Self-Assembling Cyclic Peptide Cylinders as Nuclei for Crystal Engineering**

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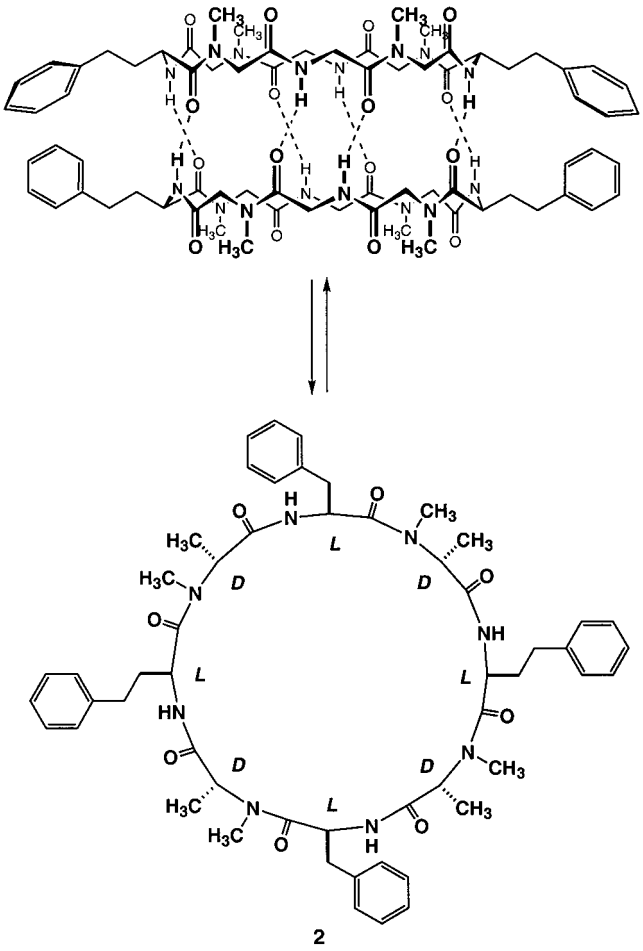
Convergent assembly strategies for creating new information surfaces are well known in Nature, especially in the organization of structural proteins[1] and gene transcription machinery.[2] Such programmed molecular recognition captures the essence of supramolecular design.[3–5] In noncovalent synthesis, achieving controlled, multidimensional self-assembly would allow the construction of ordered materials: in essence, crystal engineering.[3, 6–8] We have previously reported the propensity of cyclic peptides of alternating D,L-amino acid configuration to adopt a flat-ring structure and stack by means of backbone hydrogen bonding in an antiparallel β-sheet fashion, yielding nanometer-scale, ordered, tubular peptide assemblies.[9–11] In the present model study, we have coupled limited cylindrical assembly by means of backbone hydrogen bonding with the formation of a new, orthogonal recognition interface comprised of aromatic amino acid side chain functionality, which in turn induces higher order molecular organization in the solid state through aromatic edge-to-face interactions.

Aryl functionality recognition motifs, including weakly polar edge-to-face phenyl interactions,[12–18] cation–π,[19–22] π-π,[16, 23–27] and quadrupole–quadrupole interactions,[19, 20, 22] are excellent complements to hydrogen-bonding donor–acceptor interactions in supramolecular chemistry, as these recognition strategies can operate with minimal interference from each other. We have utilized cyclic peptide **2** (Scheme 1), with the sequence *cyclo*[(-L-Phe-D-^{Me}*N*-Ala-L-hPhe-D-^{Me}*N*-Ala)$_2$], to study aryl–aryl interactions templated by hydrogen bonding directed self-assembly. All four D-alanine residues are N-methylated, limiting the hydrogen-bonded assembly in organic solvents to D_2-symmetrical cyclic peptide dimers. The one-carbon homologation of the phenylalanine side chain to homophenylalanine (hPhe) was expected to provide the additional mobility necessary to allow the formation of cross-strand aromatic–aromatic interactions in the β-sheet dimer. Consistent with the high β-sheet propensity of Phe,[28–30] replacement of Phe with hPhe results in a peptide with reduced dimerization capacity,[31] but also more complex folding behavior.

X-ray crystallographic analysis of **2** proved extremely revealing.[32] Aryl–aryl interactions apparently do not strongly influence assembly in solution, as observed in the ^{1}H NMR spectrum in $CDCl_3$,[33] but cumulative lattice energies drove the formation of a consensus hydrogen-bonded dimer of **2** in the solid state, in which like residues are paired cross-strand with like residues (Scheme 1). As intended, the solid-state structure revealed a canonical intradimer edge-to-face cross-strand phenyl–phenyl interaction between two hPhe residues. More strikingly though, the one-carbon homologation of phenylalanine completely altered the crystal packing of **2** relative to the parent peptide *cyclo*[(-L-Phe-D-^{Me}*N*-Ala)$_4$] (**1**).[31, 34] Unlike **1**, the homophenylalanine peptide **2** packs with a dimer as the asymmetric unit with two dimers in the unit cell (Figure 1). The dimers interact by means of a cluster of aromatic side-chain interactions, twisting their cylindrical axes nearly orthogonally to one another, at an angle of 74°. The crystal lattice of **1** (Figure 2a) is less complex: C_4 symmetry and use of the more conformationally constrained phenylalanine residues in all L positions results in a lattice in which the cylindrical axes of the cyclic peptide dimers are unidirectionally aligned.[31,34,35] Peptide **3** (Figure 2b), *cyclo*[(-L-Phe-D-^{Me}*N*-Ala-L-Leu-D-^{Me}*N*-Ala)$_2$-], another C_2-symmetrical cyclic peptide,[35] similarly packs with



Scheme 1. A two-dimensional representation of the chemical structure of peptide **2** (D and L refer to amino acid chirality). The assembly equilibrium between the monomer and one of two possible dimeric species in which cross-strand aromatic interactions are possible between hPhe residues. (For clarity, the Phe side chains are not shown in the dimer.)

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Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

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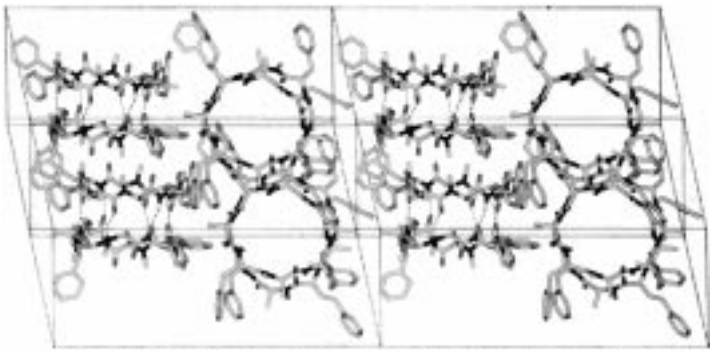

Figure 1. Stick representation of the crystal lattice of **2** viewed along one peptide cylindrical axis, with adjacent cylindrical peptide columns twisted at a 74° angle. Four unit cells are shown, with two dimers in each unit. Intradimer hydrogen bonds are shown with dotted lines.

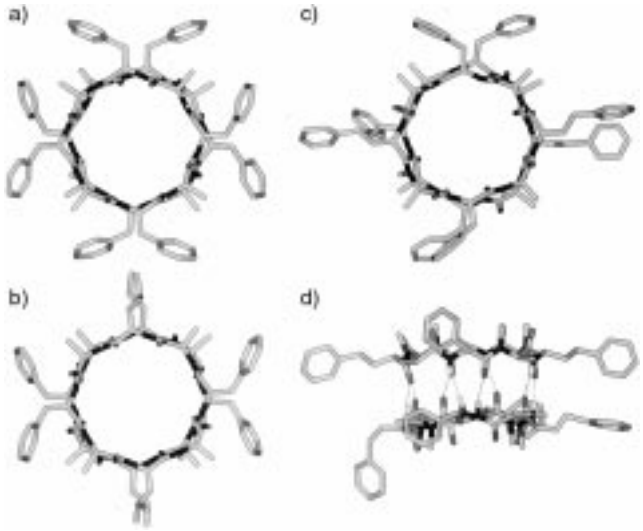

Figure 2. Crystal structures of dimeric β-sheet assemblies formed by a) *cyclo*[(-L-Phe-D-^{Me}*N*-Ala)$_4$-] (**1**); b) *cyclo*[(-L-Phe-D-^{Me}*N*-Ala-L-Leu-D-^{Me}*N*-Ala)$_2$-] (**3**); c) *cyclo*[(-L-Phe-D-^{Me}*N*-Ala-L-hPhe-D-^{Me}*N*-Ala)$_2$-] (**2**) viewed along the cylindrical axes, and d) across the dimeric interface of **2**.

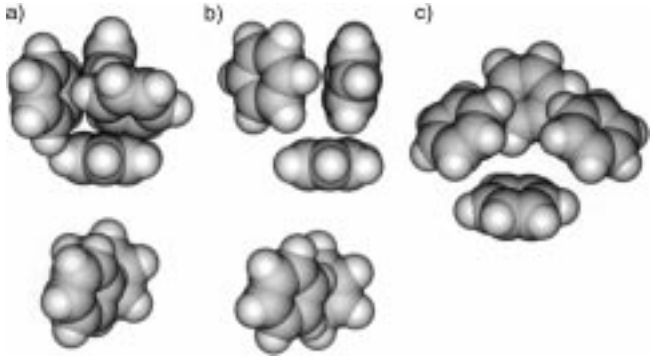

Figure 3. Space-filling representation of the principal phenyl–phenyl crystal contacts observed in a) benzene, b) peptide **2**, and c) peptides **1** and **3**.

Table 1. Comparison of benzene crystal contacts with cyclic peptide phenyl–phenyl contacts.

Crystal	Contact	Centroid–centroid distance [Å]	Interplanar angle
Benzene	Ph–Ph	5.986	86.1
		5.025	86.5
		5.812	29.4
1	F–F	5.77	45.87
		6.28	46.8
		5.77	46.26
2	hF–hF	5.12	87.2
	F–hF	4.61	45.01
		5.13	30.47
		5.83	60.04
		4.82	42.38
		6.6	76.67
		4.83	42.38
	F–F	5.61	54.71
3	F–F	5.34	31.3
		5.95	42.24
		5.97	43.69
		6.16	37.87

the C_2 cylindrical axes aligned in the crystal,[31] despite the reduced symmetry and the presence of a flexible γ-branched leucine side-chain. Presumably, the alignment is controlled by interdimer phe–phe contacts, and leu–leu contacts do not interfere with phe–phe packing. In contrast, the insertion of homophenylalanine residues in place of leucine in this C_2-symmetrical framework has a dramatic effect on dimer interactions. The one additional methylene group in homophenylalanine provides enhanced conformational freedom in the χ angle as well as a longer backbone tether, allowing more options in the lattice packing of phenyl groups. Interestingly, the recognition of side-chain phenyl rings with themselves in all three structures is very similar to the packing of benzene[36–38] with itself (Figure 3). Thus, it is as though each peptide dimer is coated with a layer of covalently bound benzene "solvent" that is assembled into interaction range by means of the noncovalent recognition of the peptide backbone (Table 1). This layer of phenyl rings from the hPhe side chains forms both intra- and interdimer contacts with both hPhe and Phe phenyl rings. These three peptide lattices display high sensitivity to side-chain functionality and perhaps also the symmetry of substitution, despite the fact that the essential backbone-directed dimer remains identical. In fact, preferred β-conformations dictated by the backbone configuration are overridden by the lattice. Homophenylalanine side chains of peptide **2** are extended to maximize interdimer contacts (Figure 2c and d), and Phe side-chain conformational preferences are overridden to introduce additional contacts. Though one cross-strand pair of Phe residues in **2** adopts the preferred χ angles of $\approx 180°$ observed in **1** and **3**, aromatic interactions with hPhe residues perturb the conformation of the other Phe cross-strand pair to yield a normally unfavorable cross-strand set of χ angles: $-176°$ and $-67°$. This places the side-chain phenyl rings in an eclipsed conformation with one another, but allows interdimer contact (Figure 2). Remarkably, the functionality displayed on the exterior of the peptide cylinder nucleus is essentially unchanged between **1** and **2**, indicating that the extreme difference in lattice morphology is driven completely by the amplified effect of an additional methylene group in two out of four phenylalanine side chains.

The cyclic peptide scaffold also serves to template leucine–leucine van der Waals contacts,[39] as observed in the crystal

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structure of **3** (Figure 4). Indeed, the γ-carbon distances are similar to those seen in the tightly packed leucine zipper cores of the dimeric coiled coil region of GCN4 and the tetrameric

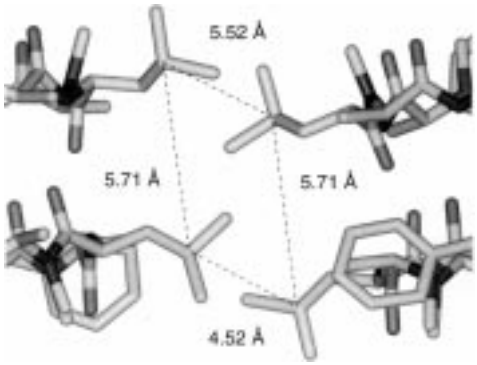

Figure 4. Stick representation of leucine – leucine interdimer lattice contacts in the crystal structure of **3**. Gamma-carbon distances are shown in Å.

variant of GCN4 (Table 2).[40] No aliphatic – aromatic contacts were found in **3**, despite the favorable energetics of interaction observed between *tert*-butyl esters and phenyl groups,[12, 13] suggesting that the construction of hydrocarbon contacts in the solid-state lattice may be more greatly influenced by shape selection rather than π-system interactions.

Table 2. Comparison of leucine – leucine contact distances in peptide **3** and leucine-core coiled coils.

Peptide (Leu – Leu contact)	γ-carbon distance [Å]
cyclo[Phe-^{Me}N-D-Ala-Leu-^{Me}N-D-Ala]$_2$	4.52, 5.52, 5.71, 5.71
GCN4 – p1	5.73, 5.42, 5.41, 5.67
GCN4 – p4	4.69, 5.23, 5.41, 5.67

Certainly, the variability of lattice organization seen within this small set of crystal structures of similar peptides indicates the subtlety of crystal growth. Nevertheless, the cylindrical dimers studied here are useful models for crystallization nuclei that can present 16 functional groups in space by self-assembly, thus enhancing control over lattice contacts by preforming a multivalent cluster of functionality. Indeed, it has been demonstrated that it is possible to access multiple crystal forms with the identical peptide backbone fold by single atom determinants of structure in the case of the Phe →hPhe double mutant **2**. Further, the dimeric peptide system can be readily studied in solution, allowing rapid identification of interactions compatible with hydrogen bonding for inducing crystal growth orthogonal to the tubular axis, enabling further crystal engineering efforts. Current studies are directed towards manipulating these self-assembled functional surfaces to gain greater control over the molecular organization of the subsequent noncovalent tubular constructs, for use in biosensors and nanotechnological and biomedical applications.[10]

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[32] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157105 (**1**), -157092 (**2**) and -157104 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Briefly, **2** crystallized in the monoclinic system, $P2_1$ space group with unit cell dimensions of $a = 13.689(3)$, $b = 15.905(3)$, $c = 29.521(6)$ Å, and $\beta = 99.18^\circ$, a volume of 6345 Å^3, and a calculated density of 1.021 Mg m^{-3} for an empirical formula of $C_{54}H_{68}N_8O_8 \cdot H_2O$, accounting for one water molecule per asymmetric unit. A full-matrix least-squares refinement was performed on $|F^2|$, converging to final R indices ($I > 2\sigma(I)$) of $R_1 = 0.1010$, $wR_2 = 0.2671$ and with all data, $R_1 = 0.1875$, $wR_2 = 0.3353$. (Two water molecules were found in the unit cell, disordered over seven positions likely accounting for the unusually high R factor.) 9280 reflections (9279 independent) were collected at 298 K, with a wavelength of 1.54178 Å with 0.89 Å dataset resolution on a Rigaku AFC6R diffractometer equipped with a rotating copper anode ($Cu_{K\alpha}$) and a highly ordered graphite monochromator. Data were corrected for Lorentzian, polarization, and absorption effects using the psi-scan method. Hydrogen

atoms were included in the ideal positions with fixed isotropic values. Calculations were performed using the programs TEXSAN (data reduction) and SHELX-97 (refinement).

[33] ^{1}H NMR spectroscopic analysis of **2** in chloroform solution at a 17-mM concentration indicated that **2** assembles to form the two expected dimeric assemblies as evidenced by two sets of hydrogen-bonded NH resonances, corresponding to two distinct sets of homophenylalanine and phenylalanine residues. Upon examination at low temperature, an additional set of hydrogen-bonded NH protons appeared possibly arising from a dimer desymmetrized by cross-strand aryl–aryl interaction, though subsequent two-dimensional ^{1}H NMR spectroscopic investigation was inconclusive (see Supplementary Information).T. D. Clark, J. M. Buriak, K. Kobayashi, M. P. Isler, D. E. McRee, M. R. Ghadiri, *J. Am. Chem. Soc.* **1998**, *120*, 8949–8962.

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A Large 24-Membered-Ring Germanate Zeolite-Type Open-Framework Structure with Three-Dimensional Intersecting Channels**

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The search for new topological microporous structures of extra-large-pore open frameworks with more than 12 tetrahedral atoms has been extremely intensive because of the widespread applications of these materials in catalysis and the separation of large molecules such as heavy oils or pharmaceuticals. Since the first molecular sieve containing 18-membered rings (18MR), aluminophosphate VPI-5, was discovered in 1988,[1] many metal phosphates and aluminosilicates with extra-large-pore open frameworks such as $AlPO_4$-8 (14MR),[2] Cloverite (20MR),[3] JDF-20 (20MR),[4] UTD-1 (14MR),[5] CIT-5 (14MR),[6] ND-1 (24MR)[7] have been synthesized. Several useful synthetic approaches have been studied to prepare such large-pore materials.[8] Among these are, for example, the use of large templates, the selection of framework elements that can form three-membered rings, such as the zincosilicates and zincophosphates,[9] or the use of tailored secondary building units (SBUs), for example, in the preparation of large-pore indium sulfide.[10] However, most of the materials with extra-large-pore frameworks have only one-dimensional (1D) channels. Germanates are of particular interest because they can form extended structures with GeO_5 trigonal bipyramids or GeO_6 octahedra, as well as GeO_4 tetrahedra.[11, 12] The high coordination numbers offer the possibility of synthesizing germanate frameworks with high charge densities, which may result in multidimensional channel systems and novel structures with large pores.[13] Unfortunately, to date extra-large-pore germanate zeolite-type structures have not been successfully prepared. According to the host–guest charge-matching concept,[14, 15] a highly charged inorganic framework should be templated by highly charged organic amines such as multiamines. Herein we report the synthesis and structure of the unique germanate zeolite analogue **1** (known as FDU-4) with a large 24-membered ring. Compound **1** was prepared by using an organic multiamine, tris-(2-aminoethyl)-amine (TREN) as a structure-directing agent in a *N*,*N*-dimethylformamide (DMF)/water mixture. Interestingly, the novel germanate open-framework structure has a three-dimensional (3D) intersecting channel system, in which each 24MR channel is surrounded by six 12MR channels, and the 12MR and 24MR channels are connected by the alternating 8MR pore windows.

$[Ge_9O_{17}(OH)_4][N(CH_2CH_2NH_3)_3]_{2/3}\,[HCON(CH_3)_2]_{1/6}\,(H_2O)_{11/3}$ **1** (FDU-4)

FDU-4 is the first germanate zeolite-type structure with the 24-member ring channels and it has a previously unknown framework topology with the space group $P6_3cm$ (No. 185, standard setting). A single-crystal X-ray diffraction analysis reveals the 3D open framework constructed from the SBU shown in Figure 1. The core of the SBU has C_{2v} symmetry and is composed of nine germanium centers, seventeen oxygen

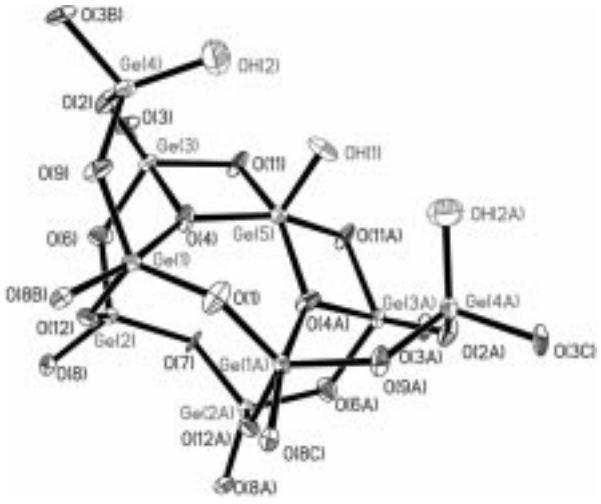

Figure 1. ORTEP view of the building block unit in crystalline FDU-4. Atoms labeled A, B, or C are symmetry generated.

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