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Synthesis and Structure of Chiral Macrocycles Containing 2,2′-Bipyridine Subunits†

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Abstract—A series of macrocyclic receptors has been prepared containing bipyridine groups linked to two amino acids. Variations in both the amino acid and the linking spacer have been made. The structure of the resulting macrocycles has been investigated using ^{1}H NMR spectroscopy and X-ray crystallography. The use of L-valine leads to an open conformation for the macrocycle in which the 2-propyl substituents are directed perpendicular to the plane of the ring leaving the bipyridine and amide groups accessible for binding to a metal or complementary substrate. Proline-based macrocycles take up a twisted arrangement with the linking chain stretched across the face of the bipyridine which takes up a *trans* conformation. The metal ion binding properties of these derivatives have been investigated and shown to occur only to the valine macrocyles which have the two pyridine rings preorganized for complexation. These macrocycles have also been shown to bind to phenolic hydroxyl groups by using hydrogen-bond donors and acceptors from the amide groups in the linking chain. Copyright © 1996 Elsevier Science Ltd

Introduction

The area of molecular recognition has been a subject of intense interest in recent years.[1] Many different strategies involving macrocyclic[2] and non-macrocyclic[3] species have been developed for the construction of receptors containing multiple recognition sites. A major goal of this work lies in the incorporation of reactive groups into the receptors and the generation of enzyme-like properties of rate acceleration and reaction specificity.[4] As part of a program[5] aimed at the development of such artificial enzymes, we sought to prepare molecular receptors in which a transition metal could be held within the framework of a chiral cavity. Our basic design is shown in Figure 1 and involves a rigid chelating unit linked to two chiral subunits and held within a macrocyclic framework.[6] The intention was to place a catalytically-active metal within a chiral environment that would influence the approach and binding of potential substrates. The most effective interaction should take place between an approaching substrate and chiral groups positioned in front of the metal center. Transition metal derivatives of these chiral receptors may find applications in metal mediated reactions including olefin epoxidation[5,7] or Lewis acid activating[8] reactions. In this paper we report the synthesis and structure of several members of this new class of macrocyclic receptor.

†Dedicated to Professor Sir Alan R. Battersby and Professor A. Ian Scott on their receipt of the 1995 Tetrahedron Prize, with particular gratitude to ARB for his mentorship to ADH during his Ph.D. (1976–1979).

Results and Discussion

Synthesis of the macrocyclic ligands

The first target structure is shown in Figure 2. Bipyridine was chosen as the chelating group owing to its ubiquitous role as a metal ligand and the ready introduction of substituents to change its electronic and spectroscopic characteristics.[9,10] The chiral residues are derived from amino acids which provide a source of potentially bulky and/or reactive substituents in enantiomerically pure form.[11] Finally a suitable diamine spacer (X in Fig. 2) completes the macrocyclic ring and may be used to modify the size and properties (i.e., rigidity, additional binding interaction, etc.) of the receptor. In addition to metal binding, the macrocyclic

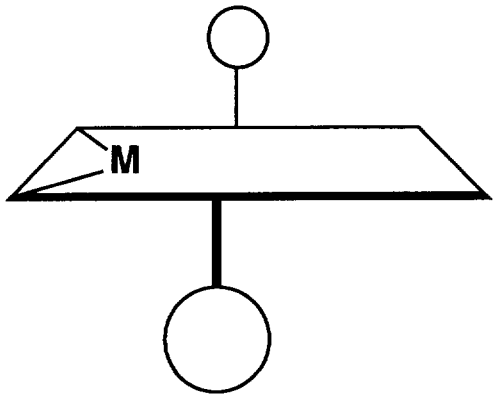


Figure 1. Schematic for receptor design.

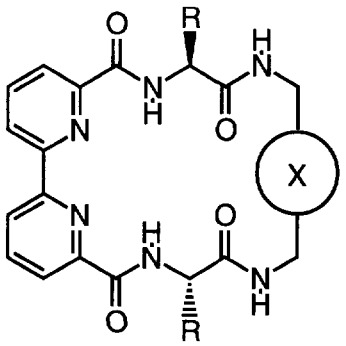
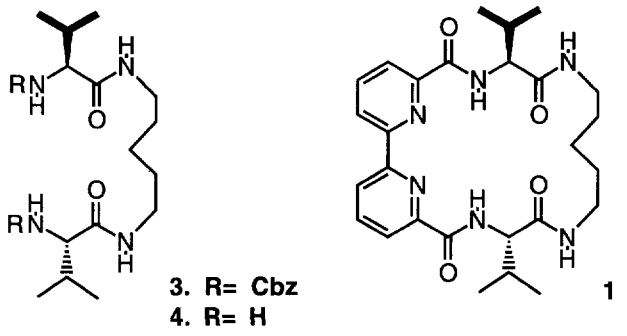


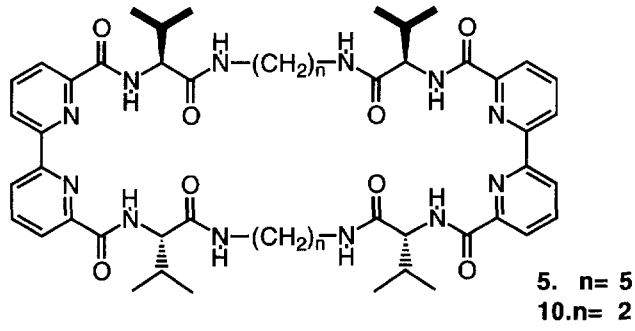
Figure 2. Design of bipyridine-amino acid macrocycles.

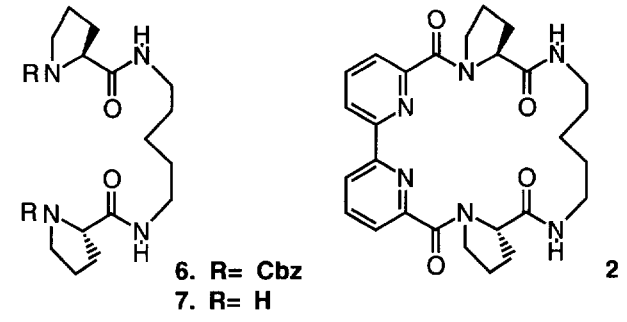
design also positions several hydrogen bond donors and acceptors on opposite sides of the ring and in a position to potentially interact with complementary substrates.

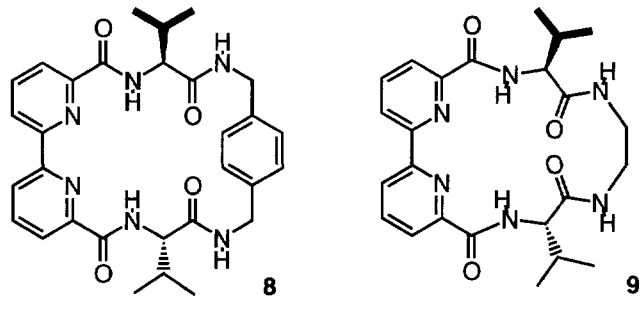
The synthetic plan was designed so that all components, chelating unit, chiral residue, and diamine spacer could be readily varied. Construction of the macrocycle involved successive double amide bond forming reactions in a stepwise route. This will be illustrated by valine-derived macrocycle **1** and proline-derived macrocycle **2**. 1,5-Diaminopentane was reacted with two equivalents of *N*-carbobenzyloxy-L-valine in refluxing CH_2Cl_2 using Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide)[12] and triethylamine to provide diamide **3** in 74% yield. Deprotection of **3** to form diamine **4** proceeded smoothly in 98% yield using catalytic hydrogenolysis (10% Pd–C) in methanol. The final cyclization step between diamine **4** and 6,6′-dichlorocarbonyl-2,2′-bipyridine[10] was carried out under high dilution conditions in CH_2Cl_2 and triethylamine. The crude product was purified by alumina chromatography (CH_2Cl_2:MeOH, 100:1) and recrystallized from CH_3CN to provide bis-valine macrocycle **1** in 83% yield. A slower moving fraction could be isolated from column chromatography and this was identified, by mass spectrometry, as cyclic dimer **5**. L-Proline-based macrocycle **2** was prepared by an exactly analogous route via bis-carbobenzyloxy-diamide **6** and diamine diamide **7**. The final cyclization step between **7** and 6,6′-dichlorocarbonyl-2,2′-bipyridine gave a 34% yield of macrocycle **2**, reduced from that of **1** presumably due to the more hindered secondary amines.

Other variations in the basic structure, besides the chiral residue, included the diamine spacer. A more rigid and open macrocycle **8** was prepared by an analogous route from *p*-xylylene diamine, with a final cyclization yield of 29%. Similarly, use of 1,2-diaminoethane as a spacer resulted in the smaller macrocycle **9** in 28% yield, in addition to the dimeric species **10** in 26% yield.









X-ray crystallography

Two macrocycles, valine **1** and proline **2**, gave crystals suitable for X-ray analysis. The structure of **1**, shown in

Figure 3, bears a close resemblance to the schematic representation in Figure 2. The two pyridine rings are almost coplanar (dihedral angle, 15.8°) and preorganized for metal complexation. The pyridine-6-carboxamides occupy the same plane while the two aliphatic amides are tilted to position the carbonyl oxygens above and below the macrocyclic ring. The most striking feature of the structure is the orientation of the two isopropyl substituents. These are positioned almost perpendicular to the plane of the macrocycle (C3–N4–C5–C26 torsion angle, 94.2°), providing a C_2-symmetrical environment around the metal binding site corresponding closely to Figure 1.

In contrast, proline macrocycle **2** shows a completely different conformation in the solid state (Fig. 4). The bipyridine takes up a *trans* arrangement with the two pyridine nitrogens pointing in 180° different directions. This causes the pentamethylene chain to be stretched across the face of the bipyridine with a deviation of the 6-carboxamide groups from its mean plane. The twisted structure is the result of the need of the macrocycle to accommodate the prolyl residues in a *cis* configuration. Normally the s-*trans* form of an acylproline is favored over the s-*cis* form.[13] However, in a macrocyclic structure of this type s-*trans* acylprolyl groups would project the pyrrolidine ring into the center of the cavity and cause serious steric congestion. This is seen clearly by considering the structure of **1** (seen in Fig. 3) in which the acylvaline residues take up the much more stable s-*trans* conformation.

NMR spectroscopy

^{1}H NMR studies on proline macrocycle **2** (Fig. 5a) show that the twisted structure seen in Figure 4 is

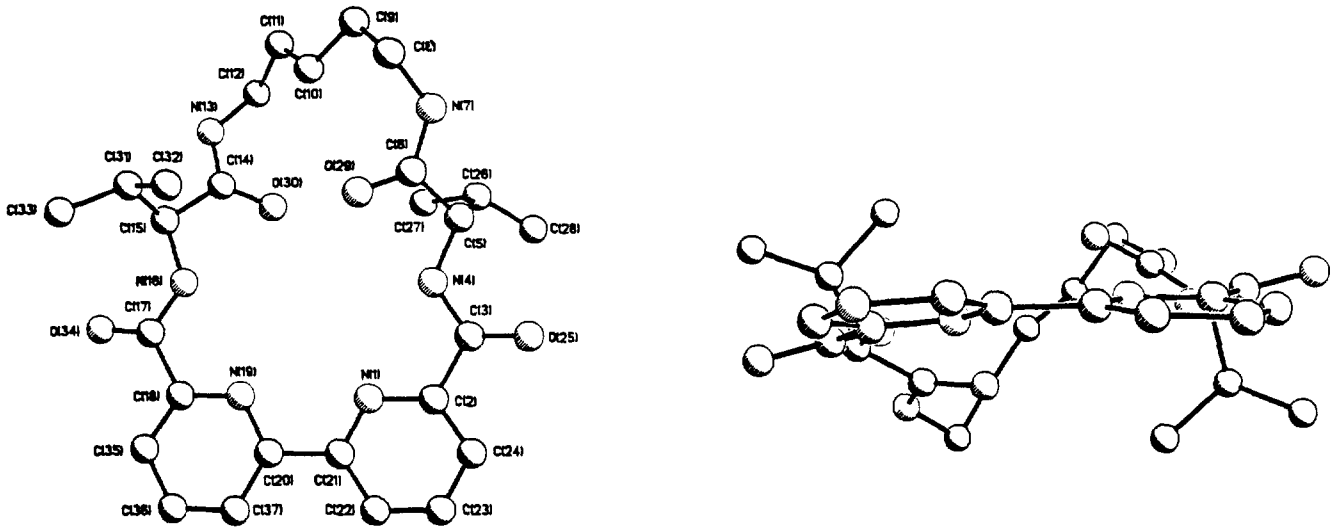


Figure 3. X-ray structure of **1**.

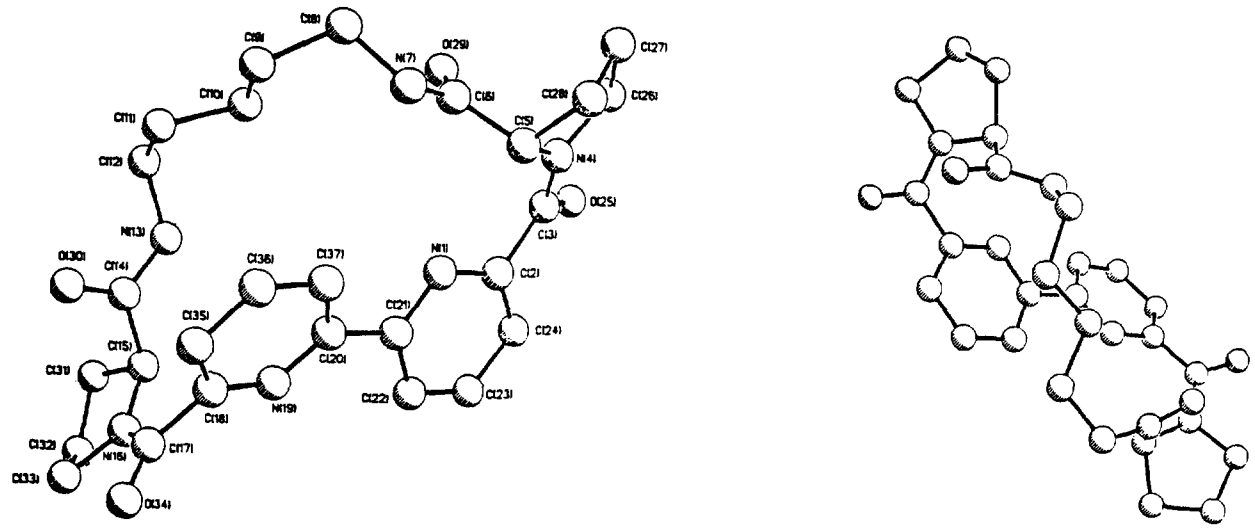


Figure 4. X-ray structure of **2**.

maintained in solution. The α, β, and γ methylene protons of the diaminopentane chain are shifted upfield by 0.27, 0.48, and 0.86 ppm, respectively, compared to the open chain analogue, **7**.[14] This is consistent with the crystal structure for **2** in which the methylene chain is stretched across the face of the bipyridine ring and so influenced by the aromatic ring current. The single central CH_2 is closest to the center of the π-system and experiences the largest upfield shift. Also, the proline-αH is more than 1 ppm further downfield in **2** than in bis-Cbz-**6** (5.39 vs. 4.35 ppm) confirming its position adjacent to the deshielding edge of the pyridine ring, as seen in the solid state structure. The resonances of the bipyridine protons in **2** occur in the order (δ values; $H_3 > H_5 > H_4$). This is different from the order in which they occur in the other macrocycles synthesized in this work and in simple 6,6′-disubstituted-2,2′-bipyridines ($H_3 > H_4 > H_5$; see Table 1).[15] The unusual downfield shift of H_5 in **2** is most likely due to the adjacent carbonyl groups which in the twisted structure are no longer coplanar with the pyridine ring.

The valine-based macrocyles show solution NMR behaviors different from **2** and much closer to those of their uncyclized precursors (Fig. 5b). For example, the diaminopentane-CH_2 groups in **1** are not shifted upfield compared to acyclic **4** and are thus held away from the effects of the bipyridine ring current. An intramolecular NOE is also seen between the isopropyl-CH_3 groups and the valine-CH, -αH, and -NH atoms. These results suggest an open conformation for the macrocycle with the isopropyl substituents perpendicular to the ring, similar to that seen in the solid state structure (Fig. 3). The other valine macrocycles show behavior very similar to **1**.

Metal ion complexation

There are dramatic differences in the coordination chemistry of the bis-valine and bis-proline macrocycles, **1** and **2**. Treatment of **1** with $Fe(ClO_4)_3$ in acetonitrile results in the formation of a deep-red Fe(III) complex with a characteristic[16] metal–ligand charge transfer band at 537 nm [$\lambda_{max}(e \times 10^{-3})$ 254 (103), 298 (55) and 537 nm (67)]. Similar treatment of **2** with $Fe(ClO_4)_3$ showed no complex formation. Other complexes (e.g., Cr(III) and Mn(III)) could be formed with **1**, but none of these metal ions reacted with **2**. These differences in coordination behavior are clearly due to the different ground state conformations of **1** and **2**. In **1**, the pyridine rings are held in a preorganized position for metal ion binding, whereas in **2**, the *trans* orientation of the pyridine-Ns and the high barrier to rotation preclude bidentate complexation.

Recognition of hydroxylic substrates

The disposition of amide and pyridine groups in **1** suggests the potential for hydrogen bonding recognition of substrates with a complementary positioning of binding sites. For example, hydroxyl groups can potentially interact with **1** by forming hydrogen bonds to the

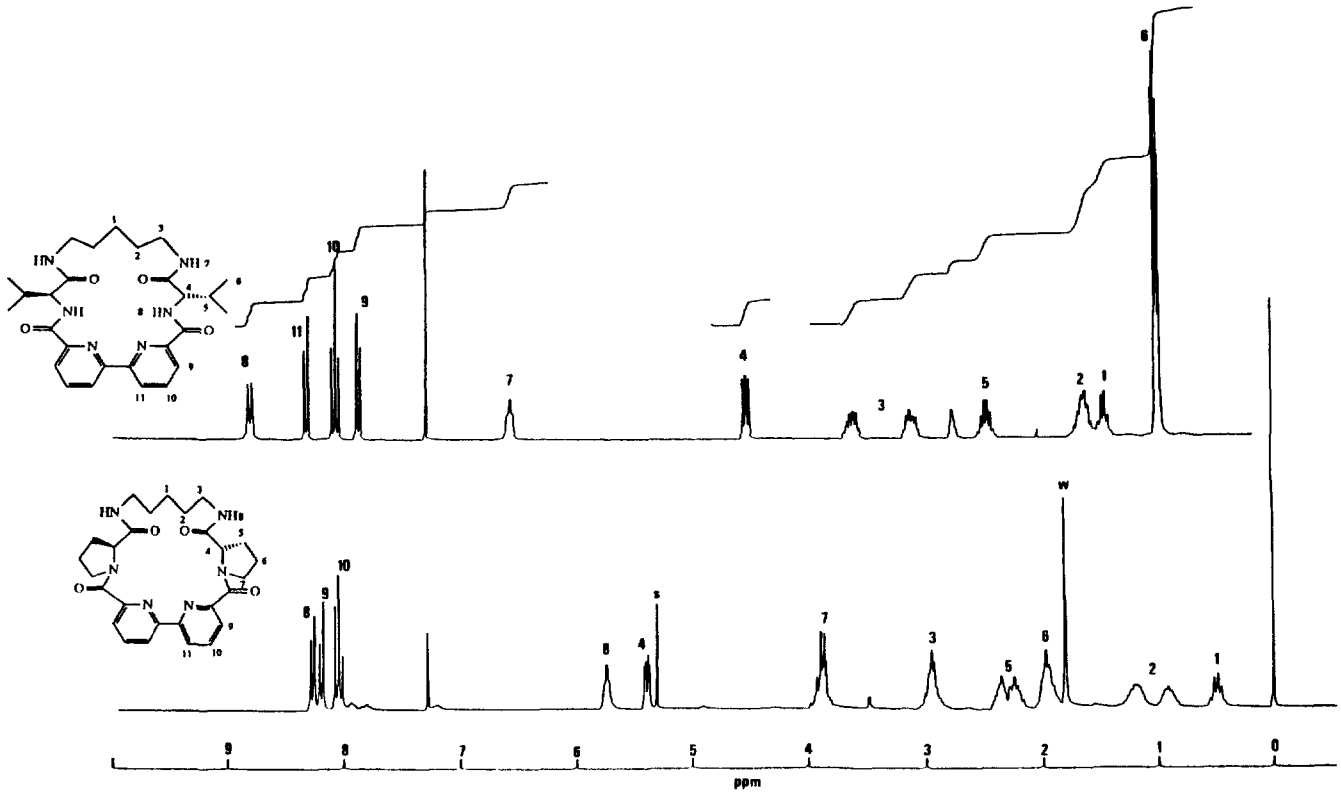


Figure 5. ^1H NMR spectra in $CDCl_3$ for (a) proline macrocycle **2**; (b) valine macrocycle **1**.

Table 1. Chemical shifts of bipyridine protons

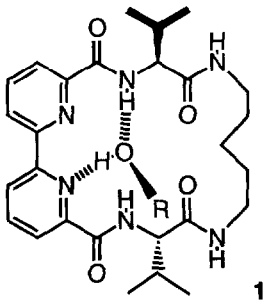
Compound	H_3	H_4	H_5
2	8.26	8.03	8.19
1	8.26	8.01	7.82
9	8.21	8.02	7.91
8	8.21	8.03	7.75
6,6′-Dimethyl-2,2′-bipyridine	8.18	7.68	7.15

pyridine-N and opposite amide-NH, as shown in **11**. A related interaction has been well characterized in the solid state[17] and has recently been seen in solution.[18]

We have investigated the interaction of **1** with *p*-nitrophenol and find that hydrogen bonding recognition occurs but not as shown in **11**. Addition of an excess of *p*-nitrophenol to a $CDCl_3$ solution of **1** (at 1.4×10^{-2} M) gives downfield shifts of the aliphatic amide-NH (0.4 ppm) and valine-αH (0.05 ppm) but an upfield shift (0.12 ppm) of the pyridine carboxamide-NH. The association constant from a corresponding titration experiment was estimated as $2.3\pm0.4\times10^{2}$ M^{-1}. The NMR results are inconsistent with a complex structure as in **11** but suggest an interaction involving amide-NH and CO groups on the aliphatic bridge, as shown in **12**. Further support for this model comes from temperature dependence studies on the chemical shift of the two pairs of amide protons in **1**. In peptides, a value of $\Delta\delta/\Delta T > 4\times10^{-3}$ ppm/K for the amide-NH resonance is considered evidence of external interaction to solvent or a guest molecule whereas $\Delta\delta/\Delta T < 3\times10^{-3}$ ppm/K suggests either the presence of an intramolecular hydrogen bond or the absence of any hydrogen bonding interactions.[19] A solution of **1** (1.4×10^{-2} M) and *p*-nitrophenol (0.7×10^{-2} M) in $CDCl_3$ gave $\Delta\delta/\Delta T = 9.8\times10^{-3}$ and -1.9×10^{-3} ppm/K for the aliphatic amide-NH and pyridine carboxamide-NH resonances, respectively. Interestingly, receptors **2** and **8** show only weak binding to *p*-nitrophenol with no discrete saturation in the titration curve. This is presumably due to the twisted conformation (for **2**) or the rigid *p*-xylylene spacer (for **8**) preventing the two amide groups in the bridge from binding cooperatively to the phenolic hydroxyl group.

Experimental

Proton NMR spectra were recorded on either a Bruker WM-250 or IBM NR 80 instrument. Unless otherwise indicated, spectra were recorded using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Mass spectra were obtained on a Kratos MS 50 instrument either in the Princeton Chemistry Instrument Facility or at the Midwest Center for Mass Spectrometry. Melting points were recorded on an electrothermal heated block melting point apparatus and are uncorrected. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All solvents were purified by standard methods before use.



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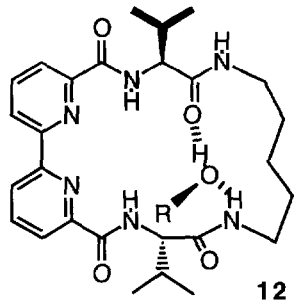

12

Bis-(*N*-Cbz-L-valyl)-1,5-pentanediamide (3). *N*-Cbz-L-valine (4.00 g, 15.9 mmol) and 2-chloro-1-methylpyridinium iodide (4.88 g, 19.1 mmol) were dissolved in 200 mL dry CH_2Cl_2 under an argon atmosphere. To this solution was added triethylamine (3.86 g, 3.82 mmol) followed by 1,5-diaminopentane (0.82 g, 7.96 mmol). The mixture was heated under reflux for 1.5 h, during which time a white floculent precipitate formed. After cooling, the solution was filtered and the precipitate washed with cold CH_2Cl_2 (25 mL) to yield 3.58 g (78%) product: mp 233–235 °C; ^{1}H NMR (DMSO-d_6): δ 0.80 (d, J=6.8 Hz, 12H, $-CH_3$), 1.30 (m, 6H, $-CH_2-$), 1.90 (m, 2H, $-CH(CH_3)_2$), 3.00 (m, 4H, $-NH-CH-$), 3.80 (m, 2H, $-CO-CH-NH$), 5.0 (s, 2H, $-CH_2-Ar$); $[\alpha]_D^{25}$ −10.6° (c 2.36×10^{-3}, $CHCl_3$). Anal. calcd for $C_{31}H_{44}N_4O_6$: C, 65.47; H, 7.80; N, 9.85. Found: C, 65.26; H, 7.84; N, 9.82.

Bis-(L-valyl)-1,5-pentanediamide (4). A suspension of **3** (1.00 g, 1.73 mmol) and 10% Pd–C (0.10 g) in 50 mL MeOH, which had been purged with argon for 15 min, was stirred under 1 atm H_2 for 20 h. At the end of this time, all the organic material had dissolved. The reaction mixture was filtered through Celite and the methanol removed on a rotary evaporator to yield a viscous oil which crystallized on standing. The product was recrystallized from EtOAc/hexanes to provide **4** as colorless needles (0.52 g, 98%): mp 82–83 °C; MS, *m/e* 300 (M^+); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.82 (d, J=6.9 Hz, 6H, $-CH_3$), 0.99 (d, J=7.1 Hz, 6H), 1.39 (m, 2H, $-CH_2-$), 1.43 (s, broad, 4H, $-NH_2$), 2.80 (m, 4H, $-CH_2-$), 3.30 (m, 2H, $-CH(CH_3)_2$), 3.22 (m, 4H, $-CH_2-N-CO-$), 3.26 (m, 2H, $-CO-CH-NH-$), 7.33 (s br, 2H, $-CO-NH-$). Anal. calcd for $C_{15}H_{32}N_4O_2\cdot0.5\ H_2O$: C, 58.22; H, 10.42; N, 18.11. Found: C, 58.48; H, 10.74; N, 18.02.

Pentamethylene-bis-(L-valyl)-bipyridine macrocycle (1). The cyclization was carried out under high dilution conditions. A solution of 6,6′-dichlorocarbonyl-2,2′-bipyridine[15] (0.236 g, 0.83 mmol) in 250 mL dry CH_2Cl_2 and a solution of **4** (0.250 g, 0.83 mmol) and triethylamine (0.185 g, 1.83 mmol) in 250 mL dry CH_2Cl_2 were simultaneously dropped into vigorously stirred dry CH_2Cl_2 (100 mL) over an eight-hour period. The reaction mixture was allowed to stir at room temperature overnight. The resultant clear solution was concentrated on a rotary evaporator and the residue was then dissolved in 50 mL of CH_2Cl_2 and washed with 2×5 mL 10% citric acid solution and 50 mL 10%

$NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the partially purified product (0.415 g). This material was further purified by column chromatography (alumina, CH_2Cl_2:MeOH, 100:1) to yield, after crystallization from CH_3CN, macrocycle **1** as a white solid (0.350 g, 83%): mp 289–291 °C; MS, *m/e* 508 (M^+); ^1H NMR: δ 0.92 (d, $J=4.2$ Hz, 6H, $-CH_3$) 0.95 (d, $J=4.2$ Hz, 6H, $-CH_3$), 1.42 (m, 2H, $-CH_2-CH_2-CH_2$), 1.58 (m, 4H, $-CH_2-CH_2-CH_2-$), 2.42 (m, 2H, $-CH(CH_3)_2$), 3.06 (m, 2H, $-NH-CH_2-$), 3.55 (m, 2H, $-NH-CH_2-$), 4.49 (dd, $J=5.4$, 8.7 Hz, 2H, $-NH-CH-CO-$), 6.59 (dd br, 2H, $J=6.0$ Hz, $-NH-CH_2$), 7.82 (d, $J=7.8$ Hz, 2H, Py-3H), 8.01 (t, $J=7.8$ Hz, 2H, Py-4H), 8.26 (d, $J=7.7$ Hz, 2H, Py-5H), 8.77 (d, $J=8.7$ Hz, 2H, $-CO-NH-CH-$); $[\alpha]_D^{25}$ −143° (*c* 1.38×10^{-2}, MeOH). Anal. calcd for $C_{27}H_{36}N_6O_4$: C, 63.76; H, 7.13; N, 16.52. Found: C, 63.85; H, 7.13; N, 16.47.

Bis-(*N*-Cbz-L-prolyl)-1,5-pentanediamide (6). To a solution of *N*-Cbz-L-proline (7.00 g, 28.1 mmol) and 2-chloro-1-methylpyridinium iodide (8.61 g, 33.7 mmol) in 200 mL dry CH_2Cl_2 were added triethylamine (6.8 g, 64.7 mmol) and 1,5-diaminopentane (1.43 g, 14.0 mmol). The clear-yellow solution was heated under reflux for 1.5 h under an argon atmosphere. After cooling to room temperature, the solution was diluted with 100 mL diethyl ether and washed with 3×100 mL 5% aqueous HCl followed by 100 mL 5% $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent removed on a rotary evaporator to give (**6**) as a light-yellow oil: ^1H NMR (DMSO-d_6): δ 1.40 (m, 8H, $-CH_2$), 1.95 (m, 8H, $-CH_2-$), 3.20–3.55 (m, 8H, $-CH_2-N-CO-$), 4.35 (dd, 2H, $-N-CH-CO-$), 5.15 (s, 4H, $Ar-CH_2-O-$), 7.30 (s, 10H, Ar-H); $[\alpha]_D^{25}$ −314° (*c* 4.61×10^{-3}, $CHCl_3$).

Bis-(L-prolyl)-1,5-pentanediamide (7). Deprotection of **6** (2.95 g, 5.22 mmol) was carried out under 1 atm H_2 with 10% Pd–C catalyst in MeOH. Compound **6** was insoluble at first, but dissolved over the course of the reaction. After stirring overnight, the reaction mixture was filtered through Celite and the solvent was removed by a rotary evaporator to yield after recrystallization from ethyl acetate/hexane 1.35 g (97%) of diamine **7**: mp 101–102 °C; ^1H NMR: δ 1.35 (m, 2H, $-CH_2-CH_2-CH_2-$), 1.53 (m, 4H, $-NHCH_2-CH_2-CH_2-$), 1.72 (m, 4H, prol. 4H), 1.90, 2.15 (m, m, 4H, prol. 3H), 2.77 (s br, 2H, prol. NH), 2.93–3.01 (m, 4H, prol. 4H), 3.22 (m, 4H, $-NH-CH_2-CH-$), 3.76 (dd, $J=9.0$, 5.4 Hz, 2H, $-CO-CH-NH$), 7.71 (s br, 2H, $-CO-NH-$). Anal. calcd for $C_{15}H_{28}N_4O_2$: C, 60.78; H, 9.52; N, 18.90. Found: C, 60.54; H, 9.56; N, 18.60.

Pentamethylene-bis-(L-prolyl)-bipyridine macrocycle (2). The high dilution method was employed in the synthesis of **2**. A solution of **7** (1.00 g, 3.73 mmol) and triethylamine (0.79 g, 7.81 mmol) in 250 mL dry CH_2Cl_2 and a solution of 6,6′-dichlorocarbonyl-2,2′-bipyridine (1.05 g, 3.73 mmol) in 250 mL dry CH_2Cl_2 were added dropwise to dry CH_2Cl_2 (100 mL). After stirring for two days, the solvent was removed on a rotary evaporator and the white solid was suspended in 50 mL CH_2Cl_2 and collected by suction filtration to yield **2** (0.64 g, 34%): mp 294–295 °C; MS, *m/e* 504 (M^+); ^1H NMR ($CDCl_3$, 250 MHz): δ 0.49 (m, 2H, $-CH_2-$), 0.91 (m, 2H, $-CH_2-$), 1.19 (m, 2H, $-CH_2-$), 1.97 (m, 4H, $-CH_2-$), 2.24 (m, 2H, $-CH_2-$), 2.35 (m, 2H, $-CH_2-$), 2.95 (m, 4H, $-CH_2-N-CO-$), 3.87 (m, 4H, $-CH_2-NH-CO-$), 5.39 (dd, $J=2.8$, 8.1 Hz, 2H, pyrrol. 2H), 5.73 (dd br, 2H, $-CH_2-NH-CO-$), 8.03 (t, $J=7.8$ Hz, 2H, Py-H), 8.19 (d, $J=7.9$ Hz, 2H, Py-H), 8.25 (d, $J=7.9$ Hz, 2H, Py-H). Anal. calcd for $C_{27}H_{32}N_6O_4\cdot H_2O$: C, 62.05; H, 6.56; N, 16.08. Found: C, 62.04; H, 6.57; N, 16.21.

Bis-(*N*-Cbz-L-valyl)-*p*-xylyldiamide. *N*-Cbz-L-valine (1.48 g, 5.87 mmol) and 2-chloro-1-methylpyridinium iodide (1.80 g, 7.05 mmol) were dissolved in 200 mL dry CH_2Cl_2 under an argon atmosphere. After adding triethylamine (1.43 g, 14.1 mmol) and *p*-xylylene diamine (0.40 g, 2.94 mmol), the mixture was heated under reflux for 1.5 h. The gelatinous precipitate which formed was collected by suction filtration, washed with CH_2Cl_2, and dried in vacuo over anhydrous Ca_2SO_4 to yield the doubly protected product (0.99 g, 56%): mp 252–253 °C; ^1H NMR (DMSO-d_6): δ 0.83 (d, $J=6.6$ Hz, 12H), 2.49 (m, 2H, $-CH(CH_3)_2$), 3.86 (m, 2H, $NH-CH-CH-$), 4.25 (m, 4H, $Ar-CH_2-NH-$), 5.03 (s, 4H, $Ar-CH_2-NH-$), 7.18 (m, 6H, Ar-H, $-NH-CO-$), 7.34 (m, 10H, Ar-H), 8.33 (br t, 2H, $Ar-CH_2-NH-CO-$); $[\alpha]_D^{25}$ +579° (*c* 1.57×10^{-3}, THF). Anal. calcd for $C_{34}H_{42}N_4O_6$: C, 67.75; H, 7.14; N, 9.30. Found: C, 67.61; H, 6.96; N, 9.21.

Bis-(L-valyl)-*p*-xylyldiamide. The foregoing diamide (0.50 g, 0.83 mmol) and 10% Pd–C (0.1 g) were stirred in methanol (20 mL) under 1 atm of H_2. The reaction was followed by the dissolution of starting material which is sparingly soluble in methanol. After three days, the reaction mixture was filtered through Celite and the solvent removed on a rotary evaporator to give the diamine product as a viscous oil (0.22 g, 79%) which was used without further purification; ^1H NMR: δ 0.83 (d, $J=6.9$ Hz, 6H, $-CH_3$), 1.00 (d, $J=6.9$ Hz, 6H, $-CH_3$), 2.36 (m, 2H, $-CO-CH-NH-$), 3.38 (d, $J=3.7$ Hz, 2H, $CH-NH_2$), 4.43 (dd, $J=4.0$, 5.9 Hz, 4H, $Ar-CH_2-$), 7.27 (s, 4H, Ar–H), 7.66 (s br, 2H, $-NH-C-$); MS, *m/e* 334 (M^+).

***p*-Xylyl-bis-(L-valyl)-bipyridine macrocycle (8).** A solution of the foregoing diamide (0.220 g, 0.658 mmol) and triethylamine (0.133 g, 1.13 mmol) in dry CH_2Cl_2 (250 mL) and a solution of 6,6′-dichlorocarbonyl-2,2′-bipyridine (0.185 g, 0.658 mmol) in dry CH_2Cl_2 (250 mL) were simultaneously added dropwise to

vigorously stirred dry CH_2Cl_2 (50 mL) over a period of 8 h. The mixture was allowed to stir overnight at room temperature, and at the end of this time the CH_2Cl_2 was removed on a rotary evaporator. The resulting white solid was dissolved in 75 mL CH_2Cl_2 and washed with brine solution (2×50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated to yield **8** (0.104 g, 29%) as a white solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.99 (d, $J=6.8$ Hz, 6H, —CH_3), 1.03 (d, $J=6.8$ Hz, 6H, —CH_3), 2.53 (m, 2H, —$CH(CH_3)_2$), 3.97 (dd, $J=3.4$, 15.0 Hz, 2H, CO—CH—NH), 4.61 (m, 4H, Ar—CH_2—), 6.50 (dd, $J=3.1$, 6.8 Hz, 2H, $ArCH_2$—NH—CO—), 6.93 (s, 4H, Ar—H), 7.75 (d, $J=7.7$ Hz, 2H, Py-3H), 8.03 (t, $J=7.7$ Hz, 2H, Py-4H), 8.21 (d, $J=7.9$ Hz, 2H, Py-5H), 8.31 (d, $J=10$ Hz, 2H, —NH—CO—Py); $[\alpha]_D^{25}$ −2.08° (*c* 4.32×10^{-3}, THF).

Ethylene-bis-(L-valyl)-bipyridine macrocycle (9) and dimer (10). These compounds were prepared by the high dilution method. A solution of 6,6′-dichlorocarbonyl-2,2′-bipyridine (0.266 g, 0.946 mmol) in dry CH_2Cl_2 (250 mL) and a solution of bis-(L-valyl)-1,2-ethylenediamide (0.243 g, 0.946 mmol) and triethylamine (0.21 g, 2.08 mmol) in dry CH_2Cl_2 (250 mL) were added dropwise to CH_2Cl_2 (100 mL) over an eight-hour period. After stirring overnight, the CH_2Cl_2 was removed on a rotary evaporator. The residue was dissolved in 50 mL CH_2Cl_2, a small amount of insoluble material was removed by suction filtration, and the filtrate was washed with citric acid (5%, 50 mL) followed by $NaHCO_3$ (5%, 50 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and the CH_2Cl_2 was evaporated to give a white residue. The crude mixture was purified by preparative thin layer chromatography (alumina, CH_2Cl_2:MeOH, 50:1) to give, as a faster moving band, **9** (0.125 g, 28%); ^{1} H NMR: δ 0.83 (d, $J=6.8$ Hz, 6H, —CH_3), 0.90 (d, $J=6.8$ Hz, 6H, —CH_3), 2.57 (m, $J=6.8$ Hz, 2H, —CH—$(CH_3)_2$), 3.10 (d br, 2H, —NH—CH_2—), 3.90 (m, 2H, —NH—CH_2), 4.78 (dd, $J=3.9$, 10.2 Hz, 2H, —NH—CH—CO—), 7.50 (s br, 2H, —CO—NH—CH_2—), 7.91 (d, $J=7.7$ Hz, 2H, Py-3H), 8.02 (t, $J=7.7$ Hz, 2H, Py-4H), 8.21 (d, $J=7.7$ Hz, 1H, Py-5H), 8.79 (d, $J=10.2$ Hz, 2H, Py—NH—CO—); MS calcd for $C_{24}H_{30}N_6O_4$: 466.1329. Found: 466.1384. The slower moving band (0.112 g, 26%) corresponded to dimer **10**; ^{1}H NMR (250 MHz, DMSO-d_6): δ 0.81 (d, $J=3.4$ Hz, 6H, —CH_3), 0.84 (d, $J=3.5$ Hz, 6H, —CH_3), 2.06 (m, 4H, —$CH(CH_3)_2$), 3.11 (m, 4H, —HN—CH_2), 3.16 (m, 4H, —NH—CH_2—CH_2), 4.32 (dd, $J_1=J_2=7.9$ Hz, 4H, —CH—$(CH_3)_2$), 8.07 (d, $J=7.6$ Hz, 4H, Py 5H), 8.15 (m, 8H, Py 4H, —NH—CH_2—), 8.48 (d, $J=7.7$ Hz, 4H, Py 3H), 8.54 (d, 4H, —CO—NH—CH—). MS calcd for $C_{48}H_{60}N_{12}O_8$: 932.4657. Found: 932.4520.

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