Noncovalent Formation of Polyglycine II-Type Structure by Hexagonal Self-Assembly of Linear Polymolecular Chains

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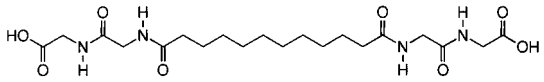
One-, two-, and three-dimensional hydrogen bonds have been ingeniously utilized as an organizing force for molecular building blocks to construct hydrogen-bonded supramolecular structures.[1] These hydrogen bonds also underlie the formation of a wide variety of complex biological structures.[2] The versatility of the biological structures can be exemplified by simple polyamide chains. For example, aliphatic polyamides (nylons) always form a parallel sheet structure stabilized by two-dimensional hydrogen bonds,[3] whereas polyglycine (nylon 2) can adopt a hexagonal array (polyglycine II) where hydrogen bonds are formed in three directions at 120°.[4] Thus, the glycine residues induce a helical structure in polyamides to form three-dimensional hydrogen-bond networks.[5] We have recently demonstrated the formation of well-defined vesicle-encapsulated microtubes[6] from oligoglycine-based bolaamphiphiles. Our strategy of the molecular building blocks is based on the use of multiple hydrogen-bonded networks provided by sugar and peptide moieties.[7−9] Interestingly, these peptide bolaamphiphiles give several kinds of molecular assemblies in equilibrium in water, including tubes, vesicles, and crystals. The formation was found to be largely influenced by the ionization state of the two terminal carboxyl groups. In the present paper, we describe critically pH-dependent crystal formation and the first noncovalent formation of polyglycine II-type structure by glycylglycine bolaamphiphile **1**.[10]



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The obtained dicarboxamide derivative with a glycylglycine moiety **1** proved to be insoluble in all organic solvents except dimethylsulfoxide and hot dimethylformamide. In analogy with usual fatty acids, the aggregation behavior of **1** in water is largely influenced by the ionization state of the carboxyl groups.[11−13] In particular, the uncharged species was found to be hardly soluble in water, whereas the fully ionized species was freely soluble. The critical micelle concentration (cmc) of the sodium salt in pure water is >50 mM at 20 °C when measured by a surface tension method. When the 10 mM aqueous solution (sodium salt, pH = ∼8) was aged at room temperature for 2−3 weeks, swarms of fibrous assemblies can evidently be seen.[6] Using dark-field light microscopy, we found many needle-like microcrystals with a length of 2−10 μm and a width of ca. 0.01 μm (Figure 1a), growing outward from the outer surface of the microtubes.

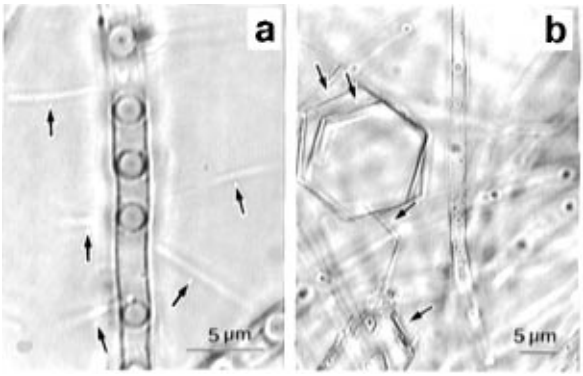

Figure 1. (a) Needle-like microcrystals of **1** (denoted by arrows) sitting on the outer surface of the microtubes, observed using phase-contrast light microscopy (at 25 °C in water, pH = 7.5). (b) A single crystal of **1** (denoted by arrows) coexisting with microtubes (pH = 5.4), which was obtained by precisely controlled protonation using the vapor diffusion method.

To investigate the effect of pH on crystallization, we evaluated the degree of ionization α of **1** using pH titration at room temperature.[14,15] The α value increases in a sigmoidal fashion with increasing the pH value of the solution. Similar behavior is observed for aqueous solutions of fatty acids[11] and amino acid surfactants.[15] The pH value of the bulk aqueous environment was around 7.5, at which we found both the microtubes and needle-like crystals. This suggests that the local decrease in pH at highly charged surfaces[12,16] plays a dominant role in producing the interesting superstructures. Thus, we successfully obtained a single crystal coexisting with vesicle-encapsulated tubes (Figure 1b) by controlled protonation (α ≈ 0.5, pH ≈ 5.4) using slow vapor diffusion of 1% acetic acid into the aqueous solution.

X-ray diffraction analysis showed that the compound crystallizes in a monoclinic space group ($P2_1/a$).[17] All molecular layers

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(10) The bolaamphiphile **1** was synthesized by the condensation of the C-terminal-protected glycylglycine with a 1,10-decanedicarboxylic acid and the subsequent deprotection of the carboxyl group. This new compound gave satisfactory ^{1}H-NMR data (270 MHz) and elemental analysis. Detailed description of the synthetic procedures will be reported elsewhere.

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(17) Crystal data for $C_{20}H_{34}O_8N_4$: monoclinic, $P2_1/a$, a = 8.678(3), b = 4.873(4), and c = 27.161(3) Å, β = 92.68(2)°, V = 1147.3(9) Å^3, Z = 2, d_{calcd} = 1.327 g cm^{-3}, at 300 K. A Rigaku AFC7R diffractometer was used to collect 2095 data points, of which 1952 data with ($F > 3.0\sigma(F)$) were used in the solution and refinement. X-ray data were corrected for absorption (λ(Cu Kα) = 1.541 78 Å). The structure was solved by direct methods which located all non-hydrogen atoms. Hydrogen atom positions were solved by differential Fourier. The structure refined to $R(F)$ = 5.1% and $R_w(F)$ = 5.5%; GOF = 2.50; highest final difference peak, 0.19 e/Å^3.

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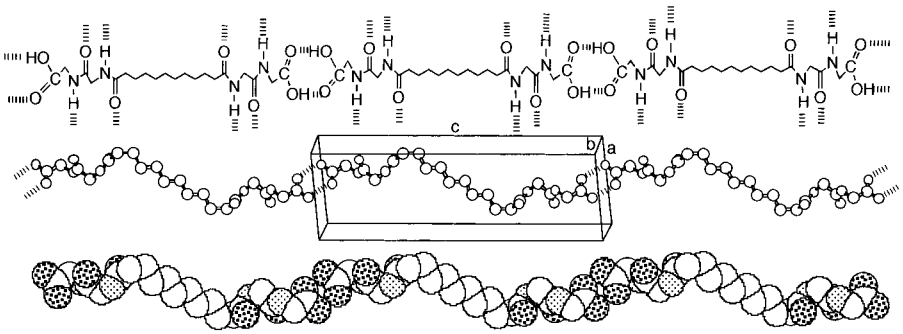

Figure 2. A linear alignment of polymolecular chains in **1** via intermolecular hydrogen bonds between two carboxylic acids. The hydrogen bonds are partly omitted for clarity.

are identical along the *c* axis. The main feature is a center of symmetry in the middle of the decamethylene segment. Thus, the glycine residues at each end have the same dihedral angles with opposite signs. The -CH_2−CH_2−CO- segment adopts a folded conformation (T$\bar{G}\bar{G}$), which remarkably differs from the usual zigzag conformation observed in linear amides.[18] A rotation of nearly 120° is observed between the amide C═O directions, which is characteristic for polyglycine II.[4] The torsion angles around the glycine residues ($\varphi = 70.0°$ and $\phi = -149.7°$) are also consistent with those of polyglycine in its form II. Furthermore, the molecules form a linear polymolecular chain via intermolecular bidentate hydrogen bonds between carboxylic acids (Figure 2).[19] It is well documented that the one dimensional, self-complementary hydrogen-bonded arrays can combine orthogonally to form two-dimensional β-networks.[20−23] In contrast, the present molecular lattice is pseudohexagonal, with similar interchain distances along the *b*, [$1\bar{1}0$], and [$1\bar{1}0$] directions (4.87, 4.99, and 4.99 Å, respectively). To the best of our knowledge, this finding provides the first example of polyglycine II-type structure made of noncovalent polymolecular chains.[24]

In addition to the four hydrogen bonds involving two terminal carboxyl functionalities, each molecule forms eight hydrogen bonds: four in the [010] direction involving the dicarboxamide carbonyls and two in each of the [$\bar{1}\bar{1}0$] and [$1\bar{1}0$] directions. Among these three directions, the dicarboxamide hydrogen-bond chains are running in antiparallel fashion with translation motif.[25] On the other hand, the side arm amide functionalities form unusual nonplanar (out of the carbonyl plane) hydrogen bonds (Figure 3). This nonplanar hydrogen bonding allows the central molecule to bond to different pairs of neighboring molecules, each related by a glide plane. Thus, all six of the close-packed

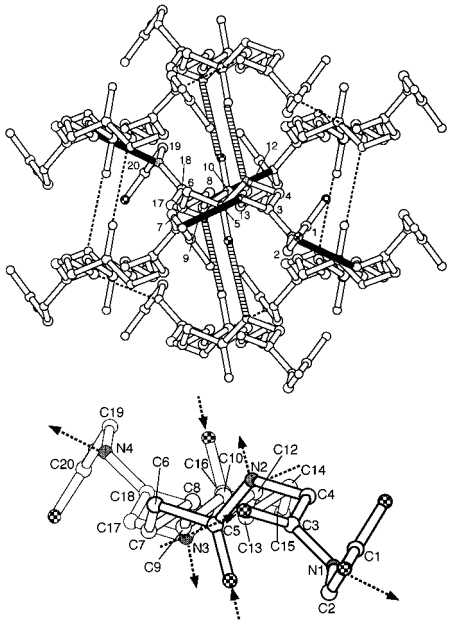

Figure 3. A hexagonal lattice of the polymolecular chains in **1**, stabilized by three-dimensional hydrogen-bonded networks. The nonplanar (out of the carbonyl plane) hydrogen bonds are denoted by bold lines (■), while the linear hydrogen bonds dashed lines (□).

neighbors are linked by hydrogen bonds. It is the nonplanar nature of the hydrogen bonds that makes the hexagonal environment possible. This situation is distinct from the linear amide hydrogen bonds to the same pair of neighboring molecules found for the similar oxalamide compound.[23] This means that hydrogen bonds are formed to only four of the six close-packed neighbors in a hexagonal lattice. The use of multiple and directional hydrogen bonds in the glycine residues will provide a molecular building block with the requisite molecular orientation in the solid state.

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Supporting Information Available: The pH dependence of α mentioned in the text and crystallographic details for the hexagonal array of **1** including tables of atomic coordinates, thermal parameters, bond angles, and bond lengths (16 pages). See any current masthead page for ordering and Internet access instructions.

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