# Synthesis, Characterization, and Stability of Manganese(II) C-Substituted 1,4,7,10,13-Pentaazacyclopentadecane Complexes Exhibiting Superoxide Dismutase Activity

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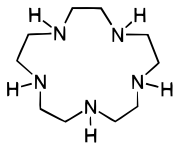
Superoxide radical anion has been demonstrated to be a mediator of many disease states, including inflammatory, autoimmune, and cancerous diseases. As a consequence, we have developed a program to design, synthesize, and test synthetic low-molecular weight superoxide dismutase (SOD) mimics as potential pharmaceutical agents. A critical feature of the design of metal-based drugs is not only high activity as an enzyme mimic but also chemical stability. In this report we describe the synthesis and characterization of a series of C-substituted 1,4,7,-10,13-pentaazacyclopentadecane, [15]aneN$_5$, ligands, **1**, and their corresponding Mn(II) complexes, **2** and **3**, as their dichloro complexes, [Mn([15]aneN$_5$)Cl$_2$]. The purpose of the work is to probe the role that substituent (methyl and fused cycloalkyl) groups exert on the catalytic activity and stability of the complexes. All of the 18 new complexes described here are catalysts for the dismutation of superoxide, and substantial substituent effects are observed with $k_{cat}$ values at pH = 7.4 varying in the range (1.4−9.1) × $10^7$ $M^{-1}$ $s^{-1}$. The kinetic and thermodynamic stabilities of these new complexes were studied by a Cu(II) ion competition spectrophotometric assay and by potentiometric titrations, respectively. It is observed that increasing the number of carbon substituents increases the kinetic stability of the complexes, while the thermodynamic stability increases, but less dramatically. The crystal structure for one of these new complexes, [Mn(2,2,3,3-Me$_4$[15]aneN$_5$)Cl$_2$], **2i**, was determined, and reveals that the Mn(II) ion is coordinated by a pentagonal bipyramid array of five macrocyclic derived nitrogen atoms in a plane with the Mn(II) center and capped by *trans*-dichloro ligands. Crystal data for $MnC_{14}H_{33}N_5Cl_2{\cdot}CH_3CH_2OH$: triclinic, $P\bar{1}$-$C_i^1$ (#2), $a$ = 9.941(2) Å, $b$ = 11.190(2) Å, $c$ = 11.613(2) Å, $V$ = 1125.4(4) Å$^3$, $Z$ = 2, $T$ = 20 ± 1 °C, for 3357 independent absorption-corrected reflections having $2\theta$(Cu K$\alpha$) < 120.0° and $I > 3\sigma(I)$, with $R_{int}$ = 0.027.

## Introduction

We have recently shown that the Mn(II) complex of the unsubstituted 1,4,7,10,13-pentaazacyclopentadecane ligand, **1a**, [Mn([15]aneN$_5$)Cl$_2$] (Figure 1), is an excellent catalyst for the dismutation of superoxide; in effect it serves as a synthetic enzyme or enzyme mimetic.[1] Our efforts in this area have focused on the design of SOD mimics which could potentially serve as human pharmaceutical agents for the treatment of diseases characterized by the overproduction of superoxide. A major thrust of our synthesis and characterization efforts has been to investigate the role that C-substituents exert on both the catalytic SOD activity and the overall chemical stability of the resultant complexes. The structural factors that affect these two key parameters are not immediately obvious; since it was not known at the outset how derivatized ligand systems would affect catalytic activity. Thus, the number of substitutents, their placement, and their stereochemistry could all be critical design elements for maximizing catalytic activity and chemical stability.

In general, we have pursued the goal of designing highly chemically stable complexes, as their end use would be as human pharmaceuticals. Our initial design goal has been to maximize the number of substituents on the macrocyclic ring,



**1a**

**Figure 1.** 1,4,7,10,13-Pentaazacyclopentadecane, **1a**.

thereby increasing the preorganizational rigidity of the macrocyclic ligand and thus increasing the stability of the Mn(L) complex to dissociation.[2] At the outset we had no way of knowing whether increasing the number of substituents on the parent macrocyclic ring would affect the catalytic activity in a beneficial or deleterious fashion. The purpose of the work described here has been to determine the effect that substitution on the macrocyclic ring has on the chemical stability as manifested by the thermodynamic and kinetic stabilities of the complex. To probe these questions, we have employed both methyl and fused-cycloalkyl substituents on macrocyclic ring carbons. We have not explored the role of N-substituents on the stability of the complexes, since, as we had noted previously,[1] the incorporation of substituents on the nitrogen centers of the macrocyclic ligand, **1**, afford Mn(II) complexes which in *all cases possess no catalytic SOD activity*.

† Monsanto Company.
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(1) Riley, D. P.; Weiss, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 387.
(2) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Brown, S. B.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 3645.

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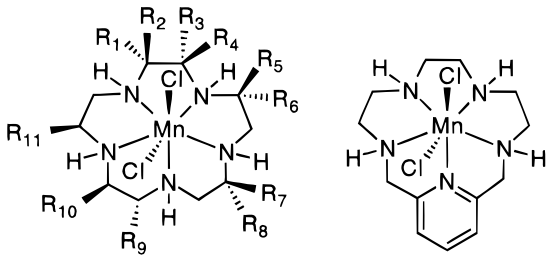


**2** **3**

a) $R_{1\text{-}11}$ = H
b) $R_1$ = Me; $R_{2\text{-}11}$ = H
c)* $R_1$, $R_4$ = Me; $R_2$, $R_3$, $R_{5\text{-}11}$ = H
d) $R_2$, $R_6$ = Me; $R_1$, $R_{3\text{-}5}$, $R_{7\text{-}11}$ = H
e) $R_2$, $R_5$ = Me; $R_1$, $R_3$, $R_4$, $R_{6\text{-}11}$ = H
f) $R_2$, $R_8$ = Me; $R_1$, $R_{3\text{-}7}$, $R_{9\text{-}11}$ = H
g) $R_2$, $R_7$ = Me; $R_1$, $R_{3\text{-}6}$, $R_{8\text{-}11}$ = H
h) $R_2$, $R_6$, $R_7$ = Me; $R_1$, $R_{3\text{-}5}$, $R_{8\text{-}11}$ = H
i) $R_{1\text{-}4}$ = Me; $R_{5\text{-}11}$ = H
j) $R_2$, $R_6$, $R_7$, $R_9$ = Me; $R_1$, $R_{3\text{-}5}$, $R_8$, $R_{10}$, $R_{11}$ = H
k) $R_1$, $R_4$, $R_9$, $R_{10}$ = Me; $R_2$, $R_3$, $R_{5\text{-}8}$, $R_{11}$ = H
l) $R_2$, $R_6$, $R_7$, $R_9$, $R_{11}$ = Me; $R_1$, $R_{3\text{-}5}$, $R_8$, $R_{10}$ = H
m)* $R_1$, $R_4$ = $-CH_2CH_2CH_2CH_2-$
n)* $R_1$, $R_4$ = $-CH_2CH_2CH_2-$
o)* $R_1$, $R_4$ = $-CH_2CH_2CH_2CH_2CH_2-$
p) $R_1$, $R_3$ = $-CH_2CH_2CH_2CH_2-$
q)* $R_1$, $R_4$ = $-CH_2CH(t\text{-}Bu)CH_2CH_2-$

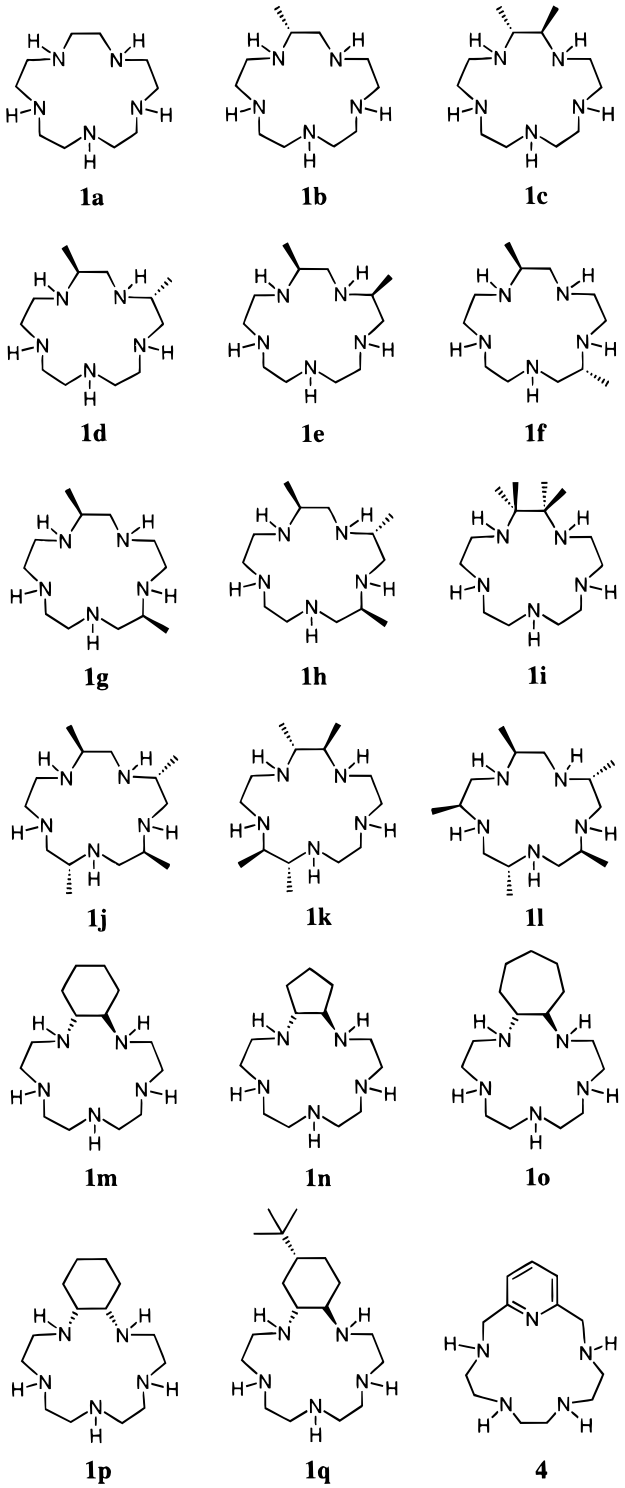
*Compounds indicated are racemic.

**Figure 2.** Structure of the [Mn([15]aneN$_5$)Cl$_2$] complexes **2a**−**q** and **3** utilized for stability and SOD catalytic activity studies.

This paper describes the synthesis and characterization of a number of new C-substituted ligands derived from **1** and their Mn(II) complexes, **2** and **3** (Figure 2). The catalytic superoxide dismutase activity at pH = 7.4 of the new C-substituted macrocyclic Mn(II) complexes is reported here, as well as the thermodynamic stability of each complex as determined by potentiometric titration. While the thermodynamic stability of the complexes is obviously important for understanding the stabilizing effect various substituent patterns exert, we also have measured for each complex its kinetic stability as a function of pH. It is this kinetic stability which is critical for the design of a drug, since it is desirable that a complex have an *in vivo* $t_{1/2}$ chemical stability greater than its clearance half-life. Finally, we report the single-crystal X-ray structure determination for one of these new complexes, [Mn(2,2,3,3-tetramethyl[15]-aneN$_5$)Cl$_2$], **2i**.

## Results

**Synthesis and Characterization of Ligands.** The novel C-substituted pentaazacyclopentadecane ligands were synthesized using a variety of methods. Chiral ligand **1b** was prepared using the macrocyclization and deprotection method of Richman and Atkins as shown in Scheme 1.[4] D-Alaninamide was reduced and tosylated to provide *N*,*N*′-bis(*p*-tolylsulfonyl)-(*R*)-1,2-diaminopropane, **6**, in 42% overall yield.[5] The protected macrocycle **10** was prepared in 45% yield via deprotonation of the chiral bis(toluenesulfonamide) **6** in situ and alkylation with 3,6,9-tris(*p*-tolylsulfonyl)-3,6,9-triazaundecane-1,11-diylbis(*p*-toluenesulfonate), **9**. The macrocycle **10** was then deprotected using 20% HBr with phenol to give R−Me−[15]aneN$_5$, **1b** in 17% yield. The remaining macrocycles **1c**−**q** were prepared



**1a** **1b** **1c**
**1d** **1e** **1f**
**1g** **1h** **1i**
**1j** **1k** **1l**
**1m** **1n** **1o**
**1p** **1q** **4**

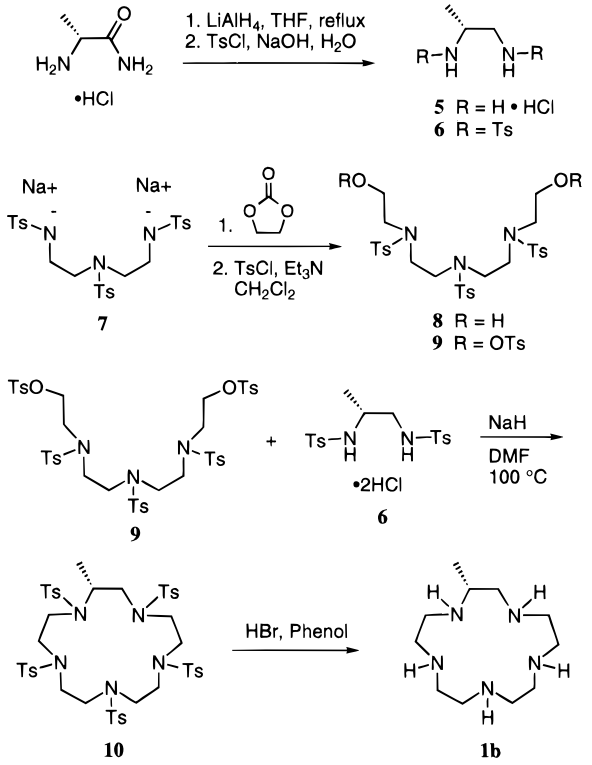
**Figure 3.** Structure of 1,4,7,10,13-pentaazacyclopentadecane ligands **1a**−**q** and **4**, which were utilized to synthesize the new Mn(II) complexes.

using one of three methods: (1) the acid chloride method, (2) the bis(chloroacetamide) method, or (3) the cyclic peptide method. In the case of ligand **1k**, a combination of these methods was used.

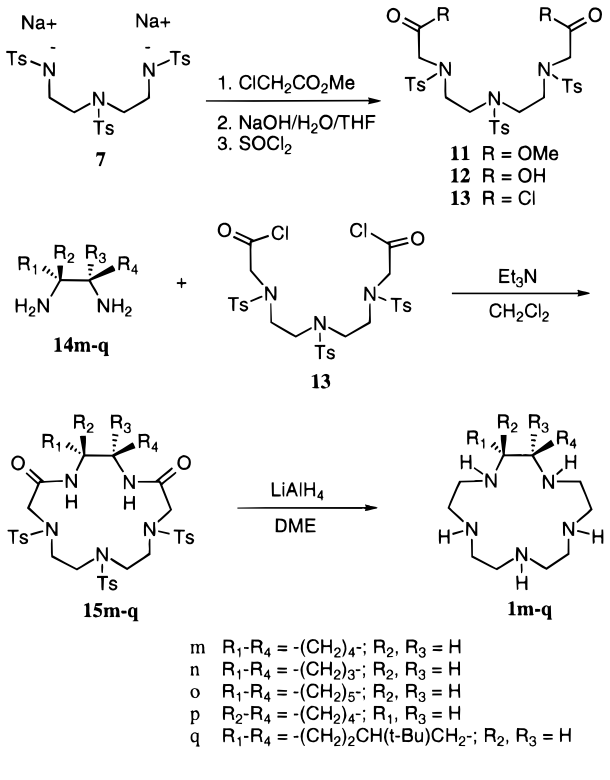
Ligands **1m**−**q** where synthesized via the acid chloride method (Scheme 2). In this method two amide bonds were formed by diacylation of vicinal diamine **14** with diacid chloride **13** to give macrocycles **15m**−**q** in yields ranging from 29% to 66%. Among the cyclic hydrocarbon diamines, both *trans*- and *cis*-cyclohexanediamines are commercially available. *trans*-Cyclopentanediamine, *trans*-cycloheptanediamine, and 4-*tert*-butylcyclohexanediamine were prepared from the cyclic ketone

(3) Atkins, T. J.; Richman, J. E.; Oettle, W. F. *Org. Synth.* **1978**, *58*, 86−99.
(4) The racemic ligand has been prepared previously: Schaeffer, Michel; Doucet, Didier; Bonnemain, Bruno; Meyer, Dominique. Eur. Pat. Appl. EP 88-400895 880413. CAN 111:69850.
(5) The presented yields have not been optimized.

**Scheme 1.** Richman−Atkins Type Synthesis

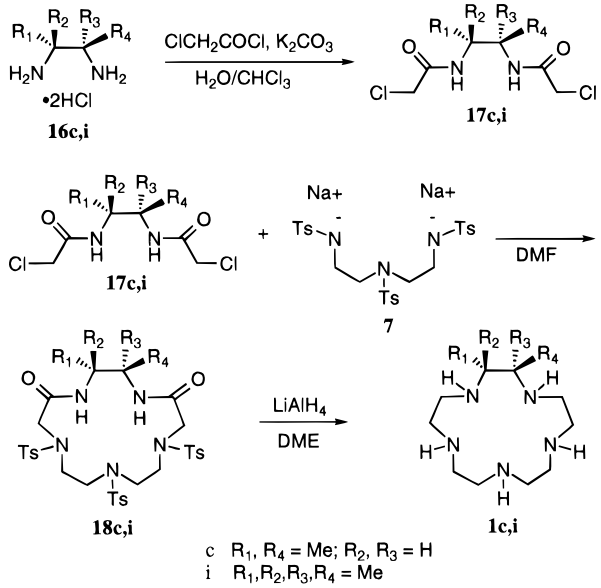



**Scheme 2.** Acid Chloride Method of Synthesis

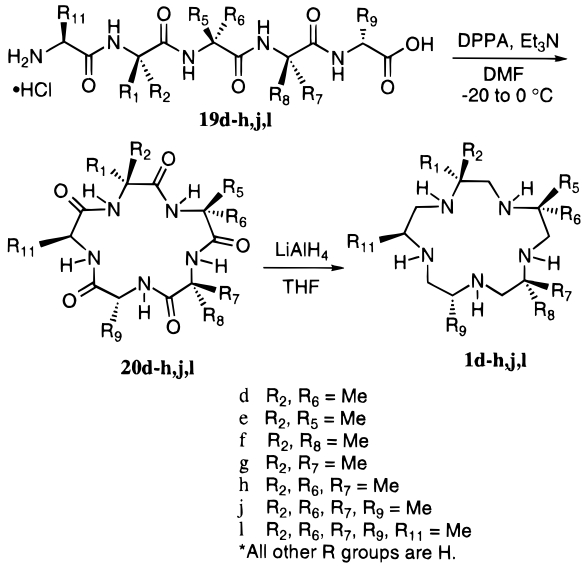



via their diketone and dioxime.[6−9] Diacid chloride **13** was prepared in high yield by alkylation of the sulfonamide dianion **7** followed by saponification and treatment of the diacid with thionyl chloride. Subsequent reduction and deprotection of the macrocycle **15** was accomplished by treatment with lithium aluminum hydride in refluxing 1,2-dimethoxyethane (DME, ethylene glycol dimethyl ether) to provide ligands **1m**−**q** in yields ranging from 22 to 50%.

**Scheme 3.** Bis(chloroacetamide) Method of Synthesis




**Scheme 4.** Cyclic Peptide Method of Synthesis

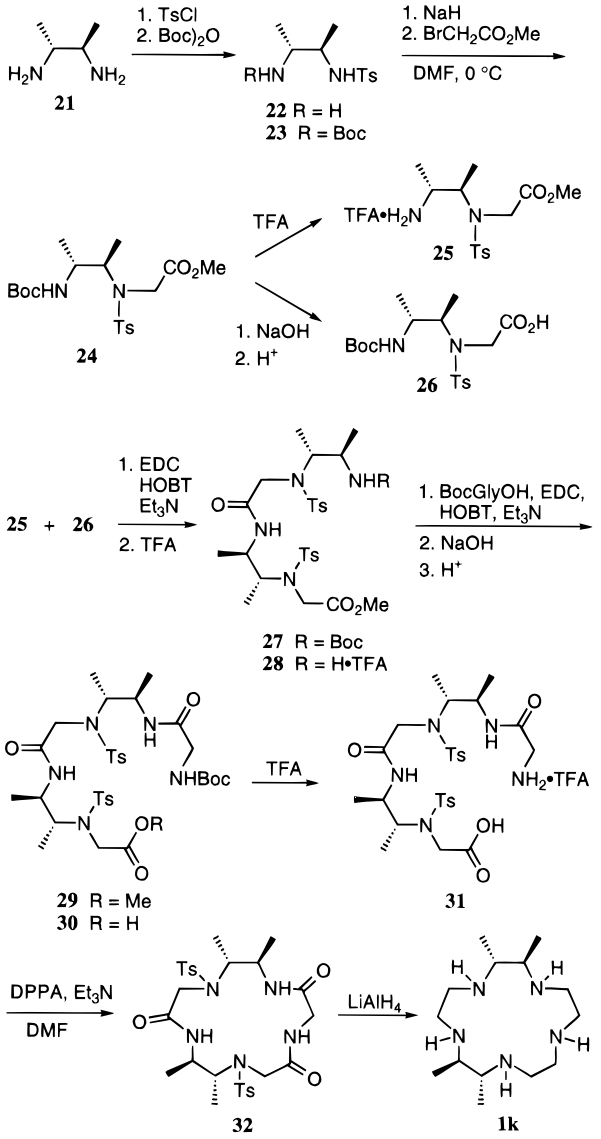



The bis(chloroacetamide) method[10] was used to synthesize ligands **1c** and **1i** (Scheme 3). Bis(chloroacetamide) **17c** or **17i** was formed in 89% yield via acylation of the diamine **16c** or **16i** with chloroacetyl chloride. Nucleophilic substitution of the tris(tosyl)diethylenetriamine dianion **7** with **17c** or **17i** gave macrocycles **18c** and **18i** in 46% and 72% yield, respectively. Lithium aluminum hydride in refluxing DME effected reduction of amide and detosylation of **18** to provide the polyaza macrocycles **1c** and **1i** in 37% and 39% yield, respectively.

In a different approach, asymmetric ligands **1d**−**h**,**j**,**l** were synthesized using the cyclic peptide method[11] (Scheme 4). Initially, the required pentapeptide, **19**, was formed in high yield using solution phase synthesis. Macrocyclization was then

(6) Cyclopentanedione: Goto, M.; Takeshita, M.; Sakai, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2589.
(7) Cyclopentanedioxime and 1,2-*trans*-cyclopentanediamine: Jaeger, F. M.; Blumendal, H. B. *Z. Anorg. Allg. Chem.* **1928**, *175*, 161.
(8) Cycloheptanedione and cycloheptanedioxime: Vander Haar, R. W.; Voter, R. C.; Banks, C. V. *J. Org. Chem.* **1949**, *14*, 836.
(9) 1,2-*trans*-Cycloheptanediamine: Belcher, R.; Hoyle, W.; West, T. S. *J. Chem. Soc.* **1961**, 667.
(10) Lennon, P. J.; Rahman, H.; Aston, K. W.; Henke, S. L.; Riley, D. P. *Tetrahedron Lett.* **1994**, *35*, 853.
(11) Aston, K. W.; Henke, S. L.; Modak, A. S.; Riley, D. P.; Sample, K. R.; Weiss, R. H.; Neumann, W. L. *Tetrahedron Lett.* **1994**, *35*, 3687.

**Scheme 5.** Combination Method of Synthesis




carried out according to the method of Veber using diphenylphosphoryl azide as the peptide coupling agent.[12] Yields of cyclic pentapeptide **20** ranged from 33 to 60%. Metal hydride reduction of cyclic pentapeptide **20** using $LiAlH_4$ in THF proved effective. Though most of the cyclic pentapeptides were insoluble in solvent alone, the peptides became soluble when the precise amount of $LiAlH_4$ was added to the suspension in THF. The methyl-substituted ligands **1d**−**h**,**j**,**l** were obtained in 39−71% yield.

A combination of peptide coupling and sulfonamide alkylation was used to prepare the tetramethyl-substituted ligand **1k** (Scheme 5). Chiral diamine **21**, prepared by literature methods,[13] was monotosylated to give compound **22** in high yield. The remaining primary amine of **22** was then protected as the *tert*-butyl carbamate, providing compound **23** in 97% yield. Alkylation of **23** with methylbromoacetate gave **24** in high yield. Next the protected amine methyl ester **24** was used to prepare both **25** and **26** by removal of the Boc protecting group and by saponification, respectively. The amine **25** and the carboxylic acid **26** were then coupled to give the tetraaza compound **27** in 85% yield. Deprotection and coupling with *N*-Boc−glycine provided **29** (69%) which was saponified to give **30** (98%). Removal of the Boc protecting group and cyclization via peptide coupling agent DPPA yielded the protected macrocycle **32** in 46% yield. Reduction and deprotection were carried out by treatment of macrocycle **32** with lithium aluminum hydride in THF to provide ligand **1k** in 39% yield.

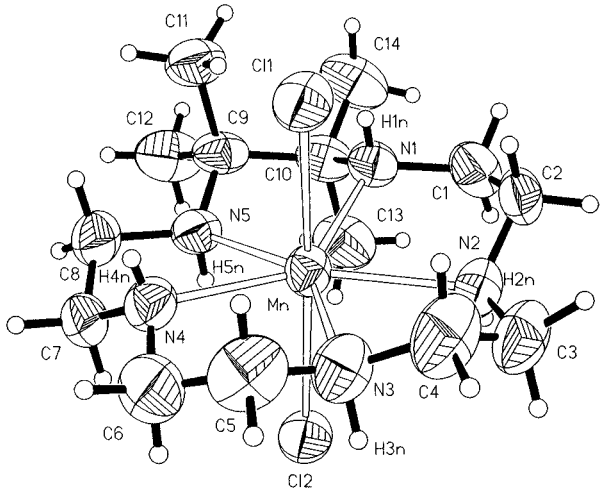



**Figure 4.** ORTEP drawing for [Mn(2,2,3,3-tetramethyl-1,4,7,10,13-pentaazacyclopentadecane)$Cl_2$], **2i**, showing the labeling scheme and the 50% probability ellipsoids for non-hydrogen atoms.

**Synthesis and Characterization of Mn(II) Complexes.** The new Mn(II) complexes, **2** and **3**, were all prepared as their dichloro complexes employing anhydrous manganese(II) chloride as the manganese source. In general, high yields of the corresponding complexes were obtained by addition of the free ligand under $N_2$ to an anhydrous methanol solution containing a stoichiometric amount (1:1) of anhydrous $MnCl_2$. Any insoluble material was removed via filtration following a short period of reflux. The order of addition did have an effect on the appearance of insoluble brown precipitate. In general, addition of $MnCl_2$ to a solution of the ligand does result in a greater amount of brown precipitate (presumably $MnO_2$). The complexes were all characterized by elemental analyses and by mass spectra. In all cases excellent agreement for the proposed structure was obtained.

The conductivity and cyclic voltammetry of these complexes was also studied in anhydrous methanol. All of the complexes exhibited molar conductances in methanol consistent with a 1:1 electrolyte, implying either a six-coordinate $[Mn(L)Cl]^+$ or seven-coordinate solvated structure, $[Mn(L)Cl(MeOH)]^+$, in solution, as reported previously for the complex derived from ligand **1,** $[Mn([15]aneN_5)Cl(MeOH)]PF_6$.[1,14] The cyclic voltammetry of each of the complexes **2** and **3** exhibits a well-defined reversible oxidation at $E_{1/2}$ in the range 0.75−0.80 V vs SHE in anhydrous MeOH containing 0.25 M *n*-$Bu_4NBF_4$ electrolyte.

**X-ray Diffraction and Crystal Structure.** The complex **2i** was crystallized from ethanol and its structure is illustrated in Figure 4, where the lattice solvent molecule is omitted for clarity. Crystallographic data are summarized in Table 1, the non-hydrogen atomic positions are listed in Table 2, the relevant bond lengths are listed in Table 3 and bond angles are listed in Table 4; additional structural data are found in the Supporting Information. The Mn(II) ion is seven coordinate with a pentagonal bipyramidal coordination geometry in which the chloro ligands lie in *trans* sites above and below the plane of the macrocyclic ligand. The greatest deviation from planarity of the ring nitrogen atoms is 6.5° as exhibited by the $Cl_1MnN_4$

(12) Veber, D. F. et al. *J. Org. Chem.* **1979**, *44*, 3101−3105.
(13) Jung, S. H.; Kohn, H. *J. Am. Chem. Soc.* **1985**, *107*, 2931−43.
(14) Newton, J. E.; Jackels, S. C. *J. Coord. Chem.* **1988**, *19*, 265.

**Table 1.** Crystallographic Data for $[Mn(2,2,3,3\text{-}Me_4[15]aneN_5)Cl_2]\cdot C_2H_5OH$, **2i**

| | | | |
|---|---|---|---|
| chem formula | $C_{16}H_{39}N_5OCl_2Mn$ | fw | 443.36 |
| *a*, Å | 9.941(2) | space group | $P\bar{1}$-$C_i^1$ (No. 2) |
| *b*, Å | 11.190(2) | *T*, °C | 20(1) |
| *c*, Å | 11.613(2) | *λ*, Å | 1.54184 |
| *α*, deg | 62.45(2) | $\rho_{calcd}$, g cm$^{-3}$ | 1.308 |
| *β*, deg | 80.47(2) | *μ*, mm$^{-1}$ | 7.06 |
| *γ*, deg | 81.33(2) | $R^a$ | 0.051 |
| *V*, Å$^3$ | 1125.4(4) | $R_w{}^b$ | 0.062 |
| Z | 2 | | |

[a] $R = \sum||F_o| - |F_c|/\sum|F_o|$. [b] $R_w = \{\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2\}^{1/2}$; $w = 1/\sigma^2_F$.

**Table 2.** Atomic Coordinates for Non-Hydrogen Atoms in Crystalline $[Mn(2,2,3,3\text{-}Me_4[15]aneN_5)Cl_2]\cdot C_2H_5OH$[a]

| atom type[b] | fractional coordinates | | | equiv isotropic thermal param *B*, Å$^2$ × 10[c] |
|---|---|---|---|---|
| | $10^4x$ | $10^4y$ | $10^4z$ | |
| Mn | 2568(1) | 2565(1) | −272(1) | 37(1) |
| $Cl_1$ | 2167(2) | 5248(2) | −1022(2) | 49(1) |
| $Cl_2$ | 2882(2) | −70(2) | 877(2) | 48(1) |
| $N_1$ | 3293(6) | 3312(6) | −2501(5) | 41(2) |
| $N_2$ | 4935(5) | 2542(6) | −488(6) | 45(2) |
| $N_3$ | 3170(6) | 2361(7) | 1664(6) | 53(2) |
| $N_4$ | 537(6) | 2508(6) | 1036(6) | 43(2) |
| $N_5$ | 862(5) | 2247(5) | −1291(5) | 40(2) |
| $C_1$ | 4809(7) | 3299(8) | −2768(7) | 59(3) |
| $C_2$ | 5375(6) | 3543(7) | −1786(7) | 52(3) |
| $C_3$ | 5467(7) | 2588(8) | 607(8) | 62(3) |
| $C_4$ | 4388(8) | 3055(9) | 1382(9) | 70(4) |
| $C_5$ | 1986(8) | 2691(9) | 2418(7) | 63(3) |
| $C_6$ | 780(7) | 2031(9) | 2386(7) | 64(3) |
| $C_7$ | −416(6) | 1760(7) | 825(6) | 48(2) |
| $C_8$ | −524(6) | 2333(7) | −602(6) | 51(3) |
| $C_9$ | 1003(7) | 2959(6) | −2733(6) | 45(2) |
| $C_{10}$ | 2584(7) | 2816(6) | −3212(6) | 48(2) |
| $C_{11}$ | 478(7) | 4441(6) | −3181(7) | 55(3) |
| $C_{12}$ | 147(9) | 2346(8) | −3310(8) | 66(3) |
| $C_{13}$ | 3096(8) | 1322(7) | −2789(8) | 62(3) |
| $C_{14}$ | 2880(10) | 3605(8) | −4683(7) | 71(3) |
| Solvent Molecule of Crystallization[d] | | | | |
| $O_{1s}$ | 3118(15) | −1094(14) | 5470(15) | 191(10) |
| $O_{1s'}$ | 3339(41) | −800(45) | 3647(35) | 82(20) |
| $C_{1s}$ | 2729(12) | −2046(17) | 5128(13) | 113(8) |
| $C_{2s}$ | 3437(11) | −3305(9) | 6033(10) | 90(4) |

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit. [b] Atoms are labeled in agreement with Figures 1 and 2. [c] This is one-third of the trace of the orthogonalized $\mathbf{B}_{ij}$ tensor. [d] The ethanol solvent molecule of crystallization is disordered with two possible orientations in the lattice. The two orientations both have carbon atoms at or near the positions specified for $C_{1a}$ and $C_{2s}$ but differ in the placement of the hydroxyl group. The major orientation has an oxygen at the position for $O_{1s}$ (85% of the time) and the minor orientation has an oxygen at the position for $O_{1s'}$ (15% of the time). The minor orientation is favorably positioned for forming a hydrogen bond with the hydrogen on $N_3$ ($H_{3n}$).

bond angle. The Mn−Cl bond distances are 2.606 and 2.695 Å, and the ClMnCl bond angle is 167.9°, considerably distorted from linear and from the 178.9° bond angle observed in the structure of the parent complex **2a**.[1] This deviation from linearity appears to be associated with the steric constraint exerted by the two *trans*-diaxial methyl groups of the tetrasubstituted chelate ring. This repulsive effect also appears to have lengthened the Mn−Cl bonds as compared to that observed in complex **2a** in which the Mn−Cl bond lengths are 2.635 and 2.571 Å.[1] The Mn−N bond lengths are observed to vary between 2.307 and 2.374 Å. This is a relatively small variation in bond lengths and suggests that the high-spin Mn(II) ion is well accommodated by the pentaaza crown cavity. In contrast, the Mn−oxygen bond distances of the corresponding pentaoxa

**Table 3.** Bond Lengths Involving Non-Hydrogen Atoms in Crystalline $[Mn(2,2,3,3\text{-}Me_4[15]aneN_5)Cl_2]\cdot C_2H_5OH$[a]

| type[b] | length, Å | type[b] | length, Å |
|---|---|---|---|
| Mn−$Cl_1$ | 2.695(2) | $N_1$−$C_1$ | 1.486(8) |
| Mn−$Cl_2$ | 2.606(2) | $N_1$−$C_{10}$ | 1.490(11) |
| | | $N_2$−$C_2$ | 1.444(8) |
| Mn−$N_1$ | 2.341(5) | $N_2$−$C_3$ | 1.480(13) |
| Mn−$N_2$ | 2.323(5) | $N_3$−$C_4$ | 1.447(11) |
| Mn−$N_3$ | 2.322(8) | $N_3$−$C_5$ | 1.454(10) |
| Mn−$N_4$ | 2.307(6) | $N_4$−$C_6$ | 1.453(10) |
| Mn−$N_5$ | 2.374(7) | $N_4$−$C_7$ | 1.471(11) |
| | | $N_5$−$C_8$ | 1.488(8) |
| $C_1$−$C_2$ | 1.496(13) | $N_5$−$C_9$ | 1.476(8) |
| $C_3$−$C_4$ | 1.477(13) | | |
| $C_5$−$C_6$ | 1.514(13) | $N_1$−$H_{1n}$ | 0.76(6) |
| $C_7$−$C_8$ | 1.492(10) | $N_2$−$H_{2n}$ | 0.70(8) |
| $C_9$−$C_{10}$ | 1.588(9) | $N_3$−$H_{3n}$ | 0.97(8) |
| $C_9$−$C_{12}$ | 1.560(13) | $N_4$−$H_{4n}$ | 0.71(7) |
| $C_9$−$C_{11}$ | 1.525(9) | $N_5$−$H_{5n}$ | 0.89(6) |
| $C_{10}$−$C_{13}$ | 1.537(9) | | |
| $C_{10}$−$C_{14}$ | 1.517(9) | | |
| Ethanol Solvent Molecule of Crystallization[c] | | | |
| $O_{1s}$−$C_{1s}$ | 1.418(29) | $C_{1s}$−$C_{2s}$ | 1.470(15) |
| $O_{1s'}$−$C_{1s}$ | 1.721(35) | | |

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit. [b] Atoms are labeled in agreement with Figures 1 and 2. [c] The ethanol solvent molecule of crystallization is disordered with two possible orientations in the lattice. The two orientations both have carbon atoms at or near the positions specified for $C_{1s}$ and $C_{2s}$ but differ in the placement of the hydroxyl group. The major orientation has an oxygen at the position for $O_{1s}$ (85% of the time) and the minor orientation has an oxygen at the position for $O_{1s'}$ (15% of the time). The minor orientation is favorably positioned for forming a hydrogen bond with the hydrogen on $N_3$ ($H_{3n}$).

macrocyclic ring analogue are shorter, in the range 2.168−2.231 Å.

**Potentiometric Titrations.** In Table 5 are listed the three p$K_a$ values observed for several of these new ligands as measured by standard potentiometric titration methodology. In addition, the best fits to the titration data in the presence of Mn(II) ion result in the calculated values for log $K_{MHL}$, log $K_{ML}$, and log $K_{MOHL}$, which are also listed in Table 5. In Figure 5 are shown the best fit complex species distribution plots as a function of pH for three representative complexes **2a**, **2m**, and **3**. It is significant that all of the complexes studied exhibit a stable monoprotonated form of the complex which possesses a four-coordinate macrocyclic ligand bound to the Mn(II) ion in solution. For all of the new ligands presented here, we observe three distinct protonation equilibria with the most basic amine ligand in this series being the 2,2,3,3-tetramethyl[15]aneN$_5$, **2i**, with p$K_{a1}$ = 11.56, while the pyridine ring-containing ligand, **4**, is the least basic macrocycle with p$K_{a1}$ = 9.43. This two order of magnitude difference in basicity is not reflected in the binding constants for the Mn(II) ion, which is 11.97 for complex **2i** and 11.54 for the pyridino complex, **3**. The inclusion of a single *trans* fused cyclohexano ring, complex **2m**, increases the thermodynamic stability by about an order of magnitude relative to that of the unsubstituted parent complex, **2a**, whereas fused cyclopentano and cycloheptano rings lower the stability. Increasing the number of methyl substituents from none to four presents no clear trend affecting the stability constant, log *K*. For example, the tetramethyl complex, **2j**, with a methyl substituent placed in each of four chelate rings has a log *K* value of 10.93 which is virtually unchanged from that of the unsubstituted complex, **2a**, where log *K* = 10.85. It must be noted that an attempt was made to perform the potentiometric titration employing the pentamethyl complex, **2l**, but due to extremely slow kinetics for the dissociation of the complex we were unable to get reproducible titration curves even over a 48 h period. Consequently, with the complex **2l**, we did not determine the log *K* value.

**Table 4.** Bond Angles Involving Non-Hydrogen Atoms in Crystalline $[Mn(2,2,3,3\text{-}Me_4[15]aneN_5)Cl_2]\cdot C_2H_5OH$[a]

| type[b] | angle, deg | type[b] | angle, deg |
|---|---|---|---|
| $Cl_1MnCl_2$ | 169.7(1) | $N_1MnN_3$ | 143.6(2) |
| $Cl_1MnN_1$ | 81.9(2) | $N_1MnN_4$ | 137.7(2) |
| $Cl_2MnN_1$ | 108.2(2) | $N_2MnN_4$ | 146.7(3) |
| $Cl_1MnN_2$ | 93.6(2) | $N_2MnN_5$ | 138.6(2) |
| $Cl_2MnN_2$ | 87.5(1) | $N_3MnN_5$ | 145.8(2) |
| $Cl_1MnN_3$ | 86.5(2) | $N_1MnN_2$ | 73.8(2) |
| $Cl_2MnN_3$ | 84.1(2) | $N_1MnN_5$ | 70.6(2) |
| $Cl_1MnN_4$ | 83.5(2) | $N_2MnN_3$ | 72.5(2) |
| $Cl_2MnN_4$ | 90.0(2) | $N_3MnN_4$ | 74.2(2) |
| $Cl_1MnN_5$ | 101.6(1) | $N_4MnN_5$ | 73.8(2) |
| $Cl_2MnN_5$ | 84.1(1) | | |
| $MnN_1C_1$ | 111.6(4) | $C_4N_3C_5$ | 118.2(8) |
| $MnN_1C_{10}$ | 116.7(4) | $MnN_4C_6$ | 111.0(4) |
| $C_1N_1C_{10}$ | 117.1(6) | $MnN_4C_7$ | 109.3(5) |
| $MnN_2C_2$ | 108.3(4) | $C_6N_4C_7$ | 115.6(5) |
| $MnN_2C_3$ | 113.9(4) | $MnN_5C_8$ | 111.0(5) |
| $C_2N_2C_3$ | 116.4(6) | $MnN_5C_9$ | 115.9(4) |
| $MnN_3C_4$ | 109.1(5) | $C_8N_5C_9$ | 117.0(5) |
| $MnN_3C_5$ | 110.7(5) | | |
| $N_1C_1C_2$ | 110.0(6) | $C_{10}C_9C_{11}$ | 111.0(5) |
| $N_2C_2C_1$ | 109.2(6) | $N_5C_9C_{12}$ | 111.5(5) |
| $N_2C_3C_4$ | 112.0(6) | $C_{10}C_9C_{12}$ | 110.5(6) |
| $N_3C_4C_3$ | 110.1(9) | $C_{11}C_9C_{12}$ | 107.6(6) |
| $N_3C_5C_6$ | 108.5(8) | $N_1C_{10}C_9$ | 105.2(6) |
| $N_4C_6C_5$ | 109.2(6) | $N_1C_{10}C_{13}$ | 107.4(6) |
| $N_4C_7C_8$ | 109.3(5) | $C_9C_{10}C_{13}$ | 110.7(5) |
| $N_5C_8C_7$ | 109.0(5) | $N_1C_{10}C_{14}$ | 112.2(6) |
| $N_5C_9C_{10}$ | 106.9(5) | $C_9C_{10}C_{14}$ | 112.0(6) |
| $N_5C_9C_{11}$ | 109.4(6) | $C_{13}C_{10}C_{14}$ | 109.3(7) |
| $MnN_1H_{1n}$ | 96(4) | $C_5N_3H_{3n}$ | 109(5) |
| $C_1N_1H_{1n}$ | 102(4) | $MnN_4H_{4n}$ | 108(5) |
| $C_{10}N_1H_{1n}$ | 110(5) | $C_6N_4H_{4n}$ | 108(7) |
| $MnN_2H_{2n}$ | 101(5) | $C_7N_4H_{4n}$ | 105(7) |
| $C_2N_2H_{2n}$ | 104(5) | $MnN_5H_{5n}$ | 99(4) |
| $C_3N_2H_{2n}$ | 113(5) | $C_8N_5H_{5n}$ | 106(3) |
| $MnN_3H_{3n}$ | 109(7) | $C_9N_5H_{5n}$ | 106(4) |
| $C_4N_3H_{3n}$ | 101(5) | | |
| Ethanol Solvent Molecule of Crystallization[c] | | | |
| $O_{1s}C_{1s}C_{2s}$ | 101.2(12) | $O_{1s}C_{1s}C_{2s}$ | 129.9(16) |

[a] The number in parentheses are the estimated standard deviations in the last significant digit. [b] Atoms are labeled in agreement with Figures 1 and 2. [c] The ethanol solvent molecule of crystallization is disordered with two possible orientations in the lattice. The two orientations both have carbon atoms at or near the positions specified for $C_{1s}$ and $C_{2s}$ but differ in the placement of the hydroxyl group. The major orientation has an oxygen at the position for $O_{1s}$ (85% of the time) and the minor orientation has an oxygen at the position for $O_{1s'}$ (15% of the time). The minor orientation is favorably positioned for forming a hydrogen bond with the hydrogen on $N_3$ ($H_{3n}$).

**Table 5.** Stability Constants of $Mn^{II}(L)$ Complexes and the $pK_a$ Values for the Free Ligands

| complex | $pK_1$ | $pK_2$ | $pK_3$ | log $K_{MHL}$ | log $K_{ML}$ | log $K_{MOHL}$ |
|---|---|---|---|---|---|---|
| **2a** | 10.31 | 9.29 | 5.93 | 5.04 | 10.85 | 11.22 |
| **2b** | 10.54 | 9.32 | 5.89 | 5.33 | 11.02 | 11.11 |
| **2c** | 10.61 | 9.37 | 5.54 | 4.99 | 11.09 | 11.14 |
| **2d** | 9.89 | 9.17 | 5.80 | 5.60 | 10.46 | 10.88 |
| **2e** | 9.96 | 9.16 | 5.80 | 5.83 | 10.19 | 10.77 |
| **2f** | 10.36 | 9.26 | 5.79 | 5.28 | 10.88 | 11.27 |
| **2h** | 11.56 | 9.41 | 5.61 | 5.82 | 11.97 | 11.32 |
| **2i** | 10.72 | 9.22 | 5.74 | 5.36 | 11.48 | 11.23 |
| **2j** | 10.33 | 9.12 | 5.67 | 5.21 | 10.93 | 11.23 |
| **2m** | 10.64 | 9.42 | 5.60 | 4.90 | 11.65 | 11.35 |
| **2n** | 10.12 | 9.18 | 5.97 | 5.34 | 10.19 | 11.35 |
| **2o** | 10.72 | 9.45 | 5.61 | 5.80 | 10.74 | 11.36 |
| **2p** | 10.61 | 9.45 | 5.99 | 5.35 | 11.09 | 10.80 |
| **3** | 9.43 | 8.80 | 5.28 | 4.20 | 11.64 | 11.54 |

**Kinetic Stabilities.** The UV−vis spectrum of the Mn(II) complexes, **2**, described here show no absorption bands above 210 nm, but dissociation of the ligand from Mn(II) followed by complexation of the ligand to Cu(II) ion in water generates a Cu(II) complex which exhibits an absorption band in the UV region ($\lambda_{max} \sim 280$ nm) with a large molar extinction coefficient ($\epsilon \sim 6000-7000$) depending upon the specific ligand utilized. The kinetic treatment for such a ligand exchange process has been described previously for the metal exchange process with porphyrin ligands and is described in eqs 1−4.[15] Application

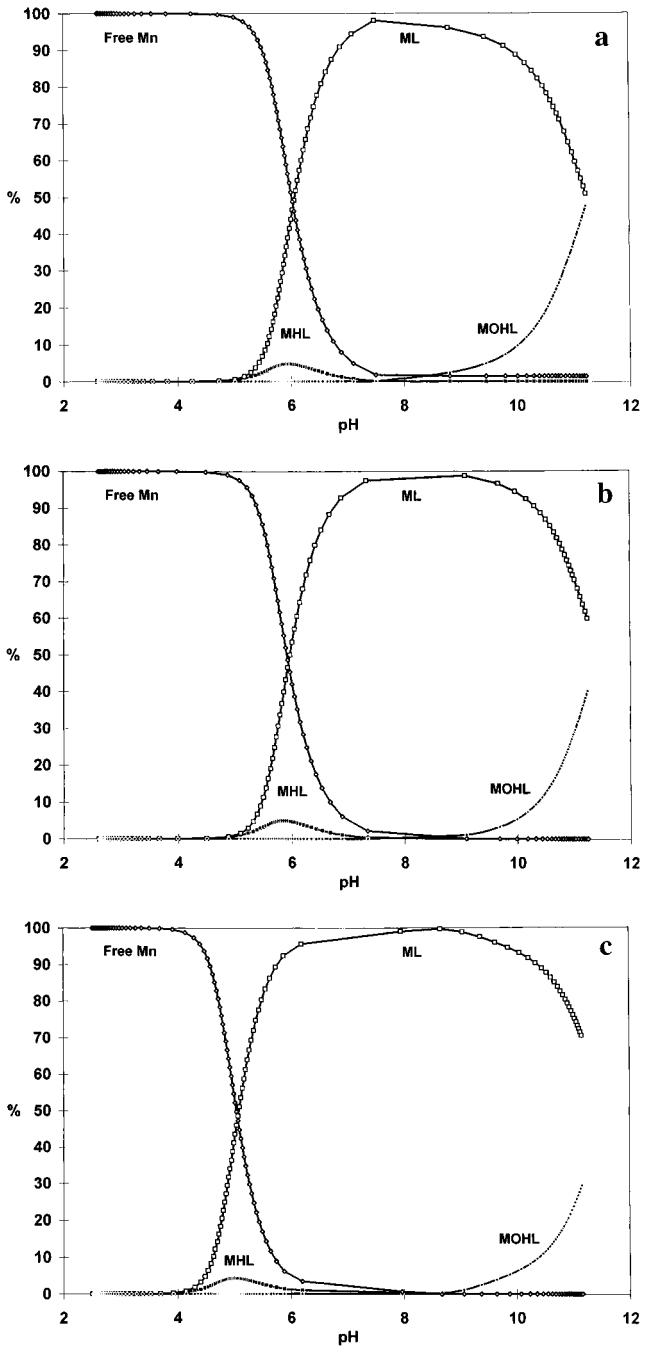



**Figure 5.** Complex species distribution as a function of pH for (a) **2a**, (b) **2m**, and (c) **3**.

$$Mn(L) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Mn(II) + L \quad (1)$$

$$Mn(L) + H^+ \xrightarrow{k_2} Mn(II) + HL^+ \quad (2)$$

$$HL^+ \underset{k_b}{\overset{k_f}{\rightleftharpoons}} H^+ + L \quad (3)$$

$$L + Cu(II) \xrightarrow{k_4} Cu(L) \quad (4)$$

(15) Baker, H.; Hambright, P.; Wagner, L.; Ross, L. *Inorg. Chem.* **1973**, *12*, 2200.

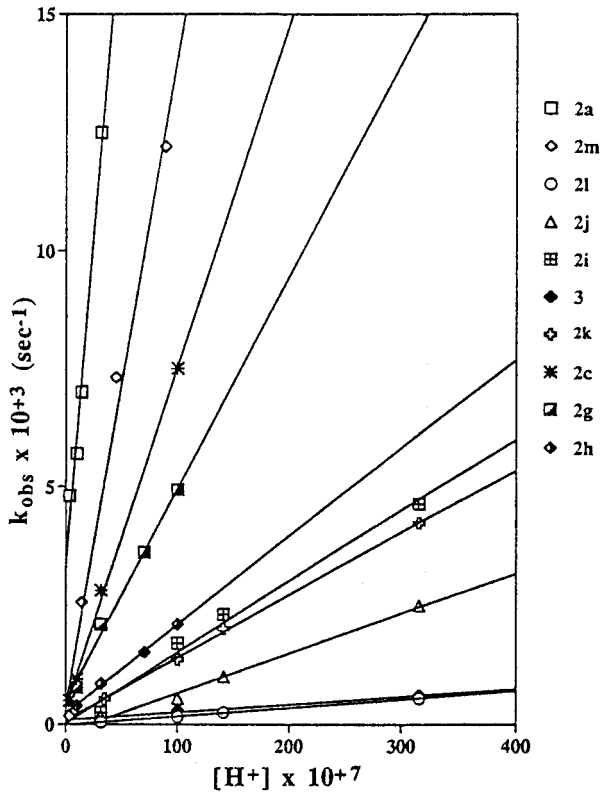



**Figure 6.** Kinetic stability of complexes **2a**, **2c**, **2g**, **2h**, **2i**, **2j**, **2k**, **2l**, and **2m** displayed as a plot of $k_{obs} \times 10^{+3}$ ($s^{-1}$) vs $10^7[H^+]$. The slope of the line gives the second-order dissociation rate constant, $k_{diss}$.

of the steady-state treatment to [L] and the recognition that $k_2[H^+] \gg k_1$ allows us to postulate that if $k_b[H^+] \ll k_4[Cu(II)]$, then $d[Cu(L)]/dt = k_2[Mn(L)][H^+] = -d[Mn(L)]/dt$. Thus, a study of the rate of formation Cu(L) as a function of $[H^+]$ allows us to determine the kinetic stability of the corresponding Mn(L) complex and the order of the proton dependence, where $k_{diss} = k_2[H^+]^n$.

The rate at which Cu(II) macrocyclic ligand complex appears at different pH's is measured by the growth of an absorbance band due to the formation of the $[Cu^{II}(L)]^{2+}$ complex at (or near) 280 nm as a function of time. This has been experimentally shown to be independent of added Cu(II) ion even with a large excess of Cu(II) present. In general, we have employed the following stoichiometry: $[Cu^{II}Cl_2]_{added} = 8[Mn^{II}(\text{macrocycle})]_{initial}$. The kinetic data are subjected to the following standard treatment. The absorbance at any time is subtracted from the absorbance at $t_\infty$ and the ln{abs $t_\infty$ − abs} is then plotted vs the time. A straight line ln{abs $t_\infty$ − abs} vs $t$ plot is obtained for over 5 half-lives, and the slope of the plot is the pseudo-first-order rate constant for dissociation at each pH. The values of $k_{diss}$ obtained for any [Mn(II)(L)] complex as a function of $[H^+]$ can be determined from the plot of $k_{obs}$ vs $[H^+]$ (Figure 6). For all the ligands studied a minimum of four different pH's over a 15-fold $[H^+]$ range were utilized to obtain the observed dependence on proton concentration. For all of these Mn(II) complexes a straight line plot was observed (Figure 6) whose slope is the second-order rate constant (first-order in $H^+$ and first-order in complex $[Mn^{II}(L)]$; units are $M^{-1}$ $s^{-1}$) for the proton-assisted dissociation of macrocyclic ligand L from the Mn(II) ion. This 2nd-order rate constant then permits the assessment of each $Mn^{II}(L)$ complex's inherent kinetic stability to dissociation via protonation (Table 6). The observed kinetic stabilities vary over a wide range. On the basis of the ratio of the $k_{diss}$ rate constants, the most stable complex, **3**, containing the pyridino ring, is over 175 times more stable than the least

**Table 6.** Second-Order Proton-Dependent Rate Constants for the Dissociation of the $Mn^{II}(L)$ Complexes at 21 °C

| complex | $\epsilon_{280}$[a] | $k_{diss}$, ($M^{-1}$ $s^{-1}$) | substituents |
|---|---|---|---|
| **2a** | 4150 | 2814 | none |
| **2b** | 5380 | 1540 | 2*R*-Me |
| **2c** | 5530 | 701 | 2*R*,3*R*-$Me_2$ |
| **2d** | 6060 | 536 | 2*S*,5*R*-$Me_2$ |
| **2e** | 5680 | 838 | 2*S*,5*S*-$Me_2$ |
| **2f** | 5720 | 473 | 2*S*,8*R*-$Me_2$ |
| **2g** | 6330 | 451 | 2*S*,8*S*-$Me_2$ |
| **2h** | 8070 | 188 | 2*S*,5*R*,8*S*-$Me_3$ |
| **2i** | 5690 | 150 | 2,2,3,3-$Me_4$ |
| **2j** | 5020 | 83 | 2*S*,5*R*,8*S*,11*R*-$Me_4$ |
| **2k** | 4750 | 131 | 2*R*,3*R*,8*R*,9*R*-$Me_4$ |
| **2l** | 4540 | 17 | 2*S*,5*R*,8*S*,11*R*,14*S*-$Me_5$ |
| **2m** | 7580 | 1375 | *trans*-cyclohexano |
| **2n** | 4960 | 3915 | *trans*-cyclopentano |
| **2o** | 3130 | 925 | *trans*-cycloheptano |
| **2p** | 5640 | 1322 | *cis*-cyclohexano |
| **2q** | 5480 | 1171 | *tert*-butyl-*trans*-cyclohexano |
| **3** | 7960 | 16 | pyridino |

[a] Molar extinction coefficient of the $Cu^{II}(L)$ complex at 280 nm at pH = 5.

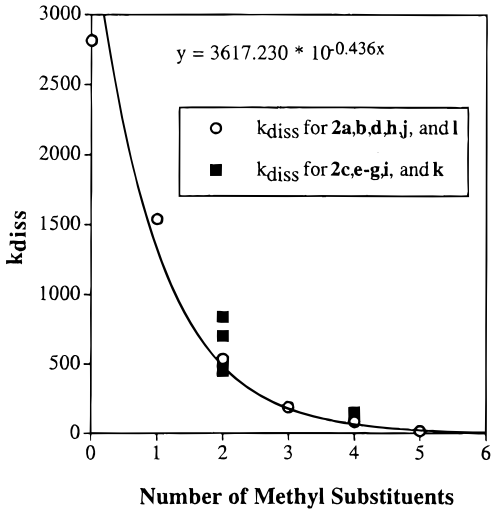



**Figure 7.** Plot of the second-order dissociation rate constant, $k_{diss}$, vs the number of methyl substituents on the chelate rings of the Mn(II)-([15]ane$N_5$) complexes.

stable complex, **2a**, at any pH. An enhanced stability comparable to that of **3** is also observed with the pentamethyl complex **2l**.

Several trends in the value of $k_{diss}$ for these complexes are readily discernable from the data. Increasing the number of hydrocarbon substituents generally increases the kinetic stability of the complex to dissociation as evidenced by lower $k_{diss}$ values. This is shown in Figure 7, where $k_{diss}$ is plotted against the number of methyl substituents for all of the methyl containing macrocyclic Mn(II) complexes. Also shown in the Figure 7, using open circles, are the complexes **2b**, **2d**, **2h**, **2j**, and **2l**, which have one through five methyl groups, on, respectively, one, two, three, four, and five adjacent chelate rings. The successive methyl groups possess alternating configurations; namely, they are derived from alternating D- and L-alanines. The observed stability enhancement is more than a simple linear effect, in fact the best fit of this data is obtained by an exponential fit.

In this [15]ane$N_5$ ring system with a given number of methyl substituents, a greater kinetic stability is observed when the number of the five-membered chelate rings which bear methyl substituents is maximized. Thus, for the dimethyl-containing macrocycles, such as complex **2c**, having two diequatorial

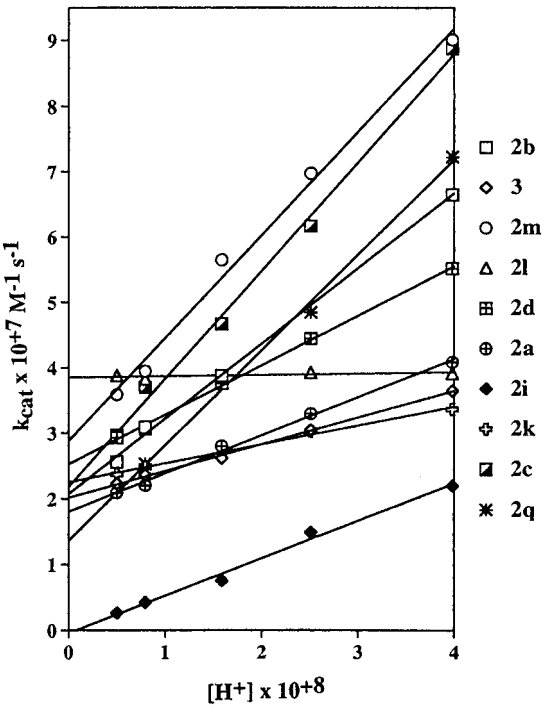



**Figure 8.** Plot of the catalytic rate constant, $k_{cat}$, vs $[H^+]$ obtained by stopped-flow method for several representative complexes.

methyls on one chelate ring is less stable (has a higher $k_{diss}$ value) than either **2f** or **2g**, each of which possesses diequatorial methyls on adjacent and alternate chelate rings, respectively. For the tetramethyl-containing macrocyclic complexes, **2i**, **2k**, and **2j**, which have four methyls on one, two, and four chelate rings, respectively, the kinetic stability increases in that same order.

It is also noteworthy that the 2,3-dimethyl complex, **2c**, has a greater kinetic stability than any of the fused cycloalkano macrocycles. The *trans*-fused cyclopentano containing macrocyclic complex **2n** is less stable than the unsubstituted parent complex **2a**. The *cis*- and *trans*-fused cyclohexano complexes, **2p** and **2m**, are of comparable stability, while the *tert*-butyl-*trans*-cyclohexano complex, **2q**, is somewhat more stable. The only fused ring cycloalkano macrocyclic complex that approaches the stability of the vicinal *trans*-2,3-dimethyl complex, **2c**, is the fused cycloheptano macrocyclic complex, **2o**, which is still about one-third less stable.

**Superoxide Dismutase Catalytic Activity.** As described in our previous publications we have found that the direct monitoring of the decay of superoxide via the stopped flow method provides a reliable method for quantitating the catalytic activity of a putative SOD catalyst. For each new complex a plot of the observed, $k_{cat}$, at a given pH vs the proton concentration yields a straight line with a nonzero *y*-intercept (Figure 8 shows a few representative complexes). From the slope of the straight line plot a proton dependent rate constant, $k_{H^+}$, is obtained and from the *y*-intercept a proton independent rate constant, $k_{ind}$, is obtained, consistent with two separate pathways for dismutation.[1] In Table 7 the $k_{H^+}$ and $k_{ind}$ rate constants are tabulated for the new complexes from the $k_{cat}$ data obtained over the pH range of 7.4−8.3; additionally, the $k_{cat}$ value at pH = 7.4 is listed for each complex. The observed rate for dismutation of superoxide observed with these complexes is shown in eq 5. We have shown previously[1] that the

$$-d[O_2^-]/dt \propto [Mn]_{tot}[O_2^-]\{k_{H^+}[H^+] + k_{ind}\} \qquad (5)$$

observed proton dependent rate constant, $k_{H^+}$, is equal to a rate constant defined as $2k_1/K_a$, where $K_a$ is the acidity constant for

**Table 7.** Representative Values for the Proton-Dependent and Proton-Independent Catalytic Rate Constants for SOD Activity Measured over the pH Range 7.4−8.3

| complex | $k_{H^+}$, $10^{15}$ $M^{-1}$ $s^{-1}$ | $k_{ind}$, $10^7$ $s^{-1}$ | $k_{cat} \times 10^{-7}$ (pH = 7.4) |
|---|---|---|---|
| **2a** | 0.58 | 1.82 | 4.13 |
| **2b** | 1.16 | 2.02 | 6.65 |
| **2c** | 1.68 | 2.18 | 8.84 |
| **2d** | 0.76 | 2.53 | 5.52 |
| **2i** | 0.56 | 0 | 2.20 |
| **2j** | 0.34 | 3.98 | 5.37 |
| **2k** | 0.28 | 2.26 | 3.37 |
| **2l** | 0 | 3.82 | 3.82 |
| **2m** | 1.56 | 2.88 | 9.09 |
| **2n** | 0.28 | 0.26 | 1.37 |
| **2o** | 1.06 | 0.84 | 5.05 |
| **2q** | 1.48 | 1.38 | 7.23 |
| **3** | 0.41 | 2.02 | 3.65 |

$HO_2^-$ ($K_a = 2.04 \times 10^{-5}$).[16] The value of $k_1$ for each catalyst is simply the observed value of $k_{H^+}$ (Table 7) times $K_a/2$ and for most of the catalysts is in the range of $10^{+9}$ $M^{-1}$ $s^{-1}$. One of these catalysts, the pentamethyl complex **2l**, is unique in that we observe no pH dependence in the catalytic rate.

## Discussion

Our initial studies suggested that the [15]aneN$_5$ core ligand structure without substitution on nitrogen was the best polyazamacrocyclic ligand for providing a Mn(II) complex which exhibits SOD catalytic activity.[1] In order to impart greater stability and higher SOD activity to the complex derived from ligand **1a**, we initiated a program to examine the effects exerted by carbon substituents. In order to probe the effects that the number, position, and stereochemistry of substituents exert on stability and stereochemistry, we employed ligands with methyl substituents and fused rings (Figure 3). Employing additional substituents on the carbon centers of the macrocycle was anticipated to provide additional "preorganization" to the ligands and hence increase the stability of their complexes.[2,17] In contrast, the effect of substituents on the SOD catalytic rate was an unknown area.

To accomplish our goal of developing an understanding of structure/function relationships within this class of catalyst, we required that a number of previously unknown ligands be synthesized. These new ligands were prepared via methodology which had not been previously utilized to make polyaza macrocyclic ligands. The 1,4,7,10,13-pentaazacyclopentadecane ligands **1a**−**q** were prepared via different methods depending upon the particular substitution pattern required. The method of Richman and Atkins was used initially to prepare the parent macrocycle **1a** (Scheme 1) and some compounds with only one carbon substituent. As ligands with more substituents were required, the chemical yields for both cyclization and detosylation using this method became unworkably low.[18] New synthetic routes to carbon substituted ligands were developed which utilized, in addition to toluenesulfonamides, amide moieties as protecting groups for the amines during the synthesis.

Fused ring substituents were also studied for their ability to rigidify the macrocyclic ligands and effect metal complex stability. Cyclopentane, cyclohexane, cycloheptane, and 4-*tert*-butylcyclohexane fused ring macrocycles were prepared to examine the effect of bite angle and flexibility of the substituted chelate ring on binding and SOD activity. Macrocyclization of these 2,3-substituted 1,4,7,10,13-pentaazacyclopentadecanes was accomplished in good yield by addition of the cycloal-

(16) Sawyer, D. T.; Valentine, J. S. *Acc. Chem. Res.* **1981**, *14*, 393.
(17) Busch, D. H. *Adv. Chem. Ser.* **1963**, *37*, 16.
(18) Lennon, P. J.; Weiss, R. H. Unpublished results.

kanediamine to the tris(*N*-tosyl)diethylenetriaminediacetyl chloride as shown in Scheme 2. One benefit of this method is the straightforward preparation of the diacid chloride, which is easy to scale up and provides the penultimate intermediate to a large family of macrocycles.

For more sterically demanding substitutions, we found that moving the site of bond formation away from the steric bulk proved effective. Thus, bis(chloroacetamides) were prepared from the substituted diamines and used in cyclization reactions with tris(*N*-tosyl)diethylenetriamine dianion as shown in Scheme 3.[10] By taking advantage of the symmetry of the macrocycle, the bis(chloroacetamide) method provides a rapid macrocycle synthesis.

In cases where one substituent per ethylene bridge is desired, the macrocyclization was carried out on a pentapeptide containing the desired substituents.[11] The cyclic pentapeptide was then reduced to provide the C-substituted 1,4,7,10,13-pentaazacyclopentadecane (Scheme 4) with no loss in stereochemical integrity at the site of C-substitution. One clear advantage to this method of ligand synthesis is the ready availability of chiral amino acids.

A combination of the peptide method with the alkylation of toluenesulfonamide anions was used effectively to produce the 2,3,8,9-tetramethyl-1,4,7,10,13-pentaazacyclopentadecane **1k** as shown in Scheme 5. The dual purpose, diamine ester **24** was prepared from the butanediamine via protection and alkylation. Compound **24** was then converted to two different fragments which are coupled to give the tetraamine ester, **27**. Compound **27** was then coupled with Boc-glycine to give the pentaamino acid which upon deprotection and cyclization provided macrocycle **32**. The reduction and deprotection of **32** provided **1k**, the desired tetrasubstituted ligand.

The effects of C-substitution on the stability of the corresponding Mn(II) complexes were assayed in both a thermodynamic (potentiometric titration) and a kinetic assay. As anticipated, the effect of additional substituents has a stabilizing effect on the Mn(II) complexes, but it is largely manifested as an increase in the kinetic stability rather than an enhanced thermodynamic stability. The stability constant ($K_{MnL}$) may be expressed directly as the ratio of the second-order formation constant ($k_f$) to the first-order dissociation rate constant ($k_d$) (eq 6). With a number of the ligands generated for this study we

$$\mathrm{Mn(II)} + \mathrm{L} \underset{k_d}{\overset{k_f}{\rightleftharpoons}} \mathrm{Mn(L)} \qquad K_{MnL} = k_f/k_d \tag{6}$$

observe that the formation constant is relatively unaffected by the degree of substitution, in particular, in the cases with a single methyl substituent per chelate ring. In contrast, increasing the number of substituents dramatically increases the kinetic stability of the complexes, thereby lowering the observed $k_{diss}$ value. This implies that in some of the ligand systems studied here the rate of formation of the Mn(II) complexes is affected by the ligand preorganization and hence is slowed by a factor similar in magnitude to that affecting the rate of ligand loss; e.g., only the *trans*-cyclohexano-containing ligand, **1m**, the pyridino-containing ligand of complex **3**, and the two tetramethyl-containing ligands, **1i** and **1h**, exhibit log *K* values greater than those observed with the unsubstituted ligand **1a**.

The stability of the ligand, **1a**, has previously been studied with a number of divalent metal ions including Zn(II),[19] Cu(II),[20] Pb(II),[19] Hg(II),[19] and Cd(II).[19] It is important to note that the thermodynamic stability (as reflected in the log *K* value) of the Mn(II) complex is inherently less than that measured for those complexes with the other common divalent metal ions listed here; e.g., log *K* of the Cu(II) complex is ~28.3[20] compared to the Mn(II) values we observe for these ligands which are in the range log $K = 10-12$.

It is precisely this thermodynamic stability difference which drives the kinetic stability assay toward the much more stable Cu(II) complex. Since the Mn(II) complexes of the [15]ane$N_5$ ligand system possess thermodynamic stabilities less than that of other divalent cations in water, it becomes a very important aspect of drug design that an understanding of the factors affecting the overall kinetic stability of the Mn(II) complexes be understood. In our studies of the rate of ligand dissociation we find that the rate law for the dissociation of these pentaaza 15-membered ring ligands from the Mn(II) ion is of the type (eq 7). This is in contrast to the rate law observed for the

$$\text{rate} = k_H[\text{complex}][H^+] \tag{7}$$

dissociation of the Ni(II) and Cu(II) complexes of the ligand **1a**, in which a second-order proton dependence is observed.[21] In any event increasing the steric congestion[22] or preorganization contributes greatly to increasing the kinetic stability of the Mn(II) complexes and retarding the rate of the proton-assisted "decomplexation" process.

The observation that carbon substituents can exert major effects on the catalytic rate suggests that mechanistic insight may well be deduced by a complete study of structure and activity. Clearly, the two independent rate-determining pathways involved in the catalytic cycle can be influenced by the number, position, and stereochemistry of the substituents. The pH-independent path was identified as an inner-sphere path in our previous paper,[1] and with this series of complexes we observe that, in general, the rates, $k_2$, associated with this pH-independent path mirror the solvent exchange rates observed for Mn(II) ion with magnitudes in the range $(1-3) \times 10^7\ s^{-1}$. The fact that the pentamethyl complex, **2l**, has no pH dependence in the rate-determining step indicates that this proton-dependent pathway is no longer operative for this highly substituted complex. Also the 2,2,3,3-tetramethyl complex, **2i**, has no proton-independent, inner-sphere pathway operative. This observation suggests that the loss of the pH-independent path may arise from the steric effect imposed by the diaxial methyl groups (observed in the X-ray structure of **2i**) blocking access of superoxide to the Mn(II) center. A steric effect arising from bis(*gem*-dimethyl) substitution has been observed in the crystal structure of the nitrate salts of the 2,2,3,3-tetramethyl substituted $Ni^{II}$(tetraaza[14]-membered ring) complexes.[22]

Of the substituent groups reported here it appears that the *trans*-cyclohexano moiety offers the best combination of enhanced catalytic rate combined with an enhanced kinetic and thermodynamic stability. For example, the *trans*-fused cyclohexano complex, **2m**, has the fastest dismutation rate constant at pH = 7.4 ($9.09 \times 10^7\ M^{-1}\ s^{-1}$) of any of the complexes reported here, and has a nearly 10-fold greater thermodynamic stability than the unsubstituted complex, **2a**. The enhanced kinetic and thermodynamic stabilities associated with *trans*-fused cyclohexano rings have also been observed previously in polythiaether macrocycles with Cu(II).[23,24] This ability of the fused *trans*-cyclohexano group to impart greater stability to the

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complex while enhancing catalytic activity may be associated with its ability to impart rigidity while permitting accessibility to the axial coordination sites on the metal. Kobira et al.[22] have shown that in a series of highly substituted Ni(II)(cyclam) complexes, the *trans*-cyclohexanocyclam Ni(II) bis(nitrate) complex is sterically unencumbered as a high-spin six-coordinate bis(nitrato) complex in the solid-state and partially so in solution. In contrast, the analogous substituted Ni(II) cyclam complexes bearing one and two tetramethylethano units in the cyclam ring show restricted coordination due to the steric crowding of the methyl groups on the axial coordination sites.

Of continuing interest to us in our design efforts is the synergy between such substituents as the *trans*-cyclohexano group and itself and other possible substituents. We are continuing these studies with the goal of understanding the key structural design features which influence the catalytic rate so that we can maximize the number of substituents and thereby maximize the ligand preorganization to achieve high chemical stability for a potential human pharmaceutical, while at the same time maintaining a high SOD catalytic activity.

## Experimental Section

**Methods.** Ligand **1a** was purchased or synthesized by the method of Richman *et al.*[3] and ligand **4** was prepared using the procedure of Stetter *et al.*[25] Analytical thin layer chromatography (TLC) was performed on Analtech 0.15 mm silica gel 60-GF plates. Visualization was accomplished with UV light, by exposure to $I_2$, or by dipping in an ethanolic phosphomolybdic acid solution followed by heating. Solvents for extraction were HPLC or ACS grade. Chromatography was performed with Merck silica gel 60 (230−400 mesh) with the indicated solvent system. Optical rotations were determined on a Rudolph Research Autopol III digital polarimeter at $\lambda = 589$ (sodium D line) at the temperature indicated and are reported as follows: $[\alpha]_\lambda$temp, concentration ($c$ = g/100 mL), and solvent. NMR spectra were collected on Varian Unity 400, VXR-400, VXR 300, and VXR-300S Spectrometers. $^1$H NMR spectra are reported in ppm from tetramethylsilane or referenced to solvent on the $\delta$ scale. Data are reported as follows: chemical shift (multiplicity where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broadened, coupling constants (Hz), relative integration). $^{13}$C NMR spectra are reported in ppm from the central deuterated solvent peak (e.g. 39.5 ppm for DMSO-$d_6$) or from internal tetramethylsilane. Data are reported as follows: chemical shift followed by multiplicity.

The following abbreviations are used throughout the experimental section: Et, ethyl; TFA, trifluoroacetic acid; DMF, dimethylformamide; HOBT·$H_2O$, 1-hydroxy-(1*H*)-benzotriazole monohydrate; EDC·HCl, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; TEA, triethylamine; THF, tetrahydrofuran; DPPA, diphenylphosphoryl azide. The following abbreviations relating to amino acids and their protective groups are in accordance with the recommendation by IUPAC-IUB Commission on Biochemical Nomenclature[26] and common usage: Ala, L-alanine; D-Ala, D-alanine; Gly, glycine; Boc, *tert*-butoxycarbonyl. Matrices used in fast-atom bombardment (FAB) mass spectroscopy include the following: NBA, 3-nitrobenzyl alcohol; DTE, dithioerythritol; DTT, dithiothreitol; GT, glutathione.

**Syntheses. Ligands. (*R*)-1,2-Diaminopropane Dihydrochloride (5).** A solution of 1.0 M lithium aluminum hydride in THF (480 mL, 0.480 mol) was added over a period of 30 min to a stirred solution of D-alaninamide hydrochloride (15.0 g, 0.120 mol) in anhydrous THF (100 mL) at room temperature under a dry argon atmosphere. The mixture was refluxed overnight. After cooling, the mixture was quenched with $H_2O$ (120 mL). The precipitate was filtered and washed with THF (300 mL) and hot methanol (2 × 600 mL). The filtrate and washes were combined and acidified with concentrated HCl. The solvent was removed *in vacuo* to give a yellow oil which was crystallized from methanol/ether to give 9.97 g (57% yield) of a white crystalline solid: mp 240−245 °C; $[\alpha]_d^{20} = +7.60°$ ($c = 0.01$, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.30 (d, $J = 6.9$ Hz, 3H), 3.09 (AB q of dd, $\delta\nu$ = 44.5 Hz, $J = 13.5$, 6.2 Hz, 2H) 3.52 (m, 1H), 8.59 (br s, 6H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 16.09, 41.43, 44.77; EI GC/MS, *m*/*z* (relative intensity) 74 ($M^+$, 2), 59 [$(M - CH_3)^+$, 22], 58 [$(M - NH_2)^+$, 13], 43 (100).

***N,N′*-Bis(*p*-tolylsulfonyl)-R-1,2-diaminopropane (6).** A suspension of *R*-1,2-diaminopropane dihydrochloride (9.76 g, 66.4 mmol) in ethyl ether (60 mL) was added to a stirred solution of NaOH (13.3 g, 332 mmol) in $H_2O$ (110 mL) at 0 °C under a dry argon atmosphere. *p*-Toluenesulfonyl chloride (27.8 g, 146 mmol) was added in portions to the mixture, which was maintained at 0 °C. The mixture was allowed to warm to room temperature and to stir overnight. After 22 h of stirring, $CH_2Cl_2$ (200 mL) was added. The layers were separated, and the $CH_2Cl_2$ layer was collected. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 75 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a white solid. The solid was recrystallized from $CHCl_3$−hexane to give 18.5 g (73% yield) of a white crystalline solid: mp 121−123 °C; $[\alpha]_d^{20} = +48.5°$ ($c = 0.01$, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.02 (d, $J = 6.9$ Hz, 3H), 2.44 (s, 6H), 2.87 (m, 1H), 2.98 (m, 1H), 3.33 (m, 1H), 4.80 (d, $J = 7.2$ Hz, 1H), 5.03 (t, $J = 6.5$ Hz, 1H), 7.30 (m, 4H), 7.73 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.93, 22.03, 48.35, 49.48, 127.11, 127.16, 129.80, 129.86, 136.71, 137.08, 143.60, 143.78; MS (FAB, NBA matrix) *m*/*z* 389 ($M + Li^+$, 100). Anal. Calcd for $C_{17}H_{22}N_2S_2O_4$: C, 53.78; H, 5.80; N, 7.32. Found: C, 53.46; H, 5.77; N, 7.37.

**1,4,7-Tris(*p*-tolylsulfonyl)-1,4,7-triazaheptane.** This compound was synthesized following the procedure of Atkins et al.[3] with slight modifications. To a stirred solution of *p*-toluenesulfonyl chloride (618 g, 3.24 mol) in pyridine (1500 mL) at 0 °C was added a solution of 1,4,7-triazaheptane (95.5 g, 0.926 mol) in pyridine (150 mL) under a dry argon atmosphere, maintaining the temperature ≤50 °C. The addition required 30 min. After the mixture was allowed to cool to room temperature slowly while stirring for 3 h, $H_2O$ (2 L) was slowly added to the cooled (ice bath) mixture. The heavy white precipitate which formed was filtered and washed thoroughly with $H_2O$. The pale yellow solid was dissolved in DMF (3 L), and 0.1 N HCl (4 L) was slowly added at 5 °C. The slurry was filtered and the pale yellow solid was washed thoroughly with $H_2O$ and dried *in vacuo* to give 486 g (93% yield) of the product: mp 180−181 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 2.39 (s, 3H), 2.40 (s, 6H), 2.84 (m, 4H), 3.04 (t, $J = 6.9$ Hz, 4H) 7.40 (d, $J = 8.1$ Hz, 4H), 7.59 (d, $J = 8.3$ Hz, 2H), 7.67 (m, 6H),

**1,4,7-Tris(*p*-tolylsulfonyl)-1,4,7-triazaheptane, 1,7-Disodium Salt (7).** This compound was synthesized following the procedure of ref 3. To a mechanically stirred slurry of 1,4,7-tris(*p*-tolylsulfonyl)-1,4,7-triazaheptane (486 g, 0.859 mol) in ethanol (1150 mL) heated to reflux under a dry argon atmosphere was added a solution of sodium ethoxide (prepared by dissolving sodium metal (39.5 g 1.72 mol) in absolute ethanol (1.0 L)) as rapidly as possible. The clear brown solution which formed rapidly was allowed to cool to room temperature and ethyl ether (1.0 L) was added. The crystals were filtered under a dry argon blanket, washed with 3:1 ethanol−ethyl ether and ethyl ether, and dried *in vacuo* to give 509 g (97% yield) of the product as a white powder: $^1$H NMR (DMSO-$d_6$) $\delta$ 2.30 (s, 6H), 2.36 (s, 3H), 2.63 (t, $J = 8.7$ Hz, 4H), 2.89 (t, $J = 7.2$ Hz, 4H), 7.11 (d, $J = 8.1$ Hz, 4H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.46 (m, 6H).

**3,6,9-Tris(*p*-tolylsulfonyl)-3,6,9-triazaundecane-1,11-diol (8).** This compound was synthesized following the procedure of ref 3 with modifications. To a stirred solution of the 1,4,7-tris(*p*-tolylsulfonyl)-1,4,7-triazaheptane 1,7-disodium salt (120 g, 0.197 mol) in anhydrous DMF (1.0 L) was added ethylene carbonate (173 g, 1.97 mol). The resulting mixture was stirred at 60 °C for 24 h. When the mixture was cooled to room temperature, $H_2O$ (100 mL) was added to quench the reaction and the solvent was removed *in vacuo*. The resulting dark yellow oil was dissolved in $CHCl_3$, was washed with $H_2O$ and saturated NaCl solution, and was then dried ($MgSO_4$). After the solution was decolorized with activated charcoal, the solvent was removed under reduced pressure to give a yellow tar. The crude product was purified by recrystallization from MeOH−$H_2O$ and dried *in vacuo* to give 124 g (96% yield) of the product as colorless needles: mp 110−112 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.43 (s, 6H), 2.44 (s, 3H), 3.24 (t, $J = 5.1$ Hz, 4 H), 3.39 (m, 8H), 3.79 (m, 4H), 7.33 (m, 6H), 7.72 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.51,49.71, 49.78, 52.62, 61.69, 127.32, 129.90, 135.37, 143.76, 143.80; MS (Thermospray), *m*/*z* 654 ($M + H)^+$.

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**3,6,9-Tris(*p*-tolylsulfonyl)-3,6,9-triazaundecane-1,11-diyl(bis-*p*-toluenesulfonate) (9).** To a stirred solution of *p*-toluenesulfonyl chloride (79.6 g, 0.418 mol) and triethylamine (42.3 g, 0.418 mol) in $CH_2Cl_2$ (300 mL) at 0 °C under a dry argon atmosphere was added a solution of 3,6,9-tris(*p*-tolylsulfonyl)-3,6,9-triazaundecane-1,11-diol (124 g, 0.190 mol) in $CH_2Cl_2$ (300 mL), maintaining the temperature below 10 °C. The addition required 30 min. The mixture was allowed to warm to room temperature and was stirred for 20 h longer. At the end of this time, the mixture was poured onto ice (1000 g) and the $CH_2Cl_2$ layer was separated. The $CH_2Cl_2$ layer was washed with 1 N HCl, $H_2O$, and a saturated NaCl solution and was dried ($MgSO_4$). After the solution was decolorized with activated charcoal, the solvent was removed under reduced pressure. The resulting tan oil was washed with hexane and then recrystallized from $CH_2Cl_2$−hexane to give 143 g (78% yield) of the product as needles: mp 158−160 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.42 (s, 6H), 2.43 (s, 6H), 2.46 (s, 3H), 3.29 (m, 8H), 3.40 (t, $J$ = 5.3 Hz, 4H), 4.15 (t, $J$ = 5.5 Hz, 4H), 7.35 (m, 10H), 7.74 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.54, 21.57, 21.66, 48.96, 49.33, 49.50, 68.78, 127.40, 127.55, 128.03, 129.99, 130.03, 132.42, 134.90, 135.15, 143.86, 143.95, 145.14; MS (FAB, NBA matrix) *m*/*z* 968 $(M + Li)^+$.

**2*R*-Methyl-1,4,7,10,13-pentakis(*p*-tolylsulfonyl)-1,4,7,10,13-pentaazacyclopentadecane (10).** Sodium hydride (2.87 g, 80% in mineral oil, 95.6 mmol) was added to a stirred solution of *N*,*N*′-bis(*p*-tolylsulfonyl)-(*R*)-1,2-diaminopropane (18.3 g, 47.8 mmol) in anhydrous DMF (480 mL) at room temperature under a dry argon atmosphere. After $H_2$ evolution was complete (60 min), the mixture was heated to 100 °C. A solution of 3,6,9-tris(*p*-tolylsulfonyl)-3,6,9-triazaundecane-1,11-diylbis(*p*-toluenesulfonate) (46.0 g, 47.8 mmol) in anhydrous DMF (240 mL) was added to the stirred mixture at 100 °C over a period of 3 h. The mixture was heated 1.5 h longer at 100 °C. After cooling, the mixture was concentrated *in vacuo* to a volume of 250 mL. A solution of 1:1 $H_2O$/MeOH (200 mL) was added dropwise, followed by $H_2O$ (1500 mL). The precipitate was collected by filtration and washed with $H_2O$. The solid was dried *in vacuo* and recrystallized from $CHCl_3$/MeOH to give 21.6 g (45% yield) of a white crystalline solid: mp 256−258 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.05 (m, 3 H), 2.42 (s, 15 H), 3.15 (m, 19 H), 7.46 (m, 10 H), 7.58 (m, 10 H); MS (FAB, NBA matrix), *m*/*z* (relative intensity) 999 $[(M + Li)^+$, 100], 851 $[(M - Ts + Li)^+$, 24], 696 $[(M - 2Ts + Li)^+$, 27], 541 $[(M - 3Ts + Li)^+$, 7]. HRMS: calcd for $C_{46}H_{57}N_5S_5O_{10}Li$ $(M + Li)^+$, 1006.2869; found, 1006.2995.

**2*R*-Methyl-1,4,7,10,13-pentaazacyclopentadecane (1b).** A mixture of 2*R*-methyl-1,4,7,10,13-pentakis(*p*-tolylsulfonyl)-1,4,7,10,13-pentaazacyclopentadecane (19.5 g, 19.4 mmol), phenol (9.13 g, 97.0 mmol), and 30% HBr in acetic acid (260 mL) was stirred for 21 h at 120 °C in a sealed Fischer & Porter bottle. A solid precipitated during the heating period. After cooling, 1:1 ethanol/ethyl ether (250 mL) was added, followed by ether (3 L). The solid was collected by filtration and was washed with ethyl ether. The solid was dissolved in $H_2O$ (1 L) and the aqueous solution was washed with ethyl ether (3 × 2 L) and concentrated under reduced pressure to 50 mL. The gradual addition of 2-propanol (900 mL) precipitated 10.6 g of the pentahydrobromide salt. This salt was filtered and dissolved in $H_2O$ (100 mL), the pH of the solution was adjusted to 11 with 10 N NaOH, and the solvent was removed on the rotary evaporator. Ethanol (2 × 500 mL) was then added and removed under reduced pressure. The resulting white oily solid was extracted with hot THF (2 × 500 mL) and filtered at room temperature. The filtrates were combined, and the solvent was removed under reduced pressure. The oil was redissolved in THF and insoluble impurities were removed by filtration. Recrystallization from cold (−20 °C) $CH_3CN$ gave 0.762 g (17% yield) of the product as a white crystalline solid: mp 88−89.5 °C; $[\alpha]_d^{20} = -38.6°$ ($c$ = 0.01, benzene); $^1$H NMR ($CDCl_3$) $\delta$ 1.02 (d, $J$ = 6.2 Hz, 3H), 1.68 (br s, 5H), 2.36 (m, 1H), 2.72 (m, 18H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.70, 46.64, 48.39, 48.55, 48.67, 48.80, 48.89, 49.09, 53.03, 56.0; MS (FAB, DTE/DTT matrix) *m*/*z* 230 $(M + H)^+$. Exact mass $(M + H)^+$: calcd, 230.2345; found, 230.2354 ($C_{11}H_{28}N_5$).

**Dimethyl 3,6,9-tris(*p*-tolylsulfonyl)-3,6,9-triazaundecanedioate (11).** 1,4,7-Tris(*p*-tolylsulfonyl)-1,4,7-triazaheptane-1,7-disodium salt (30 g, 49.2 mmol) was dissolved in dry *N*,*N*-dimethylformamide (180 mL) under argon. After this was cooled to 0 °C in an ice bath, methyl chloroacetate (15.40 g, 141.9 mmol) was added dropwise over a 10 min period. The reaction mixture became cloudy at the end of the addition and was allowed to stir overnight while the ice bath warmed to room temperature. The solvent was evaporated under reduced pressure to give a brown oil which was dissolved in ethyl acetate (450 mL), giving a milky solution. This solution was washed twice with water (500 mL and then 300 mL), and the combined water layers were back-extracted with ethyl acetate (300 mL). The combined ethyl acetate layers were washed twice with saturated sodium chloride solution (200 mL), filtered, and evaporated to dryness. This residue was dissolved in dichloromethane (200 mL) and evaporated to dryness, and placed on the vacuum line. After recrystallization from chloroform−methanol and washing with methanol and ether, an off-white solid was obtained, 27.46 g (38.68 mmol, 78.6% yield). An additional quantity of a slightly darker solid (4.7 g, 6.6 mmol, 13.5% yield) was recovered from the filtrate after removing the solvent and recrystallizing as before: mp 141−142 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.42 and 2.44 (2 s, 9H), 3.41 (br s, 8H), 3.60 (s, 6H), 4.07 (s, 4H), 7.26−7.35 (m, 6H), 7.63−7.74 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.30, 48.27, 48.90, 49.60, 51.91, 127.12, 127.20, 129.47, 129.69, 134.69, 135.46, 143.46, 143.63, 169.00. Anal. Calcd for $C_{31}H_{39}N_3O_{10}S_3$: C, 52.45; H, 5.54; N, 5.92. Found: C, 52.42; H, 5.51; N, 5.89.

**3,6,9-Tris(*p*-tolylsulfonyl)-3,6,9-triazaundecanedioic Acid (12).** Dimethyl 3,6,9-tris(*p*-tolylsulfonyl)-3,6,9-triazaundecanedioate (16 g, 22.5 mmol) was slurried in tetrahydrofuran (100 mL). Sodium hydroxide (2 N, 160 mL) was added dropwise over a 1 h period. After 72 h, the solvent was evaporated under reduced pressure, and hydrochloric acid (1 N) was added to lower the pH to 4. This aqueous phase was extracted several times with ethyl acetate. The combined ethyl acetate layers were washed twice with brine, dried ($MgSO_4$), filtered, and evaporated to give a white solid, 14.22 g (20.86 mmol, 92.7% yield): mp 177−180 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 2.38 and 2.40 (2 s, 9 H), 3.10 (m, 4 H), 3.29 (m, 4 H), 3.73 (s, 4 H), 7.37 and 7.41 (2 d, $J$ = 8.2,7.9 Hz, 6 H), 7.61 and 7.66 (2 d, $J$ = 8.0, 8.2 Hz, 6 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 20.99, 47.45, 49.17, 126.96, 127.02, 129.72, 129.94, 135.30, 136.19, 143.35, 143.63, 170.23. Anal. Calcd for $C_{29}H_{35}N_3O_{10}S_3$: C, 51.09; H, 5.17; N, 6.16. Found: C, 50.72; H, 5.29; N, 6.08.

**3,6,9-Tris(*p*-tolylsulfonyl)-3,6,9-triazaundecanedioyl Dichloride (13).** 3,6,9-Tris(*p*-tolylsulfonyl)-3,6,9-triazaundecanedioic acid (40.5 g, 59.4 mmol) was placed in a round bottom flask under argon, and oxalyl chloride (400 g, 3.15 moles) was added. This mixture, initially cloudy, became clear after a few hours and was stirred overnight at room temperature. At the end of this time it was heated to 40 °C for 30 min. Oxalyl chloride was removed on the rotary evaporator. Dichloromethane (50−60 mL) was added to dissolve the resulting solid, and was removed on the rotary evaporator. This process was repeated twice, giving 40.5 g (59.0 mmol, 99% yield) of a white solid: mp 136−137 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.43 and 2.46 (2 s, 9 H), 3.30−3.38 (m, 4 H), 3.40−3.48 (m, 4 H), 4.56 (s, 4 H), 7.30−7.40 (m, 6 H), 7.71 (d, $J$ = 8.2 Hz, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.50, 21.54, 48.03, 49.12, 58.97, 127.35, 129.98, 130.03, 134.15, 135.05, 144.26, 144.44, 170.99.

**2,3-*trans*-Cyclopentano-5,15-dioxo-7,10,13-tris(*p*-tolylsulfonyl)-1,4,7,10,13-pentaazacyclopentadecane (15n). Procedure A.** A 3 L four-neck round bottomed flask, under argon atmosphere, was equipped with a magnetic stir bar and two 500 mL dropping funnels charged with 3,6,9-tris(*p*-tolylsulfonyl)-3,6,9-triazaundecanedioyl dichloride (11.42 g, 15.9 mmol) in 320 mL of anhydrous $CH_2Cl_2$ and with 1,2-*trans*-cyclopentanediamine (1.59 g, 15.9 mmol) and triethylamine (4.43 mL, 31.8 mmol) in 320 mL of anhydrous $CH_2Cl_2$. The contents of the dropping funnels were added simultaneously over 2.5 h to the flask containing 320 mL of anhydrous $CH_2Cl_2$ cooled in an ice−water bath. White precipitate began to form after 1 h of addition. When addition was complete, the reaction mixture was allowed to slowly warm to room temperature overnight. The precipitate was then collected by suction filtration to yield 6.60 g of product. The filtrate was washed twice with 500 mL of water and 500 mL of brine, dried over $MgSO_4$, filtered, and concentrated to a tan foam. Methylene chloride was added to the tan solid and a white precipitate was collected by suction filtration to yield 0.54 g of additional product. Total yield: 7.14 g (60%). $^1$H NMR (DMSO-$d_6$) $\delta$ 1.27−1.42 (m, 2H), 1.60−1.65 (m, 2H), 1.75−1.90 (m, 2H), 2.41 (s, 6H), 2.42 (s, 3H), 2.83−2.95 (m, 2H), 3.00−3.20 (m, 6H), 3.43 (d, $J$ = 16.1 Hz, 2H), 3.83−3.96 (m, 2H), 4.02 (d, $J$ = 16.4 Hz, 2H), 7.41−7.45 (m, 6H), 7.53 (d, $J$ = 8.3 Hz, 2H), 7.68

(d, $J$ = 8.3 Hz, 4H), 7.96 (d, $J$ = 7.8 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 19.49, 20.90, 28.96, 47.07, 47.34, 51.03, 54.66, 126.71, 127.04, 129.64, 129.91, 135.04, 135.69, 143.30, 143.57, 166.74; MS (FAB, NBA matrix): $m/z$ 752 (M + Li), 596, 422. Anal. Calcd for $C_{34}H_{43}N_5S_3O_8$: C, 54.75; H, 5.81; N, 9.39; S, 12.89. Found: C, 53.81; H, 5.76; N, 9.21; S, 12.69.

**2,3-*trans*-Cyclopentano-1,4,7,10,13-pentaazacyclopentadecane (1n). Procedure B.** 2,3-*trans*-Cyclopentandiyl-5,15-dioxo-7,10,13-tritosyl-1,4,7,10,13-pentaazacyclopentadecane (3.00 g, 4.02 mmol) was placed in a 500 mL round-bottomed flask under argon atmosphere and 50 mL of anhydrous DME was added to create a slurry. The flask was placed in an ice−water bath, and $LiAlH_4$ in DME (0.5 M, 105 mL, 52.3 mmol) was added to the cooled slurry. A reflux condenser was placed on the flask and the mixture was heated to reflux. Most of the solid dissolved, and after 15 min at reflux, the mixture began to turn yellow. After 16 h at reflux, the reaction mixture, which contained much white precipitate, was allowed to cool to room temperature and then was cooled in an ice water bath. The reaction mixture was quenched by the slow addition of deionized water (2.0 mL) followed by 15% NaOH (2.0 mL) and 6.0 mL of water. After gas evolution had ceased, the mixture was allowed to warm to room temperature. After 1 h of stirring, 50 mL of THF was added to the mixture and stirring was continued for 2 h. The suspension was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in warm $CH_3CN$ and filtered. Crystals formed upon cooling overnight. Recrystallization from $CH_3CN$ provided clear, needle crystals, yield 230 mg (22%). $^1$H NMR ($CDCl_3$) $\delta$ 1.16−1.32 (m, 2H), 1.55−1.69 (m, 2H), 1.72−2.02 (m, 7H), 2.49−2.90 (m, 18H); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.73, 30.76, 47.52, 48.26, 48.56, 48.80, 65.02; MS (FAB, NBA matrix): $m/z$ 256 (M + H). HRMS exact mass: calcd for $C_{13}H_{30}N_5$, 256.2502; found, 256.2523. Anal. Calcd for $C_{13}H_{29}N_5$: C, 61.14; H, 11.44; N, 27.42. Found: C, 61.00; H, 11.40; N, 27.35.

***trans*-5,6-Cyclohexano-1,10,13-tris(*p*-tolylsulfonyl)-1,4,7,10,13-pentaazacyclopentadecan-3,8-dione (15m).** Dry dichloromethane (150 mL) was placed in a 1 L four-neck round bottom flask under argon equipped with two dropping funnels. 3,6,9-Tris(*p*-tolylsulfonyl)-3,6,9-triazaundecanedioyl dichloride (5.07 g, 7.05 mmol) was dissolved in dry dichloromethane (150 mL) and added to one of the dropping funnels. *trans*-1,2-Diaminocyclohexane (0.805 g, 7.05 mmol) and triethylamine (1.96 mL, 14.1 mmol) were dissolved in dry dichloromethane (150 mL) and added to the other dropping funnel. After the dichloromethane-containing flask was cooled in an ice bath to an internal temperature of 0−5 °C, the contents of the dropping funnels were added simultaneously to the stirred solution over 2.25 h. A white precipitate was evident before the addition was finished. At the end of this time, the ice bath was removed and the reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered, and the white precipitate was identified as pure product. The filtrate was washed twice with water (100 mL) and once with saturated sodium chloride solution (100 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. Recrystallization from dichloromethane−hexane provided additional product, along with the initial precipitate, 2.85 g (3.75 mmol): 53% yield; mp 254−255 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.15 (br s, 4 H), 1.52−1.75 (m, 4 H), 2.42 and 2.43 (2 s, 9 H), 3.04 (m, 8 H), 3.51 (d + m, $J$ = 16.5 Hz, 4 H), 4.01 (d, $J$ = 16.5 Hz, 2 H), 7.35−7.53 (m, 8 H), 7.71 (d, $J$ = 8.3 Hz, 4 H), 7.80 (br d, $J$ = 10.5 Hz, 2 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 20.94, 24.40, 32.12, 46.35, 46.46, 50.47, 51.55, 126.79, 127.24, 129.57, 129.96, 134.53, 136.16, 143.23, 143.67, 166.35.

***trans*-2,3-Cyclohexano-1,4,7,10,13-pentaazacyclopentadecane (1m).** *trans*-5,6-Cyclohexano-1,10,13-tris(*p*-tolylsulfonyl)-1,4,7,10,13-pentaazacyclopentadecane-3,8-dione (1.765 g, 2.32 mmol) was suspended in 1,2-dimethoxyethane (DME, 40 mL) under argon, and the flask was placed in a water bath. Lithium aluminum hydride (0.5 M in DME, 55 mL, 27.5 mmol) was added over a 5 min period. Five minutes later, heating with a mantle was started, and reflux began 15 min later. The reaction became almost colorless after a few minutes of reflux, later turning yellow with a white precipitate. Reflux was continued for 43.5 h, and then the reaction mixture was allowed to cool to room temperature. The reaction was quenched by the careful addition of water (0.86 mL) using a water bath for cooling. Five minutes later, 15% aqueous sodium hydroxide solution (0.86 mL) was added followed by water (2.6 mL). The slight yellowish color largely discharged during this process. One hour later, tetrahydrofuran (55 mL) was added and stirring was continued for 2 h. The quenched reaction mixture was filtered. The filtrate was evaporated under reduced pressure and placed on the vacuum line, giving a yellowish-white solid. This solid was dissolved in dichloromethane and filtered and then concentrated to a solid and placed on the vacuum line. It was recrystallized from hot acetonitrile under argon, producing white needles, 0.316 g (1.17 mmol): 50.4% yield; mp 112−113 °C (under nitrogen); $^1$H NMR ($CDCl_3$) $\delta$ 0.97 (m, 2 H), 1.22 (m, 2H), 1.39−1.96 (3 m, 7 H), 2.11 (m, 4 H), 2.49 (m, 2 H), 2.54−2.88 (several m, 12 H), 2.94 (m, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 25.12, 32.07, 46.67, 48.24, 48.62, 49.16, 62.20. Exact mass (M + H)$^+$: calcd, 270.2658; found, 270.2658 ($C_{14}H_{32}N_5$).

***cis*-5,6-Cyclohexano-1,10,13-tris(*p*-tolylsulfonyl)-1,4,7,10,13-pentaazacyclopentadecane-3,8-dione (15p).** Dry dichloromethane (250 mL) was placed in a 2 L four-necked round bottom flask under argon equipped with two dropping funnels, an argon inlet, and a magnetic stir bar. 3,6,9-Tris(*p*-tolylsulfonyl)-3,6,9-triazaundecanedioyl dichloride (9.0 g, 12.5 mmol) was dissolved in dry dichloromethane (250 mL) and added to one of the dropping funnels. *cis*-1,2-Diaminocyclohexane (1.43 g, 12.5 mmol) and triethylamine (3.5 mL, 22.25 mmol) were dissolved in dry dichloromethane (250 mL) and added to the other dropping funnel. The flask was placed in an ice bath and simultaneous dropwise addition of the contents of the two addition funnels was carried out over a 3 h period. The reaction was then allowed to warm to room temperature and stir overnight. The homogeneous solution was partially evaporated on the rotary evaporator, to a volume of about 300 mL. Water (250 mL) was added with vigorous stirring, causing a white solid to come out. After filtration and drying in a vacuum oven at 50 °C overnight, 6.21 g were recovered. Additional recovery of 0.06 g from the dichloromethane layer, after recrystallization from dichloromethane−hexane, gave a total of 6.27 g (8.25 mmol): 66% yield; mp 251−252 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.41−1.64 (br m, 6 H), 1.76 (m, 2 H), 2.45 (s, 9 H), 3.18 (m, 2 H), 3.29−3.58 (several m, 8 H), 3.82 (d, $J$ = 16.9 Hz, 2 H), 4.16 (br s, 2 H), 6.86 (d, $J$ = 7.3 Hz, 2 H), 7.31−7.40 (m, 6 H), 7.70 and 7.73 (2 d, $J$ = 8.3 and 8.3 Hz, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.57, 22.14, 28.19, 49.36, 49.72, 51.26, 54.49, 127.65, 127.80, 130.01, 130.10, 134.11, 135.65, 144.03, 144.53, 168.20. Exact mass (M + H)$^+$: calcd, 760.2509; found, 760.2550 ($C_{35}H_{45}N_5O_8S_3$).

***cis*-5,6-Cyclohexano-1,4,7,10,13-pentaazacyclopentadecane (1p).** *cis*-5,6-Cyclohexano-1,10,13-tris(*p*-tolylsulfonyl)-1,4,7,10,13-pentaazacyclopentadecan-3,8-dione (4.0 g, 5.26 mmol) was suspended in 1,2-dimethoxyethane (DME, 90 mL) and stirred under argon in a three-necked round bottom flask while the lithium aluminum hydride (0.5 M in DME, 125 mL, 62.5 mmol) was added over a 5 min period using a water bath for cooling. The reaction mixture became almost colorless before the end of the addition. After 5 min more in the water bath, heating in a mantle was started, and reflux was attained 15 min later. The reaction became yellow after a few minutes of reflux and soon showed a white precipitate. After 43 h, reflux was stopped and the reaction mixture was cooled to room temperature. Water (1.95 mL) was carefully added dropwise, using a water bath for cooling. Five minutes later, 15% aqueous sodium hydroxide solution (1.95 mL) was added, followed by more water (5.75 mL). The slight yellowish color largely discharged during this process. Stirring was continued for 1.25 h, nitrogen-saturated tetrahydrofuran (120 mL) was added, and stirring was continued. The quenched reaction mixture was filtered, and the filtrate was concentrated. About halfway through the concentration, the filtrate was filtered again to remove some solid which had been present after the previous filtration. On completion of solvent removal and drying on the vacuum line, a white solid was obtained (1.31 g). NMR showed that 20−30% of the *trans* isomer was present in addition to the desired compound. After several recrystallizations from acetonitrile, the amount of the *trans* isomer present had decreased. A final recrystallization of several combined fractions from hot hexane gave nearly pure *cis* isomer containing less than 4% of the *trans* isomer, 400 mg (1.485 mmol): 28.2% yield, mp 114−115 °C (under nitrogen); $^1$H NMR ($CDCl_3$) $\delta$ 1.23−1.88 (several m, 13 H), 2.53−2.92 (several m, 18 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 22.27, 27.90, 46.68, 48.38, 48.76, 49.20, 57.40. Exact mass (M + H)$^+$: calcd, 270.2658; found, 270.2701 ($C_{14}H_{32}N_5$).

**2,3-*trans*-Cycloheptano-5,15-dioxo-7,10,13-tritosyl-1,4,7,10,13-pentaazacyclopentadecane (15o).** Using procedure A, 1,2-diaminocycloheptane (3.50 g, 27.3 mmol) was cyclized with 3,6,9-tris(*p*-

tolylsulfonyl)-3,6,9-triazaundecanedioyl dichloride (19.6 g, 27.3 mmol) to yield 6.1 g of 2,3-*trans*-cycloheptano-5,15-dioxo-7,10,13-tritosyl-1,4,7,10,13-pentaazacyclopentadecane (29%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.30−1.64 (m, 10H), 2.39 (s, 6H), 2.40 (s, 3H), 2.90−3.15 (m, 8H), 3.48 (d, $J$ = 16.1 Hz, 2H), 3.65−3.75 (m, 2H), 3.97 (d, $J$ = 16.1 Hz, 2H), 7.31−7.35 (m, 6H), 7.50 (d, $J$ = 8.1 Hz, 2H), 7.70 (d, $J$ = 8.1 Hz, 4H), 7.92 (d, $J$ = 7.8 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 20.88, 23.96, 27.99, 31.94, 46.29, 46.51, 50.45, 54.03, 126.67, 127.16, 129.55, 129.90, 134.82, 136.13, 143.21, 143.61, 166.01. Anal. Calcd for $C_{36}H_{47}N_5S_3O_8$: C, 55.87; H, 6.12; N, 9.05; S, 12.43. Found: C, 55.93; H, 6.07; N, 9.04; S, 12.36.

**2,3-*trans*-Cycloheptano-1,4,7,10,13-pentaazacyclopentadecane (1o).** Using procedure B, 2,3-*trans*-cycloheptano-5,15-dioxo-7,10,13-tritosyl-1,4,7,10,13-pentaazacyclopentadecane (6.00 g, 7.75 mmol) was reduced with $LiAlH_4$ in DME (0.5M, 202 mL, 101 mmol) to yield 2,3-*trans*-cycloheptano-1,4,7,10,13-pentaazacyclopentadecane. Recrystallization from $CH_3CN$ provided 808 mg of fine needle crystals (37%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.31−1.46 (m, 4H), 1.48−1.56 (m, 2H), 1.60−1.71 (m, 2H), 1.74−1.84 (m, 2H), 2.01 (br s, 5H), 2.18−2.25 (m, 2H), 2.45−2.54 (m, 2H), 2.57−2.77 (m, 10H), 2.79−2.86 (m, 2H), 2.91−2.98 (m, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 24.02, 28.50, 29.82, 46.86, 47.98, 48.37, 48.73, 64.98. Anal. Calcd for $C_{15}H_{33}N_5$: C, 63.56; H, 11.73; N, 24.71. Found: C, 63.46; H, 11.66; N, 24.72.

**2*R**,3*R**-(4′*R**-*tert*-Butylcyclohexano)-5,15-dioxo-7,10,13-tritosyl-1,4,7,10,13-pentaazacyclopentadecane (15q).** Using procedure A, 1*R**,2*R**-diamino-4*R**-*tert*-butylcyclohexane (1.59 g, 9.33 mmol) was cyclized with 3,6,9-tris(*p*-tolylsulfonyl)-3,6,9-triazaundecanedioyl dichloride (6.71 g, 9.33 mmol) to yield the crude product. Column purification on silica gel using 2:1 ethyl acetate/hexanes provided 4.15 g of 2*R**,3*R**-(4′*R**-*tert*-butylcyclohexano)-5,15-dioxo-7,10,13-tritosyl-1,4,7,10,13-pentaazacyclopentadecane (55%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.80 (s, 9H), 0.90−1.30 (m, 4H), 1.67−1.80 (m, 1H), 1.89−2.04 (m, 2H), 2.40 (s, 9H), 3.05−3.96 (m, 14H), 6.50−6.63 (m, 2H), 7.23−7.36 (m, 6H), 7.59−7.72 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.50, 21.52, 21.53, 25.47, 27.39, 31.69, 32.21, 33.25, 46.45, 49.54, 49.60, 50.74, 50.93, 53.18, 53.26, 54.05, 54.07, 127.41, 127.55, 127.56, 129.85, 129.98, 129.99, 133.96, 134.02, 134.21, 143.82, 144.32, 144.34, 168.08, 168.17. HRMS: *m*/*z* calcd for $C_{39}H_{54}N_5S_3O_8$ (M + H)$^+$, 816.3135; found, 816.3112.

**2*R**,3*R**-(4′*R**-*tert*-Butylcyclohexano)-1,4,7,10,13-pentaazacyclopentadecane (1q).** Using procedure B, 2*R**,3*R**-(4′*R**-*tert*-butylcyclohexano)-5,15-dioxo-7,10,13-tritosyl-1,4,7,10,13-pentaazacyclopentadecane (2.70 g, 3.31 mmol) was reduced with $LiAlH_4$ in DME (0.5 M, 86.0 mL, 43.0 mmol) to yield 2*R**,3*R**-(4′*R**-*tert*-butylcyclohexano)-1,4,7,10,13-pentaazacyclopentadecane. Recrystallization from hexanes provided 360 mg of fine white powder (33%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.70−0.92 (m, 1H), 0.84 (s, 9H), 0.92−1.13 (m, 3H), 1.70−1.81 (m, 1H), 2.00−2.90 (m, 23H), 2.94−3.08 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.76, 27.53, 31.64, 32.33, 32.92, 46.53, 46.58, 46.60, 48.11, 48.14, 48,45, 48.53, 48.97, 49.05, 61.95, 62.23. HRMS: *m*/*z* calcd for $C_{18}H_{40}N_5$ (M + H)$^+$, 326.3284; found, 326.3276.

**D,L-*N*,*N*′-Bis(chloroacetyl)-2,3-diaminobutane, (17c).** To a stirred solution of D,L-2,3-diaminobutane dihydrochloride (8.05 g, 50.0 mol) in $H_2O$ (50 mL) was added alcohol-free $CHCl_3$ (250 mL). Solutions of chloroacetyl chloride (17.3 g, 154 mmol) in alcohol-free $CHCl_3$ (100 mL) and $K_2CO_3$ (19.6 g, 142 mmol) in $H_2O$ (200 mL) were added simultaneously under an Ar atmosphere over 1.5 h at 0 °C. The mixture was allowed to warm to room temperature while being stirred for an additional 2 h. The layers were then separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 300 mL). The combined $CHCl_3$ solutions were washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was removed *in vacuo* to give 11.3 g of a white solid. Recrystallization from $CHCl_3$−hexanes gave 10.7 g (89% yield) of the product as colorless needles: mp 159−160 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (d, $J$ = 6.2 Hz, 6 H), 3.95 (m, 2 H), 4.01 (s, 2 H), 4.02 (s, 2 H), 6.80 (br s, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.14, 42.53, 50.87, 166.49; MS (FAB, DTT/DTE matrix) *m*/*z* (relative intensity) 241 (M + H$^+$, 100), 243 (66).

**D,L-5,6-Dimethyl-1,10,13-tris(*p*-tolylsulfonyl)-1,4,7,10,13-pentaazacyclopentadecane-3,8-dione (18c).** To a stirred solution of 1,4,7-tris(*p*-tolylsulfonyl)-1,4,7-triazaheptane, 1,7-disodium salt (27.6 g, 43.7 mmol), in anhydrous DMF (1.5 L) was added a solution of D,L-*N*,*N*′-bis(chloroacetyl)-2,3-diaminobutane (10.5 g, 43.7 mmol) in anhydrous DMF (1 L) dropwise over 2.5 h under a dry argon atmosphere. The resulting cloudy mixture was stirred for 14 h. The solvent was then removed *in vacuo* and the residue was dissolved in a mixture of $CHCl_3$ (1.5 L) and $H_2O$ (1.0 L). The layers were separated, and the $CHCl_3$ layer was washed with $H_2O$ (2 × 1 L) and a saturated NaCl solution (0.5 L) and was dried ($MgSO_4$). The solution was heated and concentrated *in vacuo* to a volume of 200 mL at which time the product began to crystallize. The addition of MeOH gave 14.6 g (46% yield) of the product as colorless needles: mp 240−242 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (d, $J$ = 7.0 Hz, 6H), 2.44 (s, 9H), 3.20 (m, 4H), 3.38 (m, 2H), 3.46 (m, 2H), 3.63 (dd, $J$ = 175, 16 Hz, 4H), 3.87 (m, 2H), 6.51 (d, $J$ = 7.2 Hz, 2H), 7.34 (m, 6H), 7.71 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.51, 21.59, 49.92, 50.72, 51.58, 54.53, 127.55, 127.69, 129.98, 130.10, 133.95, 134.32, 143.97, 144.48, 169.20; MS (FAB, NBA matrix) *m*/*z* (relative intensity) 740 [(M + Li)$^+$, 100].

**D,L-2,3-Dimethyl-1,4,7,10,13-pentaazacyclopentadecane (1c).** To a stirred slurry of D,L-5,6-dimethyl-1,10,13-tris(*p*-tolylsulfonyl)-1,4,7,-10,13-pentaazacyclopentadecane (7.34 g, 10.0 mmol) in anhydrous THF (250 mL) was added a solution of lithium aluminum hydride (250 mL, 1.0 M in THF, 250 mmol). The mixture was refluxed for 48 h. The heterogeneous mixture was then cooled to 0 °C, and $H_2O$ (7.8 mL) was added dropwise, followed by 5 min of stirring. Then an aqueous solution of NaOH (8 mL, 15%) was added, followed by $H_2O$ (23 mL). The resulting slurry was stirred for 1 h, THF (500 mL) was added, and the mixture was filtered. The solid was washed with hot THF (2 × 500 mL), and the filtrate and washings were combined. Removal of the solvent *in vacuo* gave 2.86 g of a pale yellow crystalline solid. Crystallization from hexanes gave 903 mg (37% yield) of the product as colorless needles: mp 70−72 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.05 (m, 6H), 1.90 (br s, 5H), 2.23 (m, 2H), 2.50 (m, 2H), 2.64 (m, 2H), 2.73 (m, 8H), 2.96 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 17.25, 47.05, 48.08, 48.51, 49.02, 59.46; MS (FAB, GT + HCl matrix) *m*/*z* (relative intensity) 244 [(M + H)$^+$, 60], 158 [(M − 86)$^+$, 100]. Exact mass: calcd, 244.2501; found, 244.2451 ($C_{12}H_{29}N_5$).

***N*,*N*′-Bis(chloroacetyl)-2,3-diamino-2,3-dimethylbutane (17i).** To a stirred solution of 2,3-diamino-2,3-dimethylbutane (4.00 g, 21.1 mol) in $H_2O$ (20 mL) was added alcohol-free $CHCl_3$ (100 mL). Solutions of chloroacetyl chloride (7.33 g, 64.9 mmol) in alcohol-free $CHCl_3$ (40 mL) and $K_2CO_3$ (8.3 g, 60 mmol) in $H_2O$ (84 mL) were added simultaneously under an Ar atmosphere over 1 h to the solution at 0 °C. After the addition, the cooling bath was removed, and the mixture was allowed to warm to room temperature while being stirred for an additional 2 h. The clear solution was diluted with $CHCl_3$, the layers were then separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 100 mL). The combined $CHCl_3$ solutions were washed with water (100 mL) and saturated NaCl solution (100 mL) and then dried over $Na_2SO_4$. The solvent was removed *in vacuo* to give 3.55 g of the product as a white solid (62.4% yield): mp 129−130 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.39 (s, 12H), 1.14 (s, 4H), 7.73 (s, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 21.73, 43.11, 61.45, 166.60. HRMS: *m*/*z* calcd for $C_{10}H_{19}N_2O_2Cl_2$ (M + H)$^+$, 269.0824; found, 269.0826.

**3,3,4,4-Tetramethyl-8,11,14-tris(*p*-tolylsulfonyl)-2,5,8,11,14-pentaazacyclopentadecan-1,6-dione (18i).** *N*,*N*′-Bis(chloroacetyl)-2,3-diamino-2,3-dimethylbutane (5.0 g, 18.58 mmol) was dissolved in dry *N*,*N*-dimethylformamide (500 mL) and added dropwise over a period of 1.25 h to a stirred solution of disodium 1,4,7-tris(*p*-tolylsulfonyl)-1,4,7-triazaheptane (11.3 g, 18.53 mmol) in DMF (500 mL) at room temperature under argon. The reaction mixture became cloudy by the end of the addition. After overnight stirring, the solvent was removed on the rotary evaporator (water bath temperature, 45 °C). The light brown solid was dissolved in dichloromethane (350 mL) and washed with water (100 mL) four times and with saturated sodium chloride solution (100 mL). The dichloromethane layer was dried ($Na_2SO_4$) and filtered, and the solvent was removed. Recrystallization from chloroform−methanol gave 10.15 g (13.32 mmol, 71.9% yield) of the product as a white solid: mp 285−286 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.40 (12H), 2.42 (s, 9H), 3.26 and 3.19 (2 m, 8H), 7.30 (m, 6H), 3.64 (s, 4H), 7.59 (br s, 2H), 7.70 and 7.66 (2 d, $J$ = 8.1 and 8.1 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.55, 21.96, 48.23, 48.93, 54.36, 61.88, 127.34, 127.46, 129.94, 134.88, 135.53, 143.87, 144.16, 168.65.

**2,2,3,3-Tetramethyl-1,4,7,10,13-pentaazacyclopentadecane (1i).** 3,3,4,4-Tetramethyl-8,11,14-tris(*p*-tolylsulfonyl)-2,5,8,11,14-pentaazacyclopentadecane-1,6-dione (7.28 g, 9.55 mmol) was suspended in dry

1,2-dimethoxyethane (DME, 160 mL) under argon in a 1 L round bottom flask. Lithium aluminum hydride in DME (0.5 M, 228 mL, 114 mmol) was added, slowly at first and then more rapidly over a 10 min period while the reaction flask was in a water bath. The reaction mixture became homogeneous by the end of the addition. Reflux was started, and the reaction mixture became yellow and heterogeneous. After 40 h, reflux was stopped and the reaction mixture was allowed to cool. The reaction flask was placed in an ice bath, and water (3.5 mL) was cautiously added over a 10 min period. Next, 15% NaOH (3.5 mL) was added over a 5 min period, followed by more water (10.7 mL). The thick, slightly yellow, mixture was stirred out of the ice bath for an hour, then THF (225 mL) was added and stirring was continued for 2 h. The mixture was filtered, the residue was treated with more THF (150 mL) and filtered, and the process was repeated twice with THF (100 mL). After removal of solvent under reduced pressure, the residue was placed on the vacuum line. This solid was dissolved in hot hexane and filtered. The solvent was removed and the viscous liquid residue was placed on the vacuum line. This residue was recrystallized from acetonitrile starting from −25 to about −40 °C, and the crystals were washed cold with a small volume of acetonitrile and dried on the vacuum line, 1.34 g. The white solid was recrystallized from acetonitrile under argon at −10 to −15 °C as a white crystalline solid, 0.83 g (3.06 mmol): 32% yield; mp (under $N_2$) 50−50.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.05 (s, 12H), 1.29−1.94 (3 br s, 5H), 2.60−2.84 (m, 16H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.32, 41.30, 48.37, 48.69, 49.92, 58.21. Exact mass $(M + H)^+$: calcd, 272.2814; found, 272.2842 ($C_{14}H_{34}N_5$). Anal. Calcd for $C_{14}H_{33}N_5$: C, 61.95; H, 12.25; N, 25.80. Found: C, 61.70; H, 12.21; N, 26.05.

**General Procedures for Solution Phase Linear Peptide Synthesis.** All linear peptides were prepared using standard solution-phase coupling procedures (EDC·HCl, HOBT·$H_2O$) from *N*-α-Boc amino acids with suitable side-chain protection. Strategies varied according to the availability and expense of the required differentially protected amino acids and di- and tripeptides. The following synthesis of Gly-Ala-D-Ala-Gly-Gly·HCl is an example of the general procedures used.

**D-Ala-Gly-Gly-OBzl·HCl.** A suspension of D-Ala-Gly-Gly (5.0 g, 24.6 mmol) in benzyl alcohol (75 mL) was cooled to 0 °C, and anhydrous HCl gas was bubbled through the mixture for 30 min. The resulting solution was stored at ∼−30 °C overnight. The mixture was concentrated in vacuo and the resulting oil crystallized upon the addition of methanol (∼25 mL). The solid was isolated by filtration, coevaporated with water (2 × 250 mL) to remove residual methanol, and finally coevaporated with toluene (2 × 250 mL). This treatment afforded 7.10 g (88% yield) of the benzyl ester as a white powder: $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.38 (d, $J$ = 6.8 Hz, 3H), 3.81−3.95 (m, 5H), 5.14 (s, 2H), 7.38 (s, 5H), 8.33 (br s, 3H), 8.57 (t, $J$ = 5.6 Hz, 1H), 8.84 (t, $J$ = 5.5 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 16.8 (q), 40.6 (t), 41.8 (t), 48.2 (d), 65.7 (t), 127.8 (d), 128.0 (d), 128.4 (d), 135.8 (s), 168.9 (s), 169.5 (s), 169.8 (s); MS (EI) $m/z$ 300 $(M + Li)^+$.

**Boc-Gly-Ala.** To a solution of Gly-Ala (25.0 g, 171 mmol) in THF (350 mL) and 0.5 N sodium hydroxide (350 mL) at 0 °C was added $(Boc)_2O$ (41.3 g, 189 mmol). The pH was maintained at ∼10 over a 5 h period (with 1.0 N sodium hydroxide) and the reaction was stirred for 12 h thereafter at room temperature. The pH was again adjusted to ∼10 with 1.0 N sodium hydroxide, the THF layer was separated, and the aqueous solution was washed with ethyl acetate (2 × 250 mL). The pH was adjusted to 3.0 with 1.0 N sodium bisulfate, and this solution was extracted with ethyl acetate (2 × 250 mL). The combined extracts were dried (magnesium sulfate), filtered, and concentrated in vacuo to afford 38.2 g (91% yield) of the product as a white powder: $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.26 (d, $J$ = 7.3 Hz, 3H), 1.38 (s, 9H), 3.45−3.62 (m, 2H), 4.18−4.25 (m, 1H), 6.88 (t, $J$ = 5.6 Hz, 1H), 7.99 (d, $J$ = 7.2 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 17.8 (q), 28.6 (q), 43.4 (t), 47.9 (d), 78.5 (s), 156.2 (s), 169.5 (s), 174.5 (s). HRMS (FAB): $m/z$ calcd for $C_{10}H_{19}N_2O_5$ $(M + H)^+$, 247.1294; found, 247.1324 $(M + H)^+$.

**Boc-Gly-Ala-D-Ala-Gly-Gly-OBzl.** To a solution of Boc-Gly-Ala (10.2 g, 41.5 mmol) in anhydrous DMF (300 mL), was added HOBT·$H_2O$ (6.21 g, 46.0 mmol), EDC·HCl (8.81 g, 46.0 mmol) and DAla-Gly-Gly-OBzl·HCl (13.7 g, 41.5 mmol). The "pH" of the resulting solution was adjusted to ∼8 (measured by spotting the reaction mixture on moistened Hydrion paper), and the reaction mixture was allowed to stir at room temperature for 12 h thereafter. The solution was concentrated in vacuo, and the residue was dissolved in water (40 mL). The resulting solution was extracted with ethyl acetate (3 × 150 mL). The combined ethyl acetate layers were washed with 1 N sodium bisulfate (100 mL), saturated sodium bicarbonate (100 mL), and brine (100 mL). The ethyl acetate solution was dried (magnesium sulfate), filtered, and concentrated to half-volume. The product crystallized out upon standing at room temperature for 30 min. Collection of the crystals by filtration and drying at high vacuum afforded 17.4 g (80% yield) of the pure product: $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.21 (d, $J$ = 7.4 Hz, 3H), 1.23 (d, $J$ = 7.3 Hz, 3H), 1.38 (s, 9H), 3.56 (d, $J$ = 6.3 Hz, 2H), 3.75 (d, $J$ = 5.7 Hz, 2H), 3.93 (d, $J$ = 6.0 Hz, 2H), 4.24−4.34 (m, 2H), 5.14 (s, 2H), 6.98 (t, $J$ = 5.7 Hz, 1H), 7.34−7.40 (m, 5H), 7.93 (d, $J$ = 7.2 Hz, 1H), 8.17−8.24 (m, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 17.7 (q), 18.2 (q), 28.1 (q), 40.6 (t), 41.8 (t), 43.2 (t), 48.1 (d), 48.3 (d), 65.8 (t), 78.1 (s), 127.8 (d), 128.0 (d), 128.3 (d), 135.8 (s), 155.8 (s), 169.1 (s), 169.3 (s), 169.5 (s), 172.1 (s), 172.3 (s).

**Gly-Ala-D-Ala-Gly-Gly·HCl (19d).** To Boc-Gly-Ala-D-Ala-Gly-Gly-OBzl (17.2 g, 33.0 mmol) in glacial acetic acid (480 mL) was added 6 N HCl (120 mL), and the reaction mixture was stirred at room temperature for 24 h. Concentration in vacuo followed by coevaporation with water (2 × 250 mL) and toluene (2 × 250 mL) afforded 12.9 g of the product as a white powder: $^1$H NMR (300 MHz, $D_2O$) $\delta$ 1.36 (d, $J$ = 6.9 Hz, 3H), 1.38 (d, $J$ = 7.2 Hz, 3H), 3.84 (s, 2H), 3.96 (s, 2H), 3.99 (m, 2H), 4.30−4.36 (m, 2H); $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 19.2 (q), 19.4 (q), 43.2 (t), 43.8 (t), 45.2 (t), 52.7 (d), 52.8 (d), 169.7 (s), 174.6 (s), 175.8 (s), 175.9 (s), 177.7 (s), 178.2 (s). HRMS (FAB): $m/z$ 332 calcd for $C_{12}H_{21}N_5O_6$ $(M + H)^+$, 332.1570; found, 1554 $(M + H)^+$.

**General Procedure I: The Solution Phase Synthesis of Cyclic Pentapeptides.** Pentapeptide cyclizations were carried out according to the procedure of reference 12 with slight temperature and time modifications. The synthesis of cyclo-(Gly-D-Ala-Ala-Gly-Gly-) outlined below is an example of general procedure I.

**Cyclo-(Gly-Ala-D-Ala-Gly-Gly-) (20d).** To a solution of Gly-Ala-D-Ala-Gly-Gly·HCl (12.9 g, 35.0 mmol) in anhydrous DMF (4400 mL) was added enough TEA to adjust the "pH" to ∼8 (measured by spotting the reaction mixture on moistened Hydrion paper), and the resulting mixture was cooled to −50 °C. To this mixture was added DPPA (9.20 mL, 43.0 mmol) dropwise over 5 min. The reaction was stored at −25 °C (external temperature bath) for 48 h thereafter. During this time the "pH" was monitored periodically (as described above) and maintained at ∼8 by the addition of TEA. After this time the reaction mixture was allowed to stand at 0 °C for 48 h. Again the "pH" was monitored periodically and maintained at ∼8 by the addition of TEA. After this time the reaction mixture was diluted with water (4400 mL) and stirred with Bio-Rad AG 501-X8 (mixed-bed) resin (200 g) for 6 h. The resin was separated by filtration, and the solution was concentrated to dryness. Trituration of the residue with refluxing THF (250 mL) for 3 h, filtration of the hot THF, and drying at high vacuum afforded 6.61 g (60% yield) of the product as a white powder: mp 291−293 dec; $^1$H NMR (400 MHz, DMSO-$d_6$), one major conformer present, $\delta$ 1.15−1.32 (m, 6H), 3.45−4.00 (m, 6H), 4.10−4.38 (m, 2H), 7.81 (d, $J$ = 7.8 Hz, 1H), 7.97 (t, $J$ = 6.6 Hz, 1H), 8.10 (m, 2H), 8.18 (d, $J$ = 7.5 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 16.7 (q), 17.0 (q), 42.8 (t), 43.0 (t), 47.7 (d), 48.6 (d), 168.9 (s), 169.1 (s), 169.4 (s), 171.5 (s), 172.3 (s). HRMS (FAB): $m/z$ 314.1415 $(M + H)^+$, 314.1464 calcd for $C_{12}H_{20}N_5O_5$ $(M + H)^+$.

**Cyclo-(Gly-Ala-Ala-Gly-Gly-) (20e).** Prepared according to general procedure I, Gly-Ala-Ala-Gly-Gly·HCl (9.40 g, 25.6 mmol) afforded 4.2 g (52% yield) of cyclo-(Gly-Ala-Ala-Gly-Gly-) as a white powder: $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.15−1.30 (m, 6H), 3.31−4.32 (m, 8H), 7.78−8.33 (m, 5H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 17.36 (q), 17.52 (q), 42.86 (t), 42.58 (t), 43.27 (t), 47.71 (d), 50.27 (d), 168.72 (s), 168.17 (s), 168.29 (s), 171.95 (s), 172.07 (s); MS (FAB) $m/z$ 320 $(M + Li)^+$. HRMS (EI): $m/e$ calcd for $C_{12}H_{19}N_5O_5$ $(M^{\bullet+})$, 313.1386; found, 313.1398.

**Cyclo-(Gly-Ala-Gly-D-Ala-Gly-) (20f).** Prepared according to general procedure I, Gly-Ala-Gly-D-Ala-Gly·HCl (9.70 g, g, 26.4 mmol) afforded 5.00 g (60% yield) of cyclo-(Gly-Ala-Gly-D-Ala-Gly-) as a white powder: mp >300 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.16−1.25 (m, 6H), 3.38−4.23 (m, 8H), 7.55 (t, $J$ = 5.6 Hz, 1H), 7.60 (t, $J$ = 5.4 Hz, 1H), 8.20−8.25 (m, 1H), 8.40 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 16.6 (q), 16.9 (q), 42.9 (t), 43.0 (t), 43.3 (t), 49.3

(d), 49.5 (d), 169.7 (s), 169.8 (s), 169.9 (s), 172.3 (s), 172.6 (s); MS (FAB) *m*/*z* 320 $(M + Li)^+$. HRMS (EI): *m*/*z* calcd for $C_{12}H_{19}N_5O_5$ ($M^{\bullet+}$), 313.1386; found, 313.1391.

**Cyclo-(Gly-Ala-Gly-Ala-Gly-) (20g).** Prepared according to general procedure I, Gly-Ala-Gly-Ala-Gly·HCl (7.52 g, 20.5 mmol) afforded 2.30 g (36% yield) of cyclo-(Gly-Ala-Gly-Ala-Gly-) as a white powder: $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.17−1.24 (m, 6H), 3.35−3.94 (m, 6H), 4.05−4.36 (m, 2H), 7.75−8.35 (m, 5H); MS (FAB) *m*/*z* 320 $(M + Li)^+$.

**Cyclo-(Gly-Ala-D-Ala-Ala-Gly-) (20h).** Prepared according to general procedure I, Gly-Ala-D-Ala-Ala-Gly·HCl (7.94 g, 20.8 mmol) afforded 2.34 g (33% yield) of cyclo-(Gly-Ala-D-Ala-Ala-Gly-) as a white powder: $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.35−1.10 (m, 9H), 4.43−3.40 (m, 7H), 7.77 (d, $J$ = 7.7 Hz, 1H), 8.00 (coincidental d, $J$ = 5.9 Hz, 2H), 8.11 (d, $J$ = 6.7 Hz, 1H), 8.28 (m, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 16.5 (q), 16.6 (q), 17.3 (q), 43.0 (d), 43.3 (d), 47.6 (d), 47.7 (d), 48.7 (d), 168.6 (s), 169.1 (s), 171.4 (s), 171.9 (s), 172.6 (s). HRMS (FAB): *m*/*z* calcd for $C_{13}H_{21}N_5O_5Li$, 334.1703; found, 334.1734 $(M + Li)^+$.

**Cyclo-(Gly-Ala-D-Ala-Ala-D-Ala-) (20j).** Prepared according to general procedure I, Gly-Ala-D-Ala-Ala-D-Ala·HCl (15.6 g, 39.4 mmol) afforded 6.13 g (46% yield) of cyclo-(Gly-Ala-D-Ala-Ala-D-Ala-) as a white powder: $^1$H NMR (400 MHz, DMSO) $\delta$ 1.28−1.09 (m, 12H), 3.70−3.64 (m, 2H), 4.40−4.07 (m, 4H), 7.61 (d, $J$ = 7.3 Hz, 1H), 7.76 (d, $J$ = 7.8 Hz, 1H), 8.21 (m, 2H), 8.43 (d, $J$ = 5.9 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 15.5 (q), 16.5 (2 coincidental q), 17.8 (q), 43.0 (t), 47.2 (d), 47.6 (d), 48.0 (d), 49.4 (d), 168.5 (s), 171.1 (s), 171.5 (s), 172.3 (s), 172.6 (s). HRMS (FAB): *m*/*z* calcd for $C_{14}H_{23}N_5O_5Li$, 348.1859; found, 348.1875 $[M + Li]^+$.

**Cyclo-(Ala-Ala-D-Ala-Ala-D-Ala-) (20l).** By use of general procedure I, Ala-Ala-D-Ala-Ala-D-Ala·HCl (7.80 g, 19.0 mmol) afforded 3.59 g (54% yield) of product: $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.05−1.35 (m of overlapping doublets, 15H), 4.04−4.42 (m, 5H), 7.58 (d, $J$ = 7.0 Hz, 1H), 7.83 (d, $J$ = 8.4 Hz, 1H), 8.22 (d, $J$ = 6.2 Hz, 1H), 8.33 (d, $J$ = 7.8 Hz, 1H), 8.49 (d, $J$ = 6.8 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 15.2 (q), 16.7 (q), 17.0 (q), 17.4 (q), 47.1 (d), 47.4 (d), 48.1 (d), 48.5 (d), 49.9 (d), 171.0 (s), 171.4 (s), 171.8 (s), 172.0 (s), 172.1 (s). HRMS (FAB): *m*/*z* calcd for $C_{15}H_{25}N_5O_5$ $(M + H)^+$, 356.1934; found, 356.1989 $(M + H)^+$.

**General Procedure II: The Reduction of Cyclic Peptides. (2*S*,5*R*)-Dimethyl-1,4,7,10,13-pentaazacyclopentadecane (1d).** An oven-dried 500 mL flask containing a glass stir bar was allowed to cool to room temperature under argon flow and charged with cyclo-(Gly-Ala-D-Ala-Gly-Gly-) (5.10 g, 16.3 mmol) and THF (74.0 mL). To this stirred suspension was added 1.0 M $LiAlH_4$ in THF (196 mL, 196 mmol) dropwise over 10 min. The suspension was stirred for 1 h at room temperature and became homogeneous during this time. The mixture was then refluxed for 48 h. The mixture was cooled to ∼−20 °C and quenched (cautiously) with saturated sodium sulfate (50 mL). The resulting mixture was concentrated in vacuo to a dry white powder, and this mixture was triturated with methylene chloride (3 × 100 mL).[27] The combined triturates were concentrated in vacuo and the resulting residue was recrystallized from acetonitrile and then from hexanes to afford 2.23 g (56% yield) of the pure product as a white solid: mp 114−116 °C; $[\alpha]_d^{20}$ = −4.76 (*c* = 0.008, methanol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.99 (d, $J$ = 6.0 Hz, 3H), 1.00 (d, $J$ = 6.3 Hz, 3H), 1.82 (bs, 5H), 2.08 (apparent t, $J$ = 10.7 Hz, 1H), 2.30 (dd, $J$ = 11.3, 10.0 Hz, 1H), 2.45−2.95 (m, 16H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.8 (q), 18.9 (q), 46.7 (t), 48.3 (t), 48.4 (t), 48.5 (t), 48.7 (t), 48.9 (t), 54.0 (t), 54.2 (t), 54.8 (d), 56.1 (d). HRMS (FAB): *m*/*z* calcd for $C_{12}H_{29}N_5$ $(M+ H)^+$, 244.2501; found, 244.2516 $(M + H)^+$. Anal. Calcd for $C_{12}H_{29}N_5$: C, 59.22; H, 12.01; N, 28.77. Found: C, 58.76; H, 11.96; N, 28.46. Note: methylene chloride appears to be the best solvent for full extractive recovery of the products from the solid residue. In some instances the polyamine products have reacted with chlorinated solvents such as methylene chloride affording lower yields and complicating purifications.

(27) Methylene chloride appears to be the best solvent for complete extractive recovery of the products from the solid residue. In some instances the polyamine products react with polychlorinated solvents such as methylene chloride, affording lower yields and complicating purifications. In these cases THF can be substituted.

**(2*S*,5*S*)-Dimethyl-1,4,7,10,13-pentaazacyclopentadecane (1e).** By use of general procedure II, cyclo-(Gly-Ala-Ala-Gly-Gly-) (3.23 g, 10.3 mmol) afforded 1.62 g (65% yield) of (2*S*,5*S*)-dimethyl-1,4,7,10,13-pentaazacyclopentadecane after recrystallization from acetonitrile: $[\alpha]_d^{20}$ = +70.0 (*c* = 0.010, methanol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.95 (d, $J$ = 6.0 Hz, 3H), 0.97 (d, $J$ = 6.0 Hz, 3H), 1.76 (bs, 5H), 2.32 (apparent t, $J$ = 9.9 Hz, 1H), 2.44 (m, 1H), 2.53−2.86 (m, 16H); $^{13}$C NMR (75.0 MHz, $CDCl_3$) $\delta$ 18.5 (q, two coincidental), 46.4 (t), 48.2 (t), 48.5 (t, two coincidental), 48.7 (t), 48.8 (t), 51.6 (t), 52.1 (d), 52.3 (d), 55.6 (t). Anal. Calcd for $C_{12}H_{29}N_5$: C, 59.22; H, 12.01; N, 28.77. Found: C, 59.21; H, 12.01; N, 28.71.

**(2*S*,8*R*)-Dimethyl-1,4,7,10,13-pentaazacyclopentadecane (1f).** By use of general procedure II, *cyclo*-(Gly-Ala-Gly-D-Ala-Gly-) (4.00 g, 12.8 mmol) afforded 1.22 g (39%) of (2*S*,8*R*)-dimethyl-1,4,7,10,13-pentaazacyclopentadecane after acetonitrile recrystallization: mp = 130−132 °C; $[\alpha]_d^{20}$ = +2.73 (*c* = 0.011, methanol); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.95 (d, $J$ = 6.2 Hz, 6H), 1.79 (bs, 5H), 2.31 (apparent q, $J$ = 12.0 Hz, 2H), 2.50−2.84 (m, 16H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 18.59 (q), 18.63 (q), 46.14 (t), 46.36 (t), 48.65 (t), 48.77 (t), 48.86 (t), 49.02 (t), 52.67 (d), 52.70 (d), 55.90 (t), 55.93 (t); MS (FAB) *m*/*z* 250 $(M + Li)^+$. Anal. Calcd for $C_{12}H_{29}N_5$: C, 59.22; H, 12.01; N, 28.77. Found: C, 58.71; H, 11.95; N, 28.50.

**(2*S*,8*S*)-Dimethyl-1,4,7,10,13-pentaazacyclopentadecane (1g).** By use of general procedure II, cyclo-(Gly-Ala-Gly-Ala-Gly-) (1.59 g, 5.10 mmol) afforded 777 mg (63% yield) of (2*S*,8*S*)-dimethyl-1,4,7,10,13-pentaazacyclopentadecane after recrystallization from acetonitrile: $[\alpha]_d^{20}$ = +51.0 (*c* = 0.020, methanol); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.00 (d, $J$ = 2 Hz, 3H), 1.02 (d, $J$ = 2.0 Hz, 3H), 2.33 (d of t, $J$ = 18.0, 10.4 Hz, 2H), 2.48 (apparent q, $J$ = 9.2 Hz, 1H), 2.53−2.80 (m, 12H), 2.81−2.95 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 56.2 (t), 55.6 (t), 53.2 (d), 53.1 (d), 49.3 (t), 49.0 (t), 48.9 (t), 48.6 (t), 47.2 (t), 46.4 (t), 18.8 (q, two coincidental). HRMS (FAB): *m*/*z* calcd for $C_{12}H_{29}N_5$, 250.2583; found, 250.2446 $(M + Li)^+$.

**(2*S*,5*R*,8*S*)-Trimethyl-1,4,7,10,13-pentaazacyclopentadecane (1h).** By use of general procedure II, cyclo-(Gly-Ala-D-Ala-Ala-Gly-) (1.63 g, 5.00 mmol) afforded 940 mg (71% yield) of (2*S*,5*R*,8*S*)-trimethyl-1,4,7,10,13-pentaazacyclopentadecane after two recrystallizations from acetonitrile: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.98 (m, 9H), 1.87−2.12 (broad m, 8H), 2.30 (apparent t, $J$ = 10.0 Hz, 1H), 2.44−2.80 (m, 9H), 2.81−2.87 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 18.8 (q), 18.9 (q), 19.0 (q), 46.4 (t), 48.4 (t), 48.6 (t), 48.6 (t), 53.9 (d), 54.0 (d), 54.8 (d), 54.8 (t), 55.2 (t), 55.8 (t). HRMS (FAB): *m*/*z* calcd for $C_{13}H_{31}N_5$, 258.2658; found, 258.2665 $(M + H)^+$.

**(2*S*,5*R*,8*S*,11*R*)-Tetramethyl-1,4,7,10,13-pentaazacyclopentadecane (1j).** By use of general procedure II, cyclo-(Gly-Ala-D-Ala-Ala-D-Ala-) (5.53 g, 16.2 mmol) afforded 3.10 g (70% yield) of (2*S*,5*R*,8*S*,-11*R*)-tetramethyl-1,4,7,10,13-pentaazacyclopentadecane after recrystallization from acetonitrile: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.02 (m, 12H), 2.13 (apparent q, $J$ = 9.0 Hz, 3H), 2.40 (apparent t, $J$ = 9.0 Hz, 1H), 2.52−3.00 (m, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 18.8 (q, two coincidental) 19.1 (q), 19.2 (q), 46.2 (t), 48.7 (t), 53.5 (d), 53.6 (d), 54.8 (d), 54.9 (t), 55.0 (t), 55.1 (d), 55.3 (t), 55.9 (t). HRMS (FAB): *m*/*z* calcd for $C_{14}H_{33}N_5$, 272.2814; found, 272.2808 $(M + H)^+$.

**(2*S*,5*R*,8*S*,11*R*,14*S*)-Pentamethyl-1,4,7,10,13-pentaazacyclopentadecane (1l).** By use of general procedure II, cyclo-(Ala-D-Ala-Ala-D-Ala-Ala-) (3.10 g, 8.7 mmol) afforded 1.10 g (44%) of pure product as a white solid: $[\alpha]_d^{20}$ = +15.70 (*c* 0.020, chloroform); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.00 (d, $J$ = 6.0 Hz, 3H), 1.04 (d, $J$ = 6.9 Hz, 6H), 1.07 (d, $J$ = 6.3 Hz, 6H), 1.98 (br s, 5H), 2.05−2.18 (m, 3H), 2.38−2.95 (m, 12H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.6 (q), 18.8 (q), 19.1 (q), 19.2 (q), 51.5 (t), 52.2 (t), 52.5 (t), 54.3 (t), 54.5 (t), 54.5 (d), 54.6 (d), 54.9 (d), 55.1 (d), 55.4 (d). HRMS (FAB): *m*/*z* calcd for $C_{15}H_{36}N_5$, 286.2971; found, 286.3013 $(M + H)^+$.

***N*-(*p*-Tolylsulfonyl)-2*R*,3*R*-diaminobutane (22).** To a stirred solution of (*R*,*R*)-2,3-diaminobutane (32.8 g, 372 mmol) in $CH_2Cl_2$ (750 mL) at −10 °C was added a solution of *p*-toluenesulfonyl chloride (28.3 g, 149 mmol) in $CH_2Cl_2$ (750 mL) dropwise over a 6 h period, maintaining the temperature at −10 °C. The mixture was allowed to warm to room temperature while being stirred overnight. The mixture was then washed with $H_2O$ (5 × 500 mL) and was dried over $MgSO_4$. Removal of the solvent *in vacuo* gave 34.9 g (97.0% yield) of the product as a white crystalline solid: mp 91−92 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.00 (d, $J$ = 6.4 Hz, 3 H), 1.03 (d, $J$ = 6.6 Hz, 3 H), 2.42

(s, 3 H), 2.70 (br s, 3 H), 2.81 (m, 1 H), 3.03 (m, 1 H), 7.29 (d, $J$ = 9.0 Hz, 2 H), 7.77 (d, $J$ = 8.4 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 18.99, 20.61, 20.53, 50.92, 55.10, 127.08, 129.59, 138.28, 143.09; MS (FAB, NBA matrix) $m/z$ (relative intensity) 243(87) $[M + H]^+$, 249 (100) $[M + Li]^+$. HRMS: $m/z$ calcd for $C_{11}H_{19}N_2SO_2$, 243.1167; found, 243.1182 $(M + H)^+$.

***N*-(*tert*-Butyloxycarbonyl)-*N*′-(*p*-tolylsulfonyl)-2*R*,3*R*-diaminobutane (23).** To a stirred solution of *N*-(*p*-tolylsulfonyl)-2*R*,3*R*-diaminobutane, **22** (52.9 g, 218 mmol), in THF (262 mL) was added a 1 N solution of aqueous NaOH (262 mL, 262 mmol). Di-*tert*-butyl dicarbonate (50.0 g, 229 mmol) was then added, and the resulting two-phase mixture was stirred for 18 h. THF (500 mL) was added, and the layers were separated. The aqueous layer was adjusted to pH 1 with 1 N HCl and then extracted with $CH_2Cl_2$ (1 L). The extract and THF layer were combined and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a yellow crystalline solid which was purified by crystallization from an ethyl ether−hexanes mixture to give 72.4 g (96.9% yield) of the product as a white crystalline solid: mp: 121−123 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.98 (d, $J$ = 6.6 Hz, 3 H), 1.11 (d, $J$ = 6.9 Hz, 3 H), 1.43 (s, 9 H), 2.43 (s, 3 H), 3.24 (sextuplet, $J$ = 6.7 Hz, 1 H), 3.58 (sextuplet, $J$ = 6.2 Hz, 1 H), 4.51 (d, $J$ = 7.7 Hz, 1 H), 5.05 (d, $J$ = 2.5 Hz, 1 H), 7.29 (d, $J$ = 8.4 Hz, 2 H), 7.75 (d, $J$ = 8.1 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 18.57, 19.10, 21.50, 28.39, 50.74, 54.93, 126.00, 129.63, 138.34, 143.15, 156.25; MS (FAB, NBA matrix) $m/z$ 349 $[M + Li]^+$. HRMS: $m/z$ calcd for $C_{16}H_{27}N_2SO_4$, 343.1692; found, 343.1669 $(M + H)^+$.

**Methyl 1-*tert*-Butyloxycarbonyl-2*R*,3*R*-dimethyl-4-(*p*-tolylsulfonyl)-3,6-diazaheptan-6-oate (24).** To a stirred solution of *N*-(*tert*-butyloxycarbonyl)-*N*′-(*p*-tolylsulfonyl)-2*R*,3*R*-diaminobutane, **23** (72.0 g, 210 mmol), in anhydrous DMF (780 mL) at 0 °C was added NaH (7.00 g−80% in oil, 234 mmol) and the resulting mixture was stirred for 30 min. A solution of methyl bromoacetate (34.5 g, 231 mmol) in anhydrous DMF (100 mL) was then added dropwise over 30 min, and the heterogeneous mixture was allowed to warm to room temperature while being stirred overnight. After 1 h of stirring, the mixture became yellow and homogeneous. After 17 h of stirring, the solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (1 L) and $H_2O$ (1 L). The layers were separated and the ethyl acetate solution was washed with saturated $NaHCO_3$ solution, $H_2O$, and saturated NaCl solution and was dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. Crystallization by the addition of hexanes gave 9.20 g (10.6% yield) of product containing the (2*S*,3*S*) isomer, OR = +2.0° ($c$ = 1, MeOH), and 77.6 g (89.1% yield) of the desired product as an oil, OR = +10.5° ($c$ = 1, MeOH): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.94 (d, $J$ = 6.7 Hz, 3 H), 1.20 (d, $J$ = 6.4 Hz, 3 H), 1.44 (s, 9 H), 2.44 (s, 3 H), 3.60 (m, 2 H), 3.73 (s, 3 H), 3.87 (d, $J$ = 18.2 Hz, 1 H), 4.11 (d, $J$ = 18.0 Hz, 1 H), 5.01 (br d, $J$ = 5.0 Hz, 1 H), 7.32 (d, $J$ = 7.8 Hz, 2 H), 7.81 (d, $J$ = 8.3 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 16.09, 19.57, 21.57, 28.42, 44.29, 49.26, 52.34, 57.64, 79.26, 127.72, 129.67, 136.92, 143.70, 155.71, 170.86; MS (FAB, NBA matrix) $m/z$ 421 $[M + Li]^+$. HRMS: $m/z$ calcd for $C_{19}H_{30}N_2SO_6Li$, 421.1984; found, 421.1991 $(M + Li)^+$.

**Methyl 2*R*,3*R*-Dimethyl-4-(*p*-tolylsulfonyl)-3,6-diazaheptan-6-oate, TFA Salt, 25.** To a solution of methyl 1-*tert*-butyloxycarbonyl-2*R*,3*R*-dimethyl-4-(*p*-tolylsulfonyl)-3,6-diazaheptan-6-oate, **24** (10.4 g, 25.0 mmol), in $CH_2Cl_2$ (100 mL) was added trifluoroacetic acid (25.0 mL) and the resulting solution was stirred at room temperature for 30 min. The solvent was removed *in vacuo*, and residual trifluoroacetic acid was removed by coevaporation with $CH_2Cl_2$. The resulting oil was triturated with ethyl ether and hexanes (1:1 mixture), and the solvent was decanted. The resulting oil was dried *in vacuo* to give a foam. The trituration was repeated to give 10.61 g of product as a very hygroscopic foam containing trapped trifluoroacetic acid: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.84 (d, $J$ = 6.9 Hz, 3 H), 1.40 (d, $J$ = 6.5 Hz, 3 H), 2.44 (s, 3 H), 3.27 (br s, 1 H), 3.68 (d, $J$ = 18.3 Hz, 1 H), 3.83 (s, 3 H), 3.86−3.99 (m, 1 H), 4.17 (d, $J$ = 18.4 Hz, 1 H), 7.35 (d, $J$ = 8.1 Hz, 2 H), 7.73 (d, $J$ = 8.3 Hz, 2 H), 8.18 (br s, 3 H); ES MS (1:1 $H_2O$/MeOH−Li) $m/z$ 315 $[M + H]^+$.

**1-*tert*-Butyloxycarbonyl-2*R*,3*R*-dimethyl-4-(*p*-tolylsulfonyl)-3,6-diazaheptanoic Acid (26).** To a stirred solution of methyl 1-*tert*-butyloxycarbonyl-2*R*,3*R*-dimethyl-4-(*p*-tolylsulfonyl)-3,6-diazaheptan-6-oate, **24** (25.0 g, 60.3 mmol), in MeOH (500 mL) was slowly added a 1.0 N solution of aqueous NaOH (90.5 mL, 90.5 mmol), and the resulting solution was stirred for 3 h. The solvent was removed in vacuo, and the residue was dissolved in $H_2O$ (1.0 L). The solution was washed with ether (2 × 500 mL); the pH of the aqueous solution was then adjusted to 2 with 0.1 N HCl. The product was extracted with ethyl acetate (1 L), and the ethyl acetate layer was washed with $H_2O$ and saturated NaCl solution and was dried over $MgSO_4$. The solvent was removed in vacuo to give 19.5 g (80.8% yield) of the product as an off-white foam: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.88 (d, $J$ = 6.6 Hz, 3 H), 1.20 (br d, $J$ = 4.2 Hz, 3 H), 1.45 (s, 9 H), 2.44 (s, 3 H), 3.66 (m, 2 H), 3.80 (m, 2 H), 4.84 (br s, 1 H), 6.70 (br s, 1 H), 7.32 (d, $J$ = 8.1 Hz, 2 H), 7.77 (d, $J$ = 8.4 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 15.55, 19.13, 21.56, 28.42, 44.99, 58.17, 127.68, 129.81, 136.15, 143.94, 156.62, 172.85; MS (CI, $CH_4$) $m/z$ 401 $[M + H]^+$. HRMS: $m/z$ calcd for $C_{18}H_{28}N_2SO_6Li$, 407.1827; found, 407.1811 $(M + Li)^+$.

**Methyl 1-*tert*-Butyloxycarbonyl-2*R*,3*R*,8*R*,9*R*-tetramethyl-4,10-bis(*p*-tolylsulfonyl)-6,12-dioxa-1,4,7,10-tetraazadodecan-12-oate (27).** To a stirred solution of 1-*tert*-butyloxycarbonyl-2*R*,3*R*-dimethyl-4-(*p*-tolylsulfonyl)-3,6-diazaheptanoic acid, **26** (10.0 g, 25.0 mmol), in anhydrous DMF (280 mL) was added HOBT·$H_2O$ (4.05 g, 30.0 mmol) and EDC·HCl (5.75 g, 30.0 mmol). After the resulting solution was stirred for 30 min at room temperature, methyl 2*R*,3*R*-dimethyl-4-(*p*-tolylsulfonyl)-3,6-diazaheptan-6-oate, TFA salt, **25**, as the impure oil (10.6 g, 25.0 mmol) was added and the pH adjusted to 8 with TEA. After 18 h of stirring, the solvent was removed *in vacuo*. The residue was dissolved in a mixture of ethyl acetate (1 L) and $H_2O$ (500 mL) and the layers were separated. The ethyl acetate solution was washed with 0.1 N HCl, a saturated $NaHCO_3$ solution, and a saturated NaCl solution and was dried over $MgSO_4$. The solvent was removed *in vacuo* to give 14.7 g (84.5% yield) of the product as a tan foam: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.81 (d, $J$ = 6.9 Hz, 3 H), 0.93 (d, $J$ =7.0 Hz, 3 H), 1.28 (d, $J$ = 6.8 Hz, 3 H), 1.37 (d, $J$ = 6.7 Hz, 3 H), 1.40 (s, 9 H), 2.42 (s, 3 H), 2.44 (s, 3 H), 3.43 (d, $J$ = 16.4 Hz, 1 H), 3.60−3.71 (m, 2 H), 3.80 (s, 3 H), 3.88−3.90 (m, 2 H), 4.09−4.14 (m, 3 H), 4.32 (d, $J$ = 17.9 Hz, 1 H), 6.30 (br s, 1 H), 7.27−7.36 (m, 4 H), 7.69 (d, $J$ = 8.3 Hz, 2 H), 7.81(d, $J$ = 8.4 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 15.18, 15.56, 18.99, 19.33, 21.56, 28.45, 44.57, 47.08, 48.68, 50.19 (br), 52.51, 57.72, 127.33, 127.73, 129.77, 129.90, 135.98, 136.11, 143.83, 143.96, 156.00, 169.85, 172.87; MS (ES, 1:1 $H_2O$/MeOH−Li): $m/z$ 703 $[M + Li]^+$. HRMS: $m/z$ calcd for $C_{32}H_{49}N_4S_2O_9$, 697.2941; found, 697.2957 $(M + H)^+$.

**Methyl 2*R*,3*R*,8*R*,9*R*-Tetramethyl-4,10-bis(*p*-tolylsulfonyl)-6,12-dioxa-1,4,7,10-tetraazadodecan-12-oate, TFA Salt (28).** To a stirred solution of methyl 1-*tert*-butyloxycarbonyl-2*R*,3*R*,8*R*,9*R*-tetramethyl-4,10-bis(*p*-tolylsulfonyl)-6,12-dioxa-1,4,7,10-tetraazadodecan-12-oate, **27** (14.4 g, 20.7 mmol), in $CH_2Cl_2$ (80.0 mL) was added trifluoroacetic acid (19.1 mL), and the resulting solution was stirred at room temperature for 30 min. The solvent was removed *in vacuo*, and the residual trifluoroacetic acid was coevaporated with $CH_2Cl_2$ (6 × 1 L), drying *in vacuo* each time. The foam was then dried *in vacuo* overnight to give 16.6 g of the impure product as a tan foam: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.84 (d, $J$ = 7.0 Hz, 3 H), 0.87 (d, $J$ = 9.5 Hz, 3 H), 1.36 (d, $J$ = 6.3 Hz, 3 H), 1.41 (d, $J$ = 5.9 Hz, 3 H), 2.44 (s, 6 H), 3.33−3.39 (m, 1 H), 3.58−3.78 (m, 4 H), 3.82 (s, 3 H), 3.87−4.06 (m, 3 H), 7.34 (d, $J$ = 7.0 Hz, 4 H), 7.60 (d, $J$ = 6.8 Hz, 1 H), 7.71 (d, $J$ = 8.1 Hz, 2 H), 7.77 (d, $J$ = 8.1 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.08, 15.09, 15.75, 17.96, 21.54, 44.15, 45.80 (br), 50.16, 50.46, 52.74, 56.64 (br), 57.09, 109.95, 113.78, 117.61, 121.43, 127.12, 127.51, 129.99, 130.30, 135.78, 135.84, 144.38, 144.85, 160.03, 160.53, 161.05, 161.56, 171.29, 172.67; MS (ES, 1:1 $H_2O$/MeOH−Li) $m/z$ 597 $[M + H]^+$.

**Methyl 1-*tert*-Butyloxycarbonyl-5*R*,6*R*,11*R*,12*R*-tetramethyl-7,-13-bis(*p*-tolylsulfonyl)-3,9-dioxa-1,4,7,10,13-pentaazapentadecan-15-oate (29).** To a stirred solution of *N*-*tert*-butyloxycarbonylglycine (3.62 g, 20.7 mmol) in anhydrous DMF (200 mL) were added HOBT·$H_2O$ (3.35 g, 24.8 mmol) and EDC·HCl (4.75 g, 24.8 mmol). After the resulting solution was stirred for 30 min at room temperature, methyl 2*R*,3*R*,8*R*,9*R*-tetramethyl-4,10-bis(*p*-tolylsulfonyl)-6,12-dioxa-1,4,7,10-tetraazadodecan-12-oate, TFA salt, **28**, as the impure solid (16.5 g, 20.7 mmol) was added in degassed anhydrous DMF (30 mL) and the pH adjusted to 8 with TEA. After stirring for 16 h, the solvent was removed in vacuo. The residue was dissolved in a mixture of ethyl acetate (1 L) and $H_2O$ (500 mL) and the layers were separated. The

ethyl acetate solution was washed with 0.1 N HCl, a saturated $NaHCO_3$ solution, and a saturated NaCl solution and was dried over $MgSO_4$. The solvent was removed *in vacuo* to give 15.0 g of the product as a tan foam. The crude product was purified by flash chromatography using silica gel and 97:3 $CHCl_3$−MeOH mixture as eluent. The fractions containing the product were combined and the solvent was removed *in vacuo* to give 10.7 g (68.9% yield) of the product as a tan foam: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.74 (d, $J$ = 6.9 Hz, 3 H), 0.93 (d, $J$ = 6.8 Hz, 3 H), 1.30 (d, $J$ = 6.8 Hz, 3 H), 1.38 (d, $J$ = 6.4 Hz, 3 H), 1.42 (s, 9 H), 2.42 (s, 3 H), 2.44 (s, 3 H), 3.41 (d, $J$ = 16.1 Hz, 1 H), 3.58−3.78 (m, 4 H), 3.81 (s, 3 H), 3.87−4.05 (m, 4 H), 4.29 (d, $J$ = 17.9 Hz, 1 H), 5.26 (br s, 1 H), 7.30−7.35 (m, 4 H), 7.43 (d, $J$ = 8.1 Hz, 1 H), 7.67 (d, $J$ = 8.3 Hz, 2 H), 7.80 (d, $J$ = 8.3 Hz, 2 H), 8.54 (br d, $J$ = 7.7 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.77, 15.48, 18.89, 21.51, 21.54, 28.34, 44.31 (br), 44.51, 47.07, 48.77, 49.01, 52.55, 57.60, 57.84, 70.45, 127.19, 127.62, 129.83, 129.93, 135.86, 135.92, 143.99, 144.03, 155.95, 169.44, 170.03, 173.02; MS (FAB, NBA matrix) *m*/*z* 760 $[M + Li]^+$. HRMS: *m*/*z* calcd for $C_{34}H_{52}N_5S_2O_{10}$, 754.3156; found, 754.3128 $(M + H)^+$.

**1-*tert*-Butyloxycarbonyl-5*R*,6*R*,11*R*,12*R*-tetramethyl-7,13-bis(*p*-tolylsulfonyl)-3,9-dioxa-1,4,7,10,13-pentaazapentadecan-15-oic Acid (30).** To a stirred solution of methyl 1-*tert*-butyloxycarbonyl-5*R*,6*R*,-11*R*,12*R*-tetramethyl-7,13-bis(*p*-tolylsulfonyl)-3,9-dioxa-1,4,7,10,13-pentaazapentadecan-15-oate, **29** (10.1 g, 13.4 mmol), in MeOH (167 mL) was added a 1.0 N solution of aqueous NaOH (20.2 mL, 20.2 mmol), and the resulting solution was stirred for 8.0 h. The solvent was removed in vacuo, and the residue was dissolved in $H_2O$ (500 mL). The pH was adjusted to 2 with 0.1 N HCl and the solution was then extracted with ethyl acetate (1 L). The layers were separated, and the ethyl acetate layer was washed with $H_2O$ and saturated NaCl solution and was dried over $MgSO_4$. The solvent was removed *in vacuo* to give 9.72 g (97.7% yield) of the product as a colorless foam: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.78 (d, $J$ = 4.6 Hz, 3 H), 0.88 (d, $J$ = 6.7 Hz, 3 H), 1.24−1.38 (m, 6 H), 1.42 (s, 9 H), 2.39 (s, 3 H), 2.43 (s, 3 H), 3.47 (d, $J$ = 16.7 Hz, 1 H), 3.67−4.07 (m, 8 H), 4.12 (d, $J$ = 18.3 Hz, 1 H), 5.43 (br s, 1 H), 7.32 (d, $J$ = 8.1 Hz, 2 H), 7.33 (d, $J$ = 8.1 Hz, 2 H), 7.40 (br d, $J$ = 6.4 Hz, 1 H), 7.71 (d, $J$ = 7.8 Hz, 2 H), 7.77 (d, $J$ = 8.3 Hz, 2 H), 8.12 (br s, 1 H), 9.30 (br s, 1 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.92, 15.19, 18.59, 18.80, 21.52, 21.55, 28.34, 44.33, 45.00, 47.29, 49.04, 49.19, 57.96, 58.11, 79.89, 127.39, 127.53, 129.89, 130.00, 135.63, 135.80, 144.00, 156.20, 170.16, 170.43, 173.64; MS (ES, 1:1 $H_2O$/MeOH−Na) *m*/*z* 762 $[M + Na]^+$. HRMS: *m*/*z* calcd for $C_{33}H_{50}N_5S_2O_{10}$, 740.2999; found, 740.2998 $(M + H)^+$.

**5*R*,6*R*,11*R*,12*R*-Tetramethyl-7,13-bis(*p*-tolylsulfonyl)-3,9-dioxa-1,4,7,10,13-pentaazapentadecan-15-oic Acid, TFA Salt (31).** To a stirred solution of 1-*tert*-butyloxycarbonyl-5*R*,6*R*,11*R*,12*R*-tetramethyl-7,13-bis(*p*-tolylsulfonyl)-3,9-dioxa-1,4,7,10,13-pentaazapentadecan-15-oic acid, **30** (9.72 g, 13.1 mmol), in $CH_2Cl_2$ (100 mL) was added trifluoroacetic acid (13 mL), and the resulting solution was stirred for 30 min. The solvent was removed in vacuo and residual TFA was removed by coevaporation with $CH_2Cl_2$ (5 × 500 mL) to give 10.2 g of impure product as a yellow foam: $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 0.79 (d, $J$ = 6.8 Hz, 3 H), 0.88 (d, $J$ = 6.8 Hz, 3H), 1.10 (d, $J$ = 6.8 Hz, 3 H), 1.15 (d, $J$ = 6.4 Hz, 3 H), 2.40 (s, 3 H), 2.41 (s, 3 H), 3.44−3.48 (m, H), 3.77−3.85 (m, 4 H), 3.87−3.97 (quint., $J$ = 7.3 Hz, 2 H), 4.01 (d, $J$ = 18.1, 1 H), 5.40 (br s, 1 H), 7.39−7.43 (m, 4 H), 7.73−7.78 (m, 5 H), 7.97 (m, 3 H), 8.61 (d, $J$ = 8.3 Hz, 1 H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 14.28, 14.42, 17.22, 18.06, 20.91, 45.00, 46.49, 47.72, 48.07, 56.66, 57.29, 127.16, 127.33, 129.50, 129.62, 136.22, 136.67, 143.18, 143.32, 157.60, 157.93, 158.28, 158.61, 165.06, 169.58, 171.98; MS (FAB, NBA matrix) *m*/*z* 652 $[M + Li]^+$. HRMS: *m*/*z* calcd for $C_{28}H_{42}N_5S_2O_7$, 640.2475; found, 640.2469 $(M + H)^+$.

**1,10-Bis(*p*-tolylsulfonyl)-2*R*,3*R*,11*R*,12*R*-tetramethyl-5,8,14-trioxa-1,4,7,10,13-pentaazacyclopentadecane (32).** A stirred solution of 5*R*,6*R*,11*R*,12*R*-tetramethyl-7,13-bis(*p*-tolylsulfonyl)-3,9-dioxa-1,4,7,-10,13-pentaazapentadecan-15-oic acid, TFA salt, **31** (10.0 g, 13.3 mmol), in degassed anhydrous DMF (3.45 L) was adjusted to pH 8 with TEA. The solution was then cooled to −40 °C, and DPPA (4.56 g, 16.6 mmol) was added over 10 min. The solution was stirred at −40 °C for 5 h and was allowed to stand overnight at −16 °C. The pH was readjusted to 8 with TEA and the solution was cooled to −25 to −30 °C for 8 h. After the pH was readjusted as before, the solution was allowed to warm to −16 °C for 72 h. The pH was readjusted as before and the solution was allowed to warm to −8 °C. After 24 h, the pH had dropped only slightly and was readjusted as before. The solution was allowed to stand at −8 °C for another 24 h, after which time the pH had not changed. After the mixture was allowed to stand at room temperature overnight, the pH had not changed. $H_2O$ (3.45 L) and then mixed-bed ion exchange resin (1.75 kg) were added, and the mixture was stirred for 6 h. The resin was then filtered and washed with 1:1 DMF−$H_2O$, then DMF, and then $H_2O$. The filtrate and washings were combined and the solvent was then removed *in vacuo*. Residual DMF was removed by coevaporation with $H_2O$. The oily residue was triturated with $H_2O$ (500 mL), and the resulting granular solid was dissolved in warm MeOH (500 mL) and filtered to remove haziness. The solvent was removed *in vacuo*, and the crude product (9.1 g) was purified by flash chromatography using silica gel and eluted with a 97:3−95:5 $CHCl_3$−MeOH gradient. The fractions containing the product were combined and the solvent was removed *in vacuo*. Crystallization from $CH_2Cl_2$−hexanes gave 3.95 g (46.0% yield) of the product as colorless needles: mp 170 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.79 (d, $J$ = 6.4 Hz, 3 H), 0.87 (d, $J$ = 7.3 Hz, 3 H), 1.26 (d, $J$ = 5.4 Hz, 3 H), 1.43 (d, $J$ = 7.3 Hz, 3 H), 2.45 (s, 3 H), 2.46 (s, 3 H), 3.58 (m, 4 H), 4.03 (m, 6 H), 6.41 (br d, $J$ = 5.9, 1 H), 7.35 (m, 6 H), 7.71 (d, $J$ = 8.3 Hz, 2 H), 7.78 (d, $J$ = 8.3 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.37, 16.27, 18.36, 19.83, 21.61, 43.03, 47.87, 49.46, 49.57, 49.84, 58.21, 60.30 (br), 127.71, 127.92, 130.03, 130.16, 134.27, 134.31, 144.55, 144.70, 168.52, 169.66, 170.72; MS (FAB, DTT−DTE matrix) *m*/*z* 622 $[M + H]^+$. HRMS: *m*/*z* calcd for $C_{28}H_{40}N_5S_2O_7$, 622.2369; found, 633.2374 $(M + H)^+$.

**2*R*,3*R*,8*R*,9*R*-Tetramethyl-1,4,7,10,13-pentaazacyclopentadecane (1k).** To a stirred solution of 1,10-bis(*p*-tolylsulfonyl)-2*R*,3*R*,-11*R*,12*R*-tetramethyl-5,8,14-trioxa-1,4,7,10,13-pentaazacyclopentadecane, **32** (3.85 g, 6.19 mmol), in anhydrous THF (100 mL) was added dropwise a solution of 1.0 M $LiAlH_4$ in THF (77.4 mL, 77.4 mmol). The yellow homogeneous solution was refluxed for 40 h (by which time it had become heterogeneous) and was then cooled to 0 °C. The mixture was then quenched by the dropwise addition of a saturated $Na_2SO_4$ solution (10 mL) while cooling in an ice bath. Then MeOH (150 mL) was added and the mixture was stirred for 1 h. The solvent was removed *in vacuo*, and the residue was dried by azeotroping with toluene (3 × 500 mL) and then hexanes (3 × 500 mL). The solids were then refluxed with anhydrous hexanes (500 mL) for 5 min, the mixture was filtered, and the solvent was then removed *in vacuo* to give a colorless oil which crystallized on standing. The solids were then extracted as before with ethyl ether (500 mL) and THF (500 mL) and then were refluxed with THF (2 × 500 mL) for 1 and 20 h, respectively. The extracts were combined and the solvent was removed *in vacuo* to give the crude product as a yellow crystalline solid (1.21 g). The residue was extracted with hot hexanes (80 mL) and filtered to remove haziness. The solution was concentrated to a volume of 20 mL and cooled to crystallize the product, which upon recrystallization from hexanes gave 650 mg (38.7% yield) of the ligand as colorless needles: mp 110−111 °C; $^1$H NMR ($C_6D_6$, 400 MHz) $\delta$ 0.90 (d, $J$ = 6.3 Hz, 6 H), 0.95 (d, $J$ = 6.3 Hz, 6 H), 1.56 (br s, 5 H), 2.11 (m, 2 H), 2.21 (m, 2 H), 2.43 (d, $J$ = 8.3 Hz, 2 H), 2.46 (m, 2 H), 2.54 (m, 2 H), 2.67 (m, 2 H), 2.81 (m, 2 H), 2.85 (d, $J$ = 8.3 Hz, 2 H); $^{13}$C NMR ($C_6D_6$, 100 MHz) $\delta$ 17.47, 17.63, 46.94, 48.24, 49.44, 59.12, 60.12; MS (CI, $CH_4$) *m*/*z* 272 $[M + H]^+$. Anal. Calcd for $C_{14}H_{33}N_5$: C, 61.95; H, 12.25; N, 25.80. Found: C, 61.97; H, 12.22; N, 25.81.

**3,6,9,12,18-Pentaazabicyclo[12.3.1]octadeca-1(18),14,16-triene (4).** This compound was prepared according to the procedure of ref 25, with the exception that the detosylation using $H_2SO_4$ was found to be cleaner at 100 °C than at 110 °C. $^1$H NMR ($C_6D_6$) $\delta$ 2.51 (s, 4H), 2.70 (m, 8H), 0.6−3.6 (v br s, 4H), 3.78 (s, 4H), 6.60 (d, $J$ = 7.6 Hz, 2H), 7.00 (t, $J$ = 7.7 Hz, 1H); $^{13}$C NMR ($C_6D_6$) $\delta$ 48.97, 49.25, 49.47, 54.74, 120.26, 136.12, 159.99.

**Synthesis of Complexes. Dichloro[(1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2a).** Complex **2a** was prepared as described in ref 1.

**Dichloro(*R*-2-methyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2b).** A solution of (*R*)-2-methyl-1,4,7,10,13-pentaazacyclopentadecane, **1b** (0.600 g, 2.6 mmol), was added to a methanolic solution (50 mL) containing 0.33 g (2.6 mmol) of anhydrous manganese(II) chloride. The solution was refluxed under a dry nitrogen

atmosphere for 1 h and then stirred for an additional 12 h at room temperature. After cooling, the solution was taken to dryness and the solid mass was dissolved in 20 mL of a hot (~60 °C) 1:1 ethanol/THF solvent mixture. The solution was filtered through CELITE and concentrated *in vacuo*. Ethyl ether was added to the warm solution until the solution turned cloudy and the solution was allowed to sit undisturbed for several hrs. White crystals were collected by filtration, washed with ether, and dried to give 680 mg (73% yield) of a white crystalline solid: $[\alpha]_d^{20} = -21.0°$ ($c = 0.005$, methanol); MS (FAB, NBA matrix) *m*/*z* (relative intensity): 354 ($M^+$, 2), 319 [$(M - Cl)^+$, 100], 321 (30). Anal. Calcd for $C_{11}H_{27}Cl_2MnN_5$: C, 37.30; H, 7.40; N, 19.77. Found: C, 36.72; H, 7.69; N, 18.82.

**Dichloro(*trans*,*rac*-2,3-dimethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2c).** To a hot methanol solution of anhydrous manganese (II) chloride (383 mg, 3.04 mmol) was added *trans*-2,3-dimethyl-1,4,7,10,13-pentaazacyclopentadecane, **1c** (740 mg, 3.04 mmol), under a dry atmosphere. The mixture was refluxed for 1 h and then stripped to dryness. The residue was taken up in hot THF and filtered through CELITE. The filtrate was concentrated *in vacuo* to a volume of 5 mL. Ether was added to the warm solution in order to precipitate a white solid which was collected by filtration. After the solid was dried *in vacuo*, a yield of 0.81 g (72%) was obtained. MS (FAB, NBA matrix): *m*/*z* 333 $(M - Cl)^+$. Anal. Calcd for $C_{12}H_{29}N_5Cl_2Mn$: C, 39.03; H, 7.92; N, 18.97; Cl, 19.20. Found: C, 38.95; H, 7.96; N, 18.88; Cl, 19.25.

Using the methodology described for complex **2c** (unless otherwise specified), the following complexes were prepared:

**Dichloro(2*S*,5*R*-dimethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2d).** Starting with 0.367 g of ligand **1d** a yield of 0.34 g (61%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 333 $(M - Cl)^+$. Anal. Calcd for $C_{12}H_{29}N_5Cl_2Mn$: C, 39.03; H, 7.92; N, 18.97. Found: C, 39.26; H, 7.96; N, 19.00.

**Dichloro(2*S*,5*S*-dimethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2e).** Starting with 0.492 g of ligand **1e**, a yield of 0.37 g (51%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 333 $(M - Cl)^+$. Anal. Calcd for $C_{12}H_{29}N_5Cl_2Mn$: C, 39.03; H, 7.93; N, 18.97. Found: C, 39.12; H, 7.91; N, 19.00.

**Dichloro(2*S*,8*R*-dimethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2f).** Starting with 0.61 g of ligand **1f**, a yield of 0.32 g (34%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 333 $(M - Cl)^+$. Anal. Calcd for $C_{12}H_{29}N_5Cl_2Mn$: C, 39.03; H, 7.93; N, 18.97; Cl, 19.20. Found: C, 39.40; H, 7.40; N, 18.85; Cl, 19.48.

**Dichloro(2*S*,8*S*-dimethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2g).** Starting with 0.252 g of ligand **1g**, a yield of 0.18 g (47%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 333 $(M - Cl)^+$. Anal. Calcd for $C_{12}H_{29}N_5Cl_2Mn$: C, 39.03; H, 7.93; N, 18.97. Found: C, 38.93; H, 7.95; N, 18.94.

**Dichloro(2*S*,5*R*,8*S*-trimethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2h).** Starting with 0.256 g of ligand **1h**, a yield of 0.246 g (63%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 347 $(M - Cl)^+$. Anal. Calcd for $C_{13}H_{31}N_5Cl_2Mn$: C, 40.74; H, 8.15; N, 18.27. Found: C, 40.66; H, 8.20; N, 18.20.

**Dichloro(2,2,3,3-tetramethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2i).** Starting with 0.55 g of ligand **1i**, a yield of 0.612 g (76%) of the desired complex was obtained using the method of preparation outlined for complex **2a**. The complex crystallized as large colorless needles in a form suitable for X-ray diffraction studies as an ethanol solvate. MS (FAB, NBA matrix): *m*/*z* 361 $(M - Cl)^+$. Anal. Calcd for $C_{14}H_{33}N_5Cl_2Mn{\cdot}C_2H_6O$: C, 43.35; H, 8.87; N, 15.80. Found: C, 43.36; H, 8.90; N, 15.84.

**Dichloro(2*S*,5*R*,8*S*,11*R*-tetramethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2j).** Starting with 1.156 g of ligand **1j**, a yield of 1.00 g (59%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 361 $(M - Cl)^+$. Anal. Calcd for $C_{14}H_{33}N_5Cl_2Mn$: C, 42.32; H, 8.37; N, 17.63. Found: C, 42.22; H, 8.53; N, 17.19.

**Dichloro(2*S*,3*R*,8*S*,9*R*-tetramethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2k).** Starting with 0.469 g of ligand **1k**, a yield of 0.575 g (84%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 361 $(M - Cl)^+$. Anal. Calcd for $C_{14}H_{33}N_5Cl_2Mn$: C, 42.32; H, 8.37; N, 17.63; Cl, 17.85. Found: C, 42.58; H, 8.28; N, 17.05; Cl, 17.36.

**Dichloro(2*S*,5*R*,8*S*,11*R*,14*S*-pentamethyl-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2l).** Starting with 0.177 g of ligand **1l**, a yield of 0.187 g (73%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 375 $(M - Cl)^+$. Anal. Calcd for $C_{15}H_{35}N_5Cl_2Mn$: C, 43.75; H, 8.57; N, 17.01. Found: C, 43.61; H, 8.34; N, 16.84.

**Dichloro(*trans*-2,3-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2m).** Starting with 0.301 g of ligand **1m**, a yield of 0.81 g (82%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 359 $(M - Cl)^+$. Anal. Calcd for $C_{14}H_{31}N_5Cl_2Mn$: C, 42.56; H, 7.93; N, 17.65; Cl, 17.94. Found: C, 42.64; H, 7.93; N, 17.68; Cl, 17.75.

**Dichloro(*trans*-2,3-cyclopentano-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2n).** Starting with 0.124 g of ligand **1n**, a yield of 0.110 g (59%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 345 $(M - Cl)^+$. Anal. Calcd for $C_{13}H_{29}N_5Cl_2Mn$: C, 40.96; H, 7.67; N, 18.37; Cl, 18.60. Found: C, 40.91; H, 7.64; N, 18.27; Cl, 18.64.

**Dichloro(*trans*-2,3-cycloheptano-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2o).** Starting with 0.512 g of ligand **1o**, a yield of 0.549 g (74%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 373 $(M - Cl)^+$. Anal. Calcd for 44.02; H, 8.13; N, 17.11. Found: C, 41.64; H, 7.93; N, 17.01.

**Dichloro(*cis*-2,3-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2p).** Starting with 0.35 g of ligand **1p**, a yield of 0.353 g (69%) of the desired complex was obtained. MS (FAB, NBA matrix): *m*/*z* 359 $(M - Cl)^+$. Anal. Calcd for $C_{14}H_{31}N_5Cl_2Mn$: C, 42.56; H, 7.93; N, 17.65. Found: C, 42.60; H, 8.17; N, 17.38.

**Dichloro(*trans*-(3-*tert*-butylcyclohexano)-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (2q).** Starting with 0.273 g of the ligand **1q**, a yield of 0.340 (90%) of the desired complex **2q** was obtained. MS (FAB, NBA matrix): *m*/*z* 415 $(M - Cl)^+$. Anal. Calcd for $C_{18}H_{39}N_5Cl_2Mn$: C, 47.90; H, 8.71; N, 15.52; Cl, 15.71. Found: C, 47.01; H, 8.42; N, 15.28; Cl, 15.35.

**Dichloro(2,15-pyridino-1,4,7,10,13-pentaazacyclopentadecane)manganese(II) (3).** To a hot methanol solution containing 0.130 g anhydrous $MnCl_2$ (1.035 mmol) was added 258 mg (1.035 mmol) of the free base ligand pyridino[15]aneN$_5$, **5p**, with stirring under $N_2$. The solution was refluxed for an additional hour, and then the solution was taken to dryness and the off-white solid dissolved in hot THF and filtered through CELITE. This THF solution was then reduced in volume to ~10 mL and then warmed while $Et_2O$ was slowly added to induce crystallization. After the addition of ~25 mL of $Et_2O$, the solution remained cloudy. At this point the solution was allowed to sit undisturbed for 16 h. A white crystalline solid formed which was collected by filtration and then washed with $Et_2O$ and dried in vacuo. The yield was 292 mg (75%). MS (FAB, NBA matrix): *m*/*z* (339.33, $M - Cl^+$). Anal. Calcd for $C_{13}H_{23}Cl_2MnN_5$: C, 41.62; H, 6.18; Cl, 18.90; N, 18.67. Found: C, 41.41; H, 6.36; Cl, 18.44; N, 18.44.

**X-ray Crystallographic Studies.** Single crystals of the white complex **2h** were synthesized as described above. Crystals of **2h** are, at 20 ± 1 °C, triclinic, space group $P\bar{1}$-$C_i^1$ (No. 2) with $a = 9.941(2)$ Å, $b = 11.190(2)$ Å, $c = 11.613(2)$ Å, $\alpha = 62.45(2)°$, $\beta = 80.47(2)°$, $\gamma = 81.33(2)°$, $V = 1125.4(4)$ Å$^3$, and $Z = 2$ {$d_{calcd} = 1.308$ g cm$^{-3}$; $\mu_a$(Cu K$\alpha$) = 7.06 mm$^{-1}$}. A total of 3357 independent absorption-corrected reflections having $2\theta$(Cu K$\alpha$) < 120.0° (the equivalent of 0.65 limiting Cu K$\alpha$ spheres) were collected on a computer-controlled Nicolet autodiffractometer using $\theta-2\theta$ scans and nickel-filtered Cu K$\alpha$ radiation. The structure was solved using "direct-methods" techniques with the Siemens SHELXTL-PC software package modified at Crystalytics Co. The resulting structural parameters have been refined to convergence {$R_1$ (unweighted, based on $F$) = 0.051 for 2099 independent absorption-corrected reflections having $2\theta$(Cu K$\alpha$) < 120° and $I > 3\sigma(I)$} using counterweighted full-matrix least-squares techniques and a structural model which incorporated anisotropic thermal parameters for all non-hydrogen atoms and isotropic thermal parameters for all included hydrogen atoms. Hydrogen atoms on the five nitrogen atoms were located from a difference Fourier map and refined as independent isotropic atoms. The four (nonsolvent) methyl groups were included in the structural model as rigid rotors with sp$^3$-hybridized geometry and a C−H bond length of 0.96 Å. The ethanol solvent molecule of crystallization is disordered with two possible orientations in the lattice. The two orientations both have carbon atoms

at or near the positions specified for $C_{1s}$ and $C_{2s}$ but differ in the placement of the hydroxyl group. The major orientation has an oxygen at the position for $O_{1s}$ (85% of the time), and the minor orientation has an oxygen at the position for $O_{1s'}$ (15% of the time). The minor orientation is favorably positioned for forming a hydrogen bond with the hydrogen on $N_3$ ($H_{3n}$).

**Potentiometric Titration Studies.** The free ligand concentration used for all titration studies was between 20 and 30 mM. These solutions were prepared by dissolving the ligand in an appropriate amount of 0.1 M $HClO_4$ solution. The following reagents were utilized: 0.1 M of NaOH (99.99%, Aldrich No. 30657-6), $HClO_4$ (99.999%, Aldrich No. 31142), and $H_3PO_4$ (99.99%, Aldrich No. 34524-5) solutions. The NaOH solution is prepared in boiled Milli-Q, doubly deionized (DDI) water. The concentration is standardized with primary standard potassium hydrogen phthalate (KHP, 99.99% Aldrich No. 17992-2). In addition, the carbonate content of the NaOH solution is determined using a Gran's plot for every new batch of NaOH solution, and the solutions are reprepared after more than a month of storage.[28] NaOH containing less than 1% of carbonate was used for the analysis. Both $HClO_4$ and $H_3PO_4$ solutions were standardized with NaOH reagent. The Mn(II) is prepared as a 0.01 M $MnCl_2$ (99.99%, Aldrich No. 20373-4) solution containing 0.001 M $HClO_4$ (99.99%, Aldrich No. 38122-5, 0.1 M $NaClO_4$) solution is used to maintain the ionic strength of the reaction solution during titration. The titration equipment included an Orion Ross Sure-Flow model 920A pH meter, Orion $H^+$ ion selective glass electrode, Brinkmann Dosimat E635 autotitrator and IBM compatible PC. The titration cell was equipped with temperature control and nitrogen purge setups. The electrode parameters and the slope of the titration curve, which converts the pH reading of each titration point to a hydrogen ion activity, were calibrated daily at the beginning of each study. The ionization constant for each SOD mimic ligand was measured by titrating the free ligand. The thermodynamic stability constant was measured using the manganese-free ligand titration data. A computer software program is facilitated in the system to automate the PC driven titrator. With this software program, parameters, such as starting pH, ending pH, titration increment volume size and pH drift criteria, can be selected. All the data collected from each titration are imported into a preformatted data file for the calculation of electrode parameters, protonation constants (p$K_a$'s) and log $K$ with the FORTRAN program BETA.[29] The program, which is based on the general least squares program ORGLES, calculates and minimizes the standard deviation between the observed and calculated pH values of each titration point for the entire titration range. This refinement was characterized by a goodness-of-fit which was computed using the numerically calculated square reciprocal slope as a weighing factor. The titration system is checked with a known compound, EDTA (100.9%, Fisher No. S311-100), to determine any systematic errors in the procedure. One milliliter of 0.02 M EDTA was added to 8 mL or Milli-Q DDI water containing 1 mL of 1 M $NaClO_4$. The p$K_a$'s of EDTA are 2.00, 2.67, 6.16, and 10.26. This check was performed periodically. The titration system was calibrated each time to obtain the slope coefficient of the electrode. This calibration was performed by adding 1 mL each of $H_3PO_4$ and $NaClO_4$ in 8 mL of DDI water followed by the titration of this solution with the NaOH solution. The goodness-of-fit of this titration had to be less than 0.01 to meet the calibration criteria. The thermodynamic binding constants were determined by the following procedure: 1 mL each of the free ligand solution and $NaClO_4$ in 8 mL of DDI water were mixed together, followed by addition of an appropriate amount of 0.1 M $HClO_4$ to lower the pH of the solution to about 2.5. This solution was then titrated with the NaOH solution up to pH 11.5 to determine the p$K_a$'s of the free ligand. Calculation of the exact amount of the free ligand present was done from the titration curve, and the p$K_a$'s of the ligand using the BETA program were then determined. The determination of the thermodynamic stability constant (log $K$) of each $Mn^{II}(L)$ complex was carried out with the following procedure: the pH of the ligand solution is lowered to about 2.5 by adding 0.1 M $HClO_4$. An appropriate amount of $MnCl_2$ was added to the free ligand solution (the amount of $Mn^{2+}$ added was about 95−98% of free ligand used), and the solution was then titrated with the NaOH solution to pH about 11.5. The thermodynamic stability constant (log $K$) was calculated using the BETA program. To ensure that equilibrium is reached at each of the titration point, a reverse titration is performed by titrating the above solution with 0.1 M $HClO_4$ to pH 2.5. The resultant log $K$ is then calculated and the value compared to that obtained from the forward titration. The difference between the values should be less than 0.1. The averaged log $K$ value of the forward titration and reverse titration was then reported as the log $K$ value for each Mn(L) complex.

**Determination of Kinetic Stabilities of $[Mn^{II}([15]aneN_5)Cl_2]$ Complexes.** A Beckman DU-70 spectrophotometer is utilized to record spectra as a function of time over the wavelength range of 200 nm to 700 nm. The increase in absorption at 280 nm as a function of time, arising from the $Cu^{II}(L)$ complex, is monitored until the absorbance increase is unchanged. The extinction coefficient of each $Cu^{II}$-(macrocycle) complex is independently established at each pH by prior synthesis and determination at each pH. The extinctions coefficients are generally unchanged with pH over the range of 4−6 and vary with the macrocyclic ligand employed. At pH's > 6.5 this method is not useful since Cu(II)(aquo)(hydroxo) complexes begin to precipitate. Two different buffers are used depending upon the pH range of interest: for pH = 5.4−6.5, Hepes {*N*-2-(hydroxyethyl)-piperazine-*N*′-(2-ethanesulfonic acid)}, and for pH = 3.5−5.5, Mes {[2-(*N*-morpholino)-ethanesulfonic acid)]}. In general, a buffer solution at 200 mM at a specific pH is made fresh for every kinetic experiment. The $[CuCl_2]$ utilized in all studies was $2.4 \times 10^{-3}$ M in 100 mL buffer and the concentration of complex was $3.00 \times 10^{-4}$ M.

**Determination of Superoxide Dismutase Activity.** The method utilized to determine the catalytic activity of the Mn(II) complexes reported here is based on the stopped flow kinetic assay described elsewhere.[1,30,31] The work described here utilized the same methodology as described previously and for each complex $k_{cat}$ was determined over a pH range of 7.4−8.3.

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**Supporting Information Available:** Additional crystallographic details for $[Mn(2,2,3,3\text{-}Me_4[15]aneN_5)Cl_2]$, **2i**, including anisotropic thermal parameters for non-hydrogen atoms, and atomic coordinates for hydrogen atoms (4 pages). Ordering information is given on any current masthead page.

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