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Synthesis of macrocyclic ligands incorporating sulfur and furan subunits

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Polyammonium macrocycles containing sulfur and furan units in the macrocyclic ring have been synthesized and studied for ATPase activity. The synthetic methodology involved using tosyl protection for the amines and the formation of macrocyclic lactams, followed by reduction using borane in THF. Deprotection of the tosylated forms of the macrocycle was accomplished using sodium in butanol for the furan macrocycles, and HBr in HOAc for the sulfur containing macrocycle. The macrocycles were found to be poor catalysts for ATP hydrolysis compared to other similar polyammonium macrocycles.

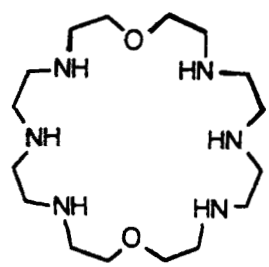
INTRODUCTION

The observation that polyammonium macrocycles form high affinity complexes with a variety of biologically relevant anions such as nucleotides led to the finding that they are also capable phosphoryl transfer catalysts.[1-4] In order to pinpoint the relationships between structure and catalysis with regard to ATPase activity, we have examined a number of macrocycles as ATPase mimics. A variety of different ring sizes, heteroatoms in the ring, and pendant groups have been explored.[2-4] The results of these studies indicate that the rates of dephosphorylation are quite dependent on ring size, number of amines in the ring, and steric hindrance. Of the polyammonium macrocycles examined to date, one of the most efficient catalysts has been 1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane, $[24]N_6O_2$, **1**.[3] At pH 7, the related 1,4,7,10,13,16-octaazacyclotetracosane, $[24]N_8$ is not as efficient a catalyst.[4] This finding led us to speculate as to role of the oxygen in the catalytic pathway. As a result, herein are reported the syntheses and kinetics of ATP hydrolysis for macrocycles closely related to **1**, but incorporating in one case two sulfur atoms in the place of the oxygens, **2**, and in the other the oxygens "tied down" or sterically constrained, **3-4**.

RESULTS AND DISCUSSION

Synthesis

The procedure developed for synthesis of the sulfur analog of **1**, $[24]N_6S_2$, **2**, utilizes the simple starting material **6**, which was reported by Atkins[5] (Scheme 1). The most logical route to the macrocycle **2** was to employ the same cyclization reactions used for $[24]N_6O_2$, namely condensation of the dimesylate **10** with 1,4,7-tris(*p*-tolylsulfonyl)-1,4,7-triazaheptane. It was anticipated that the precursor to **10**, the thiodiol **9**, could be



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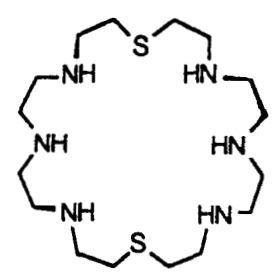

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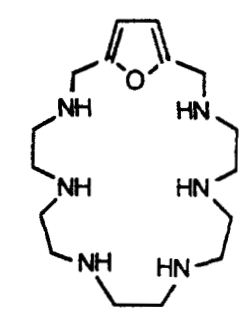

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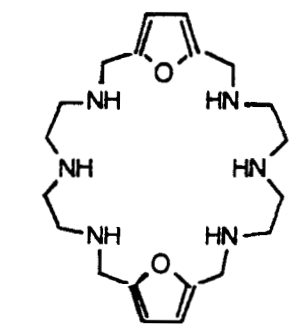

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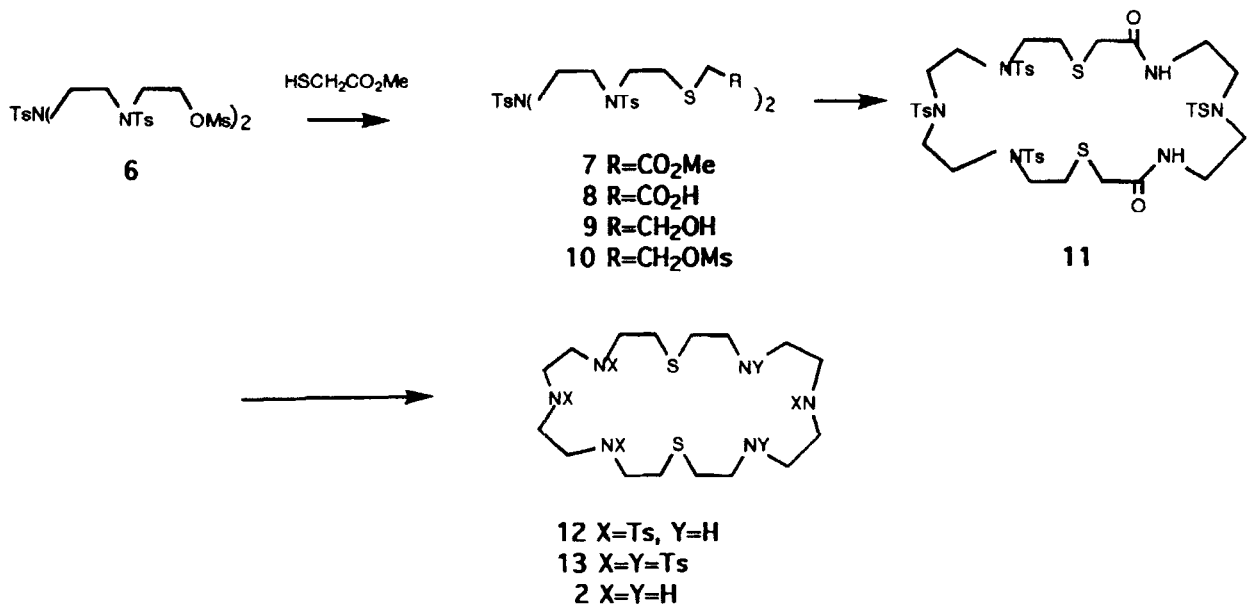
*To whom correspondence should be addressed.

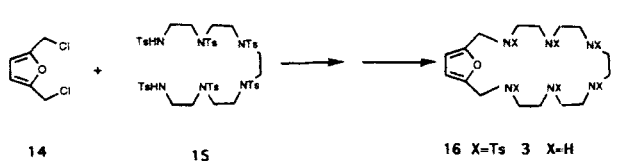


Scheme 1

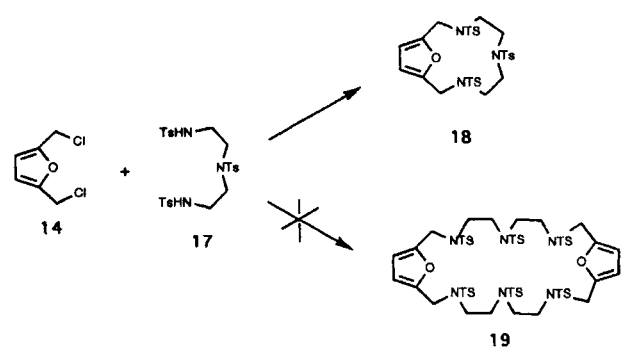
prepared by the reaction of **6** with 2-mercaptoethanol in 1the presence of NaH in THF. Unanticipated and complex reaction products were obtained, however, evidently because of the difunctional groups of 2-mercaptoethanol. Instead, reaction of **6** with methyl thioglycolate in the presence of base easily gave the diester **7** which afforded the dicarboxylic acid, **8**, after hydrolysis. The diol **9** could be readily isolated by reduction of the dicarboxylate **7** with borane in THF, and when treated with methanesulfonyl chloride in the presence of Et_3N gave the dimesylated **10**. The standard reaction of **10** with tritosylated 1,4,7-triazaheptane (**17**, Scheme 3) using established methods did not give the expected macrocycle **13**, however, since **10** was not stable at elevated temperatures and in the presence of silica gel. Hence, an alternative method was sought using our method for the formation of macrocyclic lactams.[6] This new route readily provided the lactam **11** from the diacid **8**; and **11** could be reduced to **12** using borane in THF. When detosylation was carried out in H_2SO_4, the sulfurs were partially oxidized, so HBr-HOAc was used instead to obtain the final product **2**.

The macrocycles with incorporated furan rings, **3** and **4**, were obtained commencing with 2,5-bis(chloromethyl)furan, **14**, which was prepared via chlorination of furan-2,5-dimethanol using CCl_4 in the presence of triphenylphosphine.[7] The monofuranated ring system **3** was easily obtained by treatment of **14** with the hexatosylated hexaamine, **15**, followed by detosylation (Scheme 2). The furan subunit in **18** was very sensitive to acid; however, detosylation using sodium in butanol was effective to obtain the desired monofuranated macrocycle **3**.

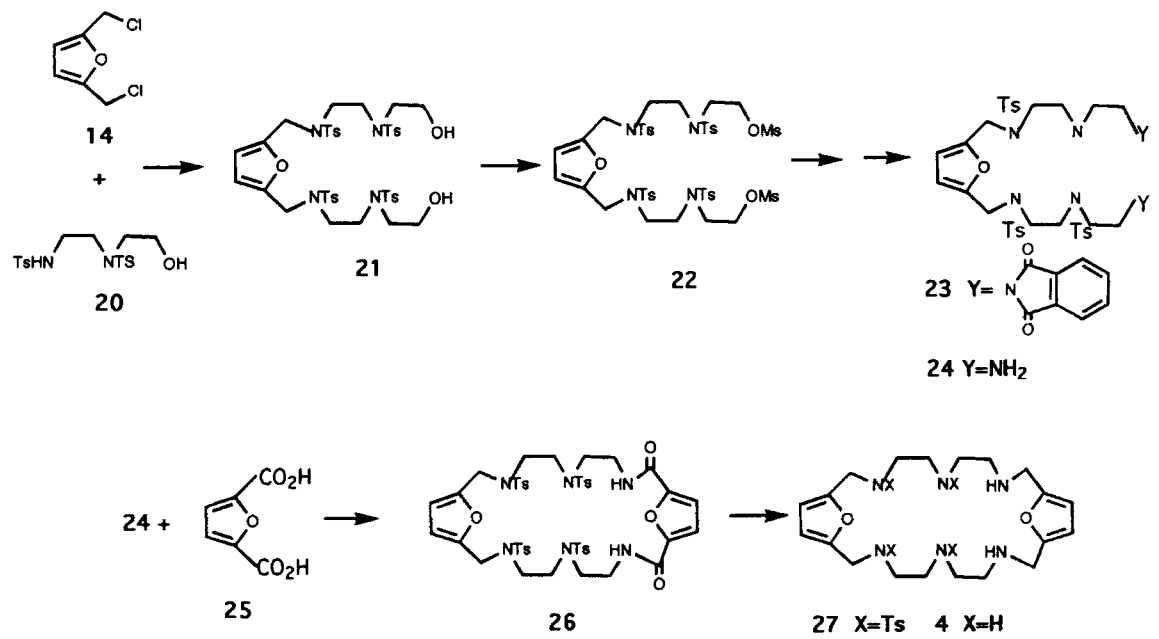
Obtaining the difuranated macrocycle by similar methods was not as straightforward since reaction of **14** with the tritosylated triamine **17** in the presence of Cs_2CO_3 in DMF gave the 1 + 1 adduct, **18**, exclusively, rather than the desired 2 + 2 adduct, **19** (Scheme 3). Chen and Martell have published an alternative method which uses a Schiff base condensation of the 2,5-furandicarboxaldehyde.[8] The procedure we developed for the synthesis of **4** with two furan subunits is shown in Scheme 4. The intermediate **24** was prepared via several steps from **14**; and 2,5-furandicarboxylic acid, **25**, was obtained by oxidation of the corresponding dialdehyde using Ag_2O.[9] The condensation between **24** and **25** gave the lactam,



Scheme 2



Scheme 3



Scheme 4

26, which was reduced with borane in THF. The deprotected macrocycle **4** was obtained from **27** using sodium in butanol.

Kinetics

Unfortunately, all of the macrocycles synthesized were poorer catalysts for ATP hydrolysis compared to macrocycle **1**. The sulfur analog was the closest to **1** with a first order rate constant, k_{obs}, at pH 7 and 70°C of 1.2×10^{-3} min^{-1} compared to 4.5×10^{-3} min^{-1} for **1**. Macrocycles **3** and **4** exhibited considerably slower rates of 7.2×10^{-4} and 9.5×10^{-4} min^{-1}, respectively. Recent crystallographic evidence indicates that the ring size and shape are extremely important.[10] Hence, since macrocycles containing sulfur are known to exhibit *exo* rather than *endo* orientations of the lone pairs on sulfur,[11] this conformational difference could be responsible for the lessened rate for **2**. The macrocycles **3** and **4** also potentially have the steric constraints because of the furan ring, which may hinder the approach of the substrate.

EXPERIMENTAL SECTION

4-*p*-Tolylsulfonyl-1,4,7-triazaheptane,[13] 1,4,7-tris(*p*-tolylsulfonyl)-1,4,7-triazaheptane (**17**),[12] 1,4,7,10,13,16-hexakis(*p*-tolylsulfonyl)-1,4,7,10,13,16-hexaazahexadecane (**15**),[12] 4,7-bis(*p*-tolylsulfonyl)-4,7-diazahexanol,[12] 2,5-furandicarboxylic acid (**25**),[9] and 2,5-bis(chloromethyl)furan (**14**)[7] were prepared as previously described. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300 at 300 and 75.43 MHz, respectively. Mass spectral data were obtained by Dr. Todd Williams of the Mass Spectrometry Laboratory at the University of Kansas. Elemental analysis for carbon, hydrogen, and nitrogen were performed at the Microanalytical Laboratory, University of Kansas by Dr. Tho Nguyen. Melting points were measured using capillary tubes without calibration.

Kinetic Analysis. A Waters Model 501 high performance liquid chromatograph together with Waters Model 481 absorbance detector and Model 740 data analyzer was used. Samples were injected on a silica column containing amine groups (Waters Bondpak-NH_2) which, in the reverse phase of operation, gives an ion-exchange-based separation. The mobile phase was a mixture of 15% acetonitrile and 85% 0.05 M ammonium phosphate at pH 4.5.

Aqueous solutions of ATP and the macrocycles (5.4×10^{-4} M in each) were examined at pH 7 and 70°C as described previously.[12]

Synthesis

Dimethyl-6,9,12-tris(*p*-tolylsulfonyl)-3,15-dithia-6,9,12-triazaheptadecanedioate (7). To a suspension of NaH (440 mg, 60% in oil, freshly washed with hexane) in DMF (50 mL) was added dropwise through a syringe methyl thioglycolate (1.06 g, 10 mmol) at room temperature. After the bubbles ceased, the dimesylate **6** (4.04 g, 5 mmol) was added, and the mixture was stirred at room temperature overnight. The DMF was removed in vacuo, and the residue was diluted with CH_2Cl_2 (50 mL), washed with water (40 mL), and dried ($MgSO_4$.) The mixture, after evaporation, was chromatographed (SiO_2,

CH_2Cl_2) to obtain the product as an oil: yield 3.75g (90%). ^{1}H NMR ($CDCl_3$) 7.75 (6 H, d, Ts), 7.36 (2 H, d, Ts), 7.33 (4 H, d, Ts), 3.72 (6 H, s, OCH_3), 3.36 (12 H, m, CH_2N), 3.29 (4 H, s, SCH_2CO), 2.86 (4 H, t, CH_2S), 2.45 (3 H, s, CH_3), 2.43 (6 H, s, CH_3) ppm. ^{13}C NMR ($CDCl_3$) 170.42, 143.62, 143.45, 135.17, 134.64, 129.62, 127.02, 126.95, 52.14, 49.47, 48.94, 48.38, 32.77, 31.00, 21.20 ppm. FABMS m/e (rel intens) 830 $(M + 1H)^+$ (12), 676(29), 429(19), 307(28), 215(54), 185(100). Anal. Calcd for $C_{35}H_{47}N_3O_{10}S_5$: C, 50.65; H, 5.71; N, 5.06. Found: C, 50.65; H, 5.59; N, 4.90.

6,9,12-Tris(*p*-tolylsulfonyl)-3,15-dithia-6,9,12-triazaheptadecanedioic acid (8). The ester **7** (2.1 g, 2.53 mmol) was dissolved in ethanol (50 mL) and 50% KOH (5 mL) and the mixture was refluxed overnight. The solution was concentrated in vacuo, and the residue was dissolved in water (50 mL) and acidified with dilute HCl (4 M) to pH 3. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and dried ($MgSO_4$). Evaporation in vacuo gave the product as a foam. Recrystallization from CH_2Cl_2-ether afforded **8** as a solid: yield 1.66 g (82%), mp 128-131°C. ^{1}H NMR ($CDCl_3$) 7.73 (4 H, d, Ts), 7.71 (2 H, d, Ts), 7.39 (2 H, d, Ts), 7.33 (4 H, d, Ts), 6.45 (2 H, br. s, COO*H*), 3.35 (12 H, m, CH_2N), 3.28 (4 H, s, SCH_2CO), 2.86 (4 H, t, CH_2S), 2.45 (3 H, s, CH_3), 2.44 (6 H, s, CH_3) ppm. ^{13}C NMR ($CDCl_3$) 174.88, 144.07, 143.86, 135.35, 134.58, 129.96, 127.27, 50.19, 49.53, 48.91, 33.30, 31.45, 21.51. Anal. Calcd for $C_{33}H_{43}N_3O_{10}S_5$: C, 49.42; H, 5.40; N, 5.24. Found: C, 49.61; H, 5.71; N, 5.40.

1,4,7,16-Tetrakis(*p*-tolylsulfonyl)-12,20-diox-10,22-dithia-1,4,7,13,16,19-hexaazacyclotetracosane (11). The diacid **8** (0.801 g, 1 mmol), 4-*p*-tolylsulfonyl-1,4,7-triazaheptane dihydrochloride (0.33 g, 1 mmol) and triethylamine (0.808 g, 8 mmol) in DMF (110 mL) were stirred at room temperature for 10 min, and diphenylphosphoryl azide (0.825 g, 3 mol) was added. The mixture was stirred for 22 h at room temperature. The DMF was then removed in vacuo and the residue was taken up into CH_2Cl_2 (50 mL). The solution was washed with $NaHCO_3$ solution twice, dried (Na_2SO_4), and chromatographed (SiO_2, CH_2Cl_2-MeOH, 100:5) to give the product as an oil: yield 0.26 g (25%). ^{1}H NMR ($CDCl_3$) 7.71 (6 H, m, Ts), 7.62 (2 H, d, Ts), 7.49 (2 H, t, NHCO), 7.31 (8 H, m, Ts), 3.49-3.20 (16 H, m, CH_2N, SCH_2CO), 2.84 (4 H, t, SCH_2), 2.42 (6 H, s, CH_3), 2.41 (3 H, s, CH_3) ppm. ^{13}C NMR ($CDCl_3$) 169.93, 143.86, 143.81, 135.20, 135.04, 134.93, 129.96, 129.73, 127.35, 127.22, 50.25, 49.97, 49.20, 39.38, 35.88, 31.84, 21.54, 21.49. FABMS (rel intens) 1023 $(M + 1H)^+$ (100), 869(62), 867(M - Ts)$^+$ (19), 722 (15), 713 (26), 429(51).

1,4,7,16-Tetrakis(*p*-tolylsulfonyl)-10,22-dithia-1,4,7,13,16,19-hexaazatetracosane (12). To a solution of the amide **11** (1.1 g, 1.08 mmol) in THF (10 mL) was added borane-THF (1M, 8 mL) under N_2 at room temperature. The mixture was then refluxed for 10 h and the excess borane was decomposed cautiously by adding 1N HCl (3mL) at 0 °C and refluxing for 1 h. The solution was concentrated in vacuo and neutrallized with 10% NaOH followed by extraction with CH_2Cl_2 (3 × 20 mL) and drying (K_2CO_3). The pure compound **12** was isolated as an oil by chromatography (SiO_2, CH_2Cl_2-MeOH, 100:9): yield 0.76 g (71%). ^{1}H NMR ($CDCl_3$) 7.74 (8 H, m, Ts), 7.38 (8 H, m, Ts), 3.40-3.32 (12 H, m, CH_2N), 3.19 (4 H, br. s, CH_2N), 2.89-2.72 (18 H, m, CH_2N, CH_2S and N*H*), 2.44 (9 H, s, CH_3), 2.42 (3 H, s, CH_3) ppm. ^{13}C NMR ($CDCl_3$) 143.95, 143.73, 143.66, 135.02, 134.63, 134.45, 129.86, 129.73, 127.29, 127.25, 50.72, 50.62, 49.76, 49.25, 48.03, 47.87, 31.20, 30.92, 21.46, 21.41 ppm. FABMS (rel intens) 995 $(M + 1H)^+$ (100), 841(37), 839(15). Anal. Calcd for $C_{44}H_{62}N_6O_8S_6$: C, 53.09; H, 6.28; N, 8.44. Found: C, 53.00; H, 6.18; N, 8.68.

10,22-Dithia-1,4,7,13,16,19-hexaazacyclotetracosane (2). A mixture of the tosylated compound **12** (680 mg, 0.67 mmol) and phenol (0.68 g, 7.1 mmol) in HBr-HOAc (12 mL, 32%) was stirred under N_2 at 80 °C for 3 d. After cooling to room temperature, ether (40 mL) was poured to precipitate the salt. The solid was collected by suction, rinsed several times with ether, dissolved in water (10 mL), and extracted with ether (3 × 20 mL). The aqueous layer was concentrated in vacuo to about 2 mL. The residue was passed through an anion exchange resin (OH-form, Dowex) to obtain the free amine **2**: yield 234 mg (92%). ^{1}H NMR ($CDCl_3$) 2.78-2.72 (32 H, m, CH_2N and CH_2S), 2.23 (6 H, s, N*H*) ppm. ^{13}C NMR ($CDCl_3$) 48.61, 48.52, 48.35, 32.59 ppm. EIMS (rel intens) 379 $(M + 1H)^+$ (23), 334 (27), 310(18), 276(91), 233(70). HRMS m/e for $C_{16}H_{38}N_6S_2$+ 1H requires: 379.2675. Found: 379.2668. The free amine was converted to the HBr salt by adding HBr solution, evaporating to dryness, and recrystallizing from MeOH-H_2O. Anal. Calcd for $C_{16}H_{38}N_6S_2 \cdot 6HBr \cdot MeOH \cdot 2H_2O$: C, 21.90; H, 5.62; N, 9.02. Found: C, 21.80; H, 5.60; N, 9.20.

6,9,12,15,18,21-Hexakis(*p*-tolylsulfonyl)-23-oxa-6,9,12,15,18,21-hexaazabicyclo[18.2.1^{1,4}]tricos-1,3-diene (16). A mixture of the hexakistosyl pentylenehexaamine **15** (4.624 g, 4 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) in DMF (150 mL) was stirred at 85 °C for 0.5 h. To this mixture was added 2,5-bis(chloromethyl)furan **14** (0.66 g, 4 mmol) in DMF (20 mL), and the mixture was stirred at 85 °C overnight. The DMF was removed in vacuo, and CH_2Cl_2 (100 mL) was added to the residue and washed with H_2O and brine in turn. The solution was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography (SiO_2, CH_2Cl_2:MeOH, 100:3) to give the product as a solid: yield 2.38 g (48%), mp 115-118 °C. ^{1}H NMR ($CDCl_3$) 7.72-7.61, 7.33-7.24 (12 H each, m, Ts), 6.02 (2 H, s, furan-*H*), 4.22 (4 H, s, furan-CH_2N), 3.29-3.24 (20 H, m, CH_2N), 2.41 (6 H, s, CH_3), 2.40 (12 H, s, CH_3). ^{13}C NMR 150.17, 143.68,

143.55, 143.41, 135.53, 134.97, 134.84, 129.76, 129.70, 129.62, 127.40, 127.25, 127.13, 109.93, 49.92, 49.81, 49.49, 48.12, 45.82, 21.40 ppm. FABMS (rel intens) 1249 $(M + 1H)^+$ (22), 1095 (100), 942 (35), 940 (35), 592 (72). Anal. Calcd for $C_{58}H_{68}N_6O_{13}S_6$: C, 55.75; H, 5.48; N, 6.73. Found: C, 55.57; H, 5.50; N, 6.38.

23-Oxa-6,9,12,15,18,21-hexaazabicyclo[18.2.1^{1,4}] tricos-1,3-diene (3). The tosylated compound **16** (2.9 g, 2.3 mmol) was dissolved in THF (100 mL) and butanol (350 mL), and sodium (19.5 g, 0.85 mol) was added in portions. After addition was complete, the solution was refluxed until the sodium disappeared (about 3 h), and concentrated in vacuo. Water (100 mL) was added and the solution was concentrated to dryness. The solid which formed was washed thoroughly with CH_2Cl_2 (200 mL), and the resulting solution was extracted with 4M HCl (2 × 20 mL) and concentrated to obtain a brownish solid. The solid was recrystallized from MeOH-ether: yield 0.63 g (46%). ^{1}H NMR (D_2O) 6.80 (2 H, s, furan-*H*), 4.52 (4 H, s, furan-CH_2N), 3.76-3.64 (20 H, m, CH_2N) ppm. ^{13}C NMR 148.83, 117.48, 46.74, 46.60, 46.27, 46.19, 46.13, 45.42 ppm. FABMS (rel intens) 325$(M + 1H)^+$ (51), 207(49), 185(92), 115(100). Anal. Calcd for $C_{16}H_{32}N_6O \cdot 6HCl \cdot MeOH \cdot H_2O$: C, 34.42; H, 7.48; N, 14.16. Found: C, 34.14; H, 7.68; N, 13.90.

6,9,12-Tris(*p*-tolylsulfonyl)-15-oxa-6,9,12-triazabicyclo[9,2,1^{1,4}]-pentadec-1,3-diene (18). A mixture of the tritosylated diethylenetriamine **17** (2.825 g, 5 mmol), 2,5-bis(chloromethyl)furan **14** (0.825 g, 5 mmol) and Cs_2CO_3 (8.15 g, 25 mmol) in DMF (100 mL) was stirred at 85°C for 20 h. The DMF was removed in vacuo. The residue was diluted with CH_2Cl_2 (100 mL) and washed with water (50 mL) and brine (50 mL), and dried (Na_2SO_4). After evaporation the mixture was purified by chromatography (SiO_2, CH_2Cl_2-MeOH, 100:2) to give the product as a yellowish foam: yield 2.9 g (88%). ^{1}H NMR ($CDCl_3$) 7.70, 7.31 (2 H, d, Ts), 7.66, 7.33 (4 H, d, Ts), 6.27 (2 H, s, furan-*H*), 4.24 (4 H, s, furan-CH_2N), 3.12, 3.02 (4 H each, m, CH_2N), 2.44 (9 H, s, CH_3) ppm. ^{13}C NMR 149.62, 143.86, 143.49, 136.55, 135.06, 129.92, 129.83, 127.16, 127.09, 111.75, 47.82, 45.95, 45.54, 21.50 ppm. FABMS 658, 504.

3,6,12,15-Tetrakis(*p*-tolylsulfonyl)-8,12-furano-9-oxa-3,6,12,15-tetraazaheptadecane-1,17-diol (21). A mixture of 2,5-bis(chloromethyl)furan (**14**) (0.224 g, 1.35 mmol), the ditosylated alcohol **20** (1.12 g, 2.7 mmol) and K_2CO_3 (0.93 g, 6.75 mmol) in DMF (30 mL) was stirred at 85 °C for 20 h. After removal of solvents, the resulting residue was chromatographed (SiO_2, CH_2Cl_2-MeOH, 100:4) to obtain the product as a solid: yield 0.345 g (28%), mp 160-162 °C. ^{1}H NMR ($CDCl_3$) 7.67, 7.64 (4 H each, d, Ts), 7.32 (8 H, d, Ts), 6.19 (2 H, s, furan-*H*), 4.27 (4 H, s, furan-CH_2N), 3.69 (4 H, t, CH_2OH), 3.45 (4 H, t, CH_2N), 3.19 (8 H, m, CH_2N), 2.89 (2 H, s, O*H*), 2.41 (12 H, s, CH_3) ppm. ^{13}C NMR 149.77, 143.52, 135.44, 135.21, 129.68, 129.61, 127.12, 127.02, 110.55, 60.94, 52.25, 48.84, 47.38, 45.18, 21.32. FABMS (positive) (rel intens) 939 $(M + Na)^+$ (12), 917 $(M + 1H)^+$ (8), 761 $(M - Ts)^+$ (12), 505 (30), 350 (100). Anal. Calcd for $C_{42}H_{52}N_4O_{11}S_4$: C, 55.00; H, 5.71; N, 6.11. Found: C, 55.08; H, 5.87; N, 6.28.

1,17-Dimethanesulfoxy-3,6,12,15-tetrakis(*p*-tolylsulfonyl)-8,12-furano-9-oxa-3,6,12,15-tetraaza heptadecane (22). The diol **21** (4.77 g, 5.21 mmol) was treated with methanesulfonyl chloride (1.19 g, 10.42 mmol) in CH_2Cl_2 (250 mL) and Et_3N (3.16 g, 31.3 mmol) at 0°C with stirring under N_2. The product was purified by chromatography (SiO_2, CH_2Cl_2-MeOH, 100:2) to give a solid: yield 5.58 g (99%), mp 146-147°C. ^{1}H NMR ($CDCl_3$) 7.68 (4H, d, Ts), 7.64 (4 H, d, Ts), 7.32 (8 H, d, Ts), 6.21 (2 H, s, furan-*H*), 4.34 (4 H, t, CH_2O), 4.26 (4 H, s, furan-CH_2N), 3.41 (4 H, t, CH_2N), 3.40, 3.16 (4 H each, m, CH_2N), 3.02 (6 H, s, CH_3SO$_3$), 2.42 (12 H, s, CH_3) ppm. ^{13}H NMR 149.70, 143.87, 143.58, 135.35, 134.82, 129.81, 129.67, 127.06, 110.66, 67.78, 48.90, 47.13, 4.26, 37.20, 21.30 ppm. Anal. Calcd for $C_{44}H_{56}N_4O_{15}S_6$: C, 49.24; H, 5.26; N, 5.22. Found: C, 49.18; H, 5.44; N, 5.35.

1,17-Diphthalimido-3,6,12,15-tetrakis(*p*-tolylsulfonyl)-8,12-furano-9-oxa-3,6,12,15-tetraazaheptadecane (23). The dimesylate **22** (5.6 g, 5.22 mmol) was treated with potassium phthalimide (3.87 g, 20.9 mmol) in DMF (300mL) at 85°C with stirring overnight. The mixture was then poured into ice-water, and the solid was collected by filtration. Chromatography (SiO_2, CH_2Cl_2-MeOH, 100:2) gave the product: yield 5.52 g (90%), mp 102-104°C. ^{1}H NMR ($CDCl_3$) 7.80-7.68 (12 H, m, Phthaloyl and Ts), 7.56, 7.35, 7.15 (4 H each, d, Ts), 4.36 (4 H, s, furan-CH_2N), 3.80 (4 H, t, CH_2N), 3.50-3.30 (12 H, m, CH_2N), 2.43, 2.30 (6 H each, s, CH_3) ppm. ^{13}C NMR 167.78, 149.75, 143.35, 143.21, 135.56, 135.45, 133.67, 131.69, 129.54, 129.44, 127.16, 126.81, 122.93, 110.64, 47.72, 47.02, 46.70, 45.13, 36.05, 21.24 ppm. Anal. Calcd for $C_{58}H_{58}N_6O_{13}S_4$: C, 58.78; H, 4.97; N, 7.15. Found: C, 58.89; H, 5.08; N, 7.18.

3,6,12,15-Tetrakis(*p*-tolylsulfonyl)-8,12-furano-9-oxa-1,3,6,12,15,17-hexaazaheptadecane (24). The phthalimide **23** (5.46 g, 4.65 mmol) was refluxed in ethanol (60mL) in the presence of hydrazine (4 mL, 85%) overnight. The solid which formed was filtered, and the filtrate was concentrated in vacuo. The resulting residue was taken up into CH_2Cl_2 (50 mL) and washed with 10% NaOH solution and dried (K_2CO_3). Evaporation gave a foam: yield 4.03 g (95%). ^{1}H NMR ($CDCl_3$) 7.71, 7.67 (4 H each, d, Ts), 7.34 (8 H, m, Ts), 6.27 (2 H, s, furan-*H*), 4.33 (4 H, s, furan-CH_2N), 3.32 (4 H, m, CH_2N), 3.15 (8 H, m, CH_2N), 2.85 (4 H, t, CH_2N), 2.46 (12 H, s, CH_3), 1.69 (4 H, br. s, NH_2) ppm. ^{13}C NMR 149.73, 143.52, 143.43, 135.47, 135.31, 129.64, 127.10, 126.99, 110.63, 53.03, 48.45, 47.45, 45.26, 40.53, 21.31 ppm. FABMS (rel intens 915 $(M + 1H)^+$ (100). HRMS

m/z for $C_{42}H_{54}N_6O_9S_4$ requires: 915.2913. Found: 915.2900.

6,9,22,25-Tetrakis(p-tolylsulfonyl)-13,18-dioxo-27,28-dioxa-6,9,22,25-tetraazatricyclo[22.2.1^{1,4}.1^{14,17}] octacos-1,3,14,16-tetraene (26). A mixture of the diamine **24** (1.36 g, 1.48 mmol), the dicarboxylic acid **25** (0.23 g, 1.48 mmol), DPPA (1.63 g, 5.92 mmol) and Et_3N (0.75 g, 7.3 mmol) was stirred in DMF (100 mL) at room temperature for 2 d. The resulting residue, after evaporation in vacuo, was chromatographed (SiO_2, CH_2Cl_2-MeOH, 100:2) to give the product as a foam: yield 0.86g (56%). ^{1}H NMR ($CDCl_3$) 7.68, 7.65, 7.31, 7.28 (4 H each, d, Ts), 7.46 (2 H, t, CON*H*), 7.10, 6.20 (2 H each, s, furan-*H*), 4.29 (4 H, s, furan-C*H*$_2$N), 3.54 (4 H, m, C*H*$_2$N), 3.38-3.21 (12 H, m, C*H*$_2$N), 2.42, 2.39 (6 H each, s, C*H*$_3$) ppm. ^{13}C NMR 157.87, 149.69, 148.01, 143.97, 135.10, 135.03, 129.95, 129.86, 127.40, 127.20, 115.18, 111.01, 48.89, 48.22, 47.36, 45.58, 38.13, 21.51 ppm. Anal. Calcd for $C_{48}H_{54}N_6O_{12}S_4$: C, 55.69; H, 5.26; N, 8.12. Found: C, 55.40; H, 5.40; N, 8.09.

6,9,22,25-Tetrakis(*p*-tolylsulfonyl)-27,28-dioxa-6,9,22,25-tetraazatricyclo[22.2.1^{1,4}.1^{14,17}]octacos-1,3,14,16-tetraene (27) The diamide **26** (1.23 g, 1.19 mmol) was treated with borane-THF (10 mL, 1 M) in THF (50 mL) at reflux temperature for 10 h under N_2. The excess borane was decomposed cautiously with dilute HCl (2M, 4 mL), and the mixture was then refluxed for 1 h. The residue, after evaporation in vacuo, was made basic with NaOH (10%) and extracted with CH_2Cl_2 (3 × 30 mL) and dried (K_2CO_3). The pure product was isolated by chromatography (SiO_2, CH_2Cl_2-MeOH, 100:6 to 100:15) as a foam: yield 0.55g (46%). ^{1}H NMR ($CDCl_3$) 7.66, 7.30 (8 H each, m, Ts), 6.16, 6.05 (2 H each, s, furan-*H*), 4.30, 3.67 (4 H each, s, furan-C*H*$_2$N), 3.33 (4 H, br. s, C*H*$_2$N), 3.15 (8 H, br. s, C*H*$_2$N), 2.72 (4 H, br. s, C*H*$_2$N), 2.43 (12 H, s, C*H*$_3$), 2.20 (2 H, br. s, N*H*) ppm. ^{13}C NMR 152.61, 149.94, 143.44, 135.65, 135.14, 129.64, 129.55, 127.18, 127.11, 110.44, 107.72, 49.89, 48.79, 47.23, 45.39, 45.21, 21.34 ppm. FABMS (rel intens) 1007 $(M + 1H)^+$ (100), 851 $(M - Ts)^+$ (11), 504 (80). Anal. calcd for $C_{48}H_{58}N_6O_{10}S_4$: C, 57.24; H, 5.80; N, 8.34. Found: 57.40; H, 6.10; N, 7.98.

27,28-Dioxa-6,9,22,25-tetraazatricyclo[22.2.1^{1,4}.1^{14,17}]octacos-1,3,14,16-tetraene (4) To a solution of **27** (100 mg, 0.1 mmol) in butanol (20 mL) was added sodium (0.7 g, 30 mmol). The mixture was refluxed for 3 h until the sodium disappeared. Water (20 mL) was added, and the mixture was concentrated in vacuo to dryness. The resulting residue was taken up in water (10 mL), acidified with dilute HCl to pH 1, and extracted with ether (3 × 20 mL). The aqueous layer was made basic with NaOH (10%), extracted with CH_2Cl_2 (5 × 20 mL), and dried (K_2CO_3). Concentration gave a yellowish oil: yield 30 mg (77%). ^{1}H NMR ($CDCl_3$) 6.08 (4 H, s, furan), 3.75 (8 H, s, furan-C*H*$_2$N), 2.70 (16 H, s, C*H*$_2$N), 2.41 (6 H, s, N*H*) ppm. ^{13}C NMR 153.02, 107.64, 48.79, 48.04, 46.12 ppm. FABMS (rel intens) 391 (M^+ + 1H, 100). HRMS m/e for $C_{20}H_{34}N_6O_2$ + 1H requires: 391.2819. Found: 391.2818. For elemental analysis the free base was converted into the HCl salt and recrystallized from MeOH-ether. Anal. Calcd for $C_{20}H_{34}N_6O_2 \cdot 6HCl \cdot 3.5H_2O \cdot MeOH$: C, 35.81; H, 7.30; N, 11.93. Found: C, 35.85; H, 7.42; N, 11.80.

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