Synthesis and Structural Aspects of Macrocyclic Polyamines Containing 2,2'-Bipyridinyl Unit(s)

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Received May 27, 1983

A one-step, general procedure to aza-crown analogues **3** containing 2,2'-bipyridinyl unit(s), by reaction of 6,6'-bis(chloromethyl)-2,2'-bipyridine (**1**) with oligomers of ethylenediamine tosylate or mesylate disodium salts (**2**) in *N,N*-dimethylformamide, is described. Detosylation or demesylation of **3** to give the free macrocyclic polyamines **4** was achieved in excellent yield by hydrolysis with concentrated H_2SO_4. A novel synthetic route to symmetrical multidentate macrocyclic diamines such as the hexaaza-18-crown-6 analogue **6** is also reported. ^1H NMR spectra of the 15- to 18-membered macrocycles suggest a syn orientation of bipyridinyl unit(s), whereas the 24-membered 2:2-macrocycle **3a** is shown by single-crystal X-ray diffraction to adopt a "stacked" conformation, with the bipyridinyl moieties in the anti configuration. Polyamine **3a** possesses triclinic space group $P\bar{1}$ with cell constants of a = 11.550 (3) Å, b = 12.267 (3) Å, c = 12.427 (3) Å, α = 83.64 (2)°, β = 66.16 (2)°, γ = 74.29 (2)°; Z = 1; d_c = 1.280 g cm^{-3}. Mass spectral aspects of these cyclic amines are also discussed.

Introduction

Numerous synthetic routes have been developed for producing new macrocyclic polyamines and their metal complexes.[3-6] Interests in the synthesis of modified structures with cation selective properties have led to the incorporation of heterocyclic subunits into the macrocyclic framework. The most popular mode of construction of these systems is via a routine Schiff base condensation of heteroaromatic dialdehydes or diketones with bis primary amines, preferably in the presence of a metal ion as a template[7,8] or by employing high dilution techniques.[9-13] This specific synthetic procedure has not been employed for the introduction of the 2,2'-bipyridinyl subunit(s) into macrocycles due to the inaccessibility of 6,6'-diformyl- (or 6,6'-acyl-) 2,2'-bipyridine.[14] Diamide macrocycles and cryptands, however, have been prepared by the classic amidation of 6,6'-bis(chlorocarbonyl)-2,2'-bipyridine with a variety of bis primary amines,[15a] diazacrown ethers,[15b] and thioethers.[16] The high temperature cyclization of 6,6'-dichloro-2,2'-bipyridine with ammonium tetrachlorozincate to produce specific porphyrin-like macrocycles has been also reported.[17]

We now report a general one-step synthesis of aza-crown analogues of **3** containing the 2,2'-bipyridinyl moiety by condensation of the disodium salts of the tosylate or mesylate derivative of polyamines (**2**), with 6,6'-bis(chloromethyl)-2,2'-bipyridine (**1**). The 1:1- or 2:2-macrocycles are prepared by this method depending on the length of polyamine. Thus, hexaaza-crown analogues have recently been obtained by a novel and simple procedure, which appears to be general[10,18] for the preparation of symmetrical multidentate macrocyclic diamines.

Results and Discussion

Incorporation of heteroaromatic subunits into a macrocyclic framework could be readily facilitated by utilization of the readily available starting materials, e.g., 6,6'-bis(chloromethyl)-2,2'-bipyridine[19] and sulphonamides **2**. Tosyl and mesyl groups were chosen as the nitrogen protecting groups due to (a) their ease in preparation, (b) enhanced acidity of the geminal hydrogen, and (c) their stability as well as corresponding salts. The most serious drawback is the difficulty in hydrolysis of the amide to afford free amine.

The cyclization step of **1** with the appropriate polyethyleneamine tosylate or mesylate disodium salts **2** was conducted in anhydrous *N,N*-dimethylformamide (DMF) at 120 °C, as outline in Scheme I. The general reaction afforded **3a-c** in reasonable yields, *without* the use of high dilution techniques. The reaction of **1** with **2a** gave the 2:2-macrocycle **3a**; no evidence for the corresponding 1:1-macrocycle was observed, probably due to the inability to form the 12-membered ring. Several factors could be operative: (a) The cyclization step may be reversible under the reaction conditions. (b) The bridging distance is too small. Salts **2b** or **2d** with **1** afforded the desired 1:1-

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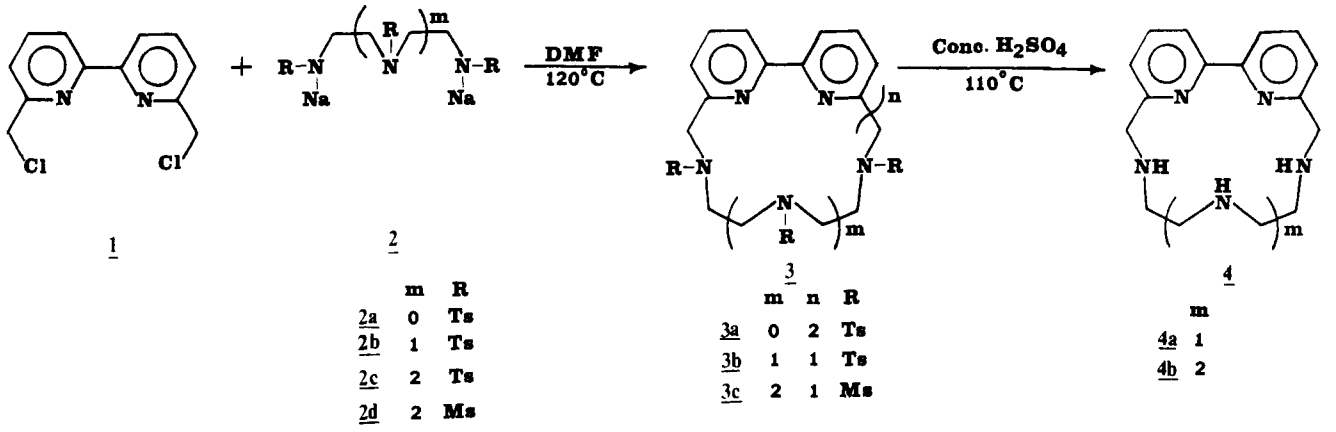
0022-3263/83/1948-4848$01.50/0

Scheme I



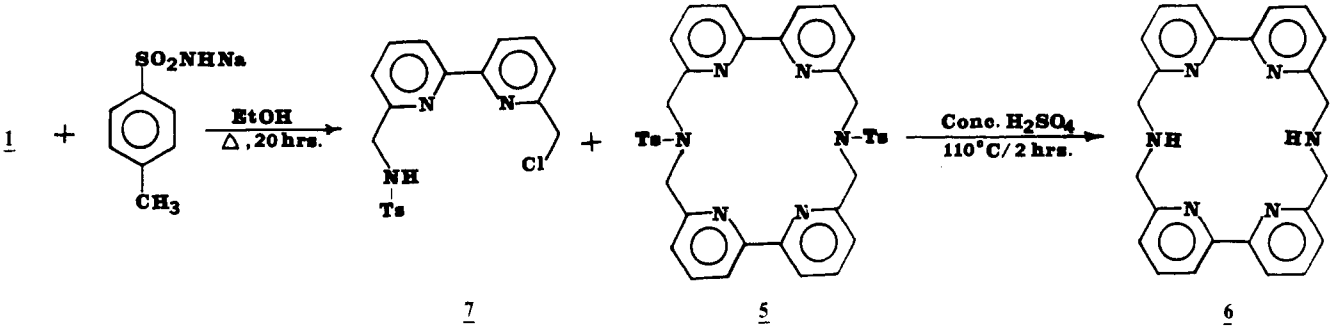
1 2 3 4

	m	R
2a	0	Ts
2b	1	Ts
2c	2	Ts
2d	2	Ms

	m	n	R
3a	0	2	Ts
3b	1	1	Ts
3c	2	1	Ms

	m
4a	1
4b	2

Scheme II



1 7 5 6

macrocycle **3b** (30%) or **3c** (16%), respectively. The inability of **2c** to give cyclic products may be due to steric crowding caused by the bulky tosyl groups.

A survey of the detosylation procedures showed that a number of techniques could be used, but none was generally the best.[9,10,20] Detosylation or demesylation of macrocycles **3** to the free aza-crown analogues **4** was achieved (72–90%) by heating (110 °C) in concentrated H_2SO_4 for 2 h.

Much more intriguing is the synthetic route which led to the formation of hexaaza-18-crown-6 analogue **5**. Macrocycle **5** was isolated (19%) in an attempt to prepare the intermediate *N,N*-ditosyl-6,6′-bis(aminomethyl)-2,2′-bipyridine by treatment of **1** with tosylamide monosodium salt in refluxing absolute EtOH (Scheme II). Surprisingly, from the reaction mixture a high melting crystalline precipitate was obtained, which was shown to be analytically pure **5**! This is best envisioned as proceeding through the intermediate monoalkylated **7** (isolated in low yield), which quickly underwent a selfcondensation in the presence of tosylamide monosodium salt, as the base. Detosylation of **5** in concentrated H_2SO_4 afforded (~100%) macrocyclic diamine **6**, which was obtained as a monohydrate. We are currently investigating the generality of this novel one-step procedure for obtaining symmetrical multidentate macrocyclic di- and polyamines.

The structures of the new macrocycles were assigned on the basis of microanalytical and spectral data. 2:2 macrocycle **3a** was further characterized by a single crystal X-ray diffraction study.

The ^1H NMR spectrum of macrocycle **3b** shows two different tosyl groups as evidenced by the 2:1 arylmethyl singlets at δ 2.44 and 2.36. Crown **3c** possesses four mesyl groups of two types; singlets at δ 2.89 (6 H) and 2.96 (6 H) support the cyclic structures. For the larger 2:2 macrocycle

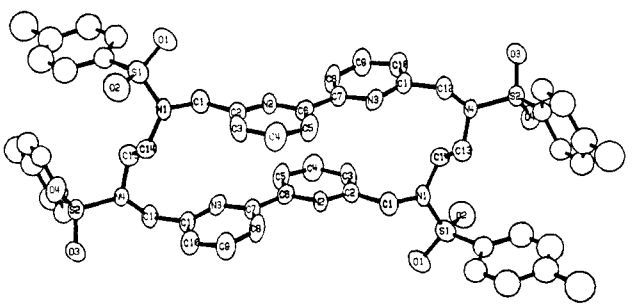


Figure 1. ORTEP drawing of 2:2 macrocycle (**3a**). Hydrogen atoms have been omitted for clarity.

3a all four tosyls are equivalent and the arylmethyl groups appear as a spike at δ 2.25. The α-methylene protons in *all* macrocycles are found to be equivalent at 25 °C as suggested by the singlet in the ranges δ 4.43–4.54 for **3** and δ 3.97–4.07 for **4** and **6**. It is interesting to note that all the heteroaromatic hydrogens in these macrocycles are shifted to higher field as compared to the open chain analogue (e.g., **1**); the most dramatic shifts are for H-3, which absorbs at δ 7.72 ± 0.02 for **4** and **6** as compared to δ 8.22 for **1**. This sharp upfield shift for H-3 clearly demonstrates that the orientation of the bipyridinyl moiety in the small macrocycles is approaching a syn conformation. The bipyridine moiety generally possesses the anti orientation as is evident from the chemical shift of H-3, which is subjected to the directed nitrogen electrons of the adjacent ring.[19]

Structure Description: 3a·Methylcyclohexane. Figure 1 shows a perspective view of 2:2-macrocycle **3a**, which, in the crystal, exists in a "stacked" conformation with crystallographic symmetry C_i. The bipyridinyl moieties possess the anti configuration, with NCCN torsion angle of 175.8°, and are parallel to one another, with closest transannular contacts of 3.74 Å (N2···C6′); thus, the inner cavity of **3a** is best not envisioned as a hole in a doughnut.

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Linkage of the bridging chains to the bipyridinyl units takes on two distinct conformations, with N1 being anti to pyridinyl N (the N1–C1–C2–N2 angle is −178.2°) and the N3–C11–C12–N4 torsion angle 121.2°. The two bridge amide N atoms also differ somewhat in their hybridization states; N1 is clearly sp^2 hybridized, with an average angle of 119.4°, while N4 possesses diminished sp^2 character, having an average angle of 117.0°. Average lengths for various bond types are 1.630 Å for S–N, 1.427 Å for S–O, 1.345 Å for pyridinyl C–N, 1.377 Å for pyridinyl C–C, and 1.380 Å for phenyl C–C.

The methylcyclohexane[21] solvent molecule lies on a crystallographic center of symmetry, with its methyl group (C4S) disordered into two half-populated positions, and has the chair conformation. It has no close contacts to the macrocycle. Extremely high thermal motion (average thermal parameter B = 18.3 Å^2) renders details of its structure nebulous.

Mass Spectral Aspects. Due to the presence of either the labile tosyl or mesyl groups and the relatively long polyethyleneamine bridge(s), **3** displays a very low stability under electron impact, thus, the absence of molecular ions. Facile fragmentation and high molecular weights are further supported by the negligible high mass range, in which the relative abundance of peaks do not exceed 2%. Conversely, the low mass range is dominated by intense fragments, which can be attributed to the evolution of *p*-toluene- or methanesulfinic acid, and their characteristic electron impact or decompositions.

The rationale for the electron-impact MS fragmentation of **5** is shown in Scheme S1 in the supplementary Materials. The main fragmentation process arises from the breakdown of the molecular ion (absent) by loss of a tosyl radical. Subsequent loss of a neutral molecule of *p*-toluenesulfinic acid gives the intense (30%) imine ion. This process may proceed via a 5-membered cyclic transition state by an α-methylene hydrogen transfer to the adjacent sulfamidic oxygen. Subsequent decomposition probably involves cleavage of the macro-ring by transfer of an α-methylene proton to the opposing pyridine nitrogen, and further α- or β-cleavage of the intermediates.

An analogous macro-ring cleavage can be envisioned for polyamines **4**, but additional peaks are observed in the high mass range attributed to the fragmentation of the polyamine chains; however, the data do not allow for a precise rationalization. In both cases, the fragment at m/e 211 is the base peak. The schemes for the fragmentation pattern and other details can be found in the supplementary materials.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Unless otherwise noted, ^{1}H NMR spectra were obtained in Me_2SO-d_6 with Me_4Si as the internal standard and recorded on an IBM-Bruker NR/80 spectrometer. Mass spectra (MS) were determined by D. Patterson on a Hewlett-Packard Model 5985 GC/MS spectrometer, obtained at 70 eV, and herein recorded as m/e (assigned fragment, relative intensity). Elemental analyses were obtained from Galbraith Laboratories.

N,N-Dimethylformamide (DMF) was purified by specific conditions to retard cyanide formation.[22] Ethylenediamine, diethylenetriamine, and triethylenetetramine (obtained from Aldrich) were tosylated by a known procedure.[23]

***N,N'*-Ditosylethylenediamine**: 80%; mp 163–164 °C (EtOH) (lit.[24] mp 160 °C); ^{1}H NMR δ 2.38 (s, Ts CH_3, 6 H), 2.77 (s, CH_2, 4 H), 7.38 (d, 2,6-Ts H, J = 7.9 Hz, 4 H), 7.65 (d, 3,5-Ts H and NH, J = 7.9 Hz, 6 H); MS, m/e 368 (M^+, 0.1), 339 (2.7), 213 (M^+ − Ts, 17), 184 ($M^+/2$, 100), 155 (Ts, 83), 91 (C_7H_7, 85), 65 (22).

***N,N',N''*-Tritosyldiethylenetriamine**: 57%; mp 172–174 °C (DMF–H_2O) (lit.[25] mp 176–177 °C); ^{1}H NMR δ 2.39 (s, Ts CH_3, 9 H), 2.94 (br s, CH_2 and NH, 10 H), 7.48 (d, 2,6-Ts H, J = 8.0 Hz, 6 H), 7.68 (d, 3,5-Ts H, J = 8.0 Hz, 6 H); MS, m/e 410 (M^+ − Ts, 5), 381 (40), 227 ($C_{10}H_{15}N_2SO_2$, 48), 209 (50), 198 ($TsNHCH_2CH_2$, 6), 184 ($TsNHCH_2$, 7), 155 (Ts, 39), 139 (26), 91 (C_7H_7, 100).

Also isolated was the *N,N,N''*-tritosyl isomer: 30%; mp 197–198 °C (CH_3CN); ^{1}H NMR δ 2.31 (s, Ts'' CH_3, 3 H), 2.41 (s, Ts CH_3, 6 H), 3.01 (br s, CH_2CH_2 and NH, 10 H), 7.11 (d, 2,6-Ts H, J = 7.9 Hz, 4 H), 7.40 (d, 2'',6''-Ts H, J = 7.9 Hz, 2 H), 7.52 (d, 3,5-Ts H, J = 7.9 Hz, 4 H), 7.73 (d, 3'',5''-Ts H, J = 7.9 Hz, 2 H); MS, m/e 227 ($C_{10}H_{15}N_2SO_2$, 100), 209 (5), 198 ($TsNHCH_2CH_2$, 11), 155 (Ts, 14), 139 (5), 91 (C_7H_7, 50). Anal. Calcd. for $C_{25}H_{31}N_3O_6S_3$: C, 53.03; H, 5.52; N, 7.43. Found: C, 53.07; H, 5.60; N, 7.41.

***N,N',N'',N'''*-Tetratosyltriethylenetetramine**: 65%; mp 210–212 °C (DMF–H_2O) (lit.[9,26] mp not reported); ^{1}H NMR δ 2.39 (s, Ts CH_3, 12 H), 3.01 (br m, CH_2 and NH, 14 H), 7.37 (d, 2,6-Ts H, J = 7.9 Hz, 8 H), 7.63, 7.69 (2d, 3,5-Ts H, J = 7.9 Hz, 4 H each); MS, m/e 607 (M^+ − Ts, 0.2), 452 (m^+ − 2 Ts, 0.9), 381 ($M^+/2$, 11), 239 (18), 227 ($C_{10}H_{15}N_2SO_2$, 78), 209 (38), 198 ($TsNHCH_2CH_2$, 11), 184 ($TsNHCH_2$, 6), 155 (Ts, 42), 139 (30), 91 (C_7H_7, 100).

6,6'-Bis(chloromethyl)-2,2'-bipyridine was prepared[19] in 65% yield by a free radical chlorination (NCS) procedure: mp 157–158 °C.

***N,N',N'',N'''*-Tetramesyltriethylenetetramine.** To a chilled solution of triethylenetetramine (2.92 g, 20 mmol) in anhydrous pyridine (5 mL) was added dropwise a solution of mesyl chloride (9.12 g, 80 mmol) in pyridine (5 mL) under nitrogen. The mixture was stirred at 20 °C for 12 h and then concentrated in vacuo to give a slurry, which was diluted with water and acidified with 1 M HCl. The resultant precipitate was filtered, washed with H_2O, and recrystallized from AcOH to give (25%) the desired sulfamide, as fine needles: 2.3 g; mp 163–164 °C; ^{1}H NMR δ 2.93, 3.00 (2 s, Ms CH_3, 6 H each), 3.25 (m, β,γ-CH_2, 8 H), 3.34 (s, α-CH_2, 4 H), 7.10 (br t, NH, J = 5 Hz, 2 H); MS, m/e 379 (M^+ − Ms, 2), 350 (M^+ − $MsNHCH_2$, 8), 300 (M^+ − 2Ms, 5), 271 (20), 270 (18), 229 ($M^+/2$, 94), 192 (41), 151 ($C_4H_{11}N_2O_2S$, 100), 133 (36), 122 (49), 85 (34), 79 (Ms, 26). Anal. Calcd. for $C_{10}H_{26}N_4O_8S_4$: C, 26.20; H, 5.68; N, 12.23. Found: C, 26.49; H, 5.78; N, 12.20.

General Procedure for the Preparation of the Tosylate or Mesylate Disodium Salts. To a stirred refluxing suspension of the amide (5 mmol) in absolute EtOH (200 mL), NaOEt (750 mg, 11 mmol) in absolute EtOH (20 mL) was added. The mixture was refluxed for 2 h and then cooled. The insoluble disodium salt was collected by rapid filtration, washed with absolute EtOH, and dried in vacuo to give >90% yield. These salts (**2a–2d**) were used without further purification.

General Macrocycle Preparation. Synthesis of Macrocycle 3a. Typically, a solution of **1** (504 mg, 2 mmol) in DMF (50 mL) was added dropwise to a stirred solution of **2a** (824 mg, 2 mmol) in DMF (100 mL) at 120 °C over the period of 3 h and then maintained at 120 °C for an additional 2 h. After cooling, the solvent was removed in vacuo to give a semisolid, which was treated with H_2O and extracted with $CHCl_3$. The combined extract was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford a viscous oil, which was column chromatographed on neutral Al_2O_3 eluting with C_7H_{16}–EtOAc (1:1) to give the 2:2-macrocycle **3a**, as colorless prisms: 55 mg (5%); mp 261 °C dec (DMF); ^{1}H NMR δ 2.25 (s, Ts CH_3, 12 H), 3.26 (s, δ-CH_2, 8 H), 4.43 (s, α-CH_2, 8 H), 7.19 (d, 5-py H, J = 7.3 Hz, 4 H), 7.26 (m, 3-pyH and 2,6-Ts H, 12 H), 7.42 (t, 4-py H, J =

(21) Macrocycle **3a** crystallizes with methylcyclohexane, present as an impurity in n-C_7H_{16}, used during the purification by column chromatography. The unsolvated host is obtained by recrystallization from *N,N*-dimethylformamide.

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7.3 Hz, 4 H), 7.56 (d, 3,5-Ts H, J = 7.9 Hz, 8 H); MS, m/e 427 (0.8), 156 (25), 139 (28), 123 (20), 107 (10), 92 (59), 91 (100). Anal. Calcd. for $C_{56}H_{56}N_8O_8S_4$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.34; H, 5.21; N, 10.11.

Macrocycle 3b. The above general procedure was followed with the disodium salt **2b** (1.22 g, 2 mmol). The resultant viscous residue was treated with H_2O, extracted with CH_2Cl_2, dried (Na_2SO_4), and filtered; slow evaporation of the solvent gave yellow crystals, which were recrystallized from DMF to afford the desired 1:1 macrocycle **3b**, as colorless prisms: 450 mg (30%); mp 215 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, ϵ-Ts CH_3, 3 H), 2.44 (s, β-Ts CH_3, 6 H), 3.41 (m, α,δ-CH_2, 8 H), 4.44 (s, α-CH_2, 4 H), 7.2–7.5 (m, Ar H, 8 H), 7.7–7.9 (m, Ar H, 10 H); ^{1}H NMR (Me_2SO-d_6) δ 2.38 (s, $TsCH_3$, 9 H), 3.43 (br s, α, δ-CH_2, 8 H), 4.45 (s, α-CH_2, 4 H), 7.38 (d, 5-py H and 2,6-Ts H, 8 H), 7.65 (t, 4-py H and 3,5-Ts H, 8 H), 7.89 (d, 3-py H, 2 H); MS, m/e 434 (0.5), 156 (TsH, 30), 139 (18), 107 (15), 92 (68), 91 (C_7H_7, 100). Anal. Calcd. for $C_{37}H_{39}N_5O_6S_3$: C, 59.58; H, 5.27; N, 9.39. Found: C, 59.34; H, 5.41; N, 9.32.

Reaction of 1 with 2c was conducted as above except for the use of **2c** (1.61 g, 2 mmol); however, cyclic products were neither detected *nor* isolated.

Macrocycle 3c. The above general procedure was followed except for the substitution of **2d** (1.00 g, 2 mmol); the resultant viscous oil was treated with H_2O, extracted with $CHCl_3$, filtered, and slowly concentrated to give a solid, which was shown (^{1}H NMR) to be unchanged **2d**. From the mother liquor, a second crop of crystals was collected and subsequently recrystallized from DMF–H_2O to give the desired 1:1 macrocycle **3c**: 150 mg (16%); mp 175–177 °C dec; ^{1}H NMR δ 2.89 (s, ϵ-Ms CH_3, 6 H), 2.96 (s, β-Ms CH_3, 6 H), 3.2 (m, CH_2, 12 H), 4.54 (s, α-CH_2, 4 H), 7.50 (dd, 4-py H, J = 7.3 Hz, 2 H), 7.98 (br d, 3,5-py H, J = 7.3 Hz, 4 H); MS, m/e 261 (1), 126 (23), 94 (56), 81 (27), 80 (MsH, 55), 79 (Ms, 55), 65 (100), 64 (55). Anal. Calcd. for $C_{22}H_{34}N_6O_8S_4$: C, 41.37; H, 5.36; N, 13.16. Found: C, 41.52; H, 5.21; N, 13.26.

Detosylation of 3b. Macrocycle 4a. Sulfamide **3b** (300 mg, 0.04 mmol) dissolved in concentrated H_2SO_4 (1 mL) was stirred at 110 °C for 2 h. After cooling, the mixture was poured into a cold brine solution containing a slight excess of NaOH. The free amine **4a**, which precipitated as an oil, was extracted with $CHCl_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give **4a** as a pale yellow oil: 84 mg (72%); ^{1}H NMR ($CDCl_3$) δ 2.86 (br s, δ-CH_2, 4 H), 3.29 (br s, γ-CH_2, 4 H), 4.07 (s, α-CH_2, 4 H); MS, m/e 283 (M^+, 11), 212 (23); 211 ($C_{12}H_{13}N_3$, 100), 199 (30), 197 (37). Anal. Calcd. for $C_{16}H_{21}N_5$: C 67.82; H, 7.47; N, 24.71. Found: C, 67.66; H, 7.61; N, 24.64.

Demesylation of 3c. Macrocycle 4b. When the above deamidation procedure was used **3c** gave **4b**, as a colorless oil: 90%; crystallizes on standing; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, ζ-CH_2, 4 H), 2.66 (m, γ,δ-CH_2, 8 H), 3.97 (s, α-CH_2, 4 H), 7.22 (dd, 4-py H, J = 7.3 Hz, 2 H), 7.70 (br d, 3,5-py H, 4 H); MS, m/e 326 (M^+, 5), 212 (32), 211 ($C_{13}H_{13}N_3$, 100), 199 (25), 198 (22), 197 (18), 184 (46). Anal. Calcd. for $C_{18}H_{26}N_6$: C, 66.23; H, 8.03; N, 25.76. Found: C, 66.10; H, 8.16; N, 25.74.

Macrocycle 5. To a boiling solution of tosylamide monosodium salt (1.16 g, 6 mmol) in absolute EtOH (200 mL), **1** (760 mg, 3 mmol) was added in one portion. The mixture was refluxed for 20 h, and after cooling the white precipitate was filtered and washed thoroughly with H_2O and then EtOH to give macrocycle **5** (200 mg, 19%), mp >260 °C. Recrystallization of **5** from high boiling polar solvents (DMF or Me_2SO) afforded an analytical sample. No ^{1}H NMR was obtained due to the insolubility of **5** at ambient temperature, in most common solvents: MS, m/e 547 (M^+ – Ts, 7), 391 (30), 246 (53), 196 (27), 184 ($C_{12}H_{12}N_2$, 10), 183 (12), 182 (13), 169 (11), 124 (28), 123 (91), 91 (100), 79 (28). Anal. Calcd. for $C_{38}H_{34}N_6O_4S_2$: C, 64.94; H, 4.88; N, 11.96. Found: C, 64.79; H, 4.91; N, 11.85.

A trace impurity of monoalkylated intermediate **7** was isolated (<1%): ^{1}H NMR ($CDCl_3$) δ 2.30 (s, Ts CH_3, 3 H), 4.40 (s, CH_2, 2 H), 4.70 (s, CH_2Cl, H), 6.00 (m, NH (exchangable with D_2O), 1 H), 7.0–8.4 (m, py H, Ts H, 10 H); MS, m/e 387 (M^+, 4), 242 (11), 232 (100), 204 (37), 196 (15), 169 (24), 91 (48).

Detosylation of 5. Macrocycle 6. Macrocycle **5** (250 mg, 0.356 mmol) was dissolved in concentrated H_2SO_4 (1 mL) and then stirred at 110 °C for 2 h. After cooling, the solution was diluted with H_2O (2 mL) and poured cautiously into an aqueous solution of NaOH (10 mL). The precipitated cyclic diamine **6** was extracted with $CHCl_3$ (5 × 5 mL), dried over anhydrous $MgSO_4$ and concentrated to dryness to give **6**, as white crystals: mp >280 °C; ^{1}H NMR ($CDCl_3$) δ 2.88 (br s, NH, H_2O, 4 H), 4.07 (s, $pyCH_2$, 8 H), 6.93 (dd, 5-py H, J = 7.8, 1.1 Hz, 4 H), 7.40 (dd, 4-py H, J = 7.8 Hz, 4 H), 7.72 (dd, 3-py H, J = 7.8, 1.1 Hz, 4 H); ($CDCl_3$ with added D_2O) δ 4.07 (s, $pyCH_2$, 8 H), 7.07 (dd, 5-py H, J = 7.2, 1.5 Hz, 4 H), 7.53 (t, 4-py H, J = 7.8, 7.2 Hz, 4 H), 7.72 (dd, 3-py H, 7.8, 1.5 Hz, 4 H); MS, m/e 394 (M^+, 12), 211 (17), 198 (29), 197 ($M^+/2$, 43), 184 ($C_{12}H_{12}N_2$, 100). Anal. Calcd. for $C_{24}H_{22}N_6 \cdot H_2O$: C, 69.88; H, 5.86; N, 20.37. Found: C, 69.86; H, 5.66; N, 20.37.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for partial support of this work.

Registry No. **1**, 74065-64-8; **2a**, 39547-86-9; **2a** (free base), 4403-78-5; **2b**, 52601-80-6; **2b** (free base), 56187-04-3; **2c**, 56187-06-5; **2c** (free base), 55442-07-4; **2d**, 87555-95-1; **2d** (free base), 87555-94-0; **3a**, 87555-96-2; **3b**, 87555-97-3; **3c**, 87555-98-4; **4a**, 87555-99-5; **4b**, 87556-00-1; **5**, 87556-01-2; **6**, 87556-03-4; **7**, 87556-02-3; *N,N,N''*-tritosyldiethylenetriamine, 87555-93-9; tosylamide monosodium salt, 18522-92-4; ethylenediamine, 107-15-3; diethylenetriamine, 111-40-0; triethylenetetramine, 112-24-3.

Supplementary Material Available: Tables of atomic coordinates, anisotropic thermal parameters, X-ray experimental and crystal data for **3a**, interatomic bond lengths (Å) and bond angles (deg) in 2:2 macrocycle **3a**, and details of mass spectral fragmentation pattern of the macrocycles (8 pages). Ordering information is given on any current masthead page.