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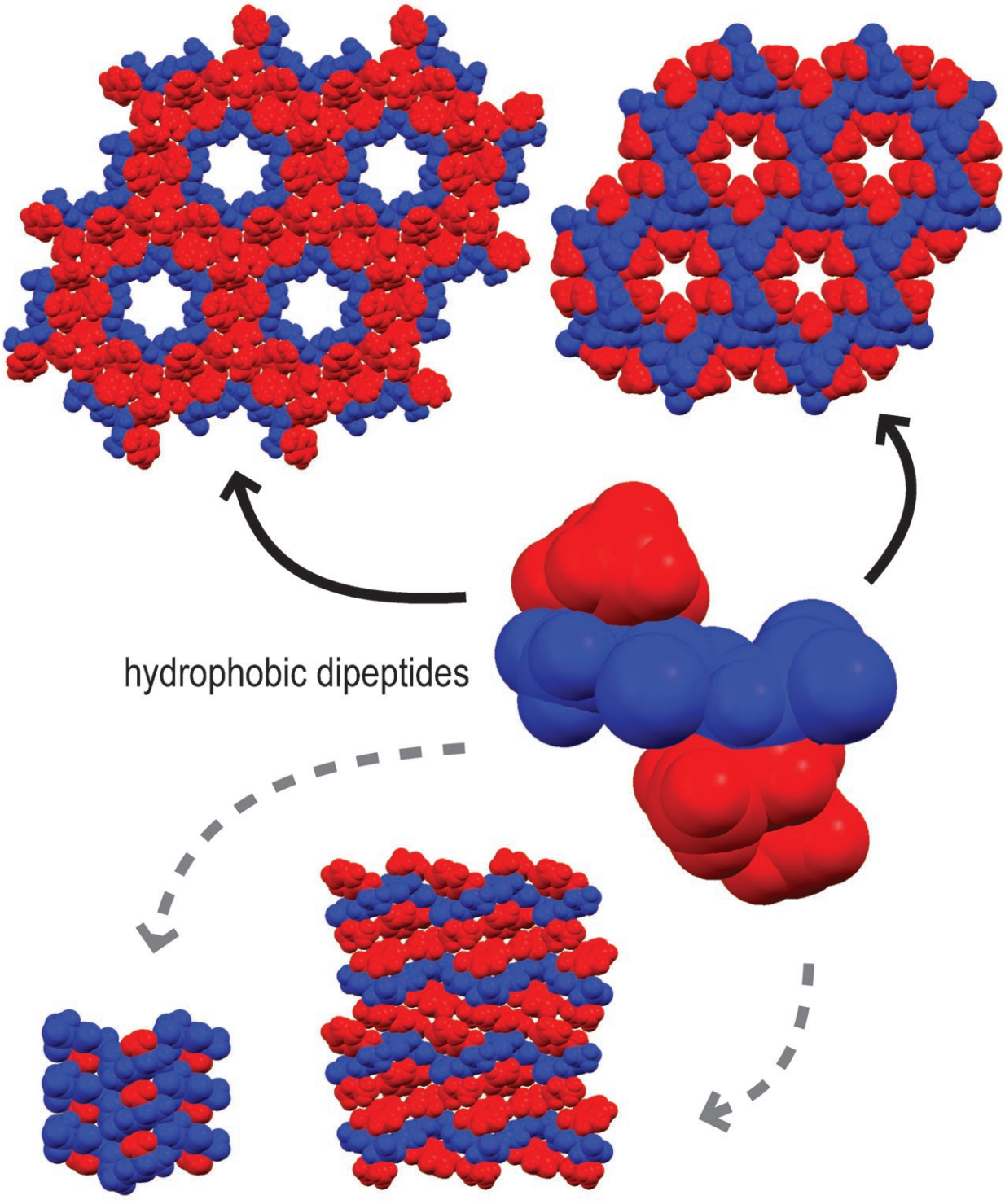

What makes dipeptides with two hydrophobic residues self-assemble not into usual crystal structures with small hydrophobic columns or distinct layers, but into two different classes of unique microporous organic materials?

Microporous Organic Materials from Hydrophobic Dipeptides

Carl Henrik Görbitz*[a]

Abstract: In the last few years dipeptides with two hydrophobic residues (hydrophobic dipeptides) have emerged as an unexpected source of stable microporous organic materials. Supramolecular self-assembly of the rather small building blocks is dictated by stringent demands on the hydrogen-bond formation by the peptide main chains and the aggregation of hydrophobic entities in the side chains. A systematic survey of structures derived from single-crystal X-ray diffraction studies has revealed the existence of two large classes of structures, differing in the dimensionality of the hydrogen-bonding patterns in the crystals and the nature of the channels. The present review summarizes the structural properties of the microporous dipeptides and discusses their potential applications.

Keywords: dipeptides · hydrogen bonds · microporous materials · self-assembly · supramolecular chemistry

Introduction

The synthesis, properties, and applications of various types of nanotubes, in particular carbon nanotubes,[1] but also various other types of inorganic[2] as well as organic nanotubes,[3] have been the subject of considerable research efforts in the last years. Nanotubes constructed by self-assembly of peptides or peptide derivatives have been investigated and developed for applications in bionanotechnology.[4] These systems are usually based on stacking of cyclic molecules through formation of intermolecular hydrogen bonds between functional groups in the peptide backbones. Pioneering work on this type of structures was carried out by Ghadiri and co-workers for cyclic D,L-peptides with 8–12 residues and van der Waals pore diameters up to 13 Å.[5] Intriguingly, these nanotubes have been shown to exert antimicrobial activity by self-assembly in bacterial membranes, thus increasing membrane permeability.[6] Various modifications of the alternating D,L-α-amino acid sequences have involved β-, γ-, δ-, and ε-amino acids,[7] as well as various non-peptidic building blocks.[8] Very different and much larger nanotubes can be formed by amphiphilic surfactant-type peptides (300–500 Å)[9] and bolamphiphilic peptides (200–10000 Å).[10]

Dipeptides with two hydrophobic residues (hydrophobic dipeptides) have recently emerged as a somewhat more unexpected source of microporous materials with pore diameters in the range 3–10 Å. The present review describes the foundations for formation of such materials, their construction, and the potential properties and applications in biotechnology and elsewhere.

Why Are Hydrophobic Dipeptides Useful Building Blocks for Microporous Materials?

The crystal structures of peptides with sizeable hydrophobic moieties in the side chains are often divided into distinct hydrophilic and hydrophobic layers.[11] The two-dimensional hydrophilic layers then typically incorporate a hydrogen-bonding motif with two $^{-}NH_3^{+}\cdots{}^{-}OOC$ head-to-tail chains, as illustrated in Figure 1 (left). The third amino H atom points straight into the adjacent hydrophobic layer, and thus cannot find a peptide main-chain acceptor. Instead, it is accepted by a functional group in one of the side chains (Figure 1, middle) or by a co-crystallized organic solvent molecule (Figure 1, right).[12,13] What might happen if either option is removed, as for dipeptides with two hydrophobic residues crystallized from solvents devoid of strong hydrogen-bond-accepting functional groups? Realization of this fundamental "packing problem" made us suspect that hydrophobic dipeptides might have unusual crystal-packing arrangements and led us to embark on a systematic investiga-

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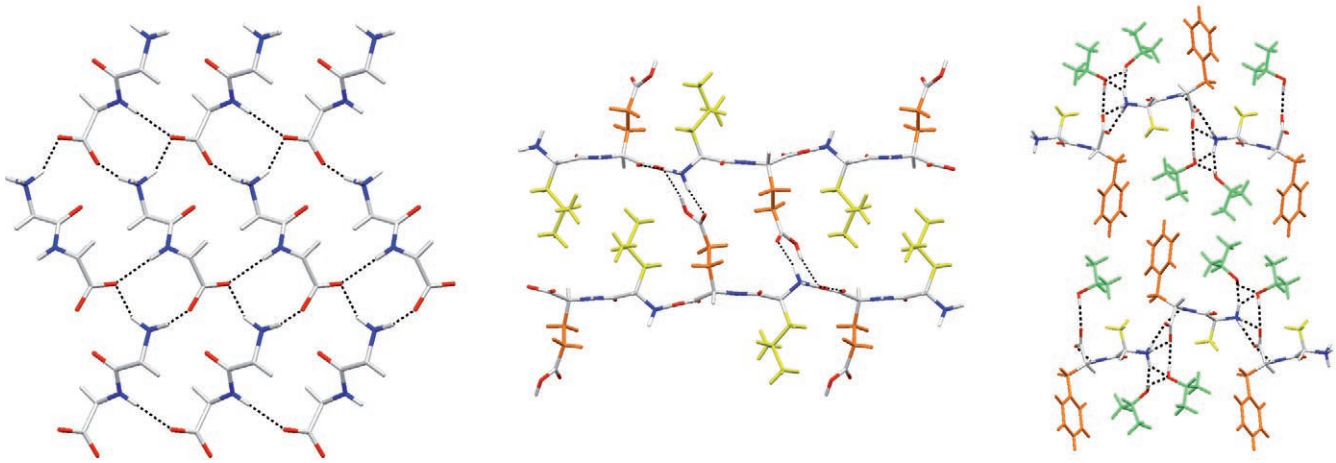


Figure 1. Left: Typical hydrophobic layer in a structure of a dipeptide with two head-to-tail $-NH_3^+\cdots{}^-OOC-$ chains. Peptide side chains are not shown. Middle: Acceptance of the third amino H atom by a side-chain carboxyl group in the structure of Val–Glu.[12] The peptide main-chain layers are seen edge-on. Right: Acceptance of the third amino H atom by a cocrystallized solvent molecule in the structure of Ala–Phe·2-propanol (1:2).[13] In this and the following illustrations the hydrophobic parts of residue 1 side chains are shown in yellow, while orange is used for residue 2. In the right-hand image the solvent molecule is shown in green.

tion of the crystal structures of dipeptides constructed from the five amino acids L-alanine (Ala), L-valine (Val), L-isoleucine (Ile), L-leucine (Leu) and L-phenylalanine (Phe). For completeness, some additional structures including L-methionine (Met) and (*S*)-2-aminobutyric acid (Abu) were also included in the study.

Solutions to the Packing Problem

Prior to our investigation only two crystal structures of hydrophobic dipeptides were known. Ala–Ala has two very small side chains (methyl groups), and manages to form three $-NH_3^+\cdots{}^-OOC$ head-to-tail chains in a tetragonal space group.[14] Met–Met forms crystals divided into layers with the third amino H atom participating only in a weak interaction with a side-chain S atom as the acceptor.[15] Figure 2 and Table 1 summarize the crystal packing arrangements of these two dipeptides and others that have been investigated as part of this project.

It can be seen that in the 5×5 matrix porous structures result when both residues are either Ala, Val, or Ile (except Ala–Ala), giving the Val–Ala class of structures,[16–18] or when both side chains are Leu or Phe (with the addition of Ile–Leu), the Phe–Phe class.[19,20]

For the remaining structures[21–30] the packing problem has been solved in various other manners, as illustrated in Figure 3, by incorporation of one or more solvent water molecules, by formation of close-packed hexagonal structures or by hydrogen-bond acceptance by the aromatic group of phenylalanine side chains.

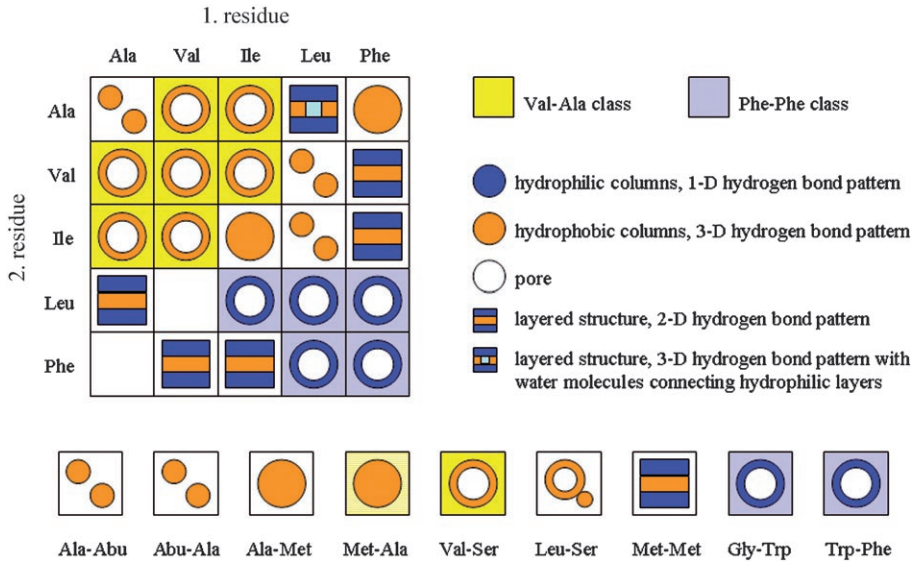


Figure 2. General description of the structures of hydrophobic dipeptides showing pattern for separation between hydrophobic and hydrophilic moieties and the presence of pores. The structures may contain co-crystallized water molecules, but not organic solvent molecules. For structures such as Leu–Val there are two different types of hydrophobic columns. References are given in Table 1. No structures are available for Val–Leu and Ala–Phe.

The Val–Ala Class

Val–Ala[16] (Figure 4, top) is the first example of a microporous dipeptide structure and was also the first member of an isostructural family that is without parallel in the Cambridge Structural Database (CSD).[31]

Table 1. Crystal data for hydrophobic dipeptides.[a] The entries have been sorted so that related structures are close to each other.

Dipeptide	Space group	Pore size [Å][b]	Z/Z′	N[c]	θ [°][d]	Reference
Ala–Ala	$I4$		8/1	3	−132	[14]
Abu–Ala	$I4$		8/1	3	−124	[36]
Ala–Abu·0.33 H_2O	$P2_1$		6/3	3	−117, −98, −89	[36]
Ala–Abu	$P2_1$		6/3	3	−179, −126, −106	[37]
Val–Ser·0.23 CF_3CH_2OH	$P2_1$	*4.6*	6/3	3	−158, 155, 172	[34]
Val–Ala·0.33 CH_3CN·0.29 H_2O	$P2_1$	*4.2*	6/3	3	−163, −142, −89	[34]
Val–Ala·0.12 CH_3CN	$P6_1$	*4.7*	6/1	3	−171	[34]
Ala–Ile·H_2O	$P6_1$	*4.7*	6/1	3	−160	[18]
Ile–Ala	$P6_1$	*3.7*	6/1	3	−179	[18]
Val–Val·H_2O	$P6_1$	*4.4*	6/1	3	−150	[18]
Val–Ile·0.22 H_2O	$P6_1$	*3.7*	6/1	3	−153	[18]
Ile–Val·0.21 H_2O	$P6_1$	*3.9*	6/1	3	−148	[18]
Ala–Val·0.35 CH_3CN	$P6_1$	*5.0*	6/1	3	−164	[17]
Ala–Val	$P6_1$	*5.0*	6/1	3	−164	[17]
Ala–Val·0.25 C_3H_7OH·0.22 H_2O	$P6_1$	*5.0*, *5.2*[e]	24/4	3	−168, −165, −162, −162	[17]
Met–Ala	$P6_1$		42/7	3	−182 to −109[f]	[41]
Leu–Val·0.75 H_2O	$P6_5$		24/4	3	−172, −166, −166, 146	[26]
Leu–Ile·0.75 H_2O	$P6_5$		24/4	3	−175, 152, 168, 172	[27]
Ala–Met·0.50 H_2O	$P2_12_12_1$		8/2	3	−121, 178	[40]
Ile–Ile·2 H_2O	$P2_12_12_1$		4/1	3	175	[23]
Phe–Ala·2 H_2O	$P2_12_12_1$		4/1	3	162	[28]
Leu–Ala·4 H_2O	$P2_12_12_1$		4/1	3	−105	[25]
Met–Met	$P2_12_12_1$		4/1	2	161	[15]
Ala–Leu·0.50 H_2O	$C2$		4/1	2	−92	[21]
Phe–Val	$P2_12_12_1$		4/1	2	−165	[29]
Val–Phe·3 H_2O	$P2_1$		16/8	2	−94, 23 [g]	[22]
Val–Phe·2 H_2O	$P2_12_12_1$		4/1	2	20	[22]
Ile–Phe·2 H_2O	$P2_1$		2/1	2	16	[24]
Phe–Ile·0.88 H_2O	$P2_1$		4/2	2	−96, 0	[30]
Ile–Leu·0.91 H_2O	$C2$	**3.2**	8/2	1	11, 15	[20]
Leu–Leu·0.87 H_2O	$P2_12_12_1$	**3.2**	8/2	1	−1, 2	[19]
Leu–Phe·0.86 H_2O	$P2_1$	**3.2**	4/2	1	0, 3	[19]
Phe–Leu·1.26 H_2O	$P2_12_12_1$	**4.2**	8/2	1	34, 35	[19]
Phe–Phe·2.47 H_2O	$P6_5$	**9.2**	6/1	1	40	[19]
Phe–Trp·0.75 H_2O	$P2_12_12_1$	**2.8**	16/4	1[h]	−13, −10, −9, 30	[46]
Trp–Gly·H_2O	$P4_1$	**4.7**	4/1	3	–[i]	[45]
Leu–Ser	$P6_5$	*4.9*	6/1	3	169	[50]

[a] Including four structures with Trp and Ser residues. Cell parameters are provided as Supporting Information. [b] Approximate van der Waals diameter, numbers in italic (Val–Ala class + Leu–Ser) identify hydrophobic pores, numbers in bold (Phe–Phe class) hydrophilic pores. [c] Dimensionality of the hydrogen-bond network. [d] θ is defined in Scheme 2. [e] Two types of pores. [f] Seven structures in the given range. [g] Average values for two groups: four structures in the range −109 to −73°, four structures in the range 22–26°. [h] Not including weak N–H···π interactions. [i] Not defined due to missing Gly side chain.

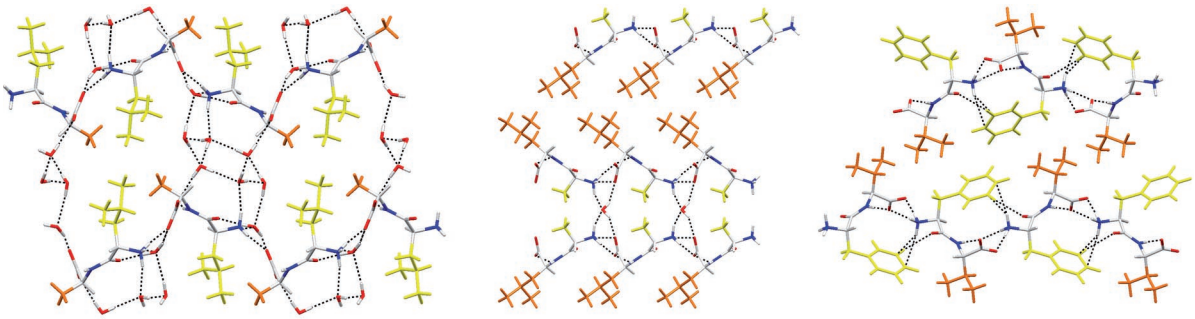


Figure 3. Left: Hydrophilic dipeptide layers connected by water molecules to give a three-dimensional hydrogen-bond pattern in the structure of Leu–Ala tetrahydrate.[25] Middle: Hydrophilic and hydrophobic layers in the structure of Ala–Leu hemihydrate.[21] The Ala side chains form independent small hydrophobic columns embedded in the hydrophilic layers. Right: The side-chain aromatic ring of Phe–Val as hydrogen-bond donor and hydrogen-bond acceptor.[29]

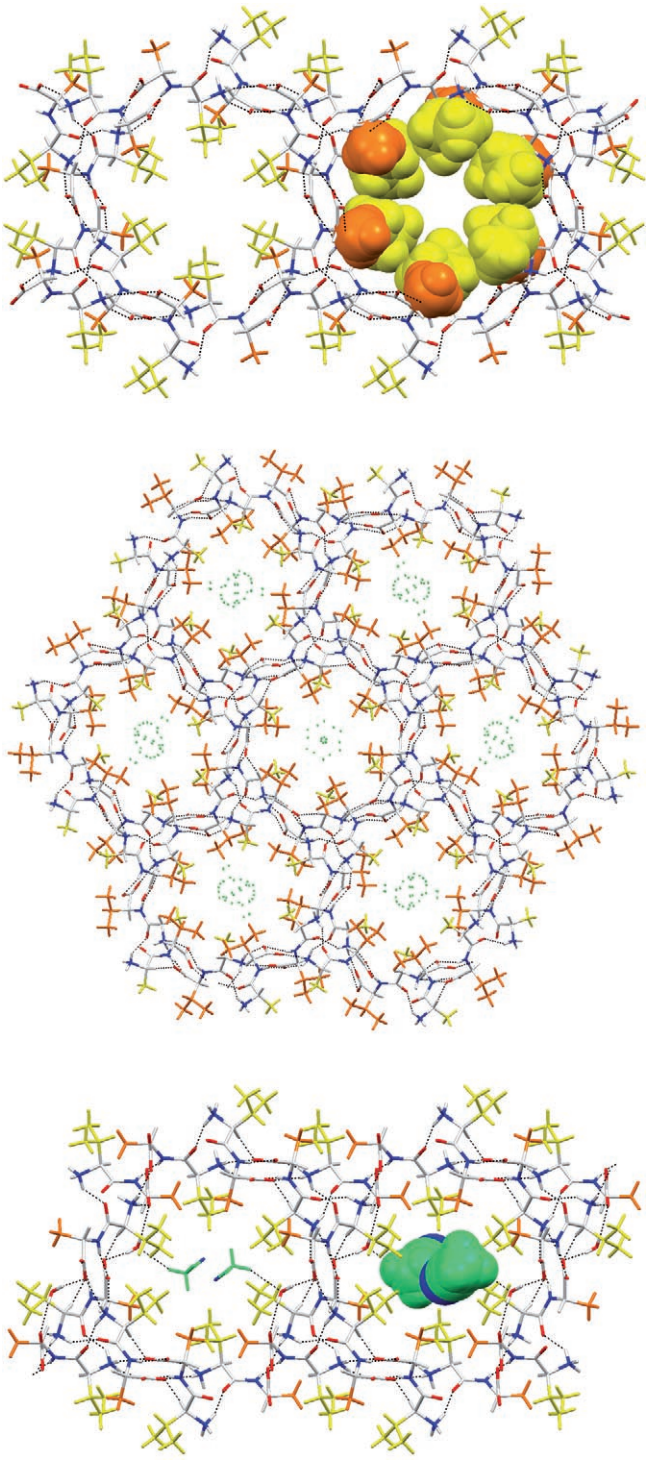
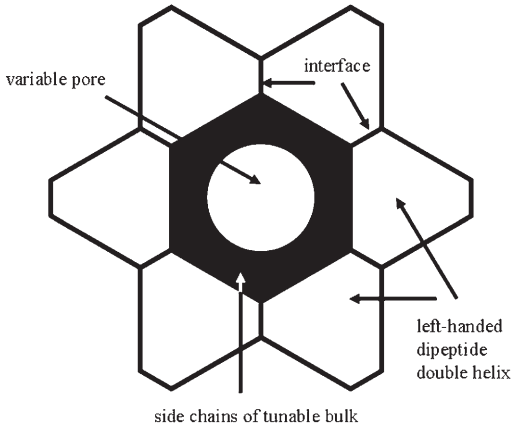


Figure 4. Crystal packing arrangement of Val-Ala (dry crystals; top),[34] Ala–Val 2-propanol solvate hydrate (middle)[17] and Val-Ala acetonitrile solvate hydrate (bottom).[34] Small dots inside the channels of Ala–Val 2-propanol solvate hydrate show refined positions for atoms in disordered solvent molecules. In the bottom image the solvent water molecules serve as acceptors in weak C–H···O interactions with acetonitrile solvent molecules.

A model for the construction of the Val–Ala class structures is given in Scheme 1.



Scheme 1.

The common honeycomb-shaped hydrogen-bonding network contains left-handed double helices of dipeptides.[32] The interface between these helices incorporate hydrogen bonds from peptide >N-H and C^{α}-H donors to carboxylate *syn* lone pairs; a rare type of interaction (Figure 5). The amino H atoms, on the other hand, are accepted by carboxylate anti-lone pairs.

Figure 5. Interaction between peptide molecules at the interface between double helices in structures belonging to the Val–Ala class.

The peptide side chains cluster around the hexagonal axes, but always leave evident central channels that are distinctly hydrophobic in nature. The van der Waals dimensions of these pores can be adjusted within a considerable range without major modifications to the main-chain scaffold and the cell dimensions by altering the bulk of the side chains.[18] Soldatov et al. calculated diameter ranges for individual structures from 3.66–3.75 Å for Val–Ile to 4.98–5.05 for Ala–Val, while their experimental values, based on absorption of He, were 3.0(2) and 5.36(8) Å, respectively.[33] The shape of the channels of the Val–Ala class also varies considerably, as illustrated in Figure 6.[33]

An extraordinary property of the Val–Ala class is that solvent guest molecules, included in a non-stoichiometric ratio inside the pores, can be removed by drying, while the peptide host remains intact. New guest molecules can subsequently be introduced, for example, by soaking the crystal in another solvent. This was illustrated in a striking manner for Ala–Val by substitution of the acetonitrile from crystallization with methanol and then, for the same crystal speci-

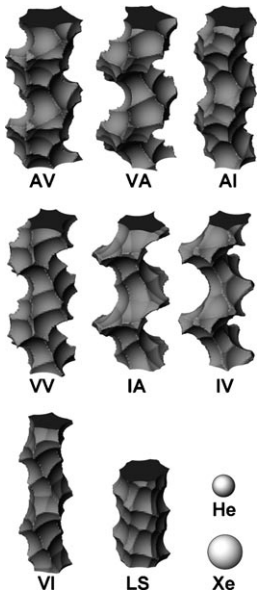


Figure 6. Illustration of pore space in dipeptides with hydrophobic channels (names are given with one-letter abbreviations).[33] The van der Waals outlines for He and Xe are given on the same scale for comparison. Reprinted with permission from reference [33] Copyright (2006) American Chemical Society.

men, further substitution of methanol with 2-propanol.[17] The latter process led to an irreversible phase transition involving a doubling of the *a* and *b* axes and transformation of the channel shapes in order to accommodate the larger alcohol molecules (Figure 4, middle).

The only crystal that shows any sign of deterioration upon solvent loss (transparent to opaque) are the crystals of Val–Ala itself.[16] Recently, it was discovered that when the alcohol was replaced by acetonitrile more stable crystals were formed, and structure refinement yielded a monoclinic modification of the acetonitrile solvate hydrate with $Z'=3$, the first non-hexagonal structure in the class (Figure 4, bottom).[34] The familiar hexagonal structure[16] is, however, obtained after solvent removal by drying, a process that is accompanied by a remarkable 6.5% increase in unit cell volume.[34]

A related structure with $Z'=3$ was subsequently found for Val–Ser[34] as part of extended search for microporous structures among dipeptides, in which one hydrophilic residue had been replaced by a hydrophilic Ser or Thr residue (Val–Ser produces a trihydrate when crystallized from aqueous solutions,[35] the porous modification was obtained using trifluoroethanol as the solvent). These crystals lose solvent very slowly and remain monoclinic even after prolonged periods of time.[34]

Ala–Abu and Abu–Ala, in which Abu is (*S*)-2-aminobutyric acid (ethyl side chain as opposed to an isopropyl chain for Val) might tentatively form larger pores than Ala–Val and Val–Ala. Both compounds have been investigated,[36] and Abu–Ala proved to form tetragonal crystals isostructural to Ala–Ala,[14] while Ala–Abu formed a 0.33 hydrate ($Z'=3$) without pores. Substitution of water with trifluoroethanol as the solvent for Ala–Abu led only to a mildly modified anhydrate.[37]

As indicated by model studies[38] a material with very small pores would result if Ile–Ile could be crystallized in a hexagonal modification, but from aqueous solution a nonporous dihydrate is easily formed.[23] Among solvent alternatives to water, liquid NH_3 was tested first. This is an excellent solvent for peptides, but its use led to proton transfer and the unprecedented formation of an ammonium salt of the peptide.[23] Trifluroethanol (TFE) was tested next, and thin needles were formed through equilibration against acetonitrile.[39] These needles were indeed porous, but did not belong to the Val–Ala class. The crystal structure of Ile–Ile·TFE is described below.

The potential incorporation of a non-branched side chain from a Met residue was finally tested by crystallization of Ala–Met and Met–Ala. The former yielded a nonporous hemihydrate,[40] while Met–Ala gave crystals related to the Val–Ala class, in the same space group ($P6_1$), but with larger cell dimensions and seven peptide molecules in the asymmetric unit (the second entry in the CSD with $Z'=7$).[41] There are two types of hydrophobic columns in this structure, and both are filled by Met side chains in more or less extended conformations so as to leave no detectable pores.

From these experiments it can be concluded that among eight different microporous compounds of the Val–Ala class Ala–Val have the largest pores, while the smallest pores occur for Val–Ile. Potential additional members of this structural family may be sought among dipeptides with Abu and Nva (Nva = norvaline) residues.

The Phe–Phe Class

Among dipeptides composed of Leu and Phe residues, Leu–Leu had prior to the present investigation been crystallized as a 2-methyl-1-propanol solvate;[42] as isomorphous ethanol, 1-propanol, and 2-propanol solvates[43]; and as a DMSO solvate,[44] while Leu–Phe had been crystallized as a 2-propanol solvate.[13] All these structures are divided into hydrophobic 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 these dipeptides form a set of completely different porous structures named after its most spectacular member Phe–Phe (Figure 7). The class also includes the structure of L-tryptophylglycine (Trp–Gly) published earlier[45] as well as the more recent structure of Phe–Trp.[46]

From a structural point of view the Phe–Phe class is somewhat more heterogenous than the Val–Ala class, with a selection of monoclinic (Leu–Phe,[19] Ile–Leu[20]), orthorhombic (Leu–Leu,[19] Phe–Leu,[19] Phe–Trp[46]), tetragonal (Trp–Gly[45]), and hexagonal (Phe–Phe[19]) crystal systems (Figure 7 and Table 1). Regardless of crystal symmetry, the hydrogen-bonding arrangement is essentially the same and unique among peptides in being one-dimensional (Trp–Gly[45] is an exception by virtue of additional hydrogen-bonding involving the side-chain N^{ε}-H donor). This arrangement is derived from wrapping a two-dimensional sheet as shown in Figure 1 (left) into a tube in the same manner that graphite can be converted into carbon nanotubes, and gives channels or pores with hydrophilic inner surfaces (rather than hydrophobic as observed for the Val–Ala class[16–18]). The packing problem is then solved by giving the third amino H atom access to water molecule acceptors inside the channels (Figure 8). When the channels are small, these water molecules are well ordered, but as the diameter increases water molecules become disordered and movable.

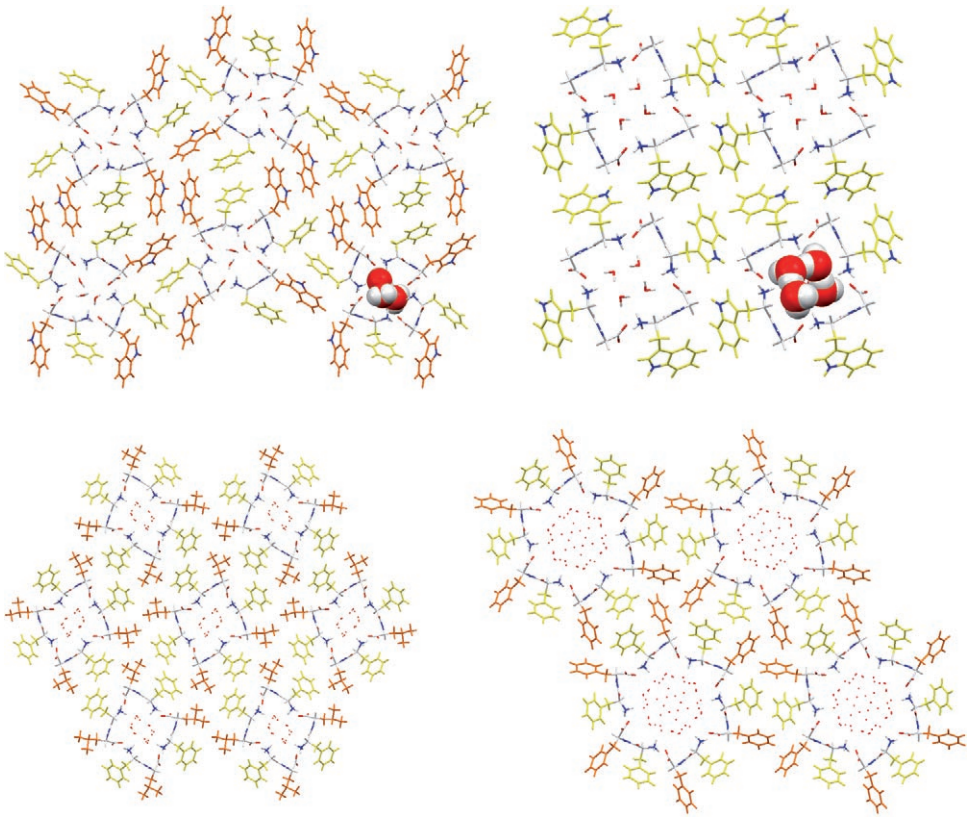


Figure 7. Structural variability within the Phe–Phe class of structures: Phe–Trp[46] (top left), Trp–Gly[45] (top right), Phe–Leu[19] (bottom left), and Phe-Phe[19] (bottom right). In the top images ordered molecules in one column have been depicted in space-fill representation. Small spheres in the bottom images represent disordered solvent positions.

Peptides in the Phe–Phe class normally have two residues that are branched at C^{γ}, in contrast to the C^{β}-branching of Ile and Val resides of the Val–Ala class. This illustrates the importance of side chain shape (Figure 9) and demonstrates that Ile is structurally much more closely related to Val, with a smaller side chain, than to Leu, with a side chain of similar bulk, but different shape. An inspection of Figure 2 accordingly reveals that Val and Ile residues can often be interchanged without major modifications to the crystal packing, while major changes always occur for interchange of Ile and Leu, except that Ile–Leu and Leu–Leu are very similar.

Apart from the difference in dimensionality of the hydrogen-bonding patterns (three-dimensional for the Val–Ala class, one-dimensional for the Phe–Phe class) and the nature of the pores (hydrophobic vs. hydrophilic), a comparison between Figures 4 and 7 reveals another oddity of the Phe–Phe class, namely the unusual molecular conformations. As detailed in Figure 10 for Ile–Leu[20] and Ile–Ile,[23] the normal dipeptide geometry puts peptide side chains on opposite sides of the peptide bond plane. If one defines the torsion angle $\theta = C_1^{\beta}$–$C_1^{\alpha}\cdots C_2^{\alpha}$–$C_2^{\beta}$ (Scheme 2), this translates to θ values close to 180°. To build a Phe–Phe class structure, both side chains must be positioned on the *same* side of the peptide bond plane, giving θ-values close to 0°, Table 1. Such values are rare among dipeptides and probably represent higher energy conformations that are nevertheless used by Phe–Phe class structures to solve the packing problem.

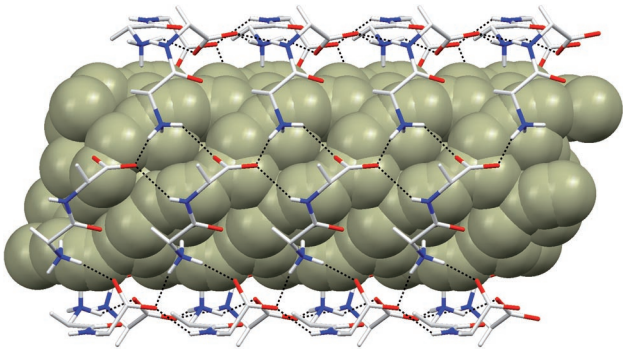


Figure 8. Water positions (with van der Waals surface) inside a channel of the Phe–Phe structure.[19] Peptide side chains have been omitted for clarity.

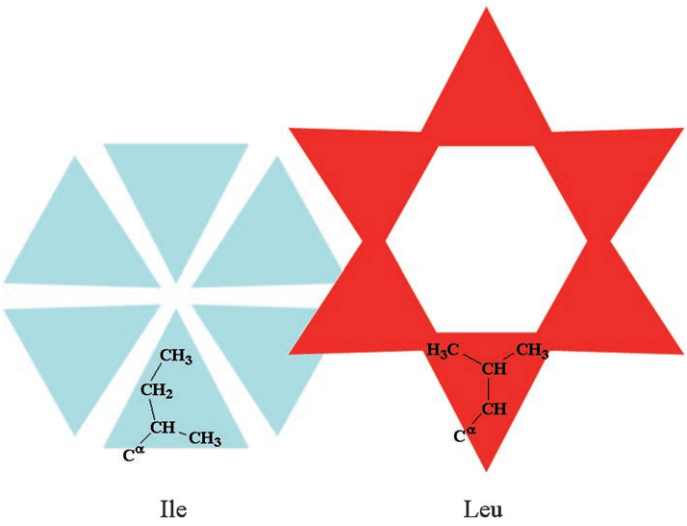
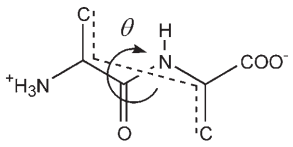


Figure 9. Schematic drawing of Ile and Leu side chains and how they can be made to fit around a hexagonal symmetry axis.

Figure 10. Different conformations of Ile-Ile[23] ($\theta = 175°$; left) and Ile-Leu[20] ($\theta = 11°$; right). The three main-chain torsion angles involved (N_1-C_1^{α}-C_1'-N_2, C_1^{α}-C_1'-N_2- C_2^{α} and C_1'-N_2-C_2^{α}-C_2) measure 145°, 169°, −143° and 137°, 175°, 50°, respectively.



Scheme 2.

Crystallization of Hydrophobic Dipeptides

Obtaining diffraction-quality crystals of the compounds studies has been one of the major obstacles in carrying out the present investigation. A few compounds, like Val–Ala[16] and Ala–Val,[17] crystallize rather easily, while most other dipeptides tend to give extremely thin, hairlike fibers unsuitable for single-crystal work. The first solution found to this problem, applied for Val–Val and Ala–Ile,[18] involved adjustment of the concentration of the peptide in vapor diffusion experiments to be just above the limiting value needed to observe precipitation. Later it was discovered that useful crystals of several peptides could be obtained by quick evaporation of aqueous solutions at elevated temperatures, up to 80 °C for Phe–Phe.[19] Many of the peptides are poorly soluble in water at room temperature, and the higher temperatures are probably needed to bring peptide concentrations to a reasonable level for crystal growth when nucleation starts. The need to carry out these experiments rather fast, 15 minutes has typically been used, may reflect a compromise between high enough concentration and peptide stability. We have not looked into detail on this matter, but have on two occasions, for Val–Leu[47] and Ile–Ile,[48] obtained crystals of a cyclic dipeptide (diketopiperazine) from a solution of the corresponding linear peptide.

When it is desirable to keep water away from the peptide, trifluoroethanol is a solvent with reasonable solubility for many peptides. Another good (but expensive) alternative, introduced by Reches and Gazit for Phe–Phe,[49] is 1,1,1,3,3,3-hexafluoro-2-propanol, which we have used to obtain crystals of Phe–Trp.[46]

Recent Developments: The Structures of Leu–Ser and Ile–Ile·Trifluoroethanol

One of the compounds studied as part of the extended investigation of dipeptides with one hydrophobic residue and one that is either Ser or Thr, was Leu–Ser. In view of the shape of the Leu side chain, which apparently makes it less suited for formation of porous structures with hydrophobic channels (see above), it was surprising to find that this particular compound forms a new type of crystal structure with hydrophobic channels that have a van der Waals diameter of 4.9 Å (Figure 11 top).[50] Co-crystallized acetonitrile solvent molecules were easily removed by drying, and the porous nature of the crystals was subsequently demonstrated in a compelling manner by soaking them in a solution of toluene saturated with I_2, whereupon the colorless crystals absorbed I_2 and turned dark brown (Figure 11, bottom). The crystal packing of Leu–Ser is sterically incompatible with side-chain branching at C^{β}, and hence Val–Ser[34,35] (see above) and Ile–Ser[51] form other types of structures. The aromatic side chain of Phe–Ser is too large to be accommodated inside the channels,[51] while Ala–Ser forms a compact structure.[52] The structure of Met–Ser is divided into layers such as Ile–Ser.[51]

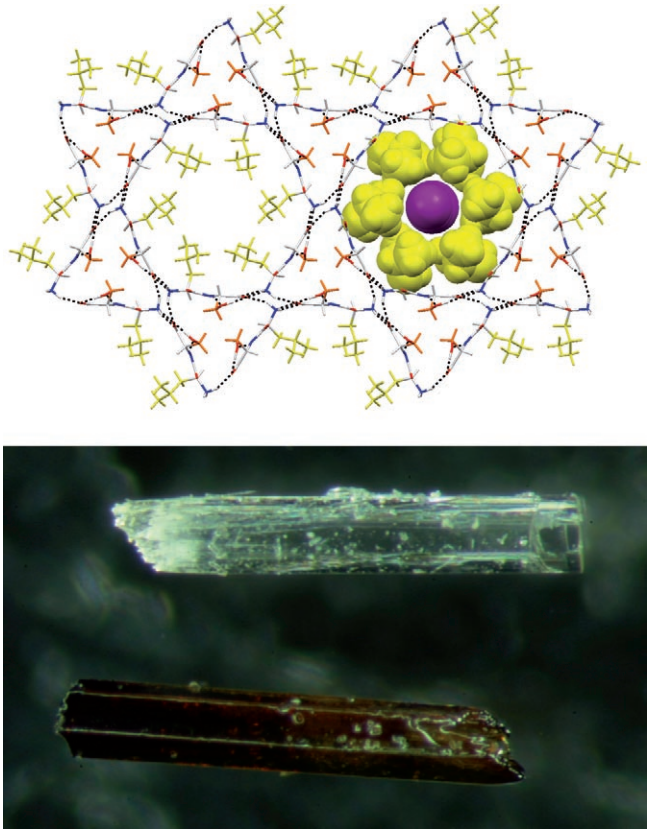


Figure 11. Top: Crystal structure of Leu-Ser.[50] Bottom: Dry crystal of Leu-Ser (above) and crystal soaked in I_2-solution (below).

A final rather spectacular example of formation of a peptide-based microporous material was recently discovered when Ile–Ile was crystallized from a solution of the peptide in trifluoroethanol (TFE), with acetonitrile as the precipitating agent. The structure formed has pores that rival Phe–Phe as the largest found for a supramolecular host of this type, 10 Å, but moreover has the unique property of possessing a co-crystallized solvent molecule on the inner surface of the channels, (Figure 12).[39] In an unprecedented experiment, this solvent molecule was replaced by soaking the crystals in *sec*-butanol, probably the first example of post-crystallization stoichiometric replacement of solvent molecule in a crystal. Moreover, *sec*-butanol is a racemate, and the observed preference for one enantiomer (the *S* form) provides a tantalizing demonstration of chiral separation by a microporous organic crystal.[38]

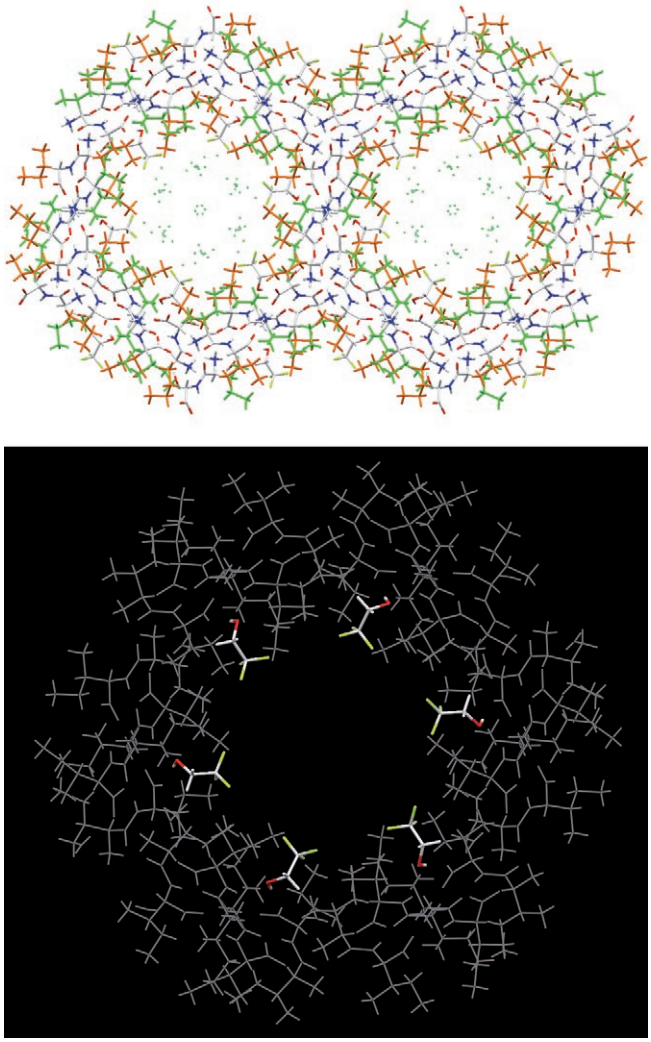


Figure 12. Top: Pores with diameter 10 Å in the structure of Ile–Ile TFE solvate hydrate.[39] Bottom: Detail showing the location of TFE molecules inside a pore.

Applications

High affinity for absorption of Xe gas has been demonstrated for Val–Ala and Ala–Val, with sorption occurring most efficiently in Val–Ala channels, although these are slightly smaller then the channels of Ala–Val (diameters 4.90 and 5.13 Å, respectively).[33,53] Peptides in the Val–Ala generally display high selectivity for CO_2(g) at ambient temperature.[33]

As for the Phe–Phe class, significant results for Phe–Phe itself show that very stiff crystalline fibers can act as casts for production of silver nanowires.,[49,55] Incorporation of platinum has also been demonstrated.[56] Furthermore, Phe–Phe can act as a model for the aggregation of aromatic groups observed in patients suffering from Alzheimer's disease.[49,57] In addition the characteristics of the nanotubes formed by Phe–Phe class of peptides resemble those formed by the cyclic D,L-peptides,[5,6] and incorporation into membranes might be achievable. A molecular dynamics study of Trp–Gly has already revealed details on the mobility of water inside the tubes.[58]

Among known microporous materials, the peptide-based structures are unique in being constructed from chiral building blocks (in distinction to metallo–organic frameworks (MOFs) and zeolites). The interior of the channels is accordingly also chiral. This opens the potential of constructing microporous materials that selectively absorb one enantiomer from a racemic mixture (chiral absorption). It should be pointed out that the materials have very low toxicity and constitute environmentally benign alternatives to inorganic materials or MOFs. Positioning of functional groups and even metal ions on the interior channel surfaces could make these materials interesting for applications in catalysis.

Conclusion

Hydrophobic dipeptides are readily available, versatile building blocks for construction of microporous materials by supramolecular self-assembly. Compared to other organic materials, the dipeptide structures are remarkably stable porous frameworks; co-crystallized solvent inside channels can often be completely removed with full retention of the peptide host lattice. Different families of hydrophobic dipeptides have different channel properties, which might find useful applications in gas storage, selective absorption, and as model compounds for membrane channels.

[1] a) Y. Ando, X. Zhao, T. Sugai, M. Kumar, *Mater. Today* **2004**, *7*, 22–29; b) K. Gong, Y. Yan, M. Zhang, L. Su, S. Xiong, L. Mao, *Anal. Sci.* **2005**, *21*, 1383–1393; c) J. A. Rojas-Chapana, M. Giersig, *J. Nanosci. Nanotechnol.* **2006**, *6*, 316–321; d) D. Tasis, N. Tagmatarchis, A. Bianco, M. Prato, *Chem. Rev.* **2006**, *106*, 1105–1136.
[2] a) C. N. R. Rao, M. Nath, *Dalton Trans.* **2003**, 1–24; b) M. Remškar, *Adv. Mater.* **2004**, *16*, 1497–1504; c) Y. Xiong, B. T. Mayers, Y. Xia, *Chem. Commun.* **2005**, 5013–5022; d) J. Goldberger, R. Fan, P. Yang, *Acc. Chem. Res.* **2006**, *39*, 239–248.

[3] a) D. T. Bong, T. D. Clark, J. R. Granja, M. R. Ghadiri, *Angew. Chem.* **2001**, *113*, 1016–1041; *Angew. Chem. Int. Ed.* **2001**, *40*, 988–1011; b) S. J. Dalgarno, G. W. V. Cave, J. L. Atwood, *Angew. Chem.* **2006**, *118*, 584–588; *Angew. Chem. Int. Ed.* **2006**, *45*, 570–574.
[4] a) J. D. Hartgerink, T. D. Clark, M. R. Ghadiri, *Chem. Eur. J.* **1998**, *4*, 1367–1372; b) S. Zhang, D. M. Marini, W. Hwang, S. Santoso, *Curr. Opin. Chem. Biol.* **2002**, *6*, 865–871; c) X. Gao, H. Matsui, *Adv. Mater.* **2005**, *17*, 2037–2050; d) C.-J. Tsai, J. Zheng, R. Nussinov, *PLoS Comput. Biol.* **2006**, *2*, 311–319.
[5] a) M. R. Ghadiri, J. R. Granja, R. A. Milligan, D. E. McRee, N. Khazanovich, *Nature* **1993**, *366*, 324–327; b) J. D. Hartgerink, J. R. Granja, R. A. Milligan, M. R. Ghadiri, *J. Am. Chem. Soc.* **1996**, *118*, 43–50; c) H. S. Kim, J. D. Hartgerink, M. R. Ghadiri, *J. Am. Chem. Soc.* **1998**, *120*, 4417–4424; d) T. D. Clark, J. M. Buriak, K. Kobayashi, M. P. Isler, D. R. McRee, M. R. Ghadiri, *J. Am. Chem. Soc.* **1998**, *120*, 8949–8962; K. Rosenthal-Aizman, G. Svensson, A. Undén, *J. Am. Chem. Soc.* **2004**, *126*, 3372–3373.
[6] a) S. Fernandez-Lopez, H.-S. Kim, E. C. Choi, M. Delgado, J. R. Granja, A. Khasanov, K. Kraehenbuehl, G. Long, D. A. Weinberger, K. M. Wilcoxen, M. R. Ghadiri, *Nature* **2001**, *412*, 452–455; b) V. Dartois, J. Sanchez-Quesada, E. Cabezas, E. Chi, C. Dubbelde, C. Dunn, J. Granja, C. Gritzen, D. Weinberger, M. R. Ghadiri, T. R. Parr, *Antimicrob. Agents Chemother.* **2005**, *49*, 3302–3310.
[7] a) I. L. Karle, B. K. Handa, C. H. Hassall, *Acta Crystallogr. Sect. B* **1975**, *31*, 555–560; b) D. Seebach, J. L. Matthews, A. Meden, T. Wessels, C. Baerlocher, L. B. McCusker, *Helv. Chim. Acta* **1997**, *80*, 173–182; c) T. D. Clark, L. K. Buehler, M. R. Ghadiri, *J. Am. Chem. Soc.* **1998**, *120*, 651–656; d) D. Gauthier, P. Baillargeon, M. Drouin, Y. L. Dory, *Angew. Chem.* **2001**, *113*, 4771–4774; *Angew. Chem. Int. Ed.* **2001**, *40*, 4635–4638; W. S. Horne, C. D. Stout, M. R. Ghadiri, *J. Am. Chem. Soc.* **2003**, *125*, 9372–9376.
[8] a) D. Ranganathan, V. Haridas, R. Gilardi, I. L. Karle, *J. Am. Chem. Soc.* **1998**, *120*, 10793–10800; b) D. Ranganathan, C. Lakshmi, I. L. Karle, *J. Am. Chem. Soc.* **1999**, *121*, 6103–6107; c) D. Ranganathan, V. Haridas, C. S. Sundari, D. Balasubramanian, K. P. Madhusudanan, R. Roy, I. L. Karle, *J. Org. Chem.* **1999**, *64*, 9230–9240; M. Amorin, L. Castedo, J. R. Granja, *Chem. Eur. J.* **2005**, *11*, 6543–6551; S. E. Gibson, C. Lecci, *Angew. Chem.* **2006**, *118*, 1392–1405; *Angew. Chem. Int. Ed.* **2006**, *45*, 1364–1377.
[9] a) S. Vauthey, S. Santoso, H. Gong, N. Watson, S. Zhang, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5355–5360; b) G. von Maltzahn, S. Vauthey, S. Santoso, S. Zhang, *Langmuir* **2003**, *19*, 4332–4337.
[10] a) M. Kogiso, S. Ohnishi, K. Yase, M. Masuda, T. Shimuzi, *Langmuir* **1998**, *14*, 4978–4986; b) H. Matsui, G. E. J. Douberly, *Langmuir* **2001**, *17*, 7918–7922; c) R. C. Claussen, B. M. Rabatic, S. I. Stupp, *J. Am. Chem. Soc.* **2003**, *125*, 12680–12681.
[11] C. H. Görbitz, M. C. Etter, *Int. J. Pept. Protein Res.* **1992**, *39*, 93–110.
[12] D. S. Eggleston, *Acta Crystallogr. Sect. C* **1984**, *40*, 1250–1252.
[13] C. H. Görbitz, *Acta Crystallogr. Sect. C* **1999**, *55*, 2171–2177.
[14] R. J. Fletterick, C. Tsai, R. E. Hughes, *J. Phys. Chem.* **1971**, *75*, 918–922.
[15] R. E. Stenkamp, L. H. Jensen, *Acta Crystallogr. Sect. B* **1975**, *31*, 857–861.
[16] C. H. Görbitz, E. Gundersen, *Acta Crystallogr. Sect. C* **1996**, *52*, 1764–1767.
[17] C. H. Görbitz, *Acta Crystallogr. Sect. B* **2002**, *58*, 849–854.
[18] C. H. Görbitz, *New J. Chem.* **2003**, *27*, 1789–1793.
[19] C. H. Görbitz, *Chem. Eur. J.* **2001**, *7*, 5153–5159.
[20] C. H. Görbitz, *Acta Crystallogr. Sect. E* **2004**, *60*, o626-o628.
[21] C. H. Görbitz, *Acta Crystallogr. Sect. C* **1999**, *55*, 9900149.
[22] C. H. Görbitz, *Acta Crystallogr. Sect. B* **2002**, *58*, 512–518.
[23] C. H. Görbitz, *Acta Crystallogr. Sect. B* **2004**, *60*, 569–577.
[24] C. H. Görbitz, *Acta Crystallogr. Sect. C* **2004**, *60*, o371-o373.
[25] C. H. Görbitz, *Acta Crystallogr. Sect. C* **1997**, *53*, 736–739.
[26] C. H. Görbitz, E. Gundersen, *Acta Chem. Scand.* **1996**, *50*, 537–543.
[27] C. H. Görbitz, *Acta Crystallogr. Sect. E* **2004**, *60*, o647-o650.
[28] C. H. Görbitz, *Acta Crystallogr. Sect. C* **2001**, *57*, 575–576.
[29] C. H. Görbitz, *Acta Crystallogr. Sect. C* **2000**, *56*, 1496–1498.
[30] C. H. Görbitz, *Acta Crystallogr. Sect. C* **2004**, *60*, o810–o812.
[31] F. H. Allen, *Acta Crystallogr. Sect. B* **2002**, *58*, 380–388.
[32] C. H. Görbitz, *Curr. Opin. Solid State Mater. Sci.* **2002**, *6*, 109–116.
[33] D. V. Soldatov, I. L. Moudrakovski, E. V. Grachev, J. A. Ripmeester, *J. Am. Chem. Soc.* **2006**, *128*, 6737–6744.
[34] C. H. Görbitz, *CrystEngComm* **2005**, *7*, 670–673.
[35] A. Johansen, R. Midtkandal, H. Roggen, C. H. Görbitz, *Acta Crystallogr. Sect. C* **2005**, *61*, o198-o200.
[36] C. H. Görbitz, *Acta Crystallogr. Sect. C* **2002**, *58*, o533-o536.
[37] C. H. Görbitz, *Acta Crystallogr. Sect. E* **2005**, *61*, o3735-o3737.
[38] Sybyl Version 7.1, Tripos, Inc., http://www.tripos.com
[39] C. H. Görbitz, unpublished results.
[40] C. H. Görbitz, *Acta Crystallogr. Sect. C* **2003**, *59*, o730-o732.
[41] C. H. Görbitz, *Acta Crystallogr. Sect. C* **2003**, *59*, o589-o592.
[42] C. H. Görbitz, *Acta Crystallogr. Sect. C* **1999**, *55*, 670–672.
[43] C. H. Görbitz, *Acta Chem. Scand.* **1998**, *52*, 1343–1349.
[44] S. N. Mitra, E. Subramanian, *Biopolymers* **1994**, *34*, 1139–1143.
[45] a) T. J. Emge, A. Agrawal, J. P. Dalessio, G. Dukovic, J. A. Inghrim, K. Janjua, M. Macaluso, L. L. Robertson, T. J. Stiglic, Y. Volovik, M. M. Georgiadis, *Acta Crystallogr. Sect. C* **2000**, *56*, e469-e471; b) H. Birkedal, D. Schwarzenbach, P. Pattison, *Angew. Chem.* **2002**, *114*, 780–782; *Angew. Chem. Int. Ed.* **2002**, *41*, 754–756.
[46] C. H. Görbitz, *Acta Crystallogr. Sect. C* **2006**, *62*, o328-o330.
[47] C. H. Görbitz, unpublished results.
[48] C. H. Görbitz, L. M. Hartviksen, *Acta Crystallogr. Sect. E* **2006**, *62*, o2358-o2360.
[49] R. Reches, E. Gazit, *Science* **2003**, *300*, 625–628.
[50] C. H. Görbitz, M. Nilsen, K. Szeto, L. W. Tangen, *Chem. Commun.* **2005**, 4288–4290.
[51] C. H. Görbitz, M. Bruvoll, S. Dizdarevic, N. Fimland, J. Hafizovic, H. T. Kalfjøs, A. Krivokapic, K. Vestli, *Acta Crystallogr. Sect. C* **2006**, *62*, o22-o25.
[52] P. G. Jones, L. Falvello, O. Kennard, *Acta Crystallogr. Sect. B* **1978**, *34*, 1939–1942.
[53] D. V. Soldatov, I. L. Moudrakovski, J. A. Ripmeester, *Angew. Chem.* **2004**, *116*, 6468–6471; *Angew. Chem. Int. Ed.* **2004**, *43*, 6308–6311.
[54] C. H. Görbitz, R. Blom, unpublished results.
[55] N. Kol, L. Adler-Abramovich, D. Barlam, R. Z. Shneck, E. Gazit, I. Rousso, *Nano Lett.* **2005**, *5*, 1343–1346.
[56] Y. Song, S. R. Challa, C. J. Medforth, Y. Qiu, R. K. Watt, D. Peña, J. E. Miller, F. van Swol, J. A. Shelnutt, *Chem. Commun.* **2004**, 1044–1045.
[57] a) A. T. Petkova, R. D. Leapman, Z. Guo, W.-M. Yau, M. P. Mattson, R. Tycko, *Science* **2005**, *307*, 262–265; b) C. H. Görbitz, *Chem. Commun.* **2006**, 2332–2334; c) V. L. Sedman, L. Adler-Abramovich, S. Allen. , E. Gazit, S. J. B. Tendler, *J. Am. Chem. Soc.* **2006**, *128*, 6903–6908.
[58] Y. Pan, H. Birkedal, P. Pattison, D. Brown, G. Chapuis, *J. Phys. Chem. B* **2004**, *108*, 6458–6466.

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