

A potential application of the synthesized macrocycles **4–8** is the extraction of ADP and ATP from aqueous solution into organic phases. Such extractions were reported for

bicyclic diammonium salts [24–27] or cyclic guanidinium salt [28]. In their tetraprotonated forms, **4–8** should bind ATP strongly and selectively and thus allow its extraction. Research along these lines is currently pursued.

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Experimental Part

General. Compounds **1** [21], **2–3** [23], **10** [21] (corresponding diol) [16]), **12** [18] [20], **16** [23], and tosylaziridine [18] [20] were prepared following published procedures. CC = column chromatography. ^{1}H-NMR and ^{13}C-NMR Spectra: *Bruker-SY-200* spectrometer; chemical shifts δ in ppm with TMS in $CDCl_3$ or *t*-BuOH in D_2O as internal standards. Mass spectra (MS) were performed by the Service de Spectrométrie de Masse, Strasbourg. Microanalyses were performed by the Service de Microanalyse, Strasbourg.

N,N′-*[(Hexadecylnitrilo)bis(ethylene)]bis[4-toluenesulfonamide]* (**9**). Hexadecylamine (12.24 g, 50.7 mmol) and tosylaziridine [18] [20] (20 g, 101.4 mmol) were refluxed in $CHCl_3$ (200 ml) for 56 h. The mixture was allowed to cool to r.t. and then evaporated. From the almost colourless residue, **9** (24.4 g, 77%) was obtained after CC (SiO_2, CH_2Cl_2/1–2% MeOH). White solid. ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, Me); 1.26 (br. *s*, 14 CH_2); 2.16 (*t*, 1 CH_2N); 2.42 (br. *s*, 2 MeC_6H_4, 2 CH_2N, 2 N*H*Ts); 2.88 (*t*, 2 CH_2NTs); 7.31, 7.78 (2*d*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 21.6 (MeC_6H_4); 26.3, 27.5, 29.8, 32.0 (Me, CH_2); 40.6, 53.0, 53.4 (CH_2N); 127.3, 129.8, 136.8, 143.4 (arom.). Anal. calc. for $C_{34}H_{57}N_3O_4S_2$ (635.96): C 64.21, H 9.03, N 6.61; found: C 64.03, H 9.16, N 6.64.

The same reaction performed in MeCN instead of $CHCl_3$ afforded a gel insoluble in all common solvents.

N,N′-*[(Palmitoylnitrilo)bis(ethylene)]bis[4-toluenesulfonamide]* (**11**). To the stirred suspension of **12** [18] [20] (21.11 g, 51.3 mmol) and Et_3N (8.6 ml) in toluene (200 ml) at r.t., palmitoyl chloride (16.92 g, 61.5 mmol) was added dropwise (1 h). Stirring at r.t. was continued for 18 h. The final reddish soln. was washed successively with 10% HCl soln. (100 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated. The residue was purified by CC (SiO_2, CH_2Cl_2/0–2% MeOH): pure **11** (24.6 g, 75%). Recrystallization from CH_2Cl_2/hexane. ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, Me); 1.25 (br. *s*, 13 CH_2); 2.32 (*t*, CH_2CO); 2.41, 2.43 (2*s*, 2 MeC_6H_4); 3.08 (*m*, 2 CH_2NTs); 3.40, 3.48 (2*t*, 2 CH_2N); 5.52 (br. *m*, 2 N*H*Ts); 7.30, 7.33, 7.68, 7.72, 7.77 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 13.9 (Me); 21.2, 22.44 (MeC_6H_4); 25.1, 29.1, 29.5, 31.6, 32.8, 40.9, 41.25, 45.8, 48.4 (CH_2); 126.7, 129.4, 129.5 (arom.); 131.3 (CO); 136.6, 142.9, 143.1 (arom.). Anal. calc. for $C_{34}H_{55}N_3O_5S_2$ (649.95): C 62.83, H 8.53, N 6.46; found: C 62.98, H 8.83, N 6.47.

7-Palmitoyl-4,10,16,19,22-pentakis(4-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (**13**). A mixture of **11** (10.46 g, 16.1 mmol), Cs_2CO_3 (26.23 g, 80.5 mmol) and DMF (300 ml) was stirred and heated to 90°. A soln. of **10** [21] (14.45 g, 16.1 mmol) in DMF (100 ml) was added dropwise (2 h) and the mixture stirred at 90° for 30 h and then allowed to cool to r.t. The solid was removed by filtration and the residue washed with DMF (100 ml). The soln. was evaporated and the residue dried, before it was partitioned between CH_2Cl_2 (250 ml) and H_2O (100 ml). The org. layer was dried ($MgSO_4$) and evaporated. Pure **13** (10.8 g, 49%) was obtained after CC (SiO_2, CH_2Cl_2/0–1% MeOH). ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, Me); 1.25 (br. *s*, 13, CH_2); 2.33, 2.39, 2.45 (*m*, CH_2CO, 5MeC_6H_4); 3.33, 3.60 (2 br. *m*, 4 CH_2O, 12 CH_2N); 7.16–7.80 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 14.2 (Me); 21.6, 22.7 (MeC_6H_4); 25.4, 29.5, 29.8, 32.0, 32.9, 46.5, 46.9, 48.4, 48.9, 49.5, 49.8 (CH_2); 69.3, 69.8, 69.9, 70.4 (CH_2O, CH_2N); 127.1, 127.3, 127.5, 129.9, 135.8, 136.1, 143.4, 143.6 (arom.); 174.0 (CO). MS: 1354 (M^+), 1199 ([M – Ts]$^+$), 1044 ([M – 2 Ts]$^+$), 889 ([M – 3 Ts]$^+$). Anal. calc. for $C_{67}H_{98}N_6O_{13}S_5$ (1355.85): C 59.35, H 7.28, N 6.19; found: C 59.07, H 7.60, N 6.09.

7-Hexadecyl-4,10,16,19,22-pentakis(4-tolylsulfonyl)-1,13-dioxa-4, 7, 10, 16, 19, 22-hexaazacyclotetracosane (**14**). Under Ar, **13** (1 g, 0.67 mmol), dry THF (50 ml), and 1M BH_3·THF (50 ml) were refluxed for 18 h. The mixture was cooled in an ice-bath, and H_2O (50 ml) was cautiously added to destroy excess B_2H_6. After evaporation, the residue was refluxed in 6N HCl (50 ml) and then evaporated. The residue was partitioned between CH_2Cl_2 (150 ml) and 2.5N NaOH (80 ml), the aq. phase further extracted with CH_2Cl_2 (100 ml), and the combined org. phase dried ($MgSO_4$) and evaporated: **14** (0.71 g, 73%) after CC (short column, SiO_2, CH_2Cl_2/0–0.5% MeOH).

Foam. ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, Me); 1.25 (br. *s*, 14 CH_2); 2.38, 2.40 (2*s*, 5 *Me*C_6H_4); 2.60 (*m*, CH_2N); 3.16, 3.25, 3.34 (*m*, 12 CH_2N); 3.54, 3.56 (*m*, 4 CH_2O); 7.27, 7.65 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 14.2 (Me); 21.6 (*Me*C_6H_4); 22.8, 27.2, 27.5, 29.8, 32.0 (CH_2); 47.8, 48.5, 49.4, 49.6, 49.8, 53.5, 54.5 (CH_2N); 70.0 (CH_2O); 127.30, 127.35, 127.4, 129.7, 129.9, 135.5, 135.6, 136.8, 143.3, 143.6 (arom.). Anal. calc. for $C_{67}H_{100}N_6O_{12}S_5$ (1341.86): C 59.97, H 7.51, N 6.26; found: C 60.17, H 7.61, N 6.20.

7-Hexadecyl-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (**4**). For 16 h, **14** (2.3 g, 1.7 mmol) and phenol (3.0 g, 32 mmol) were heated at 90° in HBr/AcOH (33%; 70 ml). The strongly colored mixture was allowed to cool to r.t., before Et_2O (200 ml) was added to precipitate the hydrobromide salt of **4**. The viscous solid was filtered, washed with Et_2O (100 ml), dried under vaccum, and partitioned between CH_2Cl_2 (200 ml) and 2.5N NaOH (100 ml). The aq. phase was further extracted with CH_2Cl_2 (100 ml) and the combined org. phase dried ($MgSO_4$) and evaporated: pure **4** (0.88 g, 90%), which was stored as hydrochloride salt. ^{1}H-NMR ($CDCl_3$): 0.81 (*t*, Me); 1.19 (br. *s*, 13 CH_2); 1.35 (*m*, CH_2); 2.15 (br., 5 NH); 2.36, 2.52, 2.61, 2.68, 2.74 (*m*, 13 CH_2N); 3.52 (br. *t*, 4 CH_2O). ^{13}C-NMR ($CDCl_3$): 14.7 (Me); 22.7, 27.2, 27.5, 29.4, 29.7, 31.9. ($CH_2CH_2CH_2$); 47.6, 48.1, 49.0, 49.3, 53.7, 55.1 (CH_2N); 70.0, 70.2 (CH_2O). Anal. calc. for $C_{32}H_{76}Cl_6N_6O_2 \cdot 3H_2O$ (843.76): C 45.55, H 9.80, N 9.96; found: C 45.25, H 9.52, N 9.25.

*2,2'-{(Palmitoylnitrilo)bis[ethylene(*N*-tosylnitrilo)ethyleneoxy]}bis[ethanol]* (**16**). For 92 h **11** (9 g, 13.8 mmol), K_2CO_3 (9.5 g, 69.2 mmol), and 1-chloroethylene glycol (50 g) were stirred and heated to 100°. After the mixture was allowed to cool to r.t., it was filtered and the solid washed with CH_2Cl_2 (200 ml). The combined filtrate and CH_2Cl_2 soln. were evaporated. The excess of 1-chloroethylene glycol was removed by distillation at 60°/reduced pressure, and the residual oil was further purified by CC (SiO_2, CH_2Cl_2/0–1% (MeOH): **16** (8.26 g, 65%). Colourless liquid. ^{1}H-NMR ($CDCl_3$): 0.86 (*t*, Me); 1.23 (br. *s*, 12 CH_2); 1.59 (br. *m*, CH_2CH_2CO); 2.38 (*t*, CH_2CO); 2.40, 2.42 (2*s*, 2 *Me*C_6H_4); 2.96 (br. *s*, 2 OH); 3.16–3.81 (*m*, 8 CH_2O, 4CH_2N); 7.28, 7.32, 7.64, 7.69 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 14.2 (Me); 21.5 (*Me*C_6H_4); 22.7, 25.4, 29.4, 29.6, 29.7, 31.9, 32.9 (CH_2); 46.9, 47.2, 48.3, 48.8, 49.7, 50.1, 61.5, 61.6, 70.3, 70.4, 72.7, 73 (CH_2O, CH_2N); 127.1, 129.9, 135.8, 143.7 (arom.); 174.5 (CO). Anal. calc. for $C_{42}H_{71}N_3O_9S_2 \cdot$MeOH (858.21): C 60.18, H 8.81, N 4.90; found: C 60.24, H 8.75, N 4.95.

*2,2'-{(Palmitoylnitrilo)bis[ethylene(*N*-tosylnitrilo)ethyleneoxy]}bis[ethyl] Bis(methanesulfonate)* (**15**). To a stirred soln. of **16** (6.67 g, 8.07 mmol) and Et_3N (4.5 ml, 32.3 mmol) in dry CH_2Cl_2 (150 ml) in an ice-bath, a soln. of MsCl (2.5 ml, 32.3 mmol) in dry CH_2Cl_2 (50 ml) was added within 1 h. The mixture was stirred at r.t. for another 2 h, before it was rapidly washed with cold 10% HCl soln. (50 ml). Washing with ice-cold H_2O (50 ml) produced an emulsion which was broken by addition of sat. NaCl soln. (50 ml). The org. layer was further extracted with sat. NaCl soln. (2 × 100 ml), dried ($MgSO_4$), and evaporated: **15** (100%) as an orange oil which was dried under vacuum overnight. The compound was sufficiently pure to be used in the next step without further purification.

7,19-Dipalmitoyl-4,10,16,22-tetrakis(4-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (**17**). To a stirred mixture of **11** (5.84 g, 9 mmol), Cs_2CO_3 (14.66 g, 45 mmol), and DMF (300 ml) at 90°, a soln. of **15** (8.2 g, 9 mmol) in DMF (100 ml) was added dropwise (2 h). The mixture was further stirred at 90° for 30 h, before it was allowed to cool to r.t. The solid was removed by filtration and washed with DMF (2 × 50 ml). The soln. was evaporated and the residue dried under vacuum, before it was partitioned between CH_2Cl_2 (250 ml) and H_2O (200 ml). The org. layer was dried ($MgSO_4$) and evaporated. Pure **17** (1.9 g, 14%) was obtained after CC (SiO_2, CH_2Cl_2/0–1% MeOH). ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, 2 Me); 1.25 (br. *s*, 24 CH_2); 1.65 (*m*, 2 CH_2CH_2CO); 2.36 (*t*, 2 CH_2CO); 2.41, 2.43 (2*s*, 4 *Me*C_6H_4); 3.12, 3.35, 3.48, 3.69, 3.77, 3.96 (br. *m*, 4 CH_2O, 12 CH_2N); 7.27–7.35, 7.62–7.70 (2*m*, 16 arom. H). ^{13}C-NMR ($CDCl_3$): 14.1 (Me); 21.5, 22.6 (*Me*C_6H_4); 25.5, 29.3, 29.7, 31.9, 33.0, 42.1, 48.7, 48.9, 50.8, 51.1, 51.8 (CH_2); 71.3, 72.6 (CH_2O). Anal. calc. for $C_{76}H_{122}N_6O_{12}S_4$ (1438.11): C 63.42, H 8.48, N 5.84; found: C 63.40, H 8.70, N 5.86.

7,19-Bis(hexadecyl)-4,10,16,22-tetrakis(4-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (**18**). As described for **14**, with **17** (1.8 g, 1.25 mmol), THF (100 ml), 1M $BH_3 \cdot$THF (50 ml; 24 h reflux). Workup (H_2O (25 ml); 2 h drying under vacuum prior to 6 h reflux in 6N HCl (100 ml); CH_2Cl_2 (200 ml)/2.5N NaOH (200 ml), then CH_2Cl_2 (100 ml)) and CC (Al_2O_3, CH_2Cl_2) gave pure **18** (1.6 g, 90%). ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, 2 Me); 1.26 (br. *s*, 28 CH_2); 2.42 (br. *s*, 2 CH_2N, 4 *Me*C_6H_4); 2.85, 3.15, 3.29 (br. *m*, 12 CH_2N); 3.80 (br. *m*, 4 CH_2O); 7.28–7.88 (*m*, 16 arom. H). ^{13}C-NMR ($CDCl_3$): 14.0 (Me); 21.5, 22.7, 29.3, 29.7, 31.9, 47.6, 49.9, 51.8, 55.1 (CH_2, CH_2N); 71.7 (CH_2O); 127.2, 129.7, 135.5, 143.4 (arom.). MS: 1411 ([M + H]$^+$), 1255 ([M + H − Ts]$^+$), 1099 ([M + H − 2 Ts]$^+$), 946 ([M + H − 3 Ts]$^+$). Anal. calc. for $C_{76}H_{126}N_6O_{10}S_4$ (1412.11): C 64.68, H 8.93, N 5.95; found: C 64.94, H 9.02, N 5.76.

7,19-Bis(hexadecyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (**5**). As described for **4** with **18** (1 g, 0.7 mmol), HBr/AcOH (33%; 30 ml), and phenol (2 g, 21.3 mmol; 12 h). Workup (Et_2O (250 ml), washing with

Et_2O (200 ml), addition of 2.5N NaOH (50 ml), extraction with CH_2Cl_2 (4 × 30 ml)) gave pure **5** (0.4 g, 73%). ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, 2 Me); 1.25 (br. *s*, 28 CH_2); 1.42 (br., 4 NH); 2.50, 2.73, 2.89 (*m*, 14 CH_2N); 3.75 (*m*, 4 CH_2O). ^{13}C-NMR ($CDCl_3$): 14.1 (Me); 22.8, 27.3, 27.4, 29.3, 29.6, 31.9 (CH_2); 47.6, 52.2, 56.0 (CH_2N); 67.4 (CH_2O). MS: 798.2 ([*M* + 2 H]$^+$). Anal. calc. for $C_{48}H_{102}N_6O_2 \cdot 2\,H_2O$ (831.41): C 69.34, H 12.85, N 10.11; found: C 69.57, H 12.85, N 10.05.

4,7,10,16,19,22-Hexapalmitoyl-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (**19**). Compound **1** · 6 HCl (0.556 g, 0.98 mmol) was passed over a *Dowex* anion-exchange column (*1X8-100*, basic form) and the free hexaamine thus obtained dried: 0.301 g of pure **1**. To a stirred mixture of **1** (0.301 g, 0.87 mmol), Et_3N (0.62 g, 6.13 mmol), and dry THF (25 ml) at r.t., a soln. of palmitoyl chloride (1.58 g, 5.75 mmol) in dry THF (10 ml) was added dropwise within 45 min. The mixture was further stirred at r.t. overnight. The solid was removed by filtration and washed with THF. The combined filtrate and washings were evaporated, the residue dissolved in CH_2Cl_2 (100 ml), and the soln. washed with H_2O (2 × 100 ml) and 10% HCl soln. (100 ml), dried ($MgSO_4$), and evaporated: 1.68 g of a slightly yellow solid. Pure **19** (1.315 g, 85%) was obtained by crystallization from CH_2Cl_2/hexane. ^{1}H-NMR ($CDCl_3$): 0.88 (br. *m*, 6 Me); 1.25 (br. *m*, 144 H, CH_2CH_2); 1.70 (br. *m*, 6 CH_2CO, 6 CH_2CH_2CO); 2.26 (br. *m*, 4 NCH_2CH_2O); 3.46 (br. *m*, 8 CH_2N, 4 CH_2O). ^{13}C-NMR ($CDCl_3$): 14.1 (Me); 22.7 (MeCH_2); 29.4–29.7 (CH_2CH_2); 32.4 (CH_2CO); 45.1 (CH_2N); 69.5 (CH_2O); 173.6 (CO). Anal. calc. for $C_{112}H_{218}N_6O_8$ (1777.02): C 75.70, H 12.37, N 4.73; found: C 75.94, H 12.09, N 4.52.

1,4,7,12,15,18-Hexapalmitoyl-1,4,7,12,15,18-hexaazacyclodocosane (**20**). Pure **20** (0.76 g, 77%) was obtained from **2** · 6 HCl (0.3 g, 0.56 mmol) following the same procedure as for **19**. ^{1}H-NMR ($CDCl_3$): 0.83 (br. *m*, 6 Me); 1.25–1.56 (2 br. *m*, 176 H, CH_2CH_2); 2.27 (br. *m*, 8 H, $NCH_2CH_2CH_2$); 3.42 (br. *m*, 16 H, NCH_2CH_2N). ^{13}C-NMR ($CDCl_3$): 13.9 (Me); 22.5 (MeCH_2); 24.6–29.8 (CH_2CH_2); 31.8 (CH_2CO); 45.7 (CH_2N); 173.6 (CO). Anal. calc. for $C_{112}H_{218}N_6O_6 \cdot 7\,CH_2Cl_2$ (2339.55): C 61.09, H 10.00; found: C 60.73, H 10.24.

1,4,7,13,16,19-Hexapalmitoyl-1,4,7,13,16,19-hexaazacyclotetracosane (**21**). Pure **21** (0.638 g, 87%) was obtained from **3** · 6 HCl (0.251 g, 0.45 mmol) following the same procedure as for **19**. ^{1}H-NMR ($CDCl_3$): 0.87 (br. *m*, 6 Me); 1.21–1.6 (2 br. *m*, 180 H, CH_2CH_2); 2.26 (br. *m*, 8 H, $NCH_2CH_2CH_2$); 3.4 (br. *m*, 16 H, NCH_2CH_2N). ^{13}C-NMR ($CDCl_3$): 14.7 (Me); 22.5 (MeCH_2); 26.7–29.8 (CH_2CH_2); 31.6 (CH_2CO); 45.7 (CH_2N); 173.8 (CO). Anal. calc. for $C_{114}H_{222}N_6O_6$ (1773.08): C 77.23, H 12.62, N 4.74; found: C 77.45, H 12.91, N 4.49.

4,7,10,16,19,22-Hexakis(hexadecyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (**6**). To a stirred soln. of **19** (1.21 g, 0.68 mmol) in dry THF (50 ml) under Ar, 1M BH_3 · THF (70 ml) was added dropwise (20 min) at r.t. The mixture was further stirred at 80° for 20 h, before it was allowed to cool down to r.t. Excess BH_3 was carefully destroyed by slow addition of H_2O (10 ml), and the mixture was evaporated. The residue was refluxed overnight in 10% HCl soln./MeOH 4:1. After evaporation, 2.5N NaOH was added until pH 13 was reached. The free hexaamine was obtained by extraction with CH_2Cl_2 (3 × 500 ml). Crystallization from CH_2Cl_2/MeOH gave pure **6** (0.87 g, 75%). ^{1}H-NMR ($CDCl_3$): 0.9 (br. *m*, 6 Me); 1.25 (br. *m*, 168 H, CH_2CH_2); 2.61 (br. *m*, 36 H, CH_2N); 3.5 (br. *m*, 8 H, CH_2O). ^{13}C-NMR ($CDCl_3$): 14.2 (Me); 22.8 (MeCH_2); 29.5–29.8 (CH_2CH_2); 32.0 (CH_2CH_2N); 53.0–55.9 (CH_2N); 69.9 (CH_2O). MS: 1693 ([*M* + H]$^+$), 1468 ([*M* + H − $C_{16}H_{33}$]$^+$). Anal. calc. for $C_{112}H_{230}N_6O_2$ (1693.12): C 79.45, H 13.69, N 4.96; found: C 79.35, H 13.90, N 4.80.

1,4,7,12,15,18-Hexakis(hexadecyl)-1,4,7,12,15,18-hexaazacyclodocosane (**7**). Pure **7** (0.497 g, 69%) was obtained from **20** (0.76 g, 0.44 mmol) following the same procedure as for **6**. ^{1}H-NMR ($CDCl_3$): 0.88 (br. *m*, 6 Me); 1.26 (br. *m*, 176 H, CH_2CH_2); 2.52 (br. *m*, 36 H, CH_2N). ^{13}C-NMR ($CDCl_3$): 14.2 (Me); 22.8 (MeCH_2); 25.2–32.0 (CH_2CH_2); 52.3–55.8 (CH_2N). MS: 1661 ([*M* + H]$^+$), 1436 ([*M* + H − $C_{16}H_{33}$]$^+$). Anal. calc. for $C_{112}H_{230}N_6$ (1661.12): C 80.98, H 13.96, N 5.06; found: C 80.97, H 13.99, N 4.77.

1,4,7,13,16,19-Hexakis(hexadecyl)-1,4,7,13,16,19-hexaazacyclotetracosane (**8**). Pure **8** (0.394 g, 73%) was obtained from **21** (0.569 g, 0.32 mmol) following the same procedure as for **6**. ^{1}H-NMR ($CDCl_3$): 0.88 (br. *m*, 18 H, Me); 1.26 (br. *m*, 180 H, CH_2CH_2); 2.51 (br. *m*, 36 H, CH_2N). ^{13}C-NMR ($CDCl_3$): 14.1 (Me); 22.8 (MeCH_2); 25.9–32.0 (CH_2CH_2); 52.3–55.8 (CH_2N). MS: 1689 ([*M* + H]$^+$), 1464 ([*M* + H − $C_{16}H_{33}$]$^+$). Anal. calc. for $C_{114}H_{234}N_6 \cdot CH_2Cl_2$ (1774.11): C 77.86, H 13.41, N 4.74; found: C 78.27, H 14.05, N 4.71.

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