# First Rigid Peptide Foldamers with an Alternating Cis−Trans Amide Sequence. An Oligomeric Building Block for the Construction of New Helices, Large-Ring Cyclic Correlates, and Nanotubes

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*Received February 28, 2001; Revised Manuscript Received April 16, 2001*

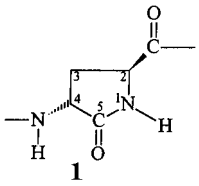
ABSTRACT: As part of a program evaluating homochiral and heterochiral amino- and carboxylic acid-substituted $\gamma$-lactams as conformationally constrained dipeptide building blocks, we have synthesized by the solid-phase technique and assessed by X-ray diffraction the crystal-state structure of the terminally blocked homotrimer from (2*S*,4*R*)-4-amino-5-oxopyrrolidine-2-carboxylic acid, characterized by a unique, alternating cis−trans amide sequence. Using computer modeling, we also showed that the rigid conformation of the trimer can be exploited as a template to construct novel linear oligopeptide foldamers and large-ring cyclic correlates with self-recognizing properties.

## Introduction

The design of compounds that fold into a predictable and well-defined 3D-structure ("foldamers") can help us learn about self-assembly motifs and self-organization processes and tailor molecules with novel functions and properties (e.g., minienzymes, new devices, drug candidates).[1] In this connection 4-amino-5-oxopyrrolidine-2-carboxylic acid (or 4-aminopyroglutamic acid, aPy) and its six-, seven-, and eight-membered ring congeners show promise of providing building blocks that are predisposed toward differently ordered secondary structures, depending on the stereochemistry of the two substituents in the lactam moiety. An interesting feature of all these systems, which may be viewed as conformationally restricted dipeptide analogues in which the two amino acid residues are fused through the side chains,[2] is that they contain an internal amide (peptide) linkage locked in the uncommon cis conformation.

The *homochiral* (*S*,*S*) and (*R*,*R*) stereoisomers, with amino and carboxyl functions in cis disposition, and the *heterochiral* (*S*,*R*) and (*R*,*S*) stereoisomers, with amino and carboxyl functions in trans disposition, of all these lactam systems have been the subject of numerous investigations which have emphasized their tendency to act as excellent $\beta$-turn mimetics (in particular of type-VI $\beta$-turns, characterized by the presence of a cis peptide bond between the $i + 1$ and $i + 2$ positions)[3] and remarkable examples of constraints for amide self-recognition (dimerization).[4] Conversely, only one study was published reporting oligomerization of such lactam dipeptide mimetics. In particular, condensation of an activated ester of the trans stereisomer of the six-membered ring ($\delta$-) lactam afforded a *polydispersed*, insoluble oligomeric material, which was not further characterized.[4f]

**Chart 1**



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In this paper, we describe the X-ray diffraction 3D-structural characterization of the *monodispersed* trimer based on the *heterochiral* $\gamma$-lactam (2*S*,4*R*)-aPy residue **1** and the results of a computer modeling study of selected higher oligomers.

## Experimental Section

**Synthesis and Characterization of Peptides.** The synthesis of Fmoc−(*S*,*R*)-aPy−OH (Fmoc, fluoren-9-ylmethoxycarbonyl) has already been reported.[5] Conventional solid-phase peptide synthesis was used to construct the terminally blocked trimer Ac[(*S*,*R*)-aPy]$_3$NH$_2$ (Ac, acetyl). In particular, we employed a methylbenzhydrylamine resin (Novabiochem), HATU [*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium] hexafluorophosphate (Perceptive Biosystem) as the coupling reagent[6] and 20% piperidine in *N*,*N*′-dimethylformamide for Fmoc N$^\alpha$-deprotection. Acetylation of the terminal amino group was achieved by means of acetic anhydride in the presence of diisopropylethylamine. The peptide was cleaved from the resin by anhydrous HF in the presence of anisole (≅10%) at 0 °C for 60 min. After removal of HF, the resin was washed several times with diethyl ether and then extracted with water. Lyophilization of the aqueous solution yielded the crude peptide, which was subsequently purified by preparative HPLC (LDC Analytical) on a reverse-phase support (Vydac C$_{18}$ column, 250 × 25 mm) with isocratic elution of 0% B in A [B, 0.038% TFA (trifluoroacetic acid) in 82% acetonitrile/water; A, 0.05% TFA in water], flow 20 mL/min. Homogeneity of the purified peptide was checked by analytical HPLC (Vydac C$_{18}$ column, 250 × 4.6 mm, isocratic elution with 100% A in 25 min; flow 1 mL/min; $R_T$ = 3.4 min) on a ThermoSeparation HPLC system equipped with an AS3000 autosampler, P4000 pump, and scanning SpectraFocus detector. The chemical structure of the pure peptide was confirmed by the FAB mass spectrum [APO Electron (Ukraine) model MI 1200 1E mass spectrometer equipped with a FAB ion source] (found [M +

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10.1021/ma010368w CCC: $20.00 
Published on Web 06/09/2001

**Table 1. Crystal Data and Structure Refinement Parameters for Ac[(*S*,*R*)-aPy]$_3$NH$_2$ Trihydrate**

| | |
|---|---|
| empirical formula | $C_{17}H_{29}N_7O_{10}$ |
| fw | 491.47 |
| temp, K | 293(2) |
| wavelength, Å | 1.54178 (Cu Kα) |
| crystal system, space group | orthorhombic, $P2_12_12_1$ |
| unit cell dimensions | $a = 10.538(3)$ Å |
| | $b = 10.906(3)$ Å |
| | $c = 19.196(4)$ Å |
| vol, Å$^3$ | 2206.1(10) |
| $Z$, calcd density, Mg/m$^3$ | 4; 1.480 |
| abs coeff, mm$^{-1}$ | 1.051 |
| $F$(000) | 1040 |
| cryst size, mm$^3$ | 0.25 × 0.10 × 0.05 |
| scan mode | $\theta - 2\theta$ |
| $\theta$ range for data collection, deg | 4.66−60.04 |
| limiting indices | $-1 \le h \le 11$ |
| | $0 \le k \le 12$ |
| | $0 \le l \le 21$ |
| no. of reflcns collected/unique | 2111/2076 [$R$(int) = 0.0417] |
| refinement method | full-matrix-block least-squares on $F^2$ |
| data/restraints/params | 2076/0/307 |
| goodness-of-fit on $F^2$ | 0.865 |
| final $R$ indices [$I \ge 2\,\sigma(I)$] | $R_1 = 0.0505$, $wR_2 = 0.1129$ |
| $R$ indices (all data) | $R_1 = 0.1417$, $wR_2 = 0.1354$ |
| largest diff peak and hole, e Å$^{-3}$ | 0.204 and −0.255 |

H]$^+$ 438, calculated 437 for $C_{17}H_{23}N_7O_7$). $[\alpha]_D^{20} = 123.3°$ (*c* 0.68, water).

**X-ray Diffraction and Computer Modeling.** Colorless single crystals of Ac[(*S*,*R*)-aPy]$_3$NH$_2$ trihydrate were grown from 2,2,2-trifluoroethanol/water by slow evaporation. Data collection was performed on a Philips PW1100 four-circle diffractometer. Intensites were corrected for Lorentz and polarization effects. No absorption correction was made ($\mu$ = 1.051 mm$^{-1}$). The structure was solved by direct methods of the SHELXS 97 program.[7a] Refinement was carried out by full-matrix-block least-squares on $F^2$, using all data, with all non-H atoms anisotropic, by application of the SHELXL 97 program,[7b] allowing the positional parameters and the anisotropic displacement parameters of the non-H atoms to refine at alternate cycles. H atoms of the peptide molecule were calculated at idealized positions and refined as riding with $U_{iso}$ set equal to 1.2 (or 1.5 for the methyl group) times the $U_{eq}$ of the parent atom. The positions of the H atoms of the W1 and W3 water molecules were recovered from a difference Fourier map, while those belonging to the W2 water molecule were calculated in agreement with a likely H-bonding scheme. The positional parameters of the H atoms for all three water molecules were not refined. Crystallographic data and structure refinement parameters are listed in Table 1.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 146011. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. Fax: (+44)1223-336-033. E-mail: deposit@ccdc.cam.ac.uk.

For the computer modeling investigation we used the program WebLab Viewer Pro 3.20 (Molecular Simulations). The models are based on the X-ray structure, by keeping bond distances and bond angles unchanged.

## Results and Discussion

Figure 1 shows the crystal-state X-ray diffraction structure of Ac[(*S*,*R*)-aPy]$_3$NH$_2$ with numbering of the atoms. The backbone $\phi$, $\psi$ torsion angles[8] are all positive (Table 2). The $\phi_2$, $\phi_4$, $\phi_6$, and the $\psi_1$, $\psi_3$, $\psi_5$ angles (all characterized by three atoms out of four within the ring system) are severely constrained at 103 ± 5 and 142 ± 2°, respectively. A slightly wider range is seen for the $\phi_1$, $\phi_3$, $\phi_5$ and $\psi_2$, $\psi_4$, $\psi_6$ angles (100 ± 15 and 138 ± 13°, respectively), all with two atoms within the ring system. The only amide[9] (peptide)[10] $\omega$ torsion angle deviating more than 2.4° from the alternating trans (180°) and cis (0°) planarities is $\omega_4$ ($|\Delta\omega| = 5.1°$).

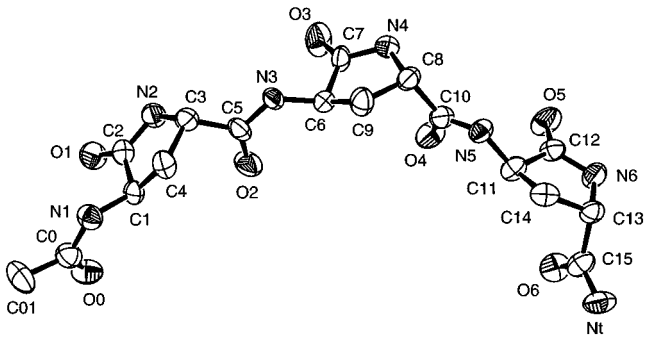


**Figure 1.** ORTEP view of the X-ray diffraction structure of the Ac[(*S*,*R*)-aPy]$_3$NH$_2$ molecule with numbering of the atoms. Anisotropic displacement ellipsoids are drawn at the 50% probability level.

**Table 2. Relevant Backbone Torsion Angles (deg) for Ac[(*S*,*R*)-aPy]$_3$NH$_2$**

| | | | | | |
|---|---|---|---|---|---|
| C01−C0−N1−C1 | $\omega_0$ | −178.2(6) | C6−C7−N4−C8 | $\omega_3$ | 2.3(8) |
| C0−N1−C1−C2 | $\varphi_1$ | 84.5(8) | C7−N4−C8−C10 | $\varphi_4$ | 99.4(7) |
| N1−C1−C2−N2 | $\psi_1$ | 140.7(6) | N4−C8−C10−N5 | $\psi_4$ | 147.2(6) |
| C1−C2−N2−C3 | $\omega_1$ | −2.4(8) | C8−C10−N5−C11 | $\omega_4$ | 174.9(6) |
| C2−N2−C3−C5 | $\varphi_2$ | 107.6(7) | C10−N5−C11−C12 | $\varphi_5$ | 85.4(8) |
| N2−C3−C5−N3 | $\psi_2$ | 126.2(6) | N5−C11−C12−N6 | $\psi_5$ | 144.0(6) |
| C3−C5−N3−C6 | $\omega_2$ | 178.2(6) | C11−C12−N6−C13 | $\omega_5$ | −0.6(9) |
| C5−N3−C6−C7 | $\varphi_3$ | 115.3(8) | C12−N6−C13−C15 | $\varphi_6$ | 97.9(7) |
| N3−C6−C7−N4 | $\psi_3$ | 142.0(6) | N6−C13−C15−NT | $\psi_6$ | 150.8(6) |

In the two surveys of crystal structures containing (*S*)-pyroglutamic acid[11] [the same isomer as in our (2*S*)-aPy residue] it was shown that the $\phi$ values are mainly close to 140° with a few examples near 100° (the latter region is that observed for our $\phi_2$, $\phi_4$, $\phi_6$ angles). Indeed, conformational energy calculations[11b] indicated the presence of two minima for the $\phi$ angle, close to the values of 110 and 140° observed. As in (*S*)-pyroglutamic acid the C$^\beta$ and C$^\gamma$ atoms are part of a cyclic system formed by condensation of the (*S*)-Glu $\gamma$-carboxyl function onto its α-amino function, some short unfavorable contacts, which would have been found between atoms of a protein (*S*)-residue with $\phi$ between 100 and 150°, are removed in the $\gamma$-lactam residue. In the same study two low-energy regions were identified for the $\psi$ angle: the lowest at about −40° and a higher-energy shallow minimum around 100° (not far from the values observed for our $\psi_2$, $\psi_4$, $\psi_6$ angles). Interestingly, these regions of the conformational space are of high energy for a protein (*S*)-residue but are acceptable conformations for a standard (*R*)-residue. It may be concluded that our crystallographic analysis confirms that a (*S*)-pyroglutamic acid residue is conformationally equivalent to a standard (*R*)-residue. This unusual result is not reproduced by our $\phi_1$, $\phi_3$, $\phi_5$ and $\psi_1$, $\psi_3$, $\psi_5$ angles [related to the (4*R*) stereocenter of our aPy isomer], which represent acceptable conformations for a standard (*R*)-residue.

Each lactam ring of Ac[(*S*,*R*)-aPy]$_3$NH$_2$ and the *following trans* peptide unit are nearly perpendicular to each other, the angles between normals to each pair of average planes being found in the range 90.3 ± 1.8°. However, the angles between normals to the average planes of each lactam ring and the *preceding trans* peptide unit are 65.7(2), 89.8(2), and 61.2(3)° (beginning from the N-terminal lactam). Therefore, a strictly orthogonal arrangement of alternating trans and cis

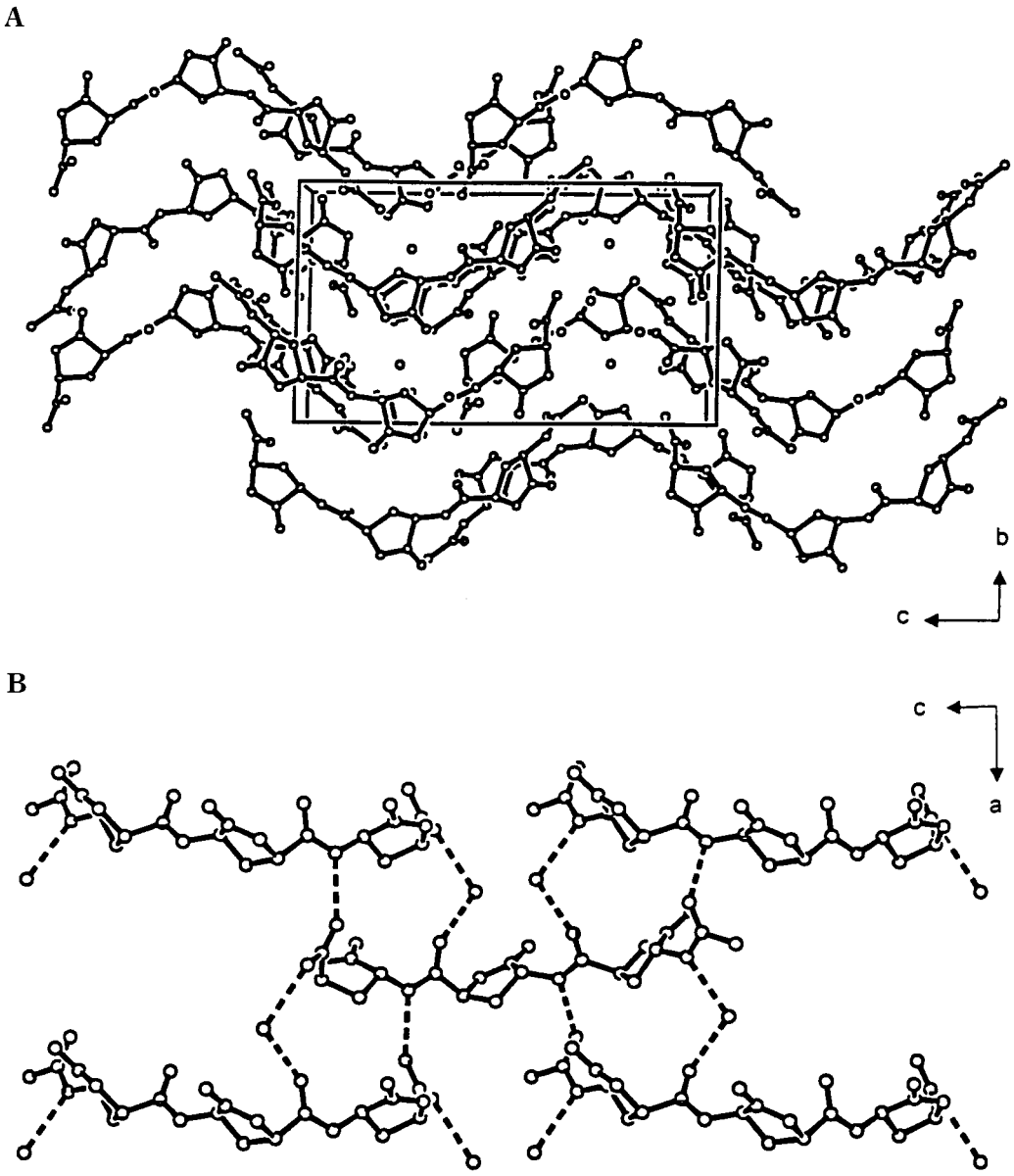


**Figure 2.** (A) Mode of packing of the Ac[(*S*,*R*)-aPy]$_3$NH$_2$ molecules projected along the *a* direction. (B) Intermolecular H-bonding network involving the trans peptide units as viewed along the *b* direction.

amide (peptide) units is observed along the central part of the trimeric molecule, whereas this arrangement is significantly distorted at either terminus.

The angles between normals to the average planes of the trans peptide units are 28.4(2), 50.6(2), and 44.3(2)°, while those between normals to the average planes of the cis lactam units are 23.8(2) and 39.2(3)°. To a large extent, these values should be correlated to the bending of the foldameric molecule.

All of the three lactam rings adopt a conformation close to the envelope ($E_4$) disposition, having the C4, C9, and C14 methylene carbon atoms mostly displaced out of their respective rings. The puckering parameters[12] are $q_2$ = 0.234(6) Å and $\varphi_2$ = 101.6(16)° for the ring encompassing the N2−C2−C1−C4−C3 atoms, $q_2$ = 0.293(7) Å and $\varphi_2$ = 110.6(12)° for the atom ring sequence N4−C7−C6−C9−C8, $q_2$ = 0.308(7) Å, and $\varphi_2$ = 105.6(14)° for the N6−C12−C11−C14−C13 ring. As a result of the modest puckering of all three pentaatomic rings, the displacement of the C4, C9, and C14 methylene carbon atoms from their average ring planes is within 0.159 −0.201 Å.

The molecules of the Ac[(*S*,*R*)-aPy]$_3$NH$_2$ trihydrate lay nearly parallel to the *bc* plane, with the trans peptide units perpendicular to it (Figure 2A). As a consequence, in the crystal packing mode the N−H and C═O groups of the trans peptide units are interconnected through either direct[13] or water-mediated[14] H-bonds to symmetry-related molecules along the *a* direction (Table 3 and Figure 2B). More specifically, the N3−H and N5−H groups are H-bonded to symmetry equivalents of the O0 and O6 atoms, respectively, while the connections between the N1−H group and a symmetry equivalent of O2 and between the Nt−Ht2 group and a symmetry equivalent of O4 are mediated through interposition of the O1W and O3W water molecules, respectively (O−H···O H-bonds).[15] The N2−H, N4−H, and N6−H groups of the cis peptide units are intermolecularly H-bonded to symmetry-equivalents of the O5, O1, and O3 carbonyl oxygen atoms, respectively, of cis peptide units. These latter intermolecular H-bonds link molecules along the *c* direction. An additional H-bond is observed between the Nt−Ht1 group and a symmetry equivalent of the O2 carbonyl oxygen atom, interconnecting molecules

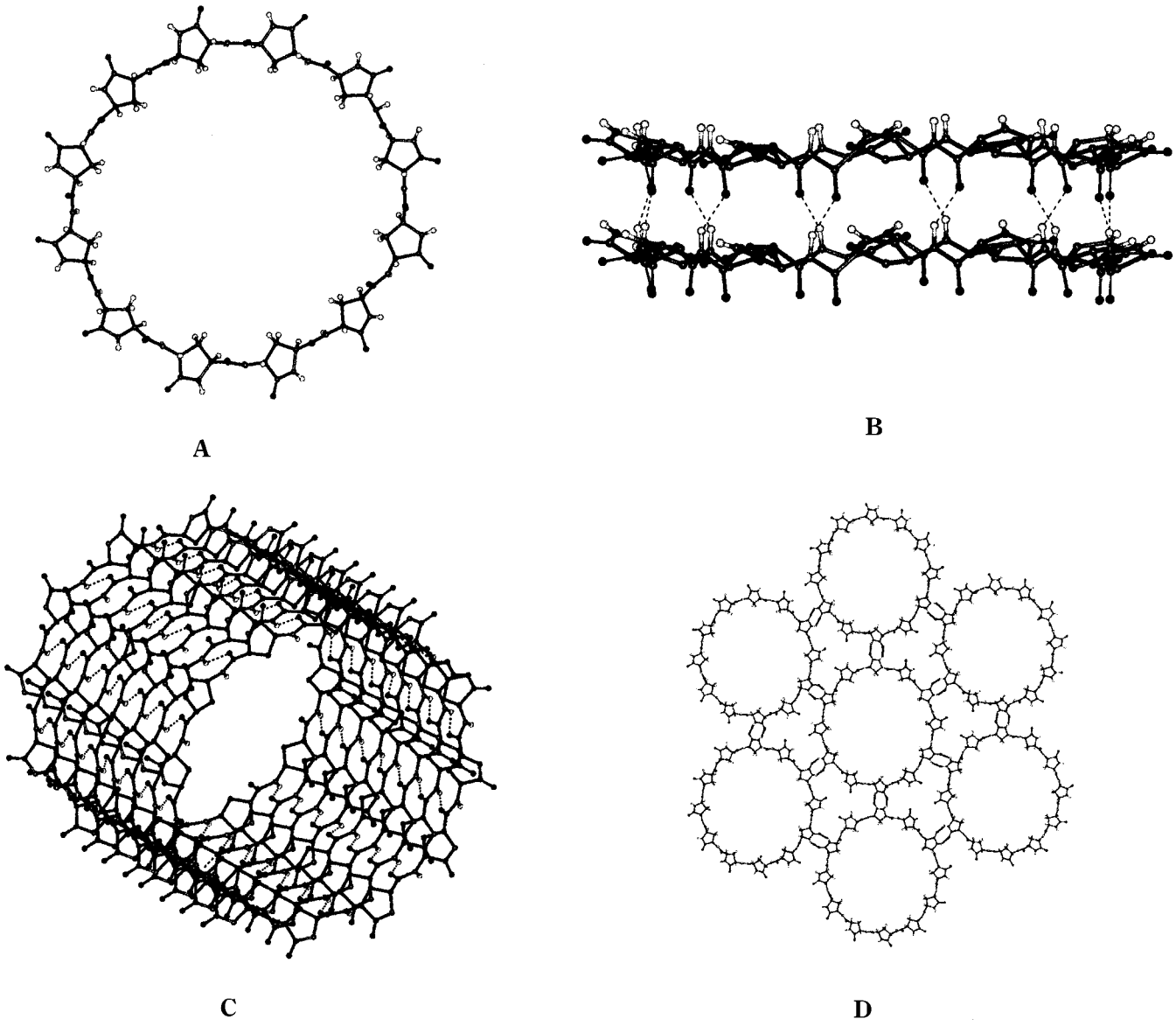


**Figure 3.** (A) Computer model of the cyclic correlate based on 12 −(*S*,*R*)-aPy− monomeric units. The idealized backbone $\phi$, $\psi$ torsion angles are 120°, 120°. (B) Computer model of the *vertical* self-assembly of two cyclic correlates emphasizing the intermolecular N−H···O═C H-bonds involving the trans amides. (C) Computer model of the nanotubular structure resulting from *vertical* self-assembling of the cyclic correlate through intermolecular N−H···O═C H-bonds involving the trans amides. (D) Computer model of the *lateral* self-assembly of cyclic correlates through intermolecular N−H···O═C H-bonds involving the cis amides.

**Table 3. Intermolecular H-Bond Parameters for Ac[(*S*,*R*)aPy]$_3$NH$_2$ Trihydrate**

| donor D−H | acceptor A | sym equiv of A | distance (Å) D···A | distance (Å) D−H···A | angle (deg) D−H···A |
|---|---|---|---|---|---|
| N1−H1 | O1W | $x, y, z$ | 2.865(8) | 2.07 | 154 |
| N2−H2 | O5 | $-x+3/2, -y+1, z-1/2$ | 2.773(7) | 2.12 | 132 |
| N3−H3 | O0 | $x+1/2, -y+3/2, -z+1$ | 2.874(7) | 2.03 | 167 |
| N4−H4 | O1 | $-x+3/2, -y+1, z+1/2$ | 2.911(7) | 2.20 | 140 |
| N5−H5 | O6 | $x+1/2, -y+3/2, -z+2$ | 2.823(8) | 1.97 | 170 |
| N6−H6 | O3 | $-x+3/2, -y+1, z+1/2$ | 2.891(8) | 2.16 | 142 |
| N6−H6 | O2W | $x, y, z$ | 3.077(9) | 2.45 | 130 |
| Nt−Ht1 | O2 | $-x+3/2, -y+2, z+1/2$ | 2.961(8) | 2.10 | 174 |
| Nt−Ht2 | O3W | $x, y, z$ | 2.899(8) | 2.06 | 164 |
| O1W−H1WA | O2 | $x+1/2, -y+3/2, -z+1$ | 2.829(8) | 2.02 | 160 |
| O1W−H1WB | O3W | $x, y, z-1$ | 2.707(9) | 2.16 | 122 |
| O2W−H2WA | O1W | $x, y, z+1$ | 2.679(11) | 1.85 | 177 |
| O2W−H2WB | O1 | $x, y, z+1$ | 3.207(10) | 2.35 | 179 |
| O3W−H3WA | O4 | $x+1/2, -y+3/2, -z+2$ | 2.766(8) | 1.93 | 178 |
| O3W−H3WB | O2W | $-x+2, y+1/2, z+5/2$ | 2.729(13) | 1.91 | 177 |

along the *b* direction. The remaining H-bonds involve only the three cocrystallized water molecules.

We have constructed a computer model of the cis−trans amide alternating foldameric structure based on

the $\phi$, $\psi$ torsion angles of the central, undistorted unit of the (*S*,*R*)-aPy trimer. We find that the curved backbone will lead to the formation of a left-handed helical structure characterized by six (*S*,*R*)-aPy residues per turn, a pitch of 13 Å, and a large hydrophilic cavity with an approximate 10 Å diameter. This rather elongated helix is not stabilized by any intramolecular N−H···O═C H-bond.

Indeed, on the basis of this new motif, a variety of hollow structures may be envisioned, in our view the most significant being a large-ring cyclic correlate (Figure 3A) based on idealized $\phi$, $\psi$ torsion angles, differing however only slightly (on the average by 20°) from those exploited for the formation of the helical structure discussed above. Creation of this macrocycle will require a homooligomer of 12 (*S*,*R*)-aPy units. Its key structural feature is the presence of pairs of orthogonal, self-complementary H-bonding amide (peptide) functionalities. Noncovalent, vertical, parallel, and in register self-assembly of two (Figure 3B) or more (Figure 3C) cyclic correlates, linked through N−H···O═C H-bonds involving the trans amide units, will eventually generate hollow, open-ended nanotubular structures,[16] characterized by a large hydrophobic cavity (diameter ≅ 21 Å). We believe that the only slightly puckered $\gamma$-lactam ring structure and the almost flat macrocyclic conformation would not prevent an efficient vertical stacking. Neighboring nanotubes will laterally self-assemble by taking advantage of the N−H···O═C H-bonding interactions arising from the orthogonal cis amide units (Figure 3D). It may be concluded that these macrocycles will provide a possible entry into nanotubes. These supramolecularly organized systems hold great promise as artificial receptors for lipophilic substances with potential applications in recognition chemistry, catalysis, and drug delivery. We are currently actively working on the synthesis of long linear and cyclic (*S*,*R*)-aPy homooligomers.

## Conclusion

Nature heavily relies on large, folded molecules to perform its sophisticated chemical operations. Therefore, the design of compounds that fold into a predictable, well-defined 3D-structure can help learn about self-assembly motifs and self-organization processes and tailor molecules with novel functions and properties.

We have designed, synthesized, and solved the X-ray diffraction structure of a crescent foldamer, namely the trimer of a lactam-based dipeptide building block characterized by a unique, alternating cis−trans sequence of amide bonds. By computer modeling we showed that higher oligomers (e.g., the dodecamer of the building block) could lead to new types of helical foldamers and cyclic correlates with large cavities. Vertical self-assembling of the ring systems will eventually produce tubular nanostructures. We believe that this work may provide a new insight into important aspects of peptide-based molecular architectures (3D-organization, molecular recognition) with a possible effect on future studies at the interface between chemistry, biology, and pharmacology.

**Supporting Information Available:** Tables giving crystal data and refinement information, atomic coordinates and isotropic thermal parameters, bond lengths and angles, anisotropic thermal parameters for non-hydrogen atoms, hydrogen atom coordinates and isotropic thermal parameters, torsion angles, and hydrogen bond data for ctf88b. This material is available free of charge via the Internet at http://pubs.acs.org.

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MA010368W