Adamantane-Constrained Novel Cyclodepsipeptides: Crystal Structure and Self-Assembling Properties of Cyclo(Adm-Ser)$_2$ and Cyclo(Adm-Ser-Xaa)$_2$, Xaa = Val/Ser

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Received March 25, 1998

Abstract: Crystallographic studies on three members of a novel class of cyclodepsipeptides, containing adamantane units in the cyclic framework, are described. While the 18-membered cyclo(Adm-Ser)$_2$ (**1**) shows a simple structure with no internal hydrogen bonds, the higher members, cyclo(Adm-Ser-Val)$_2$ (**2**) and cyclo-(Adm-Ser-Ser)$_2$ (**3**), exhibit interesting secondary structural features in the solid state. The two boat-shaped conformers of **2** assemble in a head-to-head fashion, giving rise to dimeric structures with water-filled channels, and show ion-transport properties. The molecule **3** revealed a unique intramolecular antiparallel β-sheet formed by complementary hydrogen bonding between the backbone NH groups and the side chain ester carbonyls. The self-assembly patterns in the solid state are a hydrogen-bonded chain in **1** and infinite ribbons in **2** and **3**.

Introduction

Design and synthesis of novel macrocyclic molecules capable of performing specific functions in biological systems continues to attract the attention of synthetic chemists.[1] Conformationally constrained cyclopeptides are particularly important in view of their demonstrated potential to act as regulators of membrane ion transport,[2] scaffolds/templates in the *de novo* design of artificial proteins,[3] and rigid β-turn templates for the construction of simple mimics of biologically active peptides.[4,5] Recently,[6] we introduced a novel concept in the design of membrane ion-transporting cyclopeptides, a key feature of which is the incorporation of rigid, low molecular weight, lipophilic adamantane units in the cyclic backbone. The adamantane building blocks with rigid diamondoid framework provided the desired membrane permeability and conformational constraint for efficient ion transport in lipid bilayers.

As a first illustration of this strategy, a family of adamantane-containing cystine cyclopeptides with the general structure cyclo(Adm-Cyst)$_n$ (Adm = 1,3-adamantane dicarbonyl; Cyst = L-cystine dimethyl ester; $n = 2-5$) was created in a single step by the reaction of L-cystine dimethyl ester with 1,3-adamantane dicarbonyl dichloride. These macrocycles, containing alternating repeats of cystine and adamantane units in 26-, 39-, 52-, and 65-membered rings, respectively, possess a hydrophilic interior and hydrophobic periphery and consequently were capable of transporting Na^+ and K^+ ions selectively in model membranes. The single-crystal X-ray structure of the 39-membered cyclopeptide ($n = 3$) showed that the macrocycle adopted a topologically well-defined figure-eight (double helical) motif in the solid state.[7]

Subsequently, the design strategy was exploited to construct another novel family of membrane ion-transporting peptides, the serine-based cyclodepsipeptides on adamantane building blocks.[8] This novel class of macrocyclic peptides with ring size

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S0002-7863(98)01012-9 CCC: $15.00
Published on Web 07/03/1998

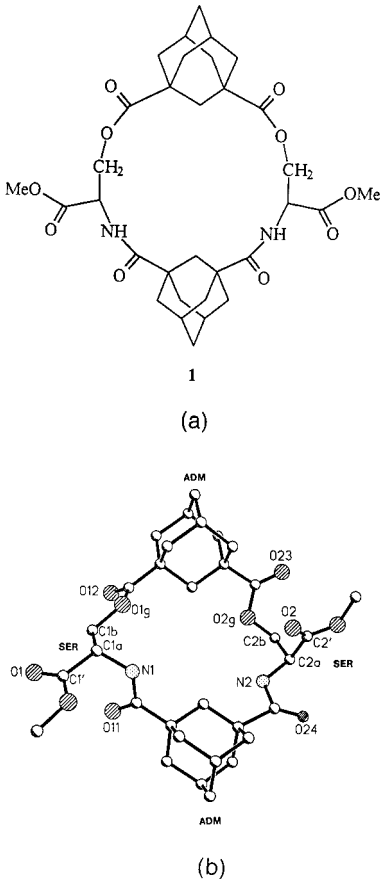

Figure 1. (a) Molecular formula of cyclo(Adm-Ser)$_2$ (**1**). (b) Crystal structure of (**1**).

varying from 18 to 36 were shown to adopt a β-turn-like conformation in solution. As anticipated, they exhibited very high efficiency in transporting Na^+, K^+, Ca^{2+}, and Mg^{2+} ions across model membranes. However, no selectivity was observed in ion transport.[8]

Results and Discussion

In this paper, we describe the X-ray crystallographic studies on three macrocyclic peptides of this novel class, namely, cyclo(Adm-Ser)$_2$ (**1**), cyclo(Adm-Ser-Val)$_2$ (**2**), and cyclo(Adm-Ser-Ser)$_2$ (**3**). These examples were particularly chosen because of increasing complexity in their structure. Thus, while 18-membered macrocycle **1** (Figure 1a) can be considered as the simplest member of this series, macrocycles **2** (Figure 3a) and **3** (Figure 8a) each contain an additional amino acid in their 24- and 26-membered ring framework, respectively. In macrocycle **2** while one adamantane unit is linked through an ester bond and the second through an amide, in all-Ser-containing cyclodepsipeptide **3**, both adamantane units are connected through ester linkages. All three molecules have an adequate number of NH and C═O groups in their cyclic backbone that may participate in internal or external hydrogen bonding. Cyclodepsipeptide **3** has an additional NH (as carbamate) on the exterior of the ring, providing an attractive model for hydrogen bonding study. Of the three macrocycles, molecule **2** was shown to be most efficient in transporting Na^+, K^+, Ca^{2+}, and Mg^{2+} ions across lipid bilayer membranes. While **1** was totally devoid of any ion-transport capability, macrocycle **3** showed only modest activity.

The crystal structure of **1** (Figure 1b) showed that the 18-membered macrocycle does not possess any internal hydrogen

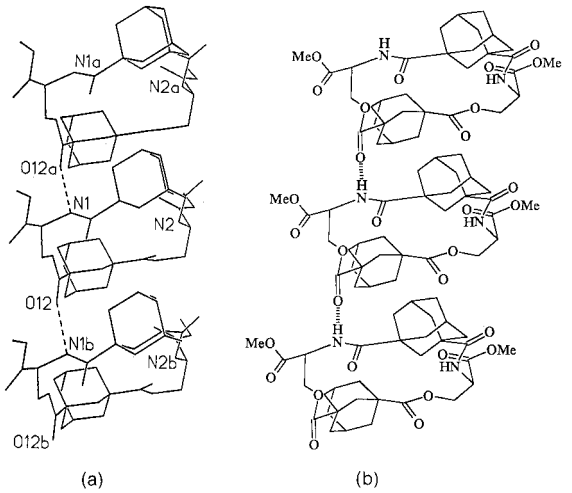

Figure 2. (a) Hydrogen-bonded chain assembly of **1** in the solid state. (b) Schematic representation of the molecular chain in **1**.

bonds. While all carbonyls in **1** are oriented outward, the amide NH groups are facing inward. Macrocycle **1** has a slight twist in the ring that enables it to participate in intermolecular hydrogen bonding. Figure 2a shows the self-assembly of **1** in the solid state. The molecules, related by translation, are connected into an infinite stack through N(1)H···O(12) hydrogen bonds (N···O, 2.966 Å; H···O, 2.19 Å). Figure 2b shows the schematic picture of the chain assembly in **1**. Only one NH group in **1** participates in hydrogen bonding. N2 is devoid of any hydrogen bond formation unless one considers the nearest approach of N2H to a possible acceptor, N2···O2g = 2.815 Å and N(2)H···O2g = 2.56 Å, as being a variation of a C_5-type hydrogen bond. The crystal structure clearly brings out the inability of **1** to complex with metal ions. The C2···C14 distance across the ring is only 4.82 Å, while the C(2)H··· C(14)H distance is only 3.30 Å. The small size of the ring cavity and orientation of all carbonyls to the outside may be the main contributing factors.

The solution state conformation of **1** as examined by ^{1}H NMR, FT-IR, and CD studies was in total agreement with the solid state structure. No evidence of intramolecular hydrogen bonding or presence of any secondary structural features was observed in the solution state. No significant cross-peaks (except weak ROE between NH and adamantane methylene) were seen in the ROESY spectra of **1**, thus corroborating the syn amide conformation observed in the solid state structure.

The crystal structure of cyclo(Adm-Ser-Val)$_2$ (**2**) revealed that the 24-membered macrocycle is present in two closely related conformational forms, molecule A and molecule B (Figure 3b). Each molecule has a syn pair (ester C═O groups) and an anti pair (amide C═O groups) of carbonyls that are adjacent to the adamantane unit. Figure 3c shows that the two conformers molecule A and molecule B, superimposed on each other, are quite similar. Torsional angles around the backbone ring are listed in Table 1.

The crystal structure further showed that the molecules of **2** adopt a boatlike conformation with no internal hydrogen bonds. The molecules A and B assemble in a head to head fashion (with concave surfaces facing each other) to form dimers filled with well-ordered water molecules. The water molecules act as bridges and stabilize the dimer through O−H···O and N−H···O hydrogen bonds (Figure 4). The water channel is perpendicular to the page as shown in Figure 4. Figure 5 shows a view into the oxygen-lined channel (with the water molecules removed). The assembly is highly hydrophobic at the exterior

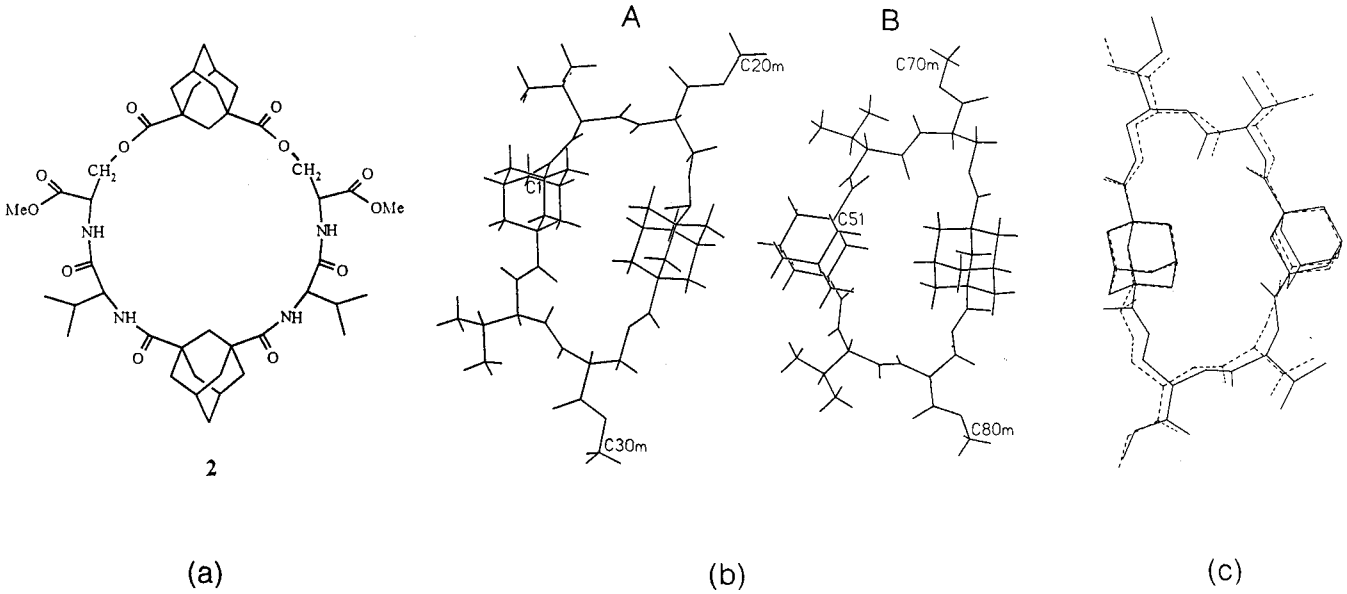

Figure 3. (a) Molecular formula of cyclo(Adm-Ser-Val)$_2$ (**2**). (b) Two conformational forms of **2**. Molecule A and molecule B have closely related conformations (for torsion angles, see Table 1). (c) The two molecules A and B superimposed on each other.

Table 1. Torsional Angles in the Cyclodepsipeptide Rings (deg)

1			**2A**	**2B**[a]	**3**[b]
C3C2C1C11	−178	C3C2C1C11	175	−179	178
C2C1C11N1	−69	C2C1C11O1g			82
C1C11N1C1a	−171	C1C11O1gC1b			−177
C11N1C1aC1b	−76	C11O1gC1bC1a			92
N1C1aC1bO1g	−63	O1gC1b C1aC1′			59
C1aC1bO1gC12	+170	C1bC1aC1′N2			−122
C1bO1gC12C13	−178	C2C1C11N1	131	63	
O1gC12C13C14	+89	C1C11N1C1a	−179	−177	
C12C13C14C15	+179	C11N1C1aC1′	142	68	
C13C14C15C23	+179	N1C1aC1′N2	−131	−144	
C14C15C23O2g	0	C1aC1′N2C2a	−177	−166	−176
C15C23O2gC2b	+179	C1′N2C2aC2b	−133	−99	81
C23O2gC2bC2a	+100	N2C2aC2bO2g	+83	55	59
O2gC2bC2aN2	+59	C2aC2bO2gC12	−124	83	144
C2bC2aN2C24	+171	C2bO2gC12C13	175	176	178
C2aN2C24C3	+171	O2gC12C13C14	169	162	46
N2C24C3C2	−23	C12C13C14C15	172	178	179
C24C3C2C1	−177	C13C14C15C23	177	178	−179
		C14C15C23O3g	149	−149	−45
		C15C23O3gC3b	−179	−171	180
		C23O3gC3bC3a	+94	−171	−154
		O3gC3bC3aN3	61	63	69
		C3bC3aN3C4′	−114	−124	77
		C3aN3C4′C4a	−173	−177	−170
		C2C3C24O4g			109
		C3C24O4gC4b			176
		C24O4gC4bC4a			78
		O4gC4bC4aC4′			47
		C4bC4aC4′N3			−120
		N3C4′C4aN4	−135	−129	
		C4′C4aN4C24	72	101	
		C4aN4C24C3	−174	178	
		N4C24C3C2	63	156	
		C24C3C2C1	180	178	175

[a] The numbering of atoms in **2B** is the same as in **2A** plus 50. [b] Approximate 2-fold rotation symmetry in molecule **3**.

upper left-hand corner and lower right-hand corner, at the positions of the adamantyl groups. Hydrogen bonds for **2** are listed in Table 2.

The water-filled dimers of **2** have a pair of NH and C═O groups extending outward on each convex face that can be self-complementary. Consequently, they assemble through pairs of direct N−H···O═C bonds into an infinite hydrogen-bonded ribbon as shown in Figure 6. To our knowledge, this finding represents the first example of a cyclopeptide or a depsipeptide

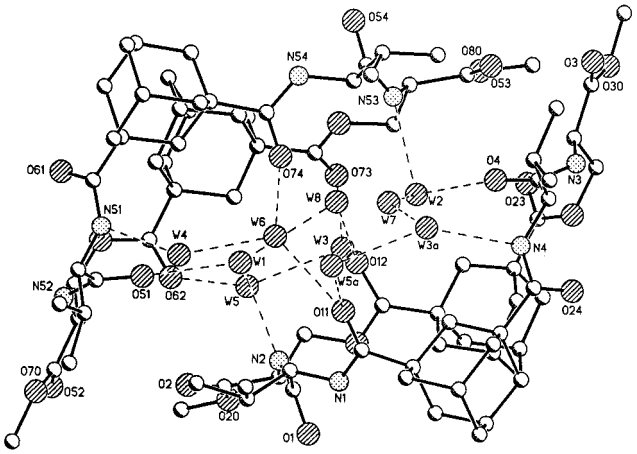

Figure 4. Dimeric structure with water-filled channel, formed by the head-to-head linking of the boat-shaped molecules A and B in **2**.

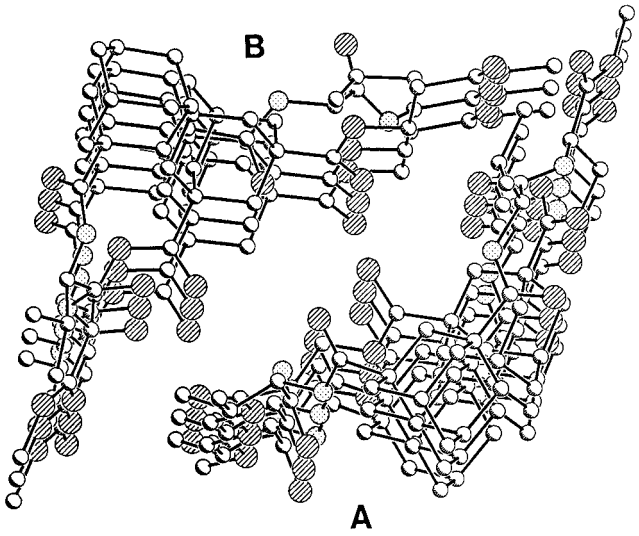

Figure 5. A view into the oxygen-lined channel formed by molecules A and B of **2**. Water molecules have been omitted.

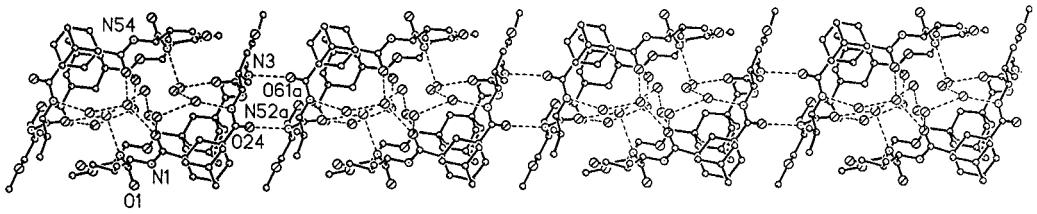

Figure 6. Hydrogen-bonded ribbon assembly of water-filled dimers. The dimers are connected through a symmetrical pair of NH···O═C bonds.

Table 2. Hydrogen Bonds in (Adm-Ser-Val)$_2$, **2**[a]

type	donor	acceptor	N···O or O···O, Å	H···O, Å
	N1	none		
C	N2	W1	2.915	2.02
BD	N3	O61[b]	2.905	2.01
C	N4	W3[c]	3.024	2.15
C	N51	W4	3.063	2.17
BD	N52	O24[d]	2.997	2.12
C	N53	W2	2.913	2.02
BD	N54	O1[e]	2.950	2.10
C	W1	O51	2.705	
C	W2	O4	2.673	
C	W3	O73	2.880	
W	W4	W6	2.617	
C	W5	O11[f]	2.891	
C	W5	O62	2.948	
C	W6	O11	2.696	
C	W6	O74	2.657	
C	W7	O11	3.135	
C	W8	O12	2.590	
C	W8	O74	2.628	
W	W1	W8	3.025	
W	W2[g]	W7	2.685	
W	W3	W5	2.721	
W	W3[g]	W7	2.952	

[a] It should be noted that W2 and W8 are mutually exclusive. The site for W8 has the lower occupancy. Hydrogen bonds between the peptide dimer and water in the channel (C); between dimer assemblies (BD); between two waters in the channel (W). [b] Symmetry equivalent at *x, y,* 1 + *z*. [c] Symmetry equivalent at x, 1 + *y, z*. [d] Symmetry equivalent at *x, y,* −1 + *z*. [e] Symmetry equivalent at 1 + *x, y, z*. [f] Symmetry equivalent at *x,* −1 + *y, z*. [g] It is not certain which water molecule donates the hydrogen to the hydrogen bond.

molecule forming dimers with water-filled channels and their further assembly into a hydrogen-bonded molecular ribbon. The ribbons are connected into sheets by the single N54H···O1 hydrogen bond (in the vertical direction in Figure 6). It is curious that N1H is directed into a hydrophobic pocket formed by two adamantyl moieties and a valine side chain and is bereft of any hydrogen bond formation, Figure 7. The highly efficient but nonselective nature of ion transport by **2** can now be rationalized, since the metal ion could easily enter the dimer cavity, displacing the water molecules, form a sandwiched complex that is adjustable in size without disrupting the conformation of the macrocycle, and be transported across the bilayer membranes by a carrier type of mechanism. However, the crystal structure does not provide a direct proof for the ion-transport mechanism, and a more detailed study on the concentraton dependence of the ion-transport ability of **2** is needed to distinguish the "dimeric carrier" from alternative mechanisms.

The ^{1}H NMR and CD spectra of **2** indicated a development of secondary structural features in the solution state. A particularly diagnostic feature which signifies the formation of β-turn structures in peptides was the presence of strong Ser NH−Val C$^\alpha$H and Val C$^\alpha$H−Ser C$^\beta$H$_2$ cross-peaks in the ROESY NMR spectra of **2** in $CDCl_3$ (Supporting Information). The presence of a strong negative band at ∼215 nm with a

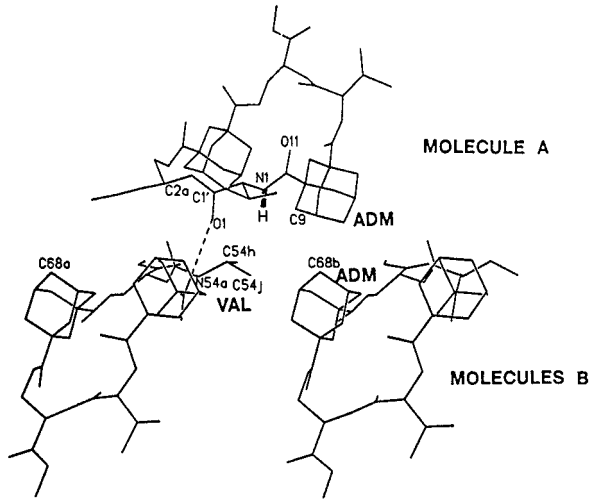

Figure 7. The hydrophobic environment surrounding the N1H moiety in **2** precludes any intermolecular hydrogen bond formation.

shoulder at ∼202 nm in the CD spectra of **2** in trifluoroethanol (Supporting Information) was supportive of a type I β-turn in cyclic peptides.[9]

The 26-membered cyclodepsipeptide **3** containing four serine residues connected to adamantane rings through ester linkages possesses two NH groups as part of the cyclic backbone and two as protected handles on the exterior of the macrocycle, Figure 8a.

Additionally, the presence of two COOMe groups on the exterior, on the opposite sides of the backbone, provides attractive opportunities for hydrogen bonding. The crystal structure of **3** revealed a unique feature, the presence of two intramolecular NH···O═C bonds enclosing a 10-membered ring, Figure 8b (N3···O2 = 3.122 Å, N3H···O2 = 2.26 Å; N2···O3 = 3.123 Å, N2H···O3 = 2.26 Å). This creates two adamantane-containing loops with 15 members in the macrocycle. The 10-membered hydrogen-bonded ring is formed by participation of backbone NH groups in complementary hydrogen bonding with side chain ester carbonyls. Interestingly, as shown in the crystal structure (Figure 8b), the cyclic backbone appears to be forced to make a reverse turn in order to form an antiparallel hydrogen-bonded sheet. To our knowledge, although cyclopeptides with pleated sheets are known to occur in nature,[2] the present example of a cyclic backbone forced into a reverse turn to form an antiparallel β-sheet-type structure with the participation of side chain groups may be the first demonstration in synthetic cyclodepsipeptides.

Interestingly, the CD spectrum of **3** shows a broad negative band at ∼220 nm which may support the sheet structure. In FT-IR ($CHCl_3$, 298 K), **3** showed two intense bands in the NH stretch region. While the band at 3422 cm^{-1} was assigned to

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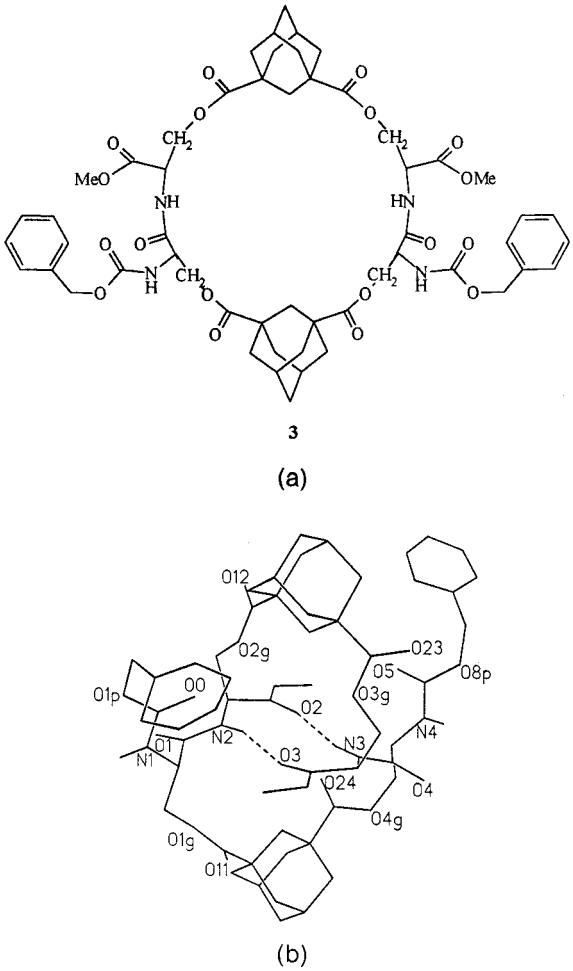

Figure 8. (a) Molecular formula of cyclo(Adm-Ser-Ser)$_2$ (**3**). (b) Crystal structure of **3**. The cyclic backbone makes a twist to form an antiparallel β-sheet through the participation of backbone NH groups in complementary hydrogen bonding with the side chain ester carbonyls. The 10-membered hydrogen-bonded ring divides the macrocycle into two adamantane-containing loops of 17 and 19 members each.

the nonbonded NH group, the more intense band at 3372 cm^{-1} may be attributed to the NH group intramolecularly bonded to an ester carbonyl.

Further examination of the crystal structure showed that the molecules of macrocycle **3** are connected into an infinite ribbon through pairs of external NH···O═C bonds (Figure 9a) (N1···O4a = 2.882 Å, N1H···O4a = 2.02 Å; N4a···O1 = 2.867 Å, N4aH···O1 = 2.06 Å). The hydrogen-bonded molecular ribbon in the self-assembly of **3** is formed by the participation of NH and O═C groups of the backbone in complementary hydrogen bonding with the ester carbonyl and carbamate NH functions of the side chains. Thus, while the ring NH participates in internal hydrogen bonding, the side chain NH connects the molecules into an infinite ribbon through intermolecular hydrogen bonding with the backbone carbonyls. The molecular ribbon is made up of a continuous array of 10-membered hydrogen-bonded rings (Figure 9c).

Conclusion

In conclusion, the present work provides the first report of the crystallographic study on the serine-based cyclodepsipeptides on adamantane scaffolds. The ion-transport activity, or non-activity, of the similar macrocycles is related to their diverse folding motifs. The novel boat-shaped structure of cyclo(Adm-Ser-Val)$_2$ (**2**) self-assembling into dimers with water-filled

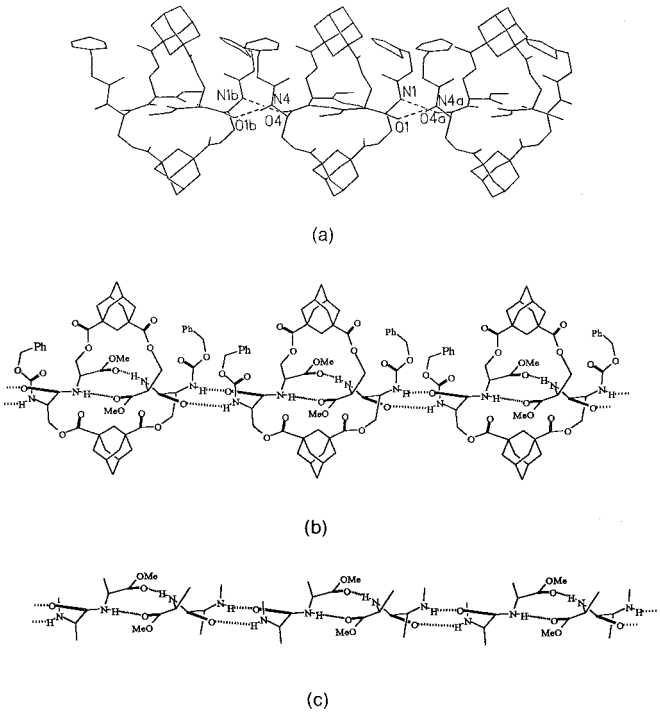

Figure 9. (a) X-ray picture of the infinite molecular ribbon in **3** formed by participation of the backbone carbonyls and side NH groups in complementary intermolecular hydrogen bonding. (b) A schematic representation of the hydrogen-bonded ribbon in **3**. (c) Continuous array of 10-membered hydrogen-bonded rings created by intra- and intermolecular hydrogen bonding between the complementary NH and CO groups.

channels provides support for the efficient yet nonselective nature of the ion transport observed with **2** in lipid bilayer membranes. The antiparallel sheet structure exhibited by **3**, to our knowledge, is the first example of a cyclodepsipeptide making a reverse fold to create an intramolecularly hydrogen-bonded 10-membered ring by complementary NH···O═C hydrogen bonding between side chain and the backbone groups.

The demonstration of the self-assembly of these macrocyclic peptides into hydrogen-bonded chains in **1** and ribbons in **2** and **3** is an additional attractive feature of the present work.

Experimental Section

All amino acids used were of L-configuration. The preparation and characterization of cyclodepsipeptides is reported elsewhere.[8] The cyclodepsipeptides **1**−**3** were crystallized from aqueous methanol.

X-ray Diffraction Analyses. X-ray data were collected on an automated diffractometer in the $\theta/2\theta$ mode, constant scan speed of 10 deg/m, 1° scan width with $2\theta_{max} = 115°$ with Cu Kα radiation (λ = 1.54178 Å). Three check reflections were monitored after every 97 measurements. The structure determinations were straightforward with direct methods as programmed in SHELXTL, Version 4.2 (Siemens Analytical X-ray Instrument Co., Madison, WI). Full-matrix anisotropic least-squares analysis on F or F^2 was performed with the hydrogen atoms placed in ideal positions and allowed to ride with the C or N atoms to which each was bonded.

The crystallographic parameters for the crystals are [(**1**) $C_{32}H_{41}N_2O_{10}$] sp. gr. $P2_12_12_1$, a = 6.460(1) Å, b = 19.670(2) Å, c = 24.147(2) Å, V = 3068.3 Å, Z = 4, d_{calc} = 1.328 g/cm^3, colorless prism, 0.10 × 0.24 × 0.40 mm, R = 5.64%, [(**2**) $[C_{42}H_{60}N_4O10]_2 \cdot 8H_2O$] sp. gr. $P1$, a = 12.604(2) Å, b = 12.623(2) Å, c = 16.575(2) Å, α = 68.48(1)°, β = 89.87(1)°, γ = 74.50(2)°, V = 2350.5(6) Å^3, Z = 1, d_{calc} = 1.216 g/cm^3, colorless prism, 0.22 × 0.27 × 0.85 mm, R_1 = 8.81%, and [(**3**) $C_{54}H_{62}N_4O_{18}$] sp. gr. $P2_1$, a = 11.664(1) Å, b = 11.657(1) Å, c = 20.715(3), β = 99.35(1)°, V = 2779.1(5) Å^3, Z = 2, d_{calc} = 1.261 g/cm^3, colorless laths, crystal size 0.09 × 0.23 × 1.2 mm, R_1 = 6.94%.

Acknowledgment. We are most grateful to Professor S. Ranganathan for valuable advice. Financial assistance from DST New Delhi, the Office of Naval Research, and the National Institutes of Health (USA), Grant-30902, is acknowledged

Supporting Information Available: ROESY spectra of **1** and **2** FT-IR spectra of **3**, CD spectra of **2** and **3** in TFE, and X-ray crystallographic coordinates, bond lengths and angles, and anisotropic thermal factors and idealized H atom coordinates for **1**, **2**, and **3** (38 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981012B