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Self-Assembling Aromatic-Bridged Serine-Based Cyclodepsipeptides (Serinophanes): A Demonstration of Tubular Structures Formed through Aromatic $\pi-\pi$ Interactions

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Abstract: A variety of 18-membered cyclodepsipeptides with alternating repeats of aromatic (phenyl or pyridyl) and Ser units in the ring have been synthesized and studied by X-ray crystallography for self-assembly patterns. Single-crystal structures of the macrocycles showed similar, relatively flat-ring structures. Those molecules containing one or two pyridine units showed self-assembly by stacking one over the other, thus creating tubular structures using aromatic $\pi-\pi$ interactions between Ph/Pyr or Pyr/Pyr as the main organizing force. The cylindrical stacks are further stabilized by water molecules acting as bridges in intermolecular hydrogen bonding. In both the macrocycle **4b,** a hybrid of benzene and pyridine units connected through ester and amide bonds, respectively, and the macrocycle **4d** with two pyridine units, the molecules form parallel cylindrical stacks wherein the aromatic rings interdigitate from one column to a neighboring one with a ~3.5-Å separation between the planes of the rings. Macrocycle **4a**, with two phenyl rings, packs in a herringbone fashion and does not form any tubes. Macrocycle **4a** does not exhibit any internal hydrogen bonds. Only **4d** forms a tube with an inner space large enough to accommodate a water molecule.

Introduction

Conformationally constrained cyclopeptides constructed from chiral amino acids represent an attractive class of macrocycles that may be exploited to create functional self-assembly[1] systems through noncovalent interactions. Perhaps, the earliest example of a cyclopeptide enforced into a well-defined supramolecular structure was provided by diketopiperazine,[2] the smallest and the simplest member of the cyclopeptide family. The two cis amide bonds in the six-membered ring force the diketopiperazine molecules to assemble into an infinite hydrogen-bonded tape through NH···O═C bonds with its neighbors. Interestingly, the largest ring cis diamide with a known crystal structure to date remains the eight-membered cyclo(di-β-alanyl), whose boat-shaped molecules with both the amide groups on the same face assemble to form a severely buckled hydrogen-bonded tape.[3] Thus, while a tape or a layer was the most common motif exhibited in the self-assembly of small-ring peptides containing all cis amide bonds, the situation changes in larger ring peptides where the amide groups prefer to adopt a trans conformation. For example, while in a cyclic tetrapeptide containing 12 atoms

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(1) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, Germany, 1995. Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37. Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229. Whitesides, G. M.; McDonald, J. C. *Chem. Rev.* **1994,** *94*, 2383.

(2) Degeilh, R.; Marsh, R. E. *Acta Crystallogr.* **1959**, *12*, 1007. Benedetti, E.; Corradini, P.; Pedone, C. *J. Phys. Chem.* **1969**, *73*, 2891.

(3) White, D. N. J.; Dunitz, J. D. *Isr. J. Chem.* **1972**, *10*, 249.

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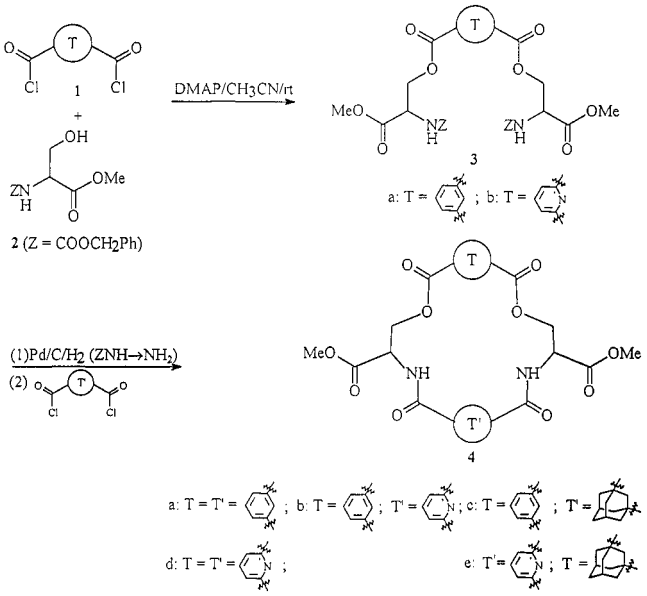
Scheme 1



in the ring, two amide groups were shown[4] in trans and two in the cis conformation, the more flexible 14-membered cyclotetrapeptide exhibited[5] all four amide groups in a trans conformation. Parenthetically, the self-assembly of the 14-membered cyclotetrapeptide L-Ser(O-*t*-Bu)-β-Ala-Gly-L-β-Asp(OMe) provided the first example[6] of a cylindrical structure formed through vertical stacking of peptide rings through NH···O═C bonds.

Rational design of cyclopeptides capable of self-assembling into hollow tubular structures was considered particularly important in the context of creating simple chemical models of channel systems for simulating important biological functions such as transport or catalysis. A beautiful illustration of tubular self-assembly formed by vertical stacking of flat peptide rings through antiparallel β-sheet-type intermolecular hydrogen bonding between complementary amide groups was provided recently in a series of papers by Ghadiri[7] et al. The flat-ring conformation, a crucial requirement for vertical stacking,[8] was achieved by arranging D- and L-amino acids in an alternating sequence in the ring.

Incorporation of small aromatic units into the backbone of a cyclopeptide was considered by us an alternate approach to create flat-ring peptides. It was envisaged that the aromatic units if properly positioned would not only induce rigidity in the structure but also help in stacking the peptide rings in a cylindrical fashion by providing $\pi-\pi$ interactions between the rings.

In this article, we provide the first illustration of this strategy and report on the design, synthesis, and crystal structure of aromatic-bridged, serine-based 18-membered macrocycles, a new class of cyclodepsipeptides, named serinophanes, containing alternating repeats of serine and aromatic units (Ph or Pyr) in the cyclic framework. The 18-membered peptide rings are demonstrated to exhibit rigid conformation with all the carbonyl groups oriented outward and amide NHs inward. Consequently, there are no internal NH···O═C bonds. The macrocycles show a strong tendency to assemble, through intermolecular interactions, into highly organized supramolecular structures. Particularly noteworthy features are the adoption of a relatively flat conformation of amide-linked pyridine-containing macrocycles and their self-assembly into layers of parallel tubular structures. Molecular modeling studies had suggested that direct stacking of serinophanes to form discrete tubes may be prevented by the projecting bulky carboxymethyl groups. The aromatic units could however take up an alternating interdigitating mode of stacking that may extend into layered structure of tubular assemblies. This expectation was fully realized in the crystal structure of **4b**,**d**. To our knowledge this is the first illustration of a tubular assembly formed in a cyclopeptide through aromatic $\pi-\pi$ interactions.

Results and Discussions

The 18-membered, serine-based cyclodepsipeptides **4a**−**e** were synthesized by a simple, two-step strategy (Scheme 1) involving first the condensation of Z-Ser-OMe (**2**) with 1,3-benzene (**1a**) or 2,6-pyridine (**1b**) dicarbonyl dichloride to give the bis-Ser derivatives **3a,b,** which after N-deprotection and recoupling with **1** afforded the desired cyclodepsipeptides in reasonable yields. The synthesis of adamantane-containing aromatic-bridged macrocycles **4c**,**e** not only showed the versatility of the design strategy but also provided models which could act as controls in the stacking studies. In terms of ring size, the macrocycles **4a**−**e** can be considered as equivalent to six-residue cyclopeptides. No unusual features were observed in the ^{1}H NMR spectra of **4a**−**e** except the large downfield shift ($\sim$1.5 δ) of the amide NHs in pyridine-bridged macrocycles **4b**,**d** as compared to rest of the macrocycles, suggesting involvement of pyridyl amide NHs in intramolecular hydrogen bonding with the ring N. The intramolecular NH···N hydrogen bonding in **4b**,**d** was also supported by the syn orientation of amide NHs as indicated by the absence of any cross-peaks between amide NHs and aromatic protons in their ROESY NMR spectra (Supporting Information). None of the 18-membered macrocycles showed any significant features in their CD spectra, indicating absence of secondary structural features as also suggested by ^{1}H NMR and FT-IR studies. Final proof for the open-ring structure in **4a**−**e** was obtained by single-crystal X-ray studies.

Suitable crystals were obtained from aqueous methanol for **4a**,**b**,**d**. Attempted crystallization of **4c**,**e** from a variety of solvents (chloroform, methanol, ethyl acetate, or a mixture of

(5) Karle, I. L.; Handa, B. K.; Hassall, C. H. *Acta Crystallogr.* **1975**, *B 31*, 555.

(6) Recently, the 16-membered cyclic tetramer of 3-aminobutanoic acid has been shown, by powder diffraction data, to adopt a tubular structure held together by NH···O═C bonds, (Seebach, D.; Mathews, J. L.; Meden, A.; Wessels, T.; Baerlocher, C.; McCusker, L. B. *Helv. Chim. Acta* **1997**, *80*, 173), as observed in ref 5.

(7) Ghadiri, M. R.; Granja, J. R.; Milligan, R. A.; McRee, D. E.; Khazanovich, N. *Nature* **1993**, *366*, 324−327. Ghadiri, M. R.; Granja, J. R.; Buehler, L. K. *Nature* **1994**, *369*, 301. Khazanovich, N.; Granja, J. R.; McRee, D. E.; Milligan, R. A.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 6011. Ghadiri, M. R.; Kobayashi, K.; Chadha, R. K.; McRee, D. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 93. Kobayashi, K.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 97. Hartgerink, J. D.; Granja, J. R.; Milligan, R. A.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 43.

(8) Although the prediction that alternating arrangement of D- and L-amino acids in a cyclopeptide would create rings with a flat conformation that may self-assemble through vertical β-sheet-like array of NH···O═C bonds into tube-like structures was made as early as 1974 (De Santis, P.; Morosetti, S.; Rizzo, R. *Macromolecules* **1974**, *7*, 52), the first designs of D,L-alternating cyclopeptides constructed from four, six, or eight Val, Leu, or Phe residues proved to be too insoluble for obtaining any conclusive evidence on their stacking profile (Tomasic, L.; Lorenzi, G. P. *Helv. Chim. Acta* **1987**, *70*, 1012. Pavone, V.; Benedetti, E.; Di Blasio, B.; Lombardi, A.; Pedone, C.; Tomasic, L.; Lorenzi, G. P. *Biopolymers* **1989**, *28*, 215). In 1982, peptide nanotubes containing vertical hydrogen bonds had been observed by the alternate stacking of the LLLL and LLDL isomers of cyclo-[-Ala-Pro-Phe-Pro] (Chiang, C. C.; Karle, I. L. *Int. J. Pept. Protein Res.* **1982**, *20*, 133). In 1993, Ghadiri constructed peptide nanotubes through the vertical stacking of an eight-residue cyclopeptide, cyclo[-(D-Ala-L-Glu-D-Ala-L-Gln)$_2$-].[7]

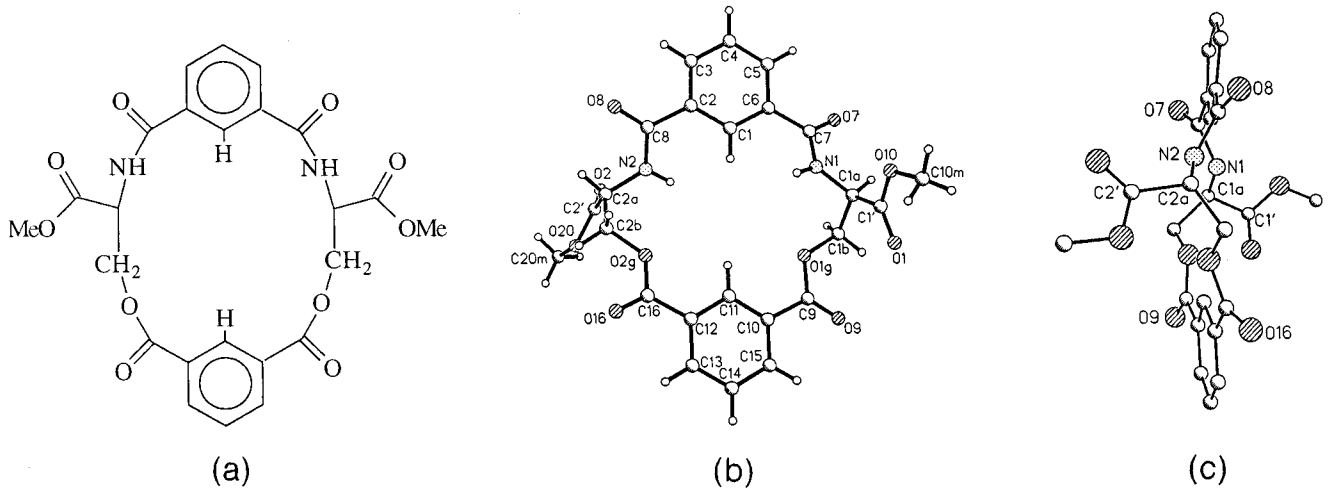


Figure 1. (a) Chemical structure of cyclo(Ph-Ser-)$_2$ (**4a**). (b) Crystal structure of **4a**, face-on view. Distances across the cavity are C1−C11, 5.24 Å; N1−O2G, 5.88 Å and N2−O1G, 5.58 Å. There are no intramolecular hydrogen bonds. (c) Side view of the molecule showing a crumpled ring structure. Hydrogen atoms have been omitted in (c) for clarity.

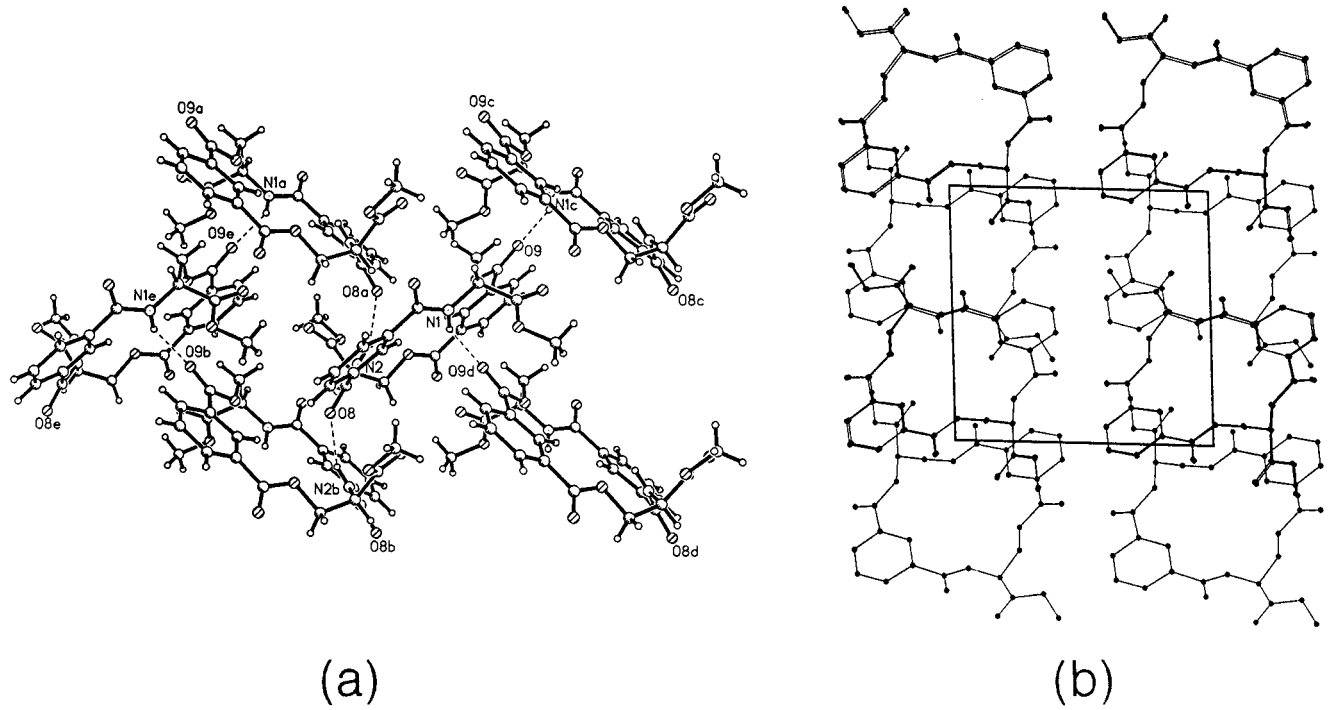


Figure 2. (a) Two-dimensional layered self-assembly in **4a**. Each molecule is surrounded by four neighbors to which it is bonded by NH···O bonds making an extended layer structure (projection is down the *c* axis). (b) Molecular packing diagram of **4a** viewed edge-on to the layer (projection is down the *b* axis).

polar and nonpolar solvents) was unsuccessful. Crystal structures showed that while **4b**,**d** macrocycles had pairs of amide NHs bonded to a ring N (NH···N, 2.68 and 2.73 Å; H···N, 2.30 and 2.35 Å), **4a** had no internal hydrogen bonds. All macrocycles showed an open-ring conformation with all carbonyl groups oriented outward and ring NHs facing inward, thus ruling out any possibility of intramolecular NH···O═C hydrogen bonding.

The macrocycle **4a** with two phenyl units in the ring (Figure 1a) adopts a slightly crumpled structure in the solid state as shown in Figure 1c. The amide NHs in this conformation are available for participating in intermolecular hydrogen bonding, creating an extended layer structure (Figure 2a), one molecule thick, wherein each molecule is bonded to four neighbors through NH···O═C bonds (N(1)···O(9), 2.934, H···O, 2.13 Å; N(2)···O(8), 2.892, H···O, 2.07 Å), Table 1. Figure 2b shows the molecular packing diagram of the layer motif.

The crystal structure of macrocycles **4b**,**d** containing an amide-linked pyridine unit revealed interesting features. Both macrocycles exhibited intramolecular NH···N (ring) hydrogen bonds that should provide added rigidity to the macrocycles **4b**,**d**. The diagrams in Figure 3 compare the planarity of the macrocycles in **4a**,**b**,**d**.

The structures of **4a** and **4b** are very similar, with **4a** having the two benzene rings in the same plane and **4b** having the benzene ring and pyridine ring in the same plane. In **4d**, the two pyridine rings are in planes that are inclined to each other by 26°. The presence of the intramolecular NH···N hydrogen bonds in **4b**,**d** is not correlated with the change, or lack thereof, of the planarity of the macrocycle. Further, in each macrocycle, the C$^\alpha$ atoms are displaced ∼1 Å from the planes of the aromatic rings. Torsional angles are listed in Table 2.

The crystal structure of **4b** (Figure 4a,b) shows the presence of two independent molecules, quite similar in conformation.

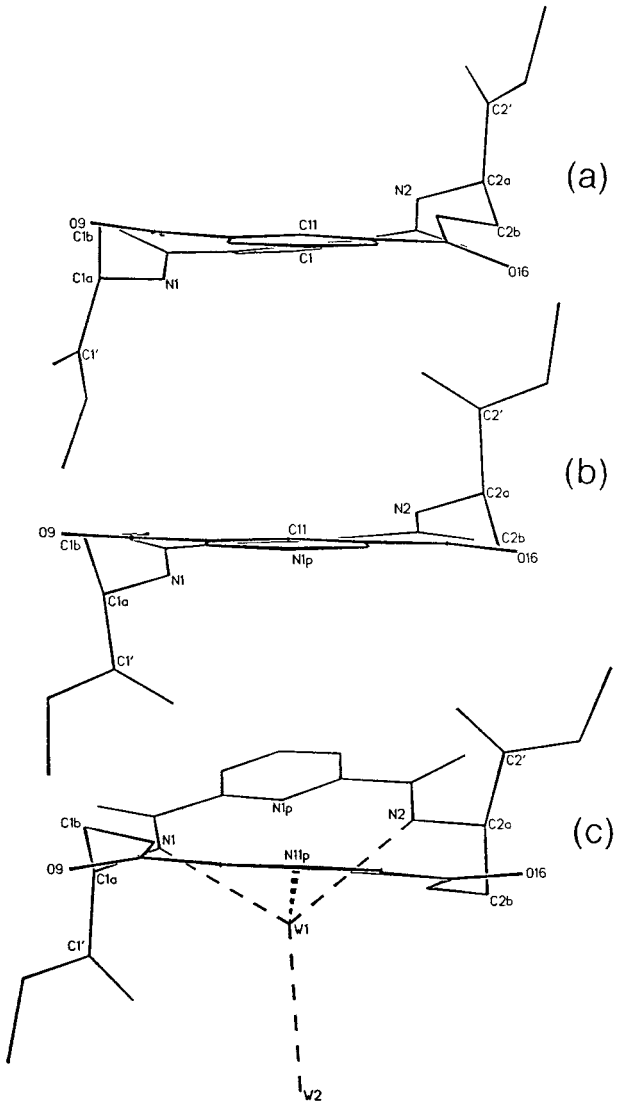


Figure 3. Diagrams showing projections of the conformations of **4a**,**b**,**d** viewed with the mean least-squares plane of the C(10) to C(15) ring perpendicular to the page. Hydrogen bonds to a water molecule below the cavity of **4d** are indicated by dashed lines.

Molecules 1 and 2 stack in separate vertical columns with pyridine and phenyl rings interdigitating from one column to the other with a ~3.5-Å separation between the planes of the rings. Molecules 1 are connected through hydrogen bonds to O2s (water 2). Molecules 2 are connected to molecules 1 by hydrogen bonds to O1s (water 1). Vertical columns of $\pi-\pi$ stacks are formed without any hydrogen bonds to neighboring stacks (Figure 5a,b). Figure 6a shows a schematic representation of the interdigitated $\pi-\pi$ stacks in **4b**.

The macrocycle **4d** (Figure 7a) containing alternating repeats of pyridine and serine units, linked through ester and amide bonds, is quite similar to **4b**, except for the inclusion of a water molecule W1 into the large ring and another water molecule W2 above W1. Further, the aromatic rings in **4d** are not coplanar, but in separate planes, as shown in Figure 3. Nevertheless, the molecules stack in columns with the pyridine rings interdigitating from separate neighboring columns. The separation between the planes of the pyridines is ~3.4 Å. The stacking of **4d** (Figure 8a,b) is almost identical to that of **4b** (Figure 5a,b), despite a tilt of the pyridine rings in the vertical $\pi-\pi$ aromatic stack. A schematic representation of the interdigitated $\pi-\pi$ stacks in **4d** is shown in Figure 6b.

Table 1. Hydrogen Bonds

crystal	type[a]	donor	acceptor	D···A (Å)	DH[b]···A (Å)
4a	inter	N1	O9[c]	2.934	2.13
	inter	N2	O8[d]	2.892	2.07
4b[e]	intra	N1	N1P	2.729	2.33
	intra	N2	N1P	2.678	2.30
	intra	N1A	N1PA	2.749	2.35
	intra	N2A	N1PA	2.685	2.30
	inter	O1s[f]	O8A	2.918	
	inter	O1s	O16[g]	2.966	
	inter	O2s[f]	O8[h]	2.690	
	inter	O2s	O2	3.041	
4d	intra	N1[i]	N1P	2.679	2.29
		N2[i]	N1P	2.723	2.21
	inter	N1	W1	2.948	2.12
	inter	N2	W1	3.086	2.21
	inter	W1	N11P	3.103	
	inter	W1	W2	3.013	
	inter	W2	O2[g]	2.939	

[a] Intermolecular or intramolecular. [b] Hydrogen atoms placed in idealized positions with N−H = 0.90 Å and O−H = 0.96 Å. [c] Coordinates at symmetry equivalent $2-x$, $^1/_2+y$, $2-z$. [d] Coordinates at symmetry equivalent $1-x$, $-^1/_2+y$, $2-z$. [e] Two independent molecules. Second molecule labeled A. [f] O1s and O2s are water molecules. [g] Coordinates at symmetry equivalents $1+x, y, z$. [h] Coordinates at symmetry equivalents $-1+x, y, z$. [i] N1H and N2H make bifurcated hydrogen bonds.

Table 2. Torsional Angles in the 18-Membered Macrocycle (deg)

	4a[a]	**4b**(1)[b]	**4b**(2)[b]	**4d**[d]
C2X1C6C7	−176	180	176	−177
X1C6C7N1	−31	−22	−16	−8
C6C7N1C1a	+174	−172	−173	177
C7N1C1aC1b	−103	−105	−115	−115
N1C1aC1bO1g	−55	−59	−61	−62
C1aC1bO1gC9	−135	−133	−147	−135
C1bO1gC9C10	−173	−175	−179	−173
O1gC9C10X11	9	0	8	−11
C9C10X11C12	179	180	178	179
C10X11C12C16	176	177	177	178
X11C12C16O2g	20	−1	+5	−7
C12C16O2gC2b	−173	−177	−180	−180
C16O2gC2bC2a	−166	−140	−140	−122
O2gC2bC2aN2	−57	−60	−63	−62
C2bC2aN2C8	−109	−117	−116	−159
C2aN2C8C2	−178	−170	−170	−178
N2C8C2X1	−25	−18	−14	+11
C8C2X1C6	176	177	179	179
C7N1C1aC1′	129	136	123	115
N1C1aC1′O10	−45	−171	−167	+179
C1a C1′O10C10M	−176	−174	−179	+177
C8N2C2aC2′	+120	+117	+121	+78
N2C2aC2′O20	+147	−163	−171	−151
C2aC2′O20C20M	+168	−177	−174	−179

[a] X1 ≡ C1, X11 ≡ C11. [b] X1 ≡ N1P, X11 ≡ C11. [d] X1 ≡ N1P, X11 ≡ N11P.

Although crystals of both **4b** and **4d** contain water molecules, the water molecules in the lattice of **4b** are between the sheets of tubes (Figure 9), while in **4d**, the water molecules are inside the tubes (Figures 8 and 9). The aromatic stacks in **4b** are aligned along a straight line, parallel to the vertical axis in Figure 9, with the result that the tubules are filled with H atoms from neighboring molecules on either side (the C4H···HC14 distance across the middle of a tubule is 2.35 Å). In **4d**, however, the tubules are rotated slightly so that the aromatic stacks form a zigzag pattern in projection. The CH atoms of the pyridine groups are directed away from the inside of the tubule, leaving enough space to accommodate two water molecules inside the tubule. Aside from hydrogen bonds, the closest approaches to the water molecules are W1···HC3a = 3.19 Å, W1···HC15a = 3.10 Å, W2···HC3a = 2.35 Å, and W2···HC14a = 2.75 Å. W1 is tetrahedrally hydrogen bonded to N1H, N2H, N11P, and

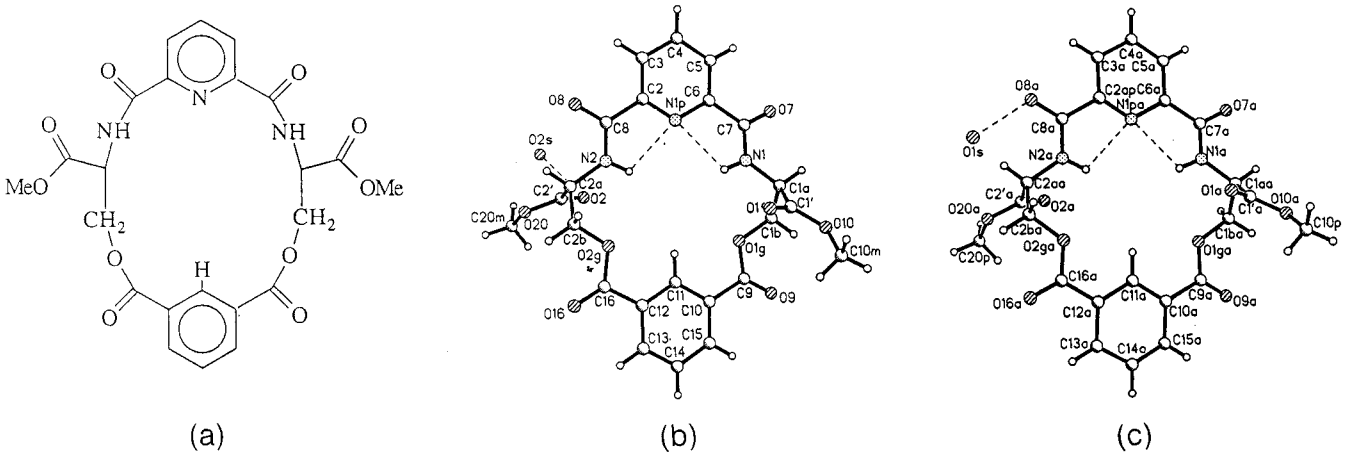


Figure 4. (a) Chemical structure of cyclo(Ph-Ser-Py-Ser-) (**4b**). (b) Crystal structure of **4b**, Molecule 1. (c) Crystal structure of **4b**, Molecule 2. The NH protons are bonded to pyridine ring N. There are two water molecules associated with molecules 1 and 2 (the hydrogen atoms for the water molecules were not located in the difference map).

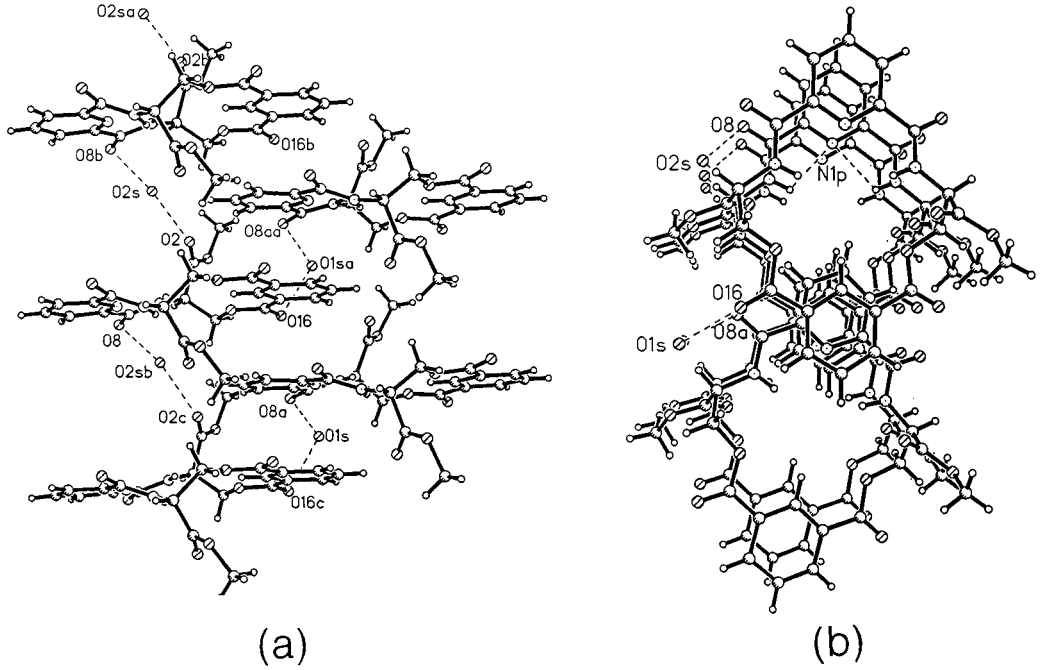


Figure 5. (a) Vertical parallel stacks in the self-assembly of **4b**. Molecules 1 and 2 stack in separate columns, but the pyridine and phenyl rings interdigitate from one column to the other with a ~3.5-Å separation between the planes of the rings. In the stacks, the molecules 1 are connected by hydrogen bonds to O2s (water 2). Molecules 2 are connected to molecules 1 by hydrogen bonds to O1s (water 1). There are no direct hydrogen bonds between the neighboring stacks. (b) Top view of a portion of a layer containing the interdigitated stacks in **4b**.

W2. In turn, W2 also forms a hydrogen bond with O2 in the same stack (Figure 10).

Conclusions

The present work provides examples of cyclopeptides capable of self-assembly into tubular structures through aromatic $\pi-\pi$ interactions. The tubes are not single but are part of a parallel assembly in a sheet. The cylindrical stacks have interdigitated aromatic rings from one column to another with 3.4−3.5 Å separation between the planes of the rings. The pairs of aromatic rings can be benzene/pyridine as in **4b** or pyridine/pyridine as in **4d**, but the macrocycle **4a**, that contains only a pair of benzene rings, does not stack. The stacks in **4b**,**d** are further stabilized by some intermolecular hydrogen bonding through water molecules acting as bridges. There are no direct hydrogen bonds between the macrocycles. Studies related to the functional properties of these assemblies are in progress in our laboratories.

Experimental Section

All amino acids used were of L-configuration. Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker WM-300 and JEOL 90-MHz instruments. The chemical shifts are reported in δ (parts per million) with TMS at 0.00 as an internal reference. FAB-MS were obtained on a JEOL SX-120/DA-6000 instrument using *m*-nitrobenzyl alcohol as the matrix. Reactions were monitored wherever possible by TLC. Silica gel G (Merck) was used for TLC, and column chromatography was done on silica gel (100−200 mesh) columns which were generally made from a slurry in hexane or a mixture of hexane and ethyl acetate. Products were eluted with either a mixture of ethyl acetate/hexane or chloroform/methanol.

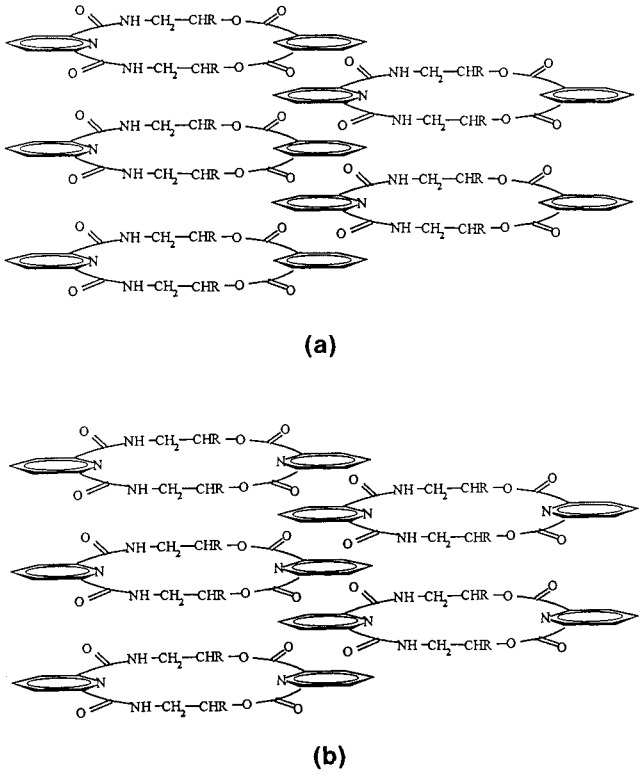


Figure 6. Schematic representation of the multiple $\pi-\pi$ stacks in the self-assembly of (a) **4b** and (b) **4d**.

General Procedure for the Preparation of 1,3-Benzene or 2,6-Pyridine Bis-Ser Depsipeptides 3a,b. A solution of 1,3-benzene or 2,6 pyridine dicarbonyl dichloride (**1**, 1 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over a period of 0.5 h to a well-stirred and ice-cooled solution of N^{α}Z-Ser-OMe (2 mmol) in dry CH_3CN (30 mL) containing *N*,*N*′-dimethyl-4-aminopyridine (DMAP, 2 mmol) and the mixture stirred at room temperature for 12 h. Solvents were evaporated in vacuo, and the residue was triturated with ethyl acetate (∼100 mL), the extract washed sequentially, with 20 mL each of ice cold 2 N H_2SO_4, H_2O, and 5% aqueous $NaHCO_3$, and the organic layer dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residue was purified on a short column of silica gel using a mixture of ethyl acetate and hexane as eluents to afford the bis-Ser peptides **3a**,**b** in nearly quantitative yields.

3a: yield 95%; syrup; IR (KBr) 3375, 2952, 1729, 1521, 1434 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.68 (s, 6H), 4.65 (brs, 4H), 4.80 (m, 2H), 5.10 (s, 4H), 6.27 (d, J = 7.5 Hz, 2H), 7.32 (10 H, brs), 7.55 (t, 1H), 8.20 (dd, J = 2.0, 9.5 Hz, 2H), 8.57 (brs, 1H).

3b: yield 86%; syrup; IR (KBr) 3375, 2962, 1730, 1586, 1533, 1453 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.67 (s, 6H), 4.77 (m, 6H), 5.09 (s, 4H), 6.62 (d, J = 7.5 Hz, 2H), 7.32 (s, 10 H), 7.95 (t, J = 7.8 Hz, 1H), 8.23 (brd, 2H).

Preparation of 18-Membered Cyclodepsipeptides 4a−e. General Procedure: (a) N-Deprotection of Aryl-Supported Bis-N^{α}Z-Ser Depsipeptides (3a,b). A solution of bis-N^{α} Z peptide (**3a,b**, 1 mmol) in dry ethyl acetate (∼10 mL) was admixed with Pd/C, 5% (peptide/catalyst 1:0.5 w/w), and hydrogenolyzed using a Parr hydrogenation apparatus. The reaction mixture after complete N^{α} deprotection (TLC) was filtered through a sintered funnel, the residue washed with dry ethyl acetate (20 mL), and the filtrate directly used for the coupling reaction in the next step.

(b) Condensation of N^{α}-Deprotected Aryl-Supported Bis-Ser Depsipeptides (3a,b) with 1. To a well-stirred and ice-cooled solution of N^{α}-deprotected bis-Ser depsipeptide (1 mmol in ∼100 mL of dry EtOAc) and NEt_3 (2 mmol) was added dropwise a solution of freshly prepared 1,3-benzene or 2,6-pyridine dicarbonyl dichloride (1 mmol in 50 mL of dry CH_2Cl_2) over a period of 0.5 h, and the mixture was stirred at room temperature for 12 h. The solvents were removed in vacuo, the residue taken up in CH_2Cl_2 (∼100 mL) and washed, sequentially, with 20 mL each of the ice-cold 2 N H_2SO_4, H_2O, and 5% aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo, and the residue was purified on a column of silica gel using either a mixture of EtOAc/hexane or $CHCl_3$/MeOH as eluents to afford aromatic-bridged Ser cyclodepsipeptides **4a**−**e** in good yields.

4a: yield 51%; mp 234−236 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 6H), 4.42 (dd, J = 3.4, 11.2 Hz, 2H), 5.21 (m, 2H), 5.34 (dd, J = 2.1, 11.4 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 7.62 (m, 2H), 8.03 (s, 1H), 8.10 (dd, J = 2.0, 9.5 Hz, 2H), 8.29 (dd, J = 2.0, 9.5 Hz, 2H), 8.49 (brs, 1H); FAB-MS: *m*/*z* (%): 499 (100) $(MH)^+$.

4b: yield 50%; mp 227−230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H), 4.36 (dd, J = 3.0, 8.4 Hz, 2H), 5.26 (m, 2H), 5.50 (dd, J = 1.5, 9.9 Hz, 2H), 7.61 (t, J = 7.8 Hz, 1H), 8.10 (t, J = 7.8 Hz, 1H), 8.29 (dd, J = 1.5, 6.3 Hz, 2H), 8.44 (d, J = 7.8 Hz, 2H), 8.53 (d, J = 9.3 Hz, 2H), 8.68 (s, 1H); FAB-MS: *m*/*z* (%): 500 (100%) $(MH)^+$.

4c: yield 52%; mp 240−242 °C; $[\alpha]^{25}_D$ +87.26 (c, 3.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.55−2.31 (m, 14H), 3.79 (s, 6H), 4.55 (dd, J = 3.42, 7.73 Hz, 2H), 4.97 (m, 4H), 6.47 (d, J = 8.0 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 8.28 (dd, J = 1.9, 7.5 Hz, 2H), 8.37 (brs, 1H); FAB-MS: *m*/*z* (%): 557 (100%) $(MH)^+$.

4d: yield 28%; mp 236−237 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H), 4.47 (brd, 2H), 5.35 (m, 4H), 8.06 (t, 2H), 8.38 (m, 4H), 9.75 (d, J = 7.8 Hz, 2H); FAB-MS: *m*/*z* (%): 501 (100) $(MH)^+$.

4e: yield 22%; semisolid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60−2.20 (m, 14H), 3.78 (s, 6H), 4.18 (d, J = 11.3 Hz, 2H), 5.04 (d, J = 8.9 Hz, 2H), 5.16 (d, J = 9.0 Hz, 2H), 8.09 (t, J = 7.9 Hz, 1H), 8.26

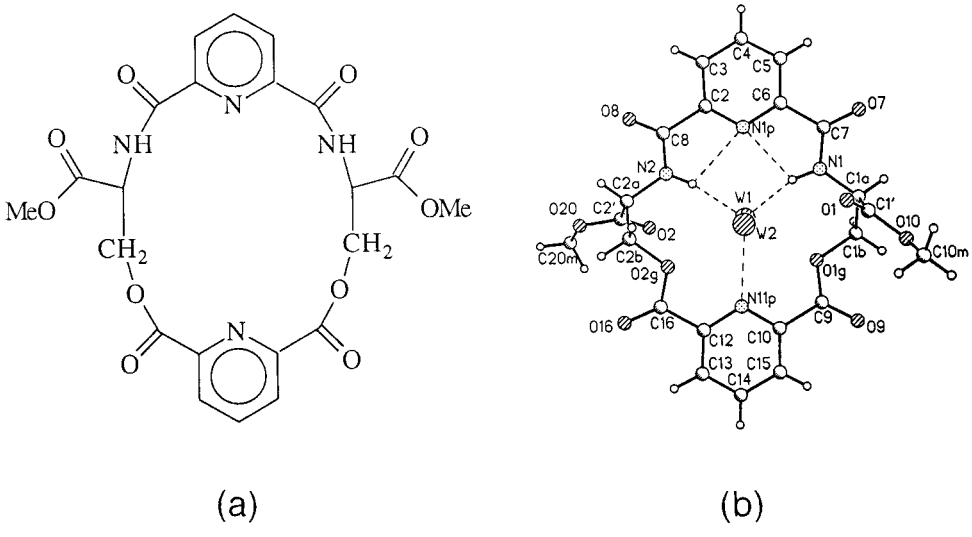


Figure 7. (a) Chemical structure of cyclo(Py-Ser-)$_2$ (**4d**). (b) Crystal structure of **4d**.

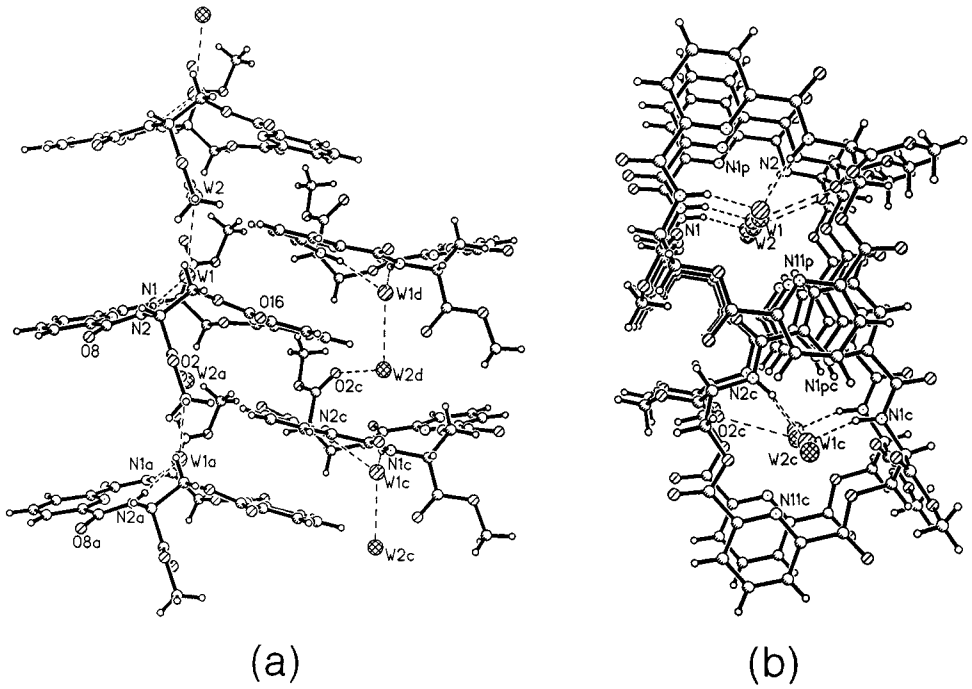


Figure 8. (a) Tubular self-assembly in **4d**. The molecules of **4d** stack one over the other and are connected by hydrogen bonds to two water molecules in a row. The main organizing force for the self-assembly is provided by the $\pi-\pi$ interactions between the pyridine rings. (b) Top view of a portion of a layer containing the interdigitated stacks in **4d**. Compare to Figure 5a,b.

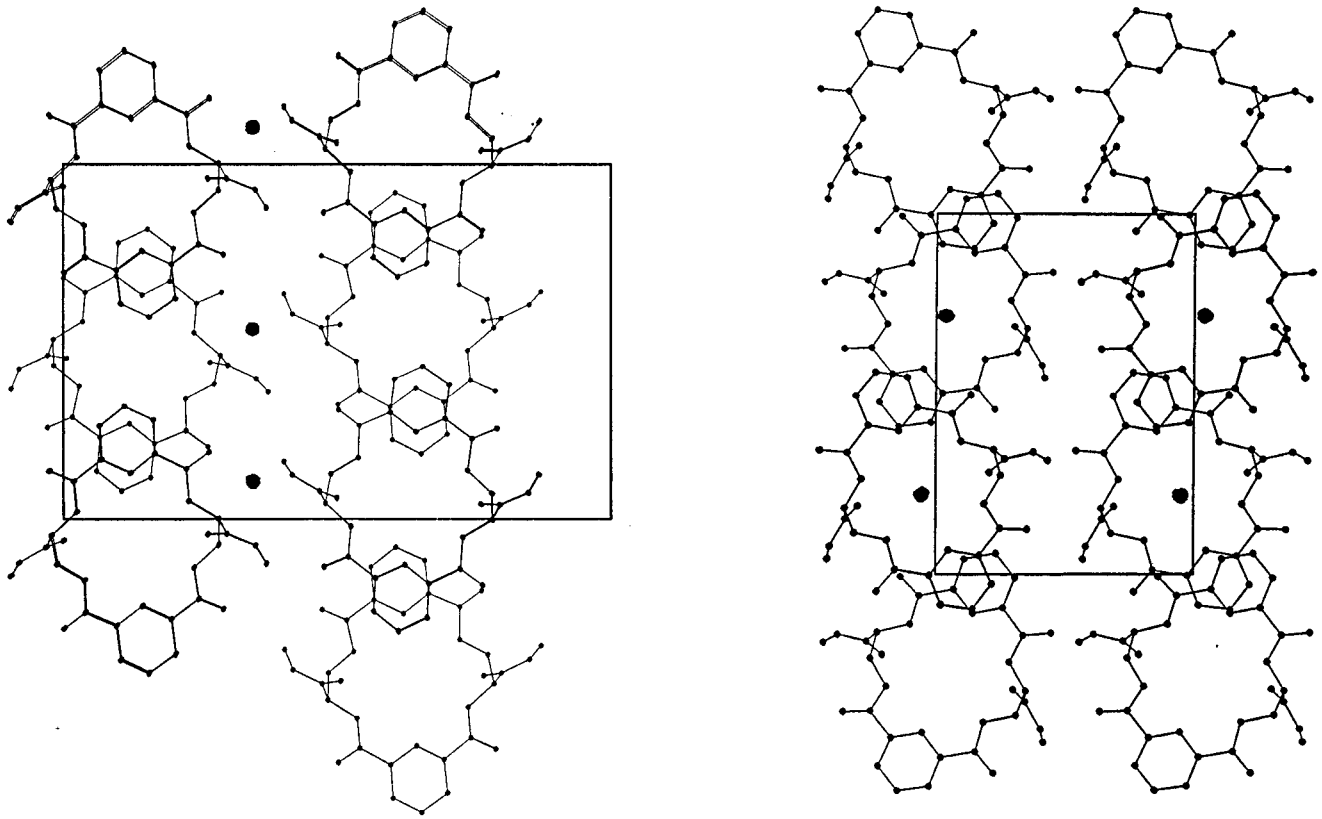


Figure 9. Comparison of the packing and $\pi-\pi$ stacking in **4b** (left) and **4d** (right). In **4b** water molecules occur between the layers, while in **4d** water molecules occur within the tubules created by the macrocyles. In each case the projection is down the *a* axis.

(d, $J = 8.9$ Hz, 2H), 8.43 (d, $J = 7.8$ Hz, 2H); FAB-MS: *m*/*z* (%): 558 (100) $(MH)^+$, 580 (73) $(M + Na^+)$.

X-ray Diffraction Analysis. X-ray structure analysis of **4a**: $C_{24}H_{22}N_2O_{10}$, $P2_1$, $a = 11.058(1)$ Å, $b = 9.290(0)$ Å, $c = 11.111(1)$ Å, $\beta = 92.920°$, $d_{calc} = 1.452$ g/cm^3, $R = 3.91\%$. X-ray structure analysis of **4b**: $C_{23}H_{19}N_3O_{10}\cdot H_2O$, $P2_1$, $a = 7.135(1)$ Å, $b = 22.751(3)$ Å, $c = 14.759(2)$ Å, $\beta = 90.10(1)°$, $d_{calc} = 1.379$ g/cm^3, $R = 12.0\%$. X-ray structure analysis of **4d**: $C_{23}H_{20}N_3O_{10}\cdot 2H_2O$, $P2_1$, $a = 7.002(0)$ Å, $b = 15.562(2)$ Å, $c = 11.202(1)$ Å, $\beta = 93.19(1)°$, $d_{calc} = 1.464$ g/cm^3, $R = 5.35\%$.

For **4a,d**, X-ray data were collected on a Siemens automated diffractometer in the $\theta/2\theta$ mode, constant scan speed of 10 deg/min, 2° scan width, and $2\theta_{max} = 116°$ (resolution 0.9 Å for Cu Kα radiation). Full-matrix anisotropic least-squares refinement was performed on the

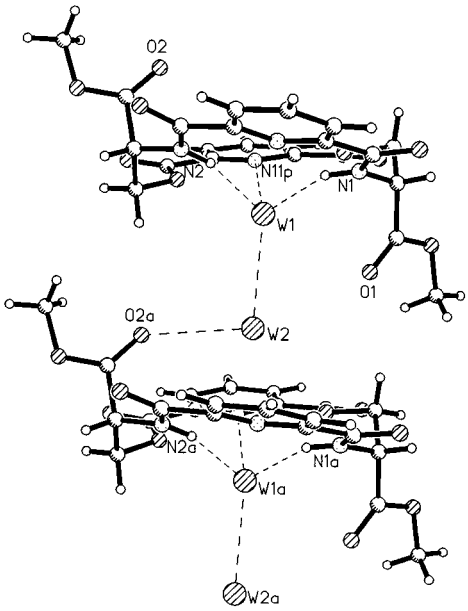


Figure 10. Side view of a partial stack of molecules of **4d** showing water molecules in the tubule. Not shown are neighboring molecules (in front and back) with their pyridine moieties inserted halfway between the pyridine moieties shown that provide $\pi-\pi$ interactions.

parameters for all the atoms except the H atoms. The H atoms were placed in idealized positions and allowed to ride with the C or N atom to which each was bonded. For **4b**, the crystals were in the form of extremely fine needles. After a number of trials, the acicular crystal that provided sufficient scattering power to measure observable data up to $2\theta = 100°$ was 0.10 × 0.04 mm in cross section. The profiles of the diffracted spots were broad, indicating either a bundle of needles with almost identical alignment, rather than a single crystal, or perhaps, some undetectable twinning since the β angle is very near 90°. The high R factor could be attributed to either of the above conditions. A structure could not be found in space groups with higher symmetry. Although the two independent molecules are quite similar, the environment around each molecule is different, thus precluding higher symmetry space groups.

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Supporting Information Available: ROESY spectra of **4a**−**c** and X-ray coordinates, bond lengths, bond angles, anisotropic thermal parameters, and coordinates for hydrogen atoms (28 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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