(0.02 g), and powdered Drierite (0.3 g) was stirred magnetically for 16 h at 25 °C (flask protected by $CaCl_2$ tube). Filtration and concentration to dryness gave 0.25 g (96%) of white prisms of crude acetal **17** with mp 70–80 °C: ^1H NMR (CD_3CN/Me_2SO-d_6) δ 4.14 (d, J = 6 Hz, 3 CH), 3.30 (s, CH_3O, 12 H), [2.85 (d, J = 12 Hz), 0.8–1.2 (m), 0.65 (q, J = 12 Hz), CH_2 + CH, 9 H]; aldehyde signal absent. On standing in ambient air, the compound produced a gummy white solid, partly soluble in $CDCl_3$ (^1H NMR of the $CDCl_3$ soluble portion revealed an aldehyde signal at δ 9.7).

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Supplementary Material Available: One figure showing full numbering used in X-ray analysis and the hydrogen atom locations; tables of (1) atom coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms, (2) anisotropic thermal parameters for non-hydrogen atoms, (3) hydrogen atom coordinates and thermal parameters, and (4) bond distances and valence angles (5 pages). Ordering information is given on any current masthead page.

Synthesis of Mono- and Difunctionalized Ditopic [24]N_6O_2 Macrocyclic Receptor Molecules

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The 24-membered macrocycle 1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane ([24]N_6O_2, **1**) as the free amine forms complexes with transition-metal cations, and in aqueous solution the polyprotonated form binds anions. Compound **1** also is an efficient catalyst in the transformation reactions of adenosine triphosphate and acetyl phosphate. A selective procedure for the preparation of derivatives of **1** containing pendant functionality is described in an effort to incorporate additional nucleophilic groups and potential general-acid–general-base catalytic sites. A convergent approach to these molecules employs 9-benzoyl-6,12-bis(*p*-tolylsulfonyl)-1,17-bis(methylsulfonyl)-6,9,12-triaza-3,15-dioxaheptadecane (**13**) in cyclization reactions with either *N'*-benzoyl-*N,N''*-bis(*p*-tolylsulfonyl)diethylenetriamine (**11**) or *N,N',N''*-tris(*p*-tolylsulfonyl)diethylenetriamine (**18**). Selective debenzoylation of these macrocycles gives respectively the protected 7,19-diamine **15** or the 7-monoamine **20**. The former was used in the preparation of the 7,19-bis(2-aminoethyl) (**2**), -(2-hydroxyethyl) (**3**), and -(2-mercaptoethyl) (**4**) derivatives of **1**. Compound **4** was isolated as the macrobicyclic disulfide **17**. The monoamine **20** was used in the preparation of the corresponding 7-monosubstituted derivatives of **1**, compounds **5**, **6**, and **7**.

The complexation of anions in chemical as well as biochemical processes has recently been explored by the use of macrocyclic and macropolycyclic polyammonium molecules.[1-3] These organic receptor molecules form stable and selective complexes with a variety of inorganic as well as organic anions.[4-12] Recently, it has been shown that macrocyclic polyammonium cations also can act as catalysts in the transformation of bound substrates such as ATP[13] and acetyl phosphate.[14] Among the various macrocyclic polyamines studied, the 24-membered dioxo hexaaza macrocycle **1**[15] presents a particularly interesting set of properties. In addition to catalyzing the hydrolysis of ATP and acetyl phosphate, pyrophosphate formation via a phosphorylated macrocyclic intermediate demonstrates the role of nucleophilic catalysis. Compound **1** acting as a supramolecular catalyst[3,16] thus performs the overall reactions catalyzed by ATPases and kinases. Recently, it was demonstrated that a third component, calcium ion, added to the complex of ATP and **1** regulates the hydrolytic reaction of ATP and allows for the formation of pyrophosphate.[17] Thus, with compound **1** three principal features of enzymatic reactions, specificity, catalysis, and regulation, have been demonstrated.

In order to gain an understanding of the catalytic behavior of the receptor–catalyst **1** and increase its efficiency, a series of new macrocycles containing additional functionality was designed. The intention was to provide

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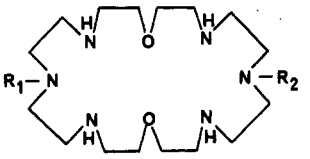
models containing additional general-acid–general-base and nucleophilic catalytic sites as single or double pendant groups attached to the parent macrocycle 1. In addition, since 1 forms dinuclear cryptate complexes with transition metals,[15,18-22] the modified macrocycles prepared in this work also would be of interest for further control over the complexation of these cations.

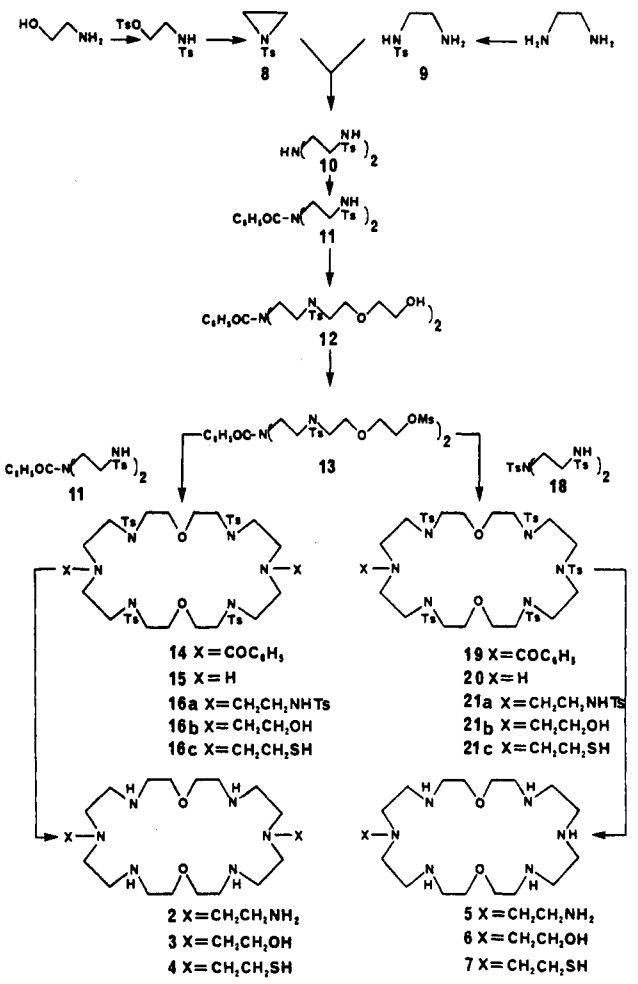
The substituents chosen for study were the amino, hydroxy, thiol, and imidazolyl groups in analogy to those present in the amino acids lysine, serine, cysteine, and histidine. Another target, a pyridine–substituted macrocycle, is planned as an entry into combining the catalytic functions with cofactor functionality. This paper describes the general strategy employed for the synthesis of the six di- and monosubstituted aminoethyl, hydroxyethyl, and mercaptoethyl macrocycles 2–7. Specific functionalization of a polyamine requires selective protection of amino groups. Among the various protective groups that can be employed, the combination of benzoyl,[23] benzyl,[24] or mesyl[25] groups with tosyl groups has been useful.



1 $R_1=R_2=H$
2 $R_1=R_2=CH_2CH_2NH_2$ 5 $R_1=H, R_2=CH_2CH_2NH_2$
3 $R_1=R_2=CH_2CH_2OH$ 6 $R_1=H, R_2=CH_2CH_2OH$
4 $R_1=R_2=CH_2CH_2SH$ 7 $R_1=H, R_2=CH_2CH_2SH$

The procedure developed for the synthesis of the target macrocycles utilizes common intermediates that can be readily converted to the various derivatives after the cyclization reaction is achieved (Scheme I). Construction of the macrocycle employs the versatile ditosylbenzoyldiethylenetriamine (11) described by Bulkowski and coworkers.[23] *N*-[2-[(*p*-Tolylsulfonyl)oxy]ethyl]-*p*-toluenesulfonamide[26] in toluene,[27] rather than benzene,[23] was treated with aqueous potassium hydroxide to give tosylaziridine (8). Reaction of 8 with monotosylethylenediamine[28] (9) followed by reaction with benzoyl chloride afforded 11. Following the procedure of Lehn and coworkers[27] the reaction of 11 with 2-(2-chloroethoxy)ethanol afforded the diol 12, which was converted to the dimesylate derivative 13. Cyclization[29,30] employed the reaction of 11

Scheme I



with the dimesylate derivative 13 in the presence of a large excess of cesium carbonate in dimethylformamide[31,32] to give the 7,19-dibenzoyl derivative 14. The diamine 15 was prepared by selective removal of the benzoyl groups by treatment of 14 with 24 equiv of potassium *tert*-butoxide and 8 equiv of water in refluxing tetrahydrofuran.[33] The overall yield for the six-step sequence starting from 8 to the common intermediate 15 was 20%; the limiting steps were the benzoylation of 10 (79%), cyclization to 14 (53%), and debenzoylation to give 15 (56%). Compound 15 had been obtained earlier by another procedure.[34]

The hexatosyl 7,19-bis(aminoethyl) derivative 16a was prepared in 88% yield by reaction of 15 with 3 equiv of tosylaziridine (8) at 70 °C for 7 days. Similarly, reaction of 15 with 12 equiv of 2-bromoethanol and 6 equiv of potassium carbonate in refluxing tetrahydrofuran gave the bis(hydroxyethyl) derivative 16b in 77% yield. The final derivative in the bis-substituted series, 16c, was formed in 70% yield by heating 15 with 2 equiv of ethylene sulfide to 90 °C in a sealed vial for 16 h. The detosylation of 16a–c was accomplished by heating in 32% hydrobromic acid–acetic acid in the presence of phenol[27,29,31,35] until TLC indicated deprotection was completed (several days).

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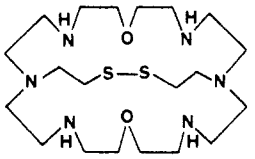
Compounds **2** and **3** were obtained as the hydrobromide salts, which were converted to the free base by anion-exchange chromatography. The hydrochloride salts were obtained by treatment of the free base with hydrochloric acid. The dithiol derivative **4** was not isolated but gave directly the bicyclic disulfide **17** presumably formed by air oxidation of the aqueous solution of the free base **4** after anion-exchange chromatography.



17

The preparation of the monosubstituted derivatives **5–7** followed the same general sequence with the exception that the cyclization reaction employed the tritosyl triamine **18** to give, after debenzoylation of **19**, the common intermediate **20**. Initial attempts to form the hydroxyethyl derivative **21b** by reaction of **20** with ethylene carbonate[30] at 160–170 °C resulted in recovered starting material.

The present work provides a facile route for the synthesis of monosubstituted or symmetrically disubstituted polyaza or polyoxaza macrocycles. In rests on the use of specific protective groups for amino functionalities, which permit the selective deprotection of the desired amino groups leading to macrocyclic compounds **15** and **20**. This strategy should be generally applicable.

Experimental Section

N-(2-Aminoethyl)-*p*-toluenesulfonamide (**9**), *N,N''*-bis(*p*-tolylsulfonyl)diethylenetriamine[27] (**10**), *N*-[[(*p*-tolylsulfonyl)-oxy]ethyl]-*p*-toluenesulfonamide,[23] *N'*-benzoyl-*N,N''*-bis(*p*-tolylsulfonyl)diethylenetriamine[23] (**11**), and *N,N',N''*-tris(*p*-tolylsulfonyl)diethylenetriamine[30] (**18**) were prepared as previously described. *N*-(*p*-Tolylsulfonyl)aziridine[23,27] (**8**) was prepared in toluene rather than in benzene by the reported procedure. All other chemicals used were high-purity commercial products.

^1H and ^{13}C NMR spectra were recorded at 300 and 75.43 MHz on a Varian XL300; chemical shifts (ppm) are relative (+, downfield) to references of tetramethylsilane or sodium 3-(trimethylsilyl)propanesulfonate. IR spectra were obtained on an IBM FT-IR. Microanalyses were obtained with use of a Hewlett-Packard 185B microanalytical instrument. Mass spectra were obtained with a Ribermag R-10-10 and a VG-ZAB spectrometer. Elemental analyses of the hydrochloride or hydrobromide salts of the final macrocycles gave varied results since these compounds were extremely hygroscopic. Evidence for the structure is based on ^1H and ^{13}C NMR for both structure and purity and high-resolution mass spectroscopy for structure.

9-Benzoyl-6,12-bis(*p*-tolylsulfonyl)-6,9,12-triaza-3,15-dioxaheptadecane-1,17-diol (12). A mixture of the triamine **11** (45 g, 87.3 mmol), 2-(2-chloroethoxy)ethanol (100 g, 0.803 mol), and K_2CO_3 (53 g, 0.384 mol) was stirred at 100 °C under an argon atmosphere for 72 h. The reaction mixture was then cooled and filtered, the solid was washed with CH_2Cl_2, and the combined filtrates were then evaporated in vacuo to remove the CH_2Cl_2 and excess 2-(2-chloroethoxy)ethanol. The resulting yellowish oil was chromatographed (SiO_2, 100% CH_2Cl_2 to 2% CH_3OH/CH_2Cl_2 gradient elution) to give **12** [56 g (92%)] as a clear, colorless viscous oil: ^1H NMR ($CDCl_3$) 7.69 (2 H, d, J = 9 Hz, aromatic), 7.55 (2 H, d, J = 9 Hz, aromatic), 7.41 (5 H, s, phenyl), 7.26 (2 H, d, J = 9 Hz, aromatic), 7.22 (2 H, d, J = 9 Hz, aromatic), 3.76 (2 H, m, OH), 3.58 (8 H, m), 3.45 (4 H, m), 3.35 (8 H, m), 3.22 (2 H, m), 3.09 (2 H, m), 2.39 (6 H, s, ArCH_3) ppm; ^{13}C NMR ($CDCl_3$) 172.6 (C=O), 143.6, 136.0, 129.8, 129.6, 128.5, 127.1, 127.0, 126.95, 126.90, 126.8, 126.6, (arom) 72.8, 72.4, 70.2, 69.9 (CH_2O) 61.6, 61.5 (CH_2OH), 49.7, 49.5, 49.2, 47.7, 47.3, 46.4 (CH_2N), 21.5 (CH_3) ppm; IR ($CHCl_3$) 3460, 3020, 2926, 2872, 1626, 1601, 1496, 1454, 1423, 1340, 1159, 1120, 1080, 1064 cm^{-1}; CIMS (NH_3) m/e (rel intens) 692 (8, M^+ + 1), 538 (11), 536 (7), 277 (14), 174 (37), 157 (13), 156 (33), 139 (100), 118 (35), 106 (39), 105 (52), 92 (34), 91 (36), 65 (11); HRMS (CI/NH_3) m/e for $C_{33}H_{45}N_3O_9S_2$ + 1 H requires 692.267, found 692.264.

9-Benzoyl-6,12-bis(*p*-tolylsulfonyl)-1,17-bis(mesyloxy)-6,9,12-triaza-3,15-dioxaheptadecane (13). The diol **12** (14 g, 20.2 mmol) was dissolved in CH_2Cl_2 (100 mL) under an argon atmosphere and the resultant mixture cooled to 0 °C. Then, triethylamine (10.2 g, 0.10 mol) was added followed by dropwise addition over 30 min of methanesulfonyl chloride (5.78 g, 50.5 mmol) in CH_2Cl_2 (30 mL). The reaction was warmed to room temperature for 2 h and then washed with cold water (90 mL), cold 10% HCl (90 mL), and cold saturated $NaHCO_3$ (90 mL). The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo to give **13** [17 g (99%)] as a red-orange foam that was used without further purification: ^1H NMR ($CDCl_3$) 7.71 (2 H, d, J = 9 Hz, aromatic), 7.57 (2 H, d, J = 9 Hz, aromatic), 7.41 (5 H, s, phenyl), 7.26–7.31 (4 H, m, aromatic), 4.28 (4 H, m, CH_2OMs), 3.05–3.80 (20 H, br m), 3.00 (6 H, s, OSO_2CH_3), 2.39 (6 H, s, ArCH_3) ppm; ^{13}C NMR ($CDCl_3$) 172.2, 143.6, 136.3, 136.0, 129.9, 129.5, 128.6, 127.1, 126.0, 69.6, 69.1, 69.0, 68.8, 68.6, 49.4, 49.2, 49.0, 47.1, 46.0, 45.9, 37.5, 21.5 ppm; IR ($CHCl_3$) 3030, 2941, 2874, 1630, 1344, 1174, 1159 cm^{-1}; CIMS (NH_3) m/e (rel intens) 848 (2, M^+ + 1), 726 (2), 598 (4), 268 (40), 192 (26), 105 (100). Anal. Calcd for $C_{35}H_{49}N_3O_{13}S_4$: C, 49.57; H, 5.82; N, 4.95. Found: C, 49.40; H, 5.85; N, 4.91.

7,19-Dibenzoyl-4,10,16,22-tetrakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (14). The dimesylate **13** (6.85 g, 7.76 mmol) in DMF (100 mL) was added dropwise over a period of 1 h to a mixture of the benzoyltriamine **11** (4.0 g, 7.76 mmol) and cesium carbonate (27.5 g, 84.4 mmol) in DMF (150 mL) at 95 °C under an argon atmosphere. After being stirred at 95 °C for 72 h, the reaction was cooled and filtered. The solid was washed with CH_2Cl_2, and the combined filtrates were washed with water and dried (Na_2SO_4). The solvent was removed in vacuo to give an orange solid that was chromatographed (SiO_2, 1% CH_3OH/CH_2Cl_2 to 2% CH_3OH/CH_2Cl_2 gradient elution) to give **14** [5.31 g (53%)] as a white solid: mp 233–234 °C; ^1H NMR ($CDCl_3$) 7.10–7.80 (26 H, m, aromatic), 3.10–3.80 (32 H, m), 2.41 (6 H, s, ArCH_3), 2.38 (3 H, s, ArCH_3), 2.35 (3 H, s, ArCH_3) ppm; ^{13}C NMR ($CDCl_3$) 172.3, 143.4, 136.4, 136.0, 135.8, 129.8, 129.3, 128.4, 127.1, 127.0, 126.8, 126.7, 69.8, 69.7, 69.1, 49.7, 49.2, 48.0, 47.9, 47.3, 47.1, 46.7, 21.5 ppm; IR (KBr) 3061, 3030, 2924, 2872, 1639, 1599, 1495, 1458, 1340, 1157, 1089 cm^{-1}. Anal. Calcd for $C_{58}H_{70}N_6O_{12}S_4 \cdot H_2O$: C, 58.57; H, 6.10; N, 7.07. Found: C, 58.70; H, 6.00; N, 7.29.

4,10,16,22-Tetrakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (15). To a solution of the macrocycle **14** (4.9 g, 4.18 mmol) in THF (150 mL) under an argon atmosphere was added water (0.6 g, 33.3 mmol) and potassium *tert*-butoxide (11.54 g, 0.103 mol). The reaction was heated at reflux for 10 h and cooled, and ice was added until two layers separated. The aqueous layer was washed thoroughly with THF and then CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to obtain an orange solid that was chromatographed (SiO_2, (1% CH_3OH + 0.5% Et_3N)/CH_2Cl_2 eluant) to give **15** [2.25 g (56%)] as a white solid: ^1H NMR ($CDCl_3$) 7.60 (8 H, d, J = 8 Hz, aromatic), 7.23 (8 H, d, J = 8 Hz, aromatic), 3.52 (8 H, m, CH_2O), 3.08–3.25 (16 H, m, CH_2NTs), 2.76 (8 H, m, CH_2NH), 2.45 (2 H, m, NH), 2.31 (12 H, s, ArCH_3) ppm; ^{13}C NMR ($CDCl_3$) 143.4, 135.8, 129.8, 127.1, 70.3, 49.6, 49.3, 48.0, 21.5 ppm; IR (KBr) 3330, 3063, 3032, 2924, 2866, 1597, 1495, 1452, 1383, 1338, 1120, 1089, 1018 cm^{-1}. Anal. Calcd for $C_{44}H_{62}N_6O_{10}S_4 \cdot H_2O$: C, 53.85; H, 6.59; N, 8.57. Found: C, 54.00; H, 6.98; N, 8.51.

7,19-Bis[2-[*N*-(*p*-tolylsulfonyl)amino]ethyl]-4,10,16,22-tetrakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (16a). A solution of the macrocycle **15** (1.05 g, 1.09 mmol) and tosylaziridine (**8**; 0.65 g, 3.27 mmol) in CH_3CN/toluene (100 mL, 1:1) was heated at reflux under an argon atmosphere for 7 days. The reaction was cooled, and the solvent was removed in vacuo. The resulting residue was chromatographed (SiO_2, 1% CH_3OH/CH_2Cl_2 to 2% CH_3OH/CH_2Cl_2 gradient elution) to give **16a** [1.30 g (88%)] as a white powder: ^1H NMR ($CDCl_3$) 7.73 (4 H, d, J = 8 Hz, aromatic), 7.67 (6 H, d, J = 8 Hz, aromatic), 7.27–7.32 (10 H, m, aromatic), 7.18 (4 H, d, J = 8 Hz, aromatic), 5.63 (2 H, br s, NH), 3.56 (8 H, m, CH_2O),

3.10–3.21 (16 H, m, CH_2NTs), 2.91 (4 H, m, CH_2NHTs), 2.64–2.75 (12 H, m, CH_2N), 2.41 (12 H, s, ArCH_3), 2.35 (6 H, s, ArCH_3-(NHTs)) ppm; ^{13}C NMR ($CDCl_3$) 143.4, 143.0, 136.9, 136.1, 129.8, 129.6, 127.1, 69.9, 54.1, 53.6, 49.5, 48.3, 41.1, 21.5 ppm; IR (KBr) 3292, 3063, 2924, 2870, 1599, 1495, 1452, 1335, 1159, 1092 cm^{-1}. Anal. Calcd for $C_{62}H_{84}N_8O_{14}S_6 \cdot H_2O$: C, 54.13; H, 6.30; N, 8.14. Found: C, 54.09; H, 6.40; N, 8.20.

7,19-Bis(2-hydroxyethyl)-4,10,16,22-tetrakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (16b). To a solution of the macrocycle **15** (0.95 g, 0.986 mmol) in THF (20 mL) under an argon atmosphere was added anhydrous K_2CO_3 (0.82 g, 5.93 mmol) and 2-bromoethanol (1.48 g, 11.8 mmol). The reaction was heated at reflux for 62 h, cooled, and taken up in CH_2Cl_2 (25 mL). This solution was extracted with water (15 mL) and dried (Na_2SO_4) and the solvent removed in vacuo to give a yellowish residue that was chromatographed (SiO_2, 100% CH_2Cl_2 to 3% CH_3OH/CH_2Cl_2 gradient elution) to give **16b** [0.80 g (77%)] as a hydroscopic white solid: ^{1}H NMR ($CDCl_3$) 7.68 (8 H, d, J = 9 Hz, aromatic), 7.30 (8 H, d, J = 9.0 Hz, aromatic), 3.52–3.59 (12 H, m, CH_2O), 3.21–3.30 (16 H, m, CH_2NTs), 2.79–2.84 (8 H, m, NCH_2CH_2NTs), 2.66–2.67 (4 H, m, NCH_2CH_2OH), 2.41 (12 H, s, ArCH_3) ppm; ^{13}C NMR ($CDCl_3$) 143.4, 136.2, 129.8, 127.1, 69.9, 59.2, 56.6, 54.0, 49.2, 48.2, 21.5 ppm; IR (KBr) 3447, 3032, 2629, 2870, 1597, 1495, 1454, 1337, 1157, 1090, 1045 cm^{-1}. Anal. Calcd for $C_{48}H_{70}N_6O_{12}S_4$: C, 54.83; H, 6.71; N, 7.99. Found: C, 54.68; H, 6.40; N, 7.68.

7,19-Bis(2-mercaptoethyl)-4,10,16,22-tetrakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (16c). A sealed vial containing a mixture of ethylene sulfide (120 mg, 1.99 mmol) and the macrocycle **15** (0.9 g, 0.93 mmol) was heated to 90–95 °C with stirring for 16 h until TLC indicated the reaction ws complete. The product was obtained in the form of a yellow residue that was chromatographed (SiO_2, 100% CH_2Cl_2 to 0.5% CH_3OH/CH_2Cl_2 gradient elution) to give **16c** [0.70 g (70%)] as a hydroscopic white solid: ^{1}H NMR ($CDCl_3$) 7.61 (8 H, d, J = 7 Hz, aromatic), 7.23 (8 H, d, J = 7 Hz, aromatic), 3.48 (8 H, s, CH_2O), 3.23 (4 H, m, CH_2S), 3.14–3.23 (16 H, m, CH_2NTs), 2.64–2.68 (12 H, m, CH_2N), 2.33 (12 H, s, ArCH_3) ppm; ^{13}C NMR ($CDCl_3$) 144.9, 137.9, 131.3, 128.6, 71.7, 59.1, 55.2, 50.6, 49.5, 24.3, 23.0 ppm; IR (KBr) 2926, 2867, 1453, 1401, 1339, 1306, 1157, 1119, 1090, 1055, 1044, 1019, 992 cm^{-1}. Anal. Calcd for $C_{48}H_{70}N_6O_{10}S_6$: C, 53.20; H, 6.52; N, 7.76. Found: C, 53.10; H, 6.40; N, 7.40.

7,19-Bis(aminoethyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (2). The macrocycle **16a** (400 mg, 0.29 mmol) and 400 mg of phenol were dissolved in 30 mL of 32% hydrobromic acid–acetic acid. The mixture was heated to 80 °C for 72 h during which time a solid formed in the mixture. The mixture was cooled, and 50 mL of ether was added to give a gray precipitate. The solid was collected, washed with cold ether, dissolved in water, and passed through a Dowex-1 (OH form) anion-exchange resin to yield, after evaporation, 90 mg of the free amine **2** (72%). The free base was converted to the hygroscopic hydrochloride salt by dissolving in water and treating with hydrochloric acid to give after evaporation a solid that was purified by crystallization from methanol: ^{1}H NMR (D_2O) 3.59 (8 H, m, CH_2O), 3.73, 2.64, 2.57 (32 H, m, CH_2N) ppm; ^{13}C NMR (D_2O) 71.48, 58.65, 55.36, 49.90, 47.90, 40.38 ppm; EIMS m/e (rel intens) 433 (7, M^+ + 1), 402 (11), 359 (4), 345 (40), 230 (25), 215 (30), 203 (20), 145 (35), 131 (25), 99 (70), 87 (100); HRMS (CI/NH_3) m/e for $C_{20}H_{48}N_8O_2$ + 1 H requires 433.397, found 433.397.

7,19-Bis(2-hydroxyethyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (3). Treatment of 200 mg of compound **16b** (0.19 mmol) according to the method described in the preparation of **2** afforded 50 mg of the free base **3** (61%): ^{1}H NMR (D_2O) 3.51, 3.22 (12 H, m, (CH_2O), 2.53–2.67 (28 H, m, CH_2N) ppm; ^{13}C NMR (D_2O) 71.95, 71.20 (CH_2O), 59.41, 55.05, 51.63, 50.17 (CH_2N) ppm; EIMS m/e (rel intens) 417 (4, M^+ + 1 H – H_2O), 398 (100), 383 (17), 342 (20), 328 (43), 273 (50), 255 (71); HRMS (CI/NH_3) m/e for $C_{20}H_{44}N_6O_3$ + 1 H – H_2O requires 417.355, found 417.352.

Note Added in Proof: The high-resolution mass spectrum for **3**, being the fragment ion derived from loss of water, does not distingush the diol **3** from the bicyclic ether that could potentially arise in the deprotection reaction. To confirm the assigned structure, the free base of **3** was treated with acetic anhydride in pyridine to give the hexaacetyl derivative of **3**: IR (KBr) 1739 (ester), 1640 cm^{-1} (amide); HRMS (EI) m/e for $C_{32}H_{58}N_6O_{10}$ requires 686.421, found 686.042.

14,25-Dioxa-4,5-dithia-1,8,11,17,22,28-hexaazabicyclo[6.11.11]triacontane (17). Treatment of 850 mg of compound **16c** (0.78 mmol) according to the method described in the preparation of **2** afforded 150 mg of the free base **17** (41%) formed by air oxidation of the expected macrocycle **4** (see text): ^{1}H NMR (D_2O) 3.60 (8 H, m, CH_2O), 2.78, 2.72 (32 H, m, CH_2N, CH_2S) ppm; ^{13}C NMR (D_2O) 71.66, 56.85, 55.14, 50.32, 48.49, 29.20 ppm; EIMS m/e (rel intens) 464 (80, M^+), 431 (100), 399 (75), 347 (46), 335 (80), 323 (74), 232 (70), 220 (44); HRMS (EI) m/e for $C_{20}H_{44}N_6O_2S_2$ requires 464.296, found 464.295.

7-Benzoyl-4,10,16,19,22-pentakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (19). The dimesylate **13** (8.9 g, 10.5 mmol) in DMF (75 mL) was added dropwise over a period of 1.75 h to a mixture of tritosyldiethylenetriamine (**18**; 5.94 g, 10.5 mmol) and cesium carbonate (34.2 g, 0.105 mol) in DMF (100 mL) at 95 °C under an argon atmosphere. After being stirred at 95 °C for 72 h, the reaction mixture was cooled and filtered. The solid was washed with CH_2Cl_2, and the combined filtrates were washed with water and dried (Na_2SO_4). The solvent was removed in vacuo to give a viscous orange oil that was chromatographed (SiO_2, 100% CH_2Cl_2 to 1% CH_3OH/CH_2Cl_2 gradient elution) to give **19** [7.15 g (55%)] as a white solid: ^{1}H NMR ($CDCl_3$) 7.64–7.71 (8 H, m, aromatic), 7.38–7.46 (7 H, m, aromatic), 7.20–7.30 (10 H, m, aromatic), 3.00–3.80 (32 H, m), 2.40 (9 H, s, ArCH_3), 2.38 (3 H, s, ArCH_3), 2.36 (3 H, s, ArCH_3) ppm; ^{13}C NMR ($CDCl_3$) 172.4, 143.5, 143.4, 136.5, 136.2, 136.1, 135.8, 135.7, 129.8, 129.5, 129.3, 128.4, 127.5, 127.3, 127.1, 127.0, 126.7, 70.0, 69.7, 69.3, 49.5, 49.2, 48.9, 48.8, 47.8, 47.2, 46.5, 21.5 ppm; IR (KBr) 3054, 3027, 2926, 2872, 1637, 1599, 1495, 1456, 1346, 1306, 1161, 1116 cm^{-1}. Anal. Calcd for $C_{58}H_{72}N_6O_{13}S_5 \cdot H_2O$: C, 56.20; H, 6.02; N, 6.78. Found: C, 56.30; H, 6.00; N, 6.80.

4,10,16,19,22-Pentakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (20). To a solution of the macrocycle **19** (9.1 g, 7.45 mmol) in THF (100 mL) under an argon atmosphere was added water (0.53 g, 29.4 mmol) and potassium *tert*-butoxide (10.27 g, 91.5 mmol). The reaction was heated at reflux for 1 h and cooled, and ice was added until two layers separated. The aqueous layer was washed thoroughly with THF and then CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to obtain an orange solid that was chromatographed (SiO_2, 1% CH_3OH/CH_2Cl_2 to 3% CH_3OH/CH_2Cl_2 gradient elution) to give **20** [6.83 g (82%)] as a white solid: ^{1}H NMR ($CDCl_3$) 7.70 (10 H, m, aromatic), 7.29 (10 H, m, aromatic), 4.30 (1 H, m, N*H*), 3.10–3.70 (26 H, m), 2.70–2.90 (8 H, m), 2.40 (15 H, s, ArCH_3) ppm; ^{13}C NMR ($CDCl_3$) 143.8, 143.6, 143.3, 136.2, 136.0, 135.8, 129.9, 129.8, 129.7, 127.2, 127.1, 126.9, 70.6, 70.5, 69.9, 49.8, 49.7, 49.6, 49.5, 49.4, 21.5 ppm; IR (KBr) 3443, 3086, 3063, 2924, 2870, 1597, 1495, 1338, 1159, 1089 cm^{-1}. Anal. Calcd for $C_{51}H_{68}N_6O_{12}S_5$: C, 54.82; H, 6.13; N, 7.52. Found: C, 54.68; H, 5.98; N, 7.30.

7-[2-[*N*-(*p*-Tolylsulfonyl)amino]ethyl]-4,10,16,19,22-pentakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (21a). A solution of the macrocycle **20** (2.0 g, 1.79 mmol) and tosylaziridine (**8**; 0.42 g, 2.15 mmol) in toluene/acetonitrile (100 mL, 1:1) under an argon atmosphere was heated at 70 °C for 5 days. The solvent was then removed in vacuo and the residue chromatographed (SiO_2, 2.5% CH_3OH/CH_2Cl_2 eluant) to give **21a** [2.31 g (98%)] as a white solid: ^{1}H NMR ($CDCl_3$) 7.55–7.72 (12 H, m, aromatic), 7.10–7.30 (10 H, m, aromatic), 7.13 (2 H, d, J = 8 Hz, aromatic), 5.68 (1 H, m, N*H*), 3.42–3.55 (8 H, m, CH_2O), 3.15–3.38 (20 H, m, CH_2NTs), 2.86 (2 H, m, CH_2NHTs), 2.59 (6 H, m, CH_2N), 2.33 (15 H, s, ArCH_3), 2.28 (3 H, s, ArCH_3(NHTs)) ppm; ^{13}C NMR ($CDCl_3$) 143.7, 143.6, 143.3, 142.9, 137.1, 136.5, 135.7, 135.6, 129.9, 129.8, 129.6, 127.4, 127.2, 127.1, 69.9, 69.5, 53.6, 53.5, 49.6, 49.1, 48.6, 47.8, 41.1, 21.5 ppm; IR (KBr) 3300, 3063, 2924, 2872, 1589, 1456, 1338, 1159, 1089 cm^{-1}. Anal. Calcd for $C_{60}H_{79}N_7O_{14}S_6$: C, 54.82; H, 6.06; N, 7.46. Found: C, 54.70; H, 6.12; N, 7.23.

7-(2-Hydroxyethyl)-4,10,16,19,22-pentakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (21b). To a solution of the macrocycle **20** (0.75 g, 0.671 mmol) in THF (10 mL) under an argon atmosphere was added anhydrous K_2CO_3 (0.28 g, 2.01 mmol) and 2-bromoethanol (0.50 g, 4.03 mmol). The reaction was heated at reflux for 72 h, cooled, and taken up

in CH_2Cl_2 (20 mL). This solution was extracted with water (15 mL) and dried (Na_2SO_4) and the solvent removed in vacuo to give a brownish residue that was chromatographed (SiO_2, 1% CH_3OH/CH_2Cl_2 to 3% CH_3OH/CH_2Cl_2 gradient elution) to give unreacted **20** (0.15 g) and **21b** [0.45 g (57%, 72% based on recovered starting material)] as a white solid: ^1H NMR ($CDCl_3$) 7.64-7.71 (10 H, m, aromatic), 7.26-7.33 (10 H, m, aromatic), 3.50-3.56 (10 H, m, CH_2O), 3.26-3.37 (20 H, m, CH_2NTs), 2.64-2.76 (6 H, m, CH_2N), 2.40 (15 H, s, $ArCH_3$) ppm; ^{13}C NMR ($CDCl_3$) 143.7, 143.5, 143.3, 137.6, 135.7, 135.5, 129.9, 129.8, 129.7, 127.4, 127.3, 127.1, 70.0, 69.7, 59.3, 56.5, 53.7, 49.7, 49.3, 48.6, 48.0, 21.6, 21.5, 21.4 ppm; IR (KBr) 3449, 3032, 2926, 2872, 1599, 1495, 1456, 1340, 1155, 1089, 995 cm^{-1}. Anal. Calcd for $C_{53}H_{72}N_6O_{13}S_5 \cdot H_2O$: C, 53.97; H, 6.32; N, 7.12. Found: C, 54.00; H, 6.40; N, 7.00.

7-(2-Mercaptoethyl)-4,10,16,19,22-pentakis(*p*-tolylsulfonyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (21c). A sealed vial containing a mixture of ethylene sulfide (26.6 mg, 0.44 mmol) and the macrocycle **20** (0.5 g, 0.44 mmol) was heated to 95 °C with stirring for 14 h when TLC indicated the reaction was completed. The product was obtained in the form of a yellow residue that was chromatographed (SiO_2, 100% CH_2Cl_2 to 1% CH_3OH/CH_2Cl_2 gradient elution) to give **21c** [0.35 g (68%)] as a white solid: ^1H NMR ($CDCl_3$) 7.63-7.71 (10 H, m, aromatic), 7.26-7.28 (10 H, m aromatic), 3.53 (8 H, m, CH_2O), 3.32, 3.25, 3.15 (22 H, m, CH_2S, CH_2NTs), 2.66 (6 H, m, CH_2N), 2.36 (15 H, s, $ArCH_3$) ppm; ^{13}C NMR ($CDCl_3$) 143.0, 142.8, 136.0, 135.0, 129.5, 129.3, 129.2, 129.1, 129.0, 128.9, 126.8, 126.7, 126.6, 126.5, 125.7, 69.47, 69.23, 52.89, 49.14, 49.00, 48.72, 48.11, 47.30, 20.93 ppm; IR (KBr) 3497, 3451, 3437, 2924, 2872, 1453, 1402, 1339, 1306, 1159, 1119, 1092, 1019, 990, 932 cm^{-1}. Anal. Calcd for $C_{53}H_{72}N_6O_{12}S_6$: C, 54.06; H, 6.16; N, 7.14. Found: C, 54.00; H, 6.18; N, 7.14.

7-(2-Aminoethyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (5). Treatment of 300 mg of the compound **21a** (0.29 mmol) according to the method described in the preparation of **2** afforded 80 mg of the free base **5**: 71%; ^1H NMR (D_2O) 3.64 (8 H, m, CH_2O), 2.70-2.92 (28 H, m, CH_2N) ppm; ^{13}C NMR (D_2O) 71.49, 71.35, 57.05, 55.04, 54.95, 50.29, 50.24, 49.97, 49.66, 48.02 ppm; EIMS *m/e* (rel intens) 389 (21, M^+), 358 (16), 315 (11), 301 (100), 114 (79); HRMS (EI) *m/e* for $C_{18}H_{43}N_7O_2$ requires 389.348, found 389.346.

7-(2-Hydroxyethyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (6). Treatment of 400 mg of the compound **21b** (0.34 mmol) according to the method described in the preparation of **2** afforded 85 mg of the free base **6**: 64%; ^1H NMR (D_2O) 3.56 (10 H, s, CH_2O), 2.48-2.72 (26 H, m, CH_2N) ppm; ^{13}C NMR (D_2O) 71.80, 71.75, 71.65 (CH_2O), 55.67, 54.59, 54.34, 50.17, 50.08, 49.85, 47.97 (CH_2N) ppm; EIMS *m/e* (rel intens) 391 (9, $M^+ + 1$), 373 (18), 316 (27), 302 (100), 247 (67), 243 (67) 229 (56); HRMS (CI/NH_3) *m/e* for $C_{18}H_{42}N_6O_3 + 1$ H requires 391.339, found 391.339.

7-(2-Mercaptoethyl)-1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (7). Treatment of 300 mg of the compound **21c** (0.25 mmol) according to the method described in the preparation of **2** afforded 65 mg of the free base **7**: 65%; ^1H NMR (D_2O) 3.6-3.7 (8 H, m, CH_2O), 2.7-2.8 (28 H, m, CH_2N, CH_2S) ppm; ^{13}C NMR (D_2O) 71.87, 71.72, 55.29, 50.40, 50.29, 50.20, 49.79, 47.41, 46.59, 40.68 ppm; EIMS *m/e* (rel intens) 407 (100, $M^+ + 1$), 373 (55), 347 (28), 329 (28), 290 (28), 229 (50); HRMS (CI/NH_3) *m/e* for $C_{18}H_{42}N_6O_2S + 1$ H requires 407.317, found 407.313.

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Reaction of Dimethyl Acetylenedicarboxylate with 3,4-Disubstituted Isoxazolin-5-ones. A New Synthesis of 1,3-Oxazin-6-ones and 2,3-Dihydro-1,3-oxazin-6-ones

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Reaction of 3,4-disubstituted isoxazolin-5-ones with dimethyl acetylenedicarboxylate affords 2,2',3,3'-tetrahydro[2,2'-bi-1,3-oxazine]-6,6'-diones. A reaction path is proposed.

The reaction of acetylenecarboxylic esters with nitrogen-containing heterocycles[1] as well as the synthesis of heterocycles through nucleophilic addition to acetylenic esters[2] have been widely studied. However the reaction of isoxazolin-5-ones with acetylene carboxylic esters has not been reported.

We have previously reported on the synthesis of 2,5-diaryl-1,3-oxazin-6-ones from 4-arylisoxazolin-5-ones[3] and of 2-(dialkylamino)-1,3-oxazin-6-ones by Vilsmeier-Haack reaction of 3,4-disubstituted isoxazolin-5-ones.[4]

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