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Self-Assembly of Dipeptidyl Ureas: A New Class of Hydrogen-Bonded Molecular Duplexes

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Control of hydrogen bonding has attracted much attention in the design of various molecular assemblies by virtue of the directionality and specificity.[1] The utilization of self-assembling properties of short peptides, which possess chiral centers and hydrogen bonding sites, is considered to be a convenient approach to a highly ordered system. We have already demonstrated that the introduction of dipeptide chains into the ferrocene scaffold permits chirality organization through the intramolecular interchain hydrogen bonding, in which a helical molecular arrangement is achieved in the crystal packing.[2] Urea functionality has been utilized to create highly organized hydrogen-bonded molecular assemblies.[3] Combination of a urea and peptide unit is envisioned to provide stable hydrogen-bonded molecular assemblies.[4] Among the numerous artificial self-assembly systems through hydrogen bonding, construction of stable hydrogen-bonded molecular duplexes is one of the important targets of current research.[5] We herein report a new class of hydrogen-bonded molecular duplexes using dipeptidyl ureas.

Our design is based on symmetrical introduction of two dipeptide chains (-L-Ala-L-Pro-) into a urea spacer as shown in Figure 1. An advantage in the use of L-alanyl-L-proline as a dipeptide unit depends on a hydrogen-bonding site and a sterically constrained proline as a well-known turn-inducer in proteins. The dipeptidyl urea **1** composed of two dipeptide chains bearing the C-terminal pyridyl moiety (-L-Ala-L-Pro-NHPy) was synthesized from the corresponding dipeptide derivatives and 1,1′-carbonyldiimidazole. X-ray crystallographic analysis of **1**·$CHCl_3$ was performed to clarify the ordered structure and self-assembling properties.[6] The crystal structure of **1**·$CHCl_3$ revealed that two molecules of **1** are held together by six intermolecular hydrogen bonds (N(1)···O(2a), 3.238 Å; N(1*)···O(2a), 3.127 Å; N(3a)···O(2*), 2.795 Å; N(1a)···O(2), 3.238 Å; N(1a*)···O(2), 3.127 Å; N(3)···O(2a*), 2.795 Å) to form a hydrogen-bonded duplex (Figure 2). It should be noted that this hydrogen-bonded duplex adopts a right-handed helical conformation. The propensity to form the chiral helicity is likely to be induced by the configuration of the peptide chains. Furthermore, each hydrogen-bonded duplex is connected by continuous intermolecular hydrogen bonds between urea CO and C-terminal amide NH to form a double helix-like arrangement as shown in Figure 3.

In the ^1H NMR spectrum of the dipeptidyl urea **1** in $CDCl_3$ (1.0×10^{-2} M) at 25 °C, only one kind of the urea NH resonance was detected at a lower field (6.75 ppm) than that of the dipeptidyl urea **2** composed of two dipeptide chains (-L-Ala-L-Pro-OEt) (1.0×10^{-2} M, 5.28 ppm). The NH protons of **1** were slightly perturbed by the addition of DMSO-d_6 to $CDCl_3$ (1.0×10^{-2} M, $CDCl_3$: 6.75 (urea NH) and 10.30 (C-terminal amide NH) ppm, $CDCl_3$/DMSO-d_6 (9:1): 6.68 (urea NH) and 10.30 (C-terminal amide NH) ppm) although a downfield shift was observed with **2** (1.0×10^{-2} M, $CDCl_3$: 5.28 (urea NH) ppm, $CDCl_3$/DMSO-d_6 (9:1): 6.10 (urea NH) ppm). These results indicate that the urea and C-terminal amide NHs of the dipeptidyl urea **1** appear to participate in the intermolecular hydrogen bonding to form a hydrogen-bonded duplex even in solution. The FT-IR spectrum of **1** in CH_2Cl_2 (1.0×10^{-2} M) showed the NH stretching bands at 3356 and 3286 cm^{-1}, which is also consistent with the formation of hydrogen bonds in **1**. The free NH stretching band of **2** was observed at 3410 cm^{-1} in CH_2Cl_2 (1.0×10^{-2} M), indicating that a similar duplex is not likely to be formed in the case of **2**. Furthermore, proton magnetic resonance

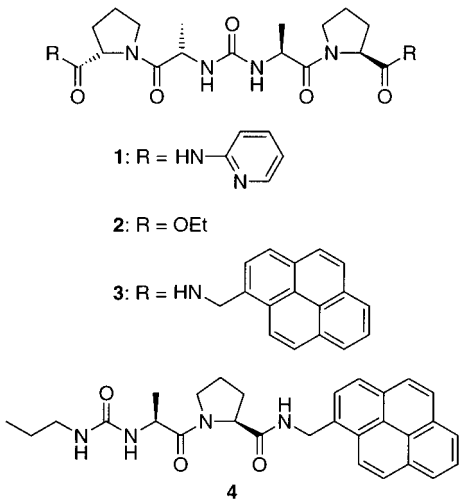

Figure 1. Dipeptidyl ureas **1**−**3** and peptidyl urea **4**.

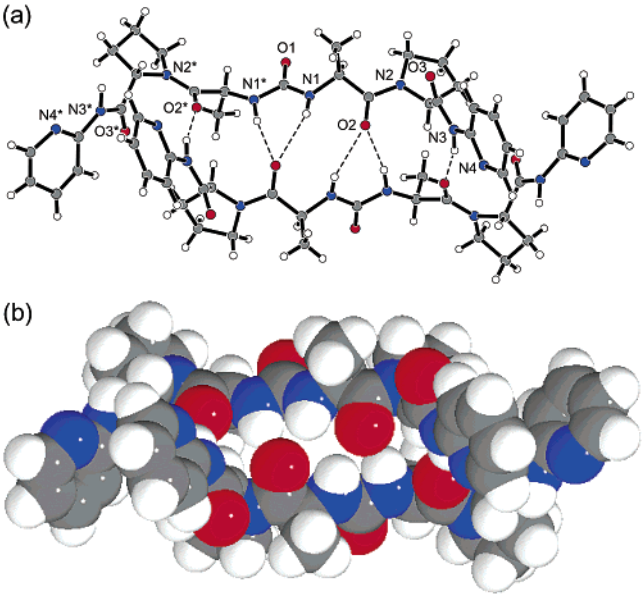

Figure 2. Molecular structure of **1**·$CHCl_3$. Chloroform molecules are omitted for clarity. (a) Ball-and-stick and (b) space-filling representations.

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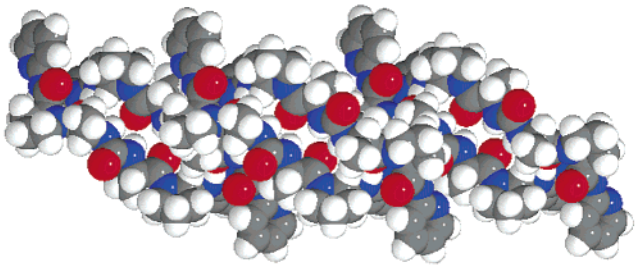

Figure 3. Layer containing the double helix-like arrangement of the crystal packing of **1**·$CHCl_3$. Chloroform molecules are omitted for clarity.

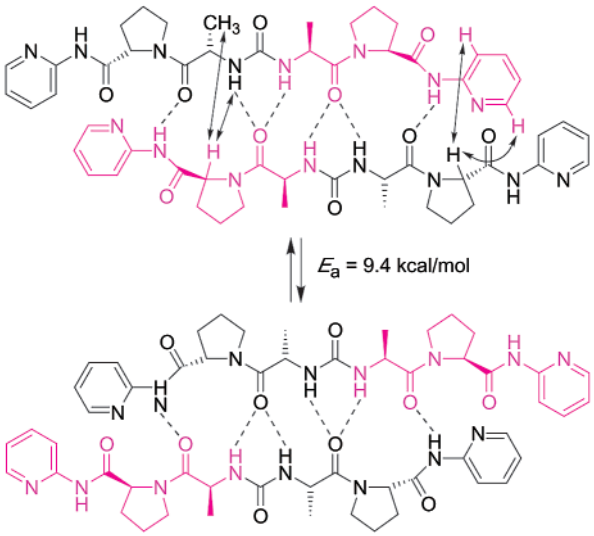

Figure 4. Shuttle-like dynamic process of **1**. NOEs observed between the dipeptidyl ureas are shown with arrows.

nuclear Overhauser effect (NOE) of **1** was studied in CD_2Cl_2 at 25 °C to support the hydrogen-bonded duplex in solution. Irradiation of Pro α-CH enhances the urea NH, Ala CH_3, and pyridyl protons at the 3- and 6-positions (Figure S1, Supporting Information), which provides diagnostic evidence for the duplex formation in solution (Figure 4). An association constant obtained by ^{1}H NMR spectra in $CDCl_3$ (20 mM ≈ 0.1 mM) was 2.9×10^4 M^{-1} for **1** and 13 M^{-1} for **2**.[7]

Variable-temperature ^{1}H NMR studies of **1** exhibited unique molecular dynamics in solution (Figure S2). As the temperature was lowered, all peaks broadened and decoalesced to give two sets of peaks. These findings indicate the nonequivalent dipeptide moieties depending on a hydrogen-bonded duplex. This molecular dynamics is accounted for by a shuttle-like dynamic process based on the recombination of hydrogen bonds as shown in Figure 4. The activation energy of this process was calculated as 9.4 kcal/mol from the Arrhenius equation.

To evaluate the effect of a combination of the urea NH and C-terminal amide NH in each side, the dipeptidyl urea **3** composed of two dipeptide chains bearing the C-terminal pyrenyl moiety (-L-Ala-L-Pro-$NHCH_2$Pyr) and the corresponding peptidyl urea **4** composed of only one dipeptide chain were synthesized similarly as mentioned above. The dipeptidyl urea **3** exhibited both monomer (377 and 396 nm) and eximer (476 nm) emissions in the fluorescence spectrum (Figure S7). On the other hand, only monomer (377 and 396 nm) emission was observed with **4**. These results also indicate the formation of a hydrogen-bonded duplex in the case of **3**. ^{1}H NMR binding studies by varying concentrations of **3** gave an association constant of 1.7×10^4 M^{-1}. A combination of the C-terminal amide NH in each side chain and the designed sequence of hydrogen-bonding sites are considered to be a crucial factor for the duplex formation.

In conclusion, dipeptidyl ureas composed of two dipeptide chains (-L-Ala-L-Pro-) were synthesized to form the chiral hydrogen-bonded duplexes in both solid and solution states. This system represents a strategy for a chiral hydrogen-bonded duplex with functional groups at C-terminals of peptides. Studies on the application of a chiral duplex including functional materials are now in progress.

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Supporting Information Available: Text giving experimental details for the syntheses and characterization of **1**−**4**, difference NOE, variable temperature ^{1}H NMR, fluorescence spectra, and tables of X-ray crystallographic data for **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Crystal data for **1**·$CHCl_3$: A single crystal of **1**·$CHCl_3$ was obtained from a chloroform−ether (1:1) solution of **1**. $C_{27}H_{34}N_8O_5$·$CHCl_3$, monoclinic, space group *C*2 (No. 5), a = 24.395(1) Å, b = 9.9578(6) Å, c = 19.812-(1) Å, β = 125.574(2)°, Z = 4, R = 0.147, R_w = 0.376. Of the 10158 reflections which were collected, 4775 were unique (R_{int} = 0.040). The final cycle of full-matrix least-squares refinement was based on 3845 observed reflections ($I > 2\sigma(I)$). The non-hydrogen atoms were refined anisotropically although the chloroform solvent molecule showed a little high-temperature factor. The crystals were of poor quality but showed no decay during measurements. The R values and remaining peaks in the final difference map (max 2.27 eÅ^{-3}) are related to the cause of the data quality.

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