Novel 1D Hydrophobic Pore Formation by C-Terminal Amide-controlled Self-assembly of Leu–Leu–Leu–NH_2 in Crystal

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A unique hydrophobic pore is generated by the self-assembly of Leu–Leu–Leu–NH_2 (**1**) in the crystal structure, in which the C-terminal amide groups induce the cylindrical arrangement of Leu side chains by intermolecular NH···O hydrogen bonds. This body-centered cubic-type pore provides a structural basis for devising the material to selectively extract low-molecular hydrophobic molecule such as methane.

Crystal engineering is defined as the study of intermolecular interactions in the context of crystal packing and the use of knowledge of such a study in the design of new solids with desired physical and chemical properties.[1] Various noncovalent intermolecular interactions markedly affect crystal structure, and the elucidation of the association between interaction type and molecular packing mode is one of the most important subjects in crystal engineering.

Organic or organometallic crystals have provided materials that can act as catalysts,[2a,2b] microporous materials,[2c,2d] and superconductors,[2e] because noncovalent molecular assemblies display unique properties such as reversible binding behaviors that are otherwise unattainable by traditional covalent synthesis.

We have been investigating the intermolecular interaction modes of C-terminal amidated peptides and comparing with those of the corresponding C-carboxylated ones to clarify the functional difference between the C-terminal amide and carboxyl groups in intermolecular assembly,[3] because the C-terminal amide group is necessary for exerting the biological function of biopeptides.[4] It was so far clarified that the amide group has a high tendency to form cyclic NH···O hydrogen bonds between the tail-to-tail-arranged neighboring molecules and expand the molecular linkage into 2D space, suggesting the possibility of forming an artificial receptor by the proper combination of hydrophobic/hydrophilic amino acid residues of peptides in the crystal structure; this is in contrast with the case of the C-carboxyl group, which prefers the linkage of head-to-tail-arranged molecules by a NH···O hydrogen bond, leading to a 1D molecular connection.

In the continuation of investigating the interaction feature in which C-terminal amide group participates, we observed the formation of a unique body-centered cubic-type hydrophobic pore by the self-assembly of Leu–Leu–Leu–NH_2 (**1**) in the crystal,[5] in which the C-terminal amide group induces the cylindrical arrangement of Leu side chains around the pore by intermolecular NH···O hydrogen bonds.

Single crystals obtained from an aqueous methanol solution belong to the space group *I*23 in the cubic crystal system and consist of two crystallographically independent peptides (molecules A and B), in which one unit cell includes 48 peptides and 16 water molecules (occupancy = 0.33), (Figure 1). The most notable feature is the formation of hydrophobic pores at the center and four corners of each unit cell; the low crystal density (0.912 g/cm^3) shows the voided structure. Because the crystal system is cubic, these pores are equivalently formed along the *a*, *b*, and *c* axes, thus leading to the formation of a body-centered cubic-type lattice (Figure 2). The pore is generated by the first and third Leu side chains of four symmetry-translated respective molecules of A and B; the isobutyl groups of these residues protrude to form a hydrophobic pore in the unit cell.

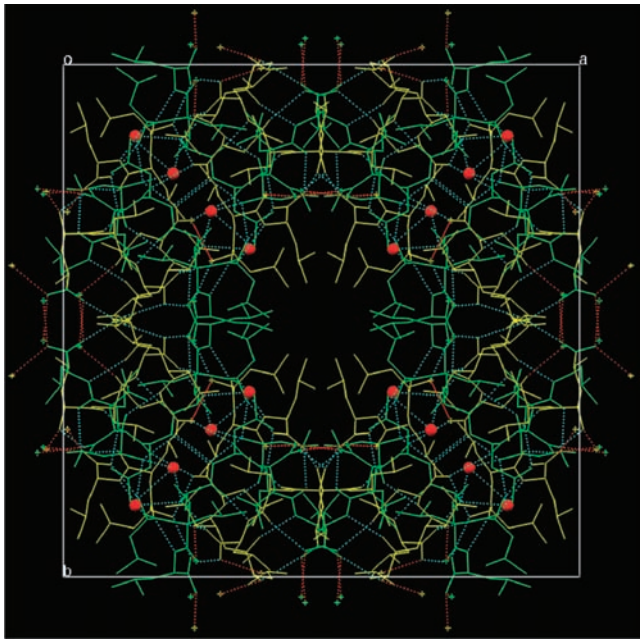
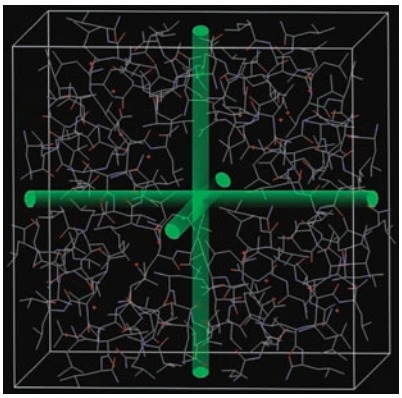
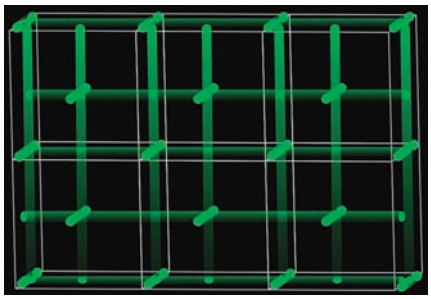


Figure 1. Crystal packing of **1**, viewed from *c* axis. The same crystal packing is drawn from the *a* and *b* axes. Two crystallographically independent molecules, A and B, are shown in yellow and green, respectively. Water molecules are shown in red circle. Hydrogen bonds are indicated as blue or red dots.

The building block necessary to form such a hydrophobic pore is generated by the unit structure of molecules A and B arranged antiparallel, which are connected by four hydrogen bonds (N1A···O3′B = 3.082, N3A···O1′B = 2.905, N1B···O3′A = 3.055, N3B···O1′A = 2.883 Å), thus, forming a concaved dimer structure (Figure 3a); two crystallographically independent molecules A and B are necessitated to form this tight and stable dimer structure, although their conformations are very similar. The C-terminal amide groups of molecules A and B connect both terminal sides of the building block with blocks symmetry-translated in the same manner via N–H···O hydrogen bonds, forming half of the pore structure. The other half is formed as a result of the two-fold symmetry running along a unit cell axis. The

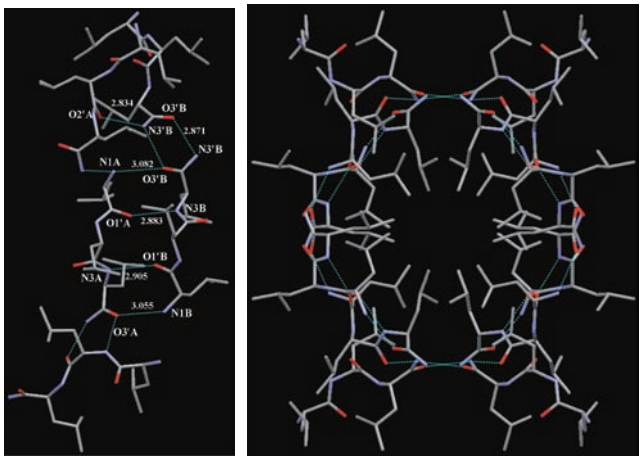


(a)



(b)

Figure 2. (a) Intersecting hydrophobic channels with a body-centered cubic-type topology. (b) Square lattice formed from hydrophobic channels.



(a) (b)

Figure 3. (a) Antiparallel dimer structure of two independent molecules A and B of **1** and the interaction mode of C-terminal amide with neighboring molecules. Hydrogen bonds are indicated as dots. (b) Hydrophobic porous column generated by eight **1** molecules. Blue dots represent hydrogen bonds between neighboring C-terminal amide groups.

two half structures are intertwined forming the unit structure of a hydrophobic pore (Figure 3b).

The blue dots in Figure 3b represent hydrogen bonds between the neighboring C-terminal amide groups. As shown in this figure, C-terminal amide groups play an important role in forming the hydrophobic pore. The major role of C-amide groups is the formation of transannular N–H···O hydrogen bonds between the neighboring C-amide groups (Figure 3a). The other important role is the connection of bifurcated hydrogen bonds between the carbamoyl NH group and the neighboring carbonyl and carbamoyl O atoms.

In order to clarify the functional difference between the C-terminal amide and carboxyl groups in forming such a hydrophobic pocket, the crystal packing of **1** was compared with that of Leu–Leu–Leu–OH.[6] A carboxyl group takes an anionic form and each of its two O atoms bifurcately forms hydrogen bonds with donor groups such as amino NH groups and water OH groups, leading to a trans-zigzag planar arrangement, from which the respective hydrophobic Leu side chains protrude alternatively and evenly.

To the best of our knowledge, this is the first example of the body-centered cubic-type hydrophobic pore generated by the amide group-controlled assembly of C-terminal amidated peptide. We believe that this result provides the structural scaffold for devising microporous materials that are able to selectively extract the hydrophobic small molecules.

References and Notes

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5 Crystal data for **1**: $C_{18}H_{56}N_4O_3 \cdot 1/3H_2O$, $M_r = 362.51$, cubic, $I23$ $a = b = c = 31.639(5)$ Å, $V = 31671(9)$ Å^3, $Z = 48$, crystal size $= 0.4 \times 0.35 \times 0.1$ mm^3, $Dx = 0.912$ g/cm^3, $F(000) = 9568$, $T = 120$ K, μ(Mo Kα) $= 0.063$ mm^{-1}, measured independent reflections 12897, reflections 9245 ($I > 2\sigma(I)$), parameters used for refinement 457, $R_1 = 0.114$ (for $I > 2\sigma(I)$), $wR_2 = 0.2764$ (for all data), GOF $= 1.628$. The positional parameters of non-H atoms were refined using the full-matrix least-squares method with anisotropic temperature parameters. The H positions, except those of water, were determined from a difference Fourier map, treated as riding with fixed isotropic displacement parameters and not included as variables for the refinement. The CIF data were deposited with CCDC 619826.

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