Nanotube Formation by Hydrophobic Dipeptides

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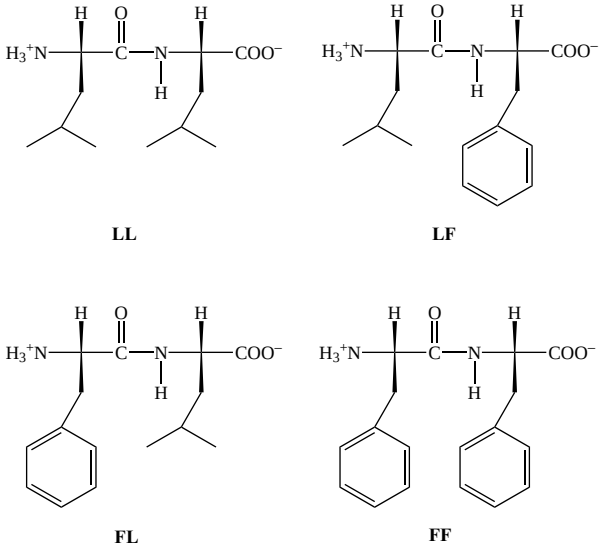
Abstract: A wide range of applications has been suggested for peptide-based nanotubes, which first attracted considerable interest as model systems for membrane channels and pores. The intriguing and unprecedented observation of nanotube formation by supramolecular self-assembly of the four dipeptides L-Leu-L-Leu, L-Leu-L-Phe, L-Phe-L-Leu and L-Phe-L-Phe is described here. These simple compounds crystallize with hydrogen-bonded head-to-tail chains in the shape of helices with four to six peptide molecules per turn. The resulting structures have chiral hydrophilic channels with a van der Waals' diameter up to 10 Å.

Keywords: nanostructures · peptides · self-assembly · supramolecular structure

Introduction

The preparation of various types of nanotubes, inorganic as well as organic, has been the subject of considerable research efforts during the last few years.[1] Peptide-based systems are of particular interest from a biological point of view as models for ion channels, membrane pores, and more.[2] For this group of compounds, tube-like structures are invariably formed by stacking of cyclic molecules through formation of intermolecular hydrogen bonds between functional groups in the peptide backbones. Pioneering work on this type of structure was carried out by Ghadiri and co-workers for cyclic D,L-peptides with eight to twelve residues.[2–6] Other research groups have introduced β-amino acids,[7] cysteine-based macrocyclic ureas,[8] and bisamides,[9] as well as aromatic rings.[10]

In the crystal structures of dipeptides, a common hydrogen bond motif is two -$NH_3^+ \cdots {}^-OOC$- head-to-tail chains in a two-dimensional sheet where the third amino H atom is accepted by a functional group in one of the side chains. When side chain acceptors are missing, as in dipeptides with two hydrophobic residues, a packing problem arises, that is, how to still position three acceptors around each amino group. As part of a systematic investigation of the structures of sixteen such hydrophobic dipeptides with residues chosen from L-Ala, L-Val, L-Leu, and L-Phe, it was discovered some time ago that L-Val-L-Ala (**VA**) forms crystals with narrow hydrophobic channels capable of hosting small organic molecules like methanol and acetonitrile.[11] This structure is conceptually very different from those mentioned above, and indeed other tubular structures as well, in that the pores are generated from the self-assembly of rather small molecules that are hydrogen-bonded, head-to-tail, into helices. Although the hydrophobic dipeptides eventually proved to constitute a surprisingly heterogeneous group as far as crystal packing arrangements are concerned,[12] structures related to **VA** were later on observed for L-Ala-L-Val, L-Val-L-Val and L-Ala-L-Ile,[13] which are structures with two fairly small side chains (L-Ala-L-Ala is a unique structure without channels[14]). The most hydrophobic members of the group selected for this study were L-Leu-L-Leu (**LL**), L-Leu-L-Phe (**LF**), L-Phe-L-Leu (**FL**) and L-Phe-L-Phe (**FF**). **LL** had previously been crystallized as a 2-methylpropan-1-ol solvate,[15] isomorphous ethanol, propan-1-ol, and propan-2-ol solvates,[16] and as a DMSO solvate,[17] while **LF** had been crystallized as a propan-2-ol solvate.[18] All these structures are divided into hydro-



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phobic and hydrophilic layers (without nanotube formation) with the alcohol/DMSO as an essential part of the hydrogen bonding network. In the absence of organic solvent molecules all four dipeptides have problematic crystallization habits, but single crystal X-ray diffraction studies have now finally been carried out. Like the **VA** family, the structures described here display very obvious channels, but with hydrophilic rather than hydrophobic inner surfaces.

Results and Discussion

In the **VA** family of structures there is head-to-tail hydrogen bonding of dipeptide molecules in helices with six dipeptide molecules per turn, shown schematically in Figure 1. The resulting 5 Å diameter channels are distinctly hydrophobic in nature since they are lined with peptide side chains. The

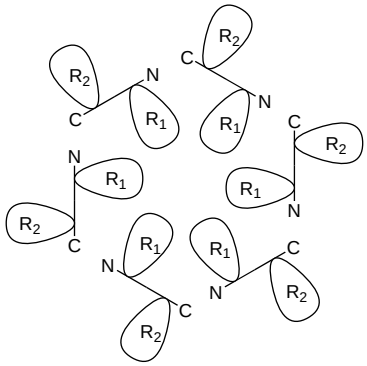

Figure 1. Molecular packing in the **VA** class of structures.

crystal structure of **VA**[11] provided an interesting new solution to the packing problem of hydrophobic dipeptides. It is evident from Figure 1, however, that accommodation of the most bulky side chains inside a channel would require an increase in the diameter of the helix formed by the peptide backbones. This cannot be done without disrupting the common hydrogen-bond pattern. Completely different packing arrangements have thus been observed for hydrophobic dipeptides containing an L-Leu or L-Phe residue,[12] although L-Leu-L-Val·¾H_2O also has hexagonal symmetry.[19]

The molecular structures of **LL**, **LF**, **FL**, and **FF** are shown in Figure 2. All bond lengths and bond angles are normal. The two molecules in the asymmetric units of **LL**, **LF**, and **FL** are very similar; root-mean-square values for the best overlap of non-H atoms are 0.098, 0.140, and 0.081 Å, respectively.

Molecular conformations: A simplified description of the conformation of a dipeptide is provided by the torsion angle $\theta = C_1^{\beta}–C_1^{\alpha}\cdots C_2^{\alpha}–C_2^{\beta}$, which defines the relative positions of the two side chains, Scheme 1. A search for zwitterionic L-Xaa-L-Xaa dipeptides (Xaa not Gly or Pro) in the Cambridge Structural Database[20] revealed that side chains usually point in almost opposite directions. This is reflected by 42 structures (out of 75) with $|\theta| > 135°$, 28 with $90° < |\theta| < 135°$, three with

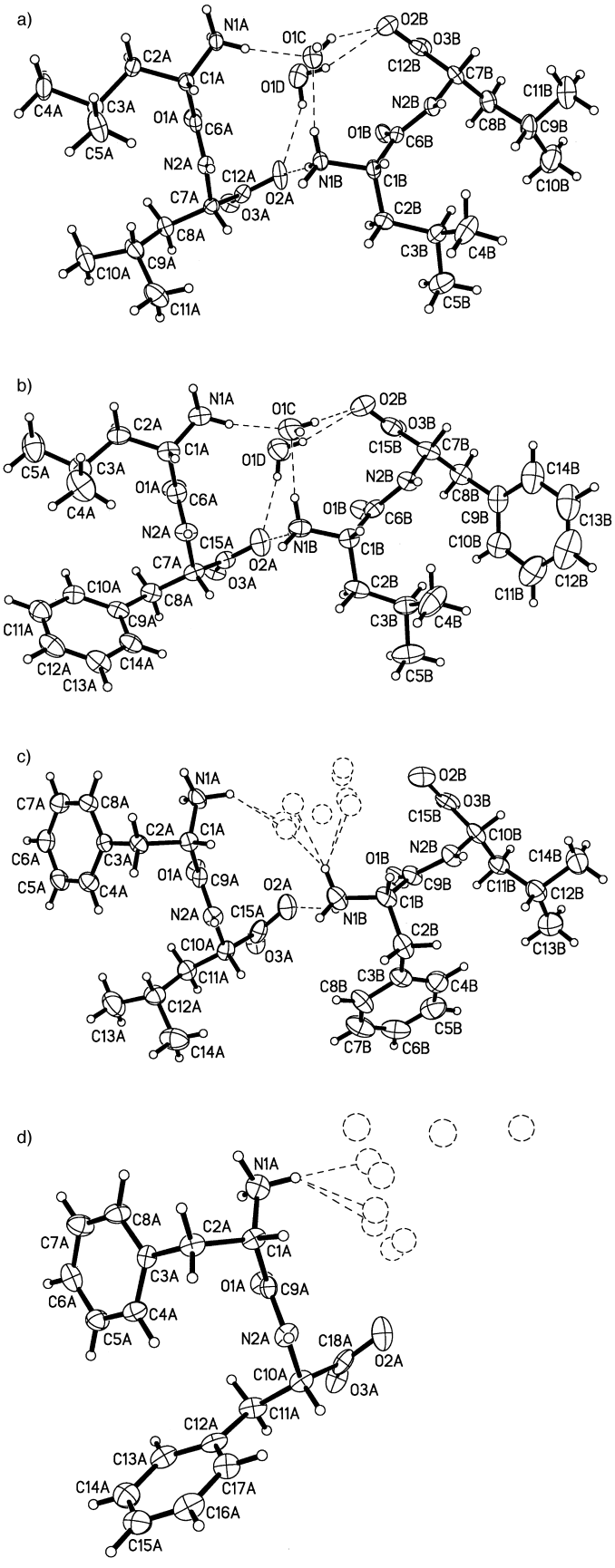

Figure 2. The molecular structure of a) **LL**, b) **LF**, c) **FL**, and d) **FF**. Displacement ellipsoids are shown at the 50% probability level. H-bonds appear as dashed lines. Partly occupied water positions are indicated by dashed circles of arbitrary size.

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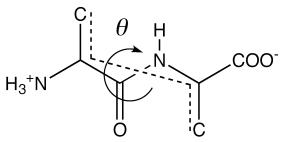

Scheme 1. Definition of the θ torsion angle in dipeptides.

$45^\circ < |\theta| < 90^\circ$ and only two, L-Ala-L-Trp[21] and L-Asp-L-Phe in its complex with L-His-Gly,[22] with $|\theta| < 45^\circ$.

It can immediately be recognized that the molecules in Figure 2 occur in most unusual conformations with both side chains located on the same side of the plane defined by the peptide bond. Indeed, all have $|\theta| < 40.2^\circ$, Table 1. The regular torsion angles, also given in Table 1, show that the rare θ values are attained primarily through a dramatic rotation around the N_2–C_2^{α} bond compared with other dipeptides, with resulting ϕ_2 torsion angles in the range 48–55°. The structures in the **VA** class[11, 13] have normal dipeptide conformations with θ between -150.5° and -169.2° and ϕ_2 between -129.0° and -150.6°. In previously investigated alcohol and DMSO solvates of **LL**[15–17] and **LF**,[18] the peptide molecules have semi-extended to extended conformations with ϕ_2 in the range -81.3° to -159.0°.

For **LL** and **LF** the side chain of the first residue is *trans*, while a less common *gauche*+ orientation is observed for **FL** and **FF**. The side chain of the second residue is *gauche*− for all four structures. As for rotation about the C^{β}–C^{γ} bond, $\chi^{2,1}$ and $\chi^{2,2}$ torsion angles for the second L-Phe residue of **FF** residue are 165.9° and −18.1°, respectively. These values are far from the energy minima at ±90°,[23] and together with the twisted backbone they make the **FF** molecule a true oddball from a conformational point of view.

Crystal structures: The reason why the dipeptides in the **FF** class occur in such unusual conformations becomes clear from the display of crystal packings in Figure 3. Very obvious channels are present in all structures: small for **LL**, **LF**, and **FL**, in which four dipeptide molecules constitute the circumference of a hydrophilic region, large in **FF**, for which translation of six molecules creates each channel. All side chains appear to emanate from the channel core, which is filled with water molecules. The structures can, on a slightly larger scale, be looked upon as idealized closepacking of hydrophobic tubes or rods. Apart from **FF**, which has crystallographic hexagonal symmetry (Figure 3d), this stacking is particularly evident for **FL**, as seen in Figure 3c. From consideration of the cell dimensions and the packing diagrams, the diameter of each rod can be roughly estimated to be in the range 17 Å ($\approx b$ for **LL**) to 24 Å ($\approx a$ and b for **FF**).

It is not uncommon that hydrophilic groups within a certain molecule segregate into columns (usually associated with hydrogen bonding) that run through a matrix of hydrophobic groups, but the title compounds are the first unblocked linear peptides to have structures with hydrophilic columns and an overall one-dimensional hydrogen-bond pattern. The water-filled nature of the columns, generated by supramolecular self-assembly of comparatively small molecules, is furthermore quite unique regardless of type or class of molecule.

Macroscopic behavior: The structures of the title compounds manifest themselves in a very illustrative manner through the macroscopic behavior of the crystals. Their hydrophobic surfaces make them extremely water repellent, and, in contrast to what is observed for other hydrophobic dipeptides, vigorous stirring is required to immerse the peptide samples in water prior to crystallization. The crystals are, on the other hand, instantly immersed in organic solvents, although the solubility is actually very low, about 0.08 mg mL^{-1} for **FF** in benzene at room temperature. Favorable aromatic interactions between the solute and the solvent can evidently not compensate for the lack of efficient shielding of the localized positive and negative charges in the zwitterions.

Hydrogen bonds: The hydrogen bond pattern between peptide molecules is qualitatively the same in all four title structures and is illustrated for **FF** in Figure 4. In graph-set terminology, a head-to-tail hydrogen-bonded chain of dipeptide molecules defines a first-level C(8) pattern,[24] that is, a chain with a repeat unit of eight atoms. In the **VA** class of structures there is just one C(8) chain, in shape of a right-handed helix. In the **FF** class there are two C(8) chains, one right-handed helix with a pitch of one unit cell length for each turn and one left-handed with a pitch of three (**LL**, **LF** and **FL**) or five (**FF**) unit cells lengths for each turn (Figure 4). Together with additional >N(amide)–H···carboxylate hydrogen bonds in a C(6) chain, the two helices create a rigid tubular scaffolding of peptide molecules in all four structures. There is a nice resemblance to hydrogen bonding in the cation

Table 1. Torsion angles [°].

	LL (A)[a]	**LL** (B)	**LF** (A)	**LF** (B)	**FL** (A)	**FL** (B)	**FF** (A)	**VA**[b]
ψ_1 (N_1-C_1^{α}-C_1'-N_2)	129.6(2)	127.8(2)	125.0(5)	124.3(5)	152.6(4)	155.3(4)	157.8(4)	162.9(6)
ω_1(C_1^{α}-C_1'-N_2-C_2^{α})	174.9(2)	177.9(2)	179.8(4)	−174.2(4)	−176.9(4)	−177.0(4)	−179.1(4)	176.0(6)
ϕ_2(C_1'-N_2-C_2^{α}-C_2')	47.9(3)	51.0(3)	47.7(6)	49.1(6)	52.6(5)	51.9(6)	55.4(5)	−150.6(6)
ψ_T (N_2-C_2^{α}-C_2'-O_2')[c]	50.6(3)	51.7(3)	52.7(7)	54.1(6)	39.2(6)	44.9(6)	43.8(5)	−28.2(9)
χ_1^1 (N_1-C_1^{α}-C_1^{β}-C_1^{γ})	176.9(2)	173.7(2)	178.4(5)	175.7(4)	63.3(5)	61.4(5)	66.8(5)	
$\chi_1^{2,1}$ (C_1^{α}-C_1^{β}-C_1^{γ}-$C_1^{\delta 1}$)	59.2(3)	60.5(3)	59.3(6)	61.5(7)	93.1(5)	93.0(6)	87.4(5)	
$\chi_1^{2,2}$ (C_1^{α}-C_1^{β}-C_1^{γ}-$C_1^{\delta 2}$)	−177.8(2)	−175.8(2)	−178.9(5)	−175.2(5)	−88.4(5)	−87.7(6)	−92.0(5)	
χ_2^1 (N_2-C_2^{α}-C_2^{β}-C_2^{γ})	−65.8(3)	−60.1(3)	−61.0(6)	−55.1(6)	−61.9(5)	−64.9(5)	−69.2(5)	
$\chi_2^{2,1}$ (C_2^{α}-C_2^{β}-C_2^{γ}-$C_2^{\delta 1}$)	168.4(2)	167.6(2)	122.9(5)	113.0(5)	167.8(4)	172.4(4)	165.9(4)	
$\chi_2^{2,2}$ (C_2^{α}-C_2^{β}-C_2^{γ}-$C_2^{\delta 2}$)	−68.7(3)	−69.2(3)	−56.5(7)	−65.2(7)	−69.9(6)	−64.7(6)	−18.1(6)	
θ (C_1^{β}-C_1^{α}···C_2^{α}-C_2^{β})	−1.5(2)	1.9(2)	−0.1(5)	3.0(5)	33.9(4)	34.9(4)	40.2(4)	−169.2(6)

[a] The label in parenthesis identifies the peptide molecule in the asymmetric unit. [b] L-Val-L-Ala.[11] [c] Measured to the O atom giving the smallest positive or negative value.

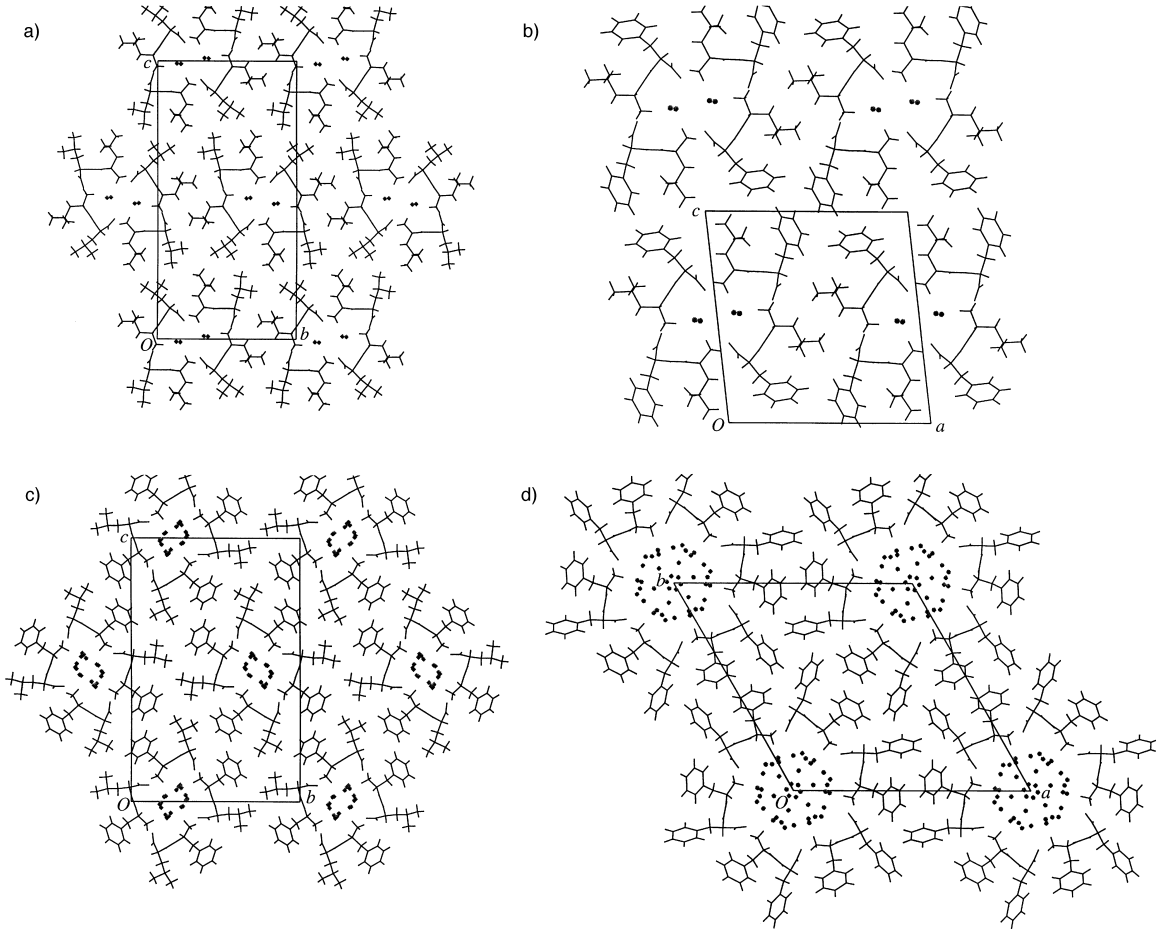

Figure 3. The unit cell and molecular packing of a) **LL** viewed along the *a* axis, b) **LF** viewed along the *b* axis, c) **FL** viewed along the *a* axis, and d) **FF** viewed along the *c* axis. Water molecules are shown as small spheres.

channel gramicidin A, which in the most recent X-ray structure[25] is shown to have a double-stranded right-handed helix with hydrogen bonds more or less parallel to the helix axis.

The inherent packing problem of hydrophobic dipeptides, as discussed above, is solved in the **FF** family of structures by donation of the third and last amino H atoms of each peptide to solvent water molecules in the channel core. Water molecules also provide additional donors for the carboxylate groups.

Solvent water: The most simple water structures are present in **LL** and **LF**. Water molecule *C* has a bridging function between the *N1A* amino group and the carboxylate *O2B* (Figure 2a and b), while molecule *D* links O atoms in two different carboxylate groups. Water molecule *D* is not fully occupied; this is presumably a result of the short H···H distance (≈2.1 Å) between H1C and H1D. It is possible, by using a molecular graphics program, to find at least three alternative orientations for molecule *D* with other sets of acceptors that would eliminate this conflict, but no trace of alternative orientations was found for **LL** in the well-defined electron density map (for **LF** it is less well defined). There are no hydrogen bonds between water molecules related by the twofold screw axis.

The slightly larger dimensions of the water channel in the **FL** structure mean that two water molecules cannot have the same bridging functions as in the structures of **LL** and **LF**. Instead, nine partially occupied water positions were found (Figure 2c), most of them quite well defined, with occupancies ranging from 0.50(3) to 0.13(2). Together, the water molecules constitute a single hydrogen bonding entity, and not two as for **LL** and **LF**. For **FF** the water structure is even more complex. The nine water molecule positions (Figure 2d), with occupancies ranging from 0.38(2) to 0.15(1) can be divided into three hydration layers (Figure 3d), one close and connected to the charged amino and carboxylate groups (layer 1), one at the hexagonal axis (layer 3) and one (layer 2) between layer 1 and layer 3. The refined isotropic displacement factors are high for all positions, and particularly for that in layer 3.

Channel structures and dimensions: The two molecules in the dimers constituting the asymmetric units of the closely related **LL** and **LF** structures are rotated almost exactly 120° relative to each other (Figure 2a and b); this means that when a dimer is rotated 180° by a twofold screw axis, there is a 60° rotation between peptide molecules at the junction between two dimers (Figure 3a and b). This gives a rectangular central channel with van der Waals' dimensions 2.5 × 6.0 Å. For **FL**, on the other hand, the relative rotations are 102° between

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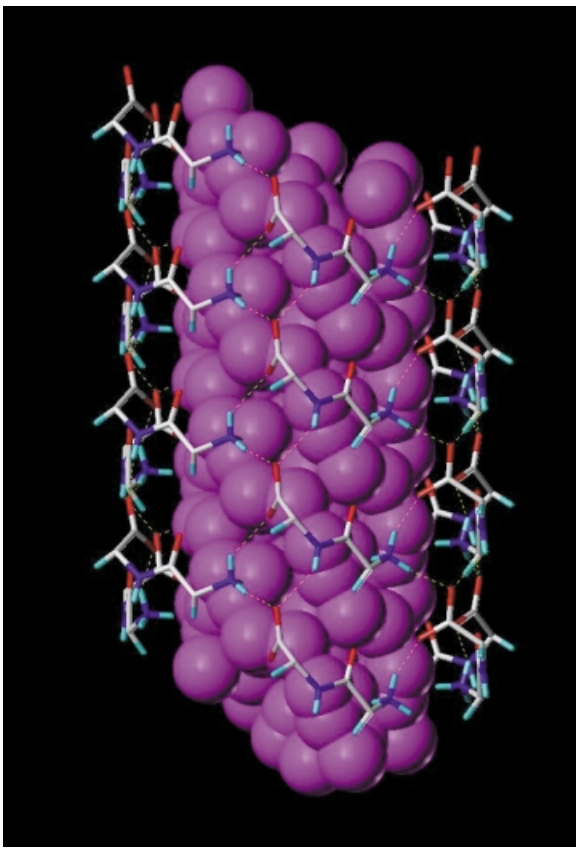

Figure 4. Water positions (with van der Waals' surface) inside a single channel in the **FF** structure. Hydrogen bonds between peptide molecules are shown as dashed lines. Peptide side chains have been omitted for clarity. Note that peptide bond >C=O groups do not accept any H atoms.

peptide molecules in the dimer and 78° between neighboring peptide molecules in opposite dimers (Figure 2c). Each hydrophobic tube then attains a conspicuous pseudotetragonal symmetry, as seen in Figure 3c. The channels dimensions are 4.0×6.0 Å.

In Figure 5 the much larger channel in the **FF** structure (diameter 10 Å) is compared with the channel of the idealized cyclo[-(L-Gln-D-Ala-L-Glu-D-Ala)$_2$-] structure (diameter 7 Å).[3] Apart from small deviations in shape, the most obvious difference between the two is that the **FF** channel is lined with hydrogen-bond donors and acceptors in charged groups (-NH_3^+ and -COO^-), while the polar but uncharged groups of the octapeptide channels are all engaged in hydrogen bonds. The same is true for the gramicidin A channels.[25]

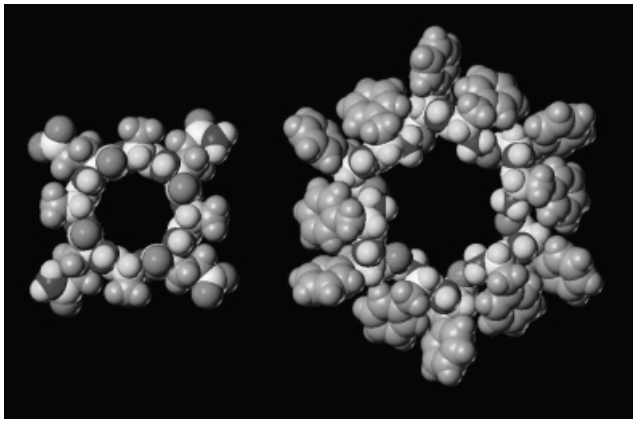

Figure 5. Comparison of the hole in the center of an idealized cyclo[-(L-Gln-D-Ala-L-Glu-D-Ala)$_2$-] molecule[3] as viewed from the top (left) with a channel in the **FF** structure (right).

A number of dipeptides (and other peptides) have crystal structures with cavities containing cocrystallized achiral organic molecules, usually the solvent used. In a special series of investigations, Ogura and co-workers have demonstrated enantioselective inclusion of alkyl phenyl sulfoxides for the dipeptide (*R*)-phenylglycine-(*R*)-phenylglycine.[26] The crystal structures of the complexes are divided into hydrophobic and hydrophilic layers. The inner surfaces of the channels formed by the title compounds are distinctly chiral, and it is not unreasonable to assume that they too could act as chiral receptors (or selectors).

Transchannel transport: For the cyclic octapeptides, not only dynamic movement of water molecules through the channels has been demonstrated,[4] but also, by incorporation into liposomes, high transport activities for K^+ and Na^+ ions.[2] In comparison, the strong hydrogen bonding of the solvent molecules of **LL** and **LF** most likely makes migration of water molecules through the channels a very slow process. The **FL** channels, however, are larger and have a number of partly occupied water positions. This indicates that some net flow of water molecules through the channels is possible. With the much larger **FF** channels, dynamic transport of a range of species can reasonably be expected. It is as yet uncertain, however, whether larger molecules such as glucose can be transported efficiently. The cyclic octapeptide lacks such activity, while the cyclic decapeptide cyclo[-(L-Trp-D-Leu)$_4$-L-Gln-D-Leu-] with a 10 Å pore size, has been shown to transport glucose efficiently.[5] Work is in progress to study incorporation of **FF** channels into biological membranes.

Conclusion

The four hydrophobic dipeptides presented here form unique crystal structures with hydrophilic channels embedded in a hydrophobic matrix created by the peptide side chains. The structure of L-Phe-L-Phe constitutes a particularly attractive candidate as a model for membrane channels due to the substantial size of the hydrophilic channels (van der Waals' diameter of about 10 Å), through which transportation of water, simple ions, and larger molecules like glucose can theoretically take place. It may also be possible to exploit the channels as chiral receptors.

Experimental Section

Crystal growth: Obtaining suitable single crystals devoid of organic solvents constituted a major obstacle in carrying out this investigation. Some experiments with acetonitrile, a less potent hydrogen bond acceptor than DMSO and the alcohols used earlier[15–18] (and a nondonor) were carried out, but evaporation from an aqueous solution of the peptide served as the main crystallization method. As a rule of thumb, the concentration of

Table 2. Crystal data, data collection and structure refinement.

	LL	**LF**	**FL**	**FF**
formula	$C_{12}H_{24}N_2O_3 \cdot 0.87\,H_2O$	$C_{15}H_{22}N_2O_3 \cdot 0.86\,H_2O$	$C_{15}H_{22}N_2O_3 \cdot 1.26\,H_2O$	$C_{18}H_{20}N_2O_3 \cdot 2.47\,H_2O$
M_r	259.84	293.84	301.22	356.87
crystal system	orthorhombic	monoclinic	orthorhombic	hexagonal
space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P6_1$
a [Å]	5.3524(5)	16.824(4)	5.2103(18)	24.0709(13)
b [Å]	16.7600(4)	5.3659(14)	19.974(7)	24.0709(13)
c [Å]	33.312(2)	17.578(5)	30.919(11)	5.4560(4)
β [°]	–	96.676(5)	–	–
V [Å^3]	2988.3(3)	1576.3(7)	3218(2)	2737.7(3)
Z	8	4	8	6
D_x [g cm^{-3}]	1.156	1.238	1.243	1.299
$\mu(Mo_{K\alpha})$ [mm^{-1}]	0.085	0.089	0.091	0.096
crystal size [mm]	$2.000 \times 0.200 \times 0.020$	$0.700 \times 0.070 \times 0.050$	$1.300 \times 0.030 \times 0.017$	$0.550 \times 0.026 \times 0.024$
transmission min/max	0.843/0.998	0.939/0.996	0.888/0.998	0.949/0.998
scan type/width [°]	ω/0.3	ω/0.3	ω/0.3	ϕ/0.2
frame exposure time [s]	60	180	240	180
reflections collected	14588	8347	16882	10937
independent reflections	5183	4710	3281	2406
observed reflections[a]	4175	2845	1802	1422
θ range [°]	2.2 – 25.2	2.4 – 25.1	1.7 – 25.0	1.0 – 25.1
$R[F^2 > 2\sigma(F^2)]$	0.0447	0.0813	0.0558	0.0595
$wR(F^2)$	0.1038	0.1942	0.1252	0.1355
goodness of fit	1.029	1.049	1.021	0.999
data/restraints/parameters	5138/37/390	4710/47/386	3281/52/416	2406/25/255
weighting scheme[b]	$1/[\sigma^2(F_o^2) + (0.0503P)^2 + 0.5369P]$	$1/[\sigma^2(F_o^2) + (0.0930P)^2]$	$1/[\sigma^2(F_o^2) + (0.0490P)^2 + 0.3665P]$	$1/[\sigma^2(F_o^2) + (0.0656P)^2]$
$\Delta\rho_{max}/\Delta\rho_{min}$ [e Å^{-3}]	0.174/ – 0.217	0.313/ – 0.312	0.221/ – 0.210	0.281/ – 0.283

[a] $F > 4.0\sigma(F)$, [b] $P = (F_o^2 + 2F_c^2)/3$.

a compound should be in the range 5 – 200 mg mL^{-1} for good crystals to form.[27] The solubility of **LL**, 23 mg mL^{-1}, is satisfactory in this respect, but the values 7.9 mg mL^{-1} for **FL** and 5.4 mg mL^{-1} for **LF** are quite low, and 2.5 mg mL^{-1} for **FF** is outside the given range. **LL** crystals could actually be grown by slow evaporation at room temperature, but the other peptides yielded needles that were far to thin (< 10 μm diameter) to be useful. To increase solubility, evaporations from warm aqueous solutions, as performed previously for, for instance, L-Tyr-L-Phe,[28] were then attempted. The required crystals failed to appear, however, until it was discovered that the speed with which the evaporation took place was a critical parameter. Surprisingly, it had to be quick rather than slow. After a series of experiments still very thin, but useful crystals were obtained for all three peptides when evaporation of 3 mL of a saturated solution took place in about 15 minutes, an astonishingly fast pace. The temperatures were 60 °C for **LF** and **FL**, and 80 °C for **FF**.

X-ray Diffraction: The crystallographic data are reported in Table 2. Data were measured at 150 K on a Siemens SMART 1000 CCD-diffractometer with MoK_α radiation ($\lambda = 0.71069$ Å). The data collection with SMART[29] nominally covered almost a sphere of reciprocal space, usually by a combination of three sets of exposures with the detector set at $2\theta = 26°$. The crystal-to-detector distance was 4.0 cm for **FF** and 5.0 cm for the other data collections. Data integration and cell refinement were carried out by SAINT,[30] while empirical absorption correction was carried out by SADABS.[31] SHELXTL[32] was used for structure solution by direct methods as well as subsequent full-matrix least-squares refinement on F^2. O, N and C atoms were refined anisotropically, except those O atoms with occupancy < 0.5 associated with solvent water molecules in **FL** and **FF**, which were refined isotropically. H atoms bonded to N in **LL** were also refined isotropically. Other H atoms were placed geometrically and either constrained to keep all C–H or N–H bond lengths as well as all C-C-H or C-N-H angles on any one C or N atom the same (H atoms bonded to C for **LL**, H atoms bonded to N for **FL** and **FF**) or kept in theoretical positions (H atoms bonded to C for **FL** and **FF**, all peptide H atoms for **LF**). Water H atoms were refined isotropically for **LL**, but could not be located in the electron density map of **LF**. H atoms were instead introduced in theoretical positions so as to mimic the hydrogen bonding of **LL**. No water H atoms were introduced for **FL** and **FF**.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 16337, CCDC 16338, CCDC 16339, and CCDC 16340 for **LL**, **LF**, **FL**, and **FF**, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

Cambridge Structural Database searches: Dipeptide structures were retrieved from the database[16] (April 2001 release) by means of the program ConQuest 1.2. Subsequent screening of the hits removed duplicate entries as well as the entries for a few mixed L-D or D-L dipeptides. When several different solvates existed for the same compound, only the number of structures representing truly different crystal packing arrangements were retained.

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