Foldectures from the Self-Assembly of Racemic Foldamers

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Self-assembling peptidic materials, which are typically composed of chiral building blocks, have attracted much attention due to their potential applications in catalysis, biomedicine, and nanoelectronics.[1−3] We have recently reported that foldamers, *i.e.*, artificial peptides, with well-defined secondary structures self-assemble in aqueous solution to provide a series of highly homogeneous and unique 3D morphologies, named foldectures.[4−8] Because they are highly crystalline, the molecular packing modes of foldecutures can be analyzed by powder X-ray diffraction analysis. For these studies, we prepared foldamer building blocks from enantiomerically pure β-amino acid monomers.

Self-assembly with racemic peptide building blocks has rarely been reported, presumably because it provides complex aggregates or assemblies with ill-defined morphologies. However, it has been reported that racemic proteins or DNAs show a higher tendency to crystallize than enantiomerically pure forms because of the propensity for enantiomers to act as "tailor-made" impurities that initiate crystallization.[9,10] Although foldectures are nonequilibrium self-assembling crystalline solids, and are different from canonical microcrystals obtained under equilibrium conditions, it remains unexplored whether self-assembly of racemic foldamers will yield structures composed of a single enantiomer or give rise to new morphologies composed of a racemic mixture of enantiomers. Herein we report that parallelogram plate shaped foldectures are obtained from an equimolar mixture of enantiomeric foldamer, while trigonal bipyramid shaped foldectures are formed from pure enantiomeric foldamer. This result highlights the fundamental differences in the morphologies of self-assembled materials composed of enantiopure and racemic mixtures of peptidic synthons.

In this study, we used heptameric foldamer (**R**) composed of aminoisobutyric acid (Aib) and a cyclic β-amino acid (1*R*,2*R*-*trans*-2-aminocyclopentane carboxylic acid, ACPC) in a 1:1 alternating sequence as the self-assembling unit (Figure 1(a)). The enantiomer (**S**) is composed of Aib and (1*S*,2*S*)-ACPC. This peptide is known to form a stable 11-helical secondary structure in both solution state and solid state.[11]

Each enantiomerically pure foldamer was synthesized according to the literature protocol.[12] Self-assembly was performed by our standard protocol[4] in P123 aqueous solution, and the morphologies of the foldecture were analyzed by scanning electron microscopy (SEM). From the self-assembly of foldamer **R** (24 g/L of P123, 2 g/L of THF as peptide stock solution), we obtained foldecture **FR1** with trigonal bipyramid shape (Figure 1(b)). When we used a MeOH stock solution of the same concentration, we obtained foldecture **FR2** with caudate trigonal bipyramid morphology (Figure 1(c)). As expected, we obtained foldectures with identical morphologies from the opposite enantiomer **S** under identical self-assembly conditions (data not shown). However, the self-assembly of a 1:1 mixture of **R** and **S** (THF stock solution) produced an elongated parallelogram plate shaped foldecture **FRS1** with side lengths of 6 and 1.5 μm, and corners of ca. 110° (Figure 1(d)). The shortened parallelogram plate shape **FRS2** (side lengths of 2.5−3.0 μm and corners of ca. 110°) was formed from the MeOH stock solution (Figure 1(e)). Interestingly, the self-assembly of a 2:1 molar mixture of **R** and **S** (THF stock solution) resulted in the simultaneous and independent formation of **FS1** and **FRS1** as a mixture in approximately the same yield, which suggested that **FRS1** was formed from 1:1 combination of **R** and **S**, and **FR1** was formed from the remaining **R**. We have not observed any other morphologies besides **FR1** and **FRS1** under these conditions, implying that there exist specific and very favorable association interactions between **R/R** (or **S/S**) and **R/S**.

To further understand these unexpected results, we analyzed the molecular structure of **FRS1** through synchrotron powder X-ray diffraction (PXRD). PXRD experiments were performed on the 9B HRPD Beamline at the Pohang Accelerator Laboratory. Through unit cell determination by our standard procedure,[5] a monoclinic cell ($a = 25.7982$ Å, $b = 18.4192$ Å, $c = 21.4044$ Å, $\alpha = \gamma = 90°$, $\beta = 101.645°$) was obtained with figure of merit value of 18.02. Unfortunately, molecular-level structure determination was not possible for this cell due to the extremely large volume ($V = 9961.637$ Å^3), an asymmetric unit composed of multiple foldamers ($Z' = 4$) and the low symmetry of the space group, which increased peak overlap. In retrospect, these results are not surprising, as large unit cells are common in foldectures, which self-assemble far from equilibrium and may thus be influenced by kinetic factors. However, the monoclinic crystal system seems to be related to the microscale morphology of the foldecture, with the *b*-axis of the unit cell orthogonal to the large

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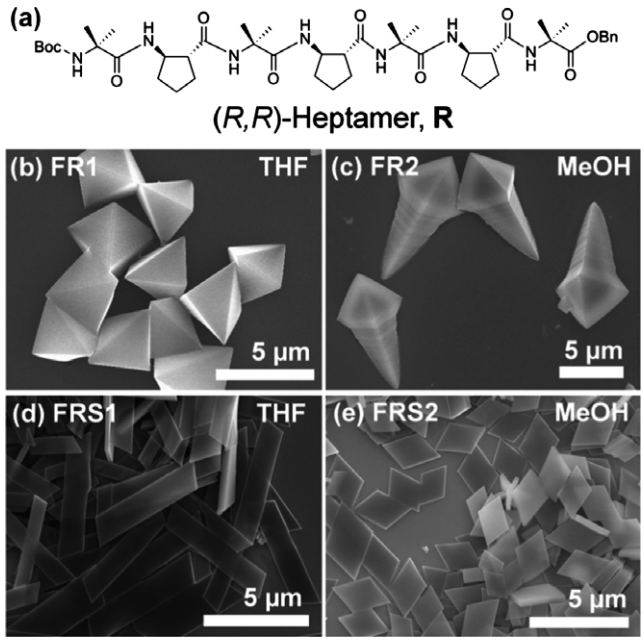

Figure 1. (a) Chemical structures of (*R*,*R*)-Heptamer, **R**. SEM images of the foldectures self-assembled in aqueous P123 solution of 24 g/L and peptide solution of 2 g/L. (b) **FR1** (THF stock solution of **R**), (c) **FR2** (MeOH stock solution of **R**), (d) **FRS1** (THF stock solution of equimolar **R/S**), (e) **FRS2** (MeOH stock solution of equimolar **R/S**).

plate faces. The similarity between the β angle (101.645°) and the foldecture corner angle (ca. 110°) is consistent with this assumption.

In conclusion, racemic foldectures composed of an equimolar mixture of foldamer enantiomers show significant morphological differences from those derived from enantiopure foldamer. Unexpectedly, self-assembly of a 2:1 molar mixture of enantiomeric foldamers resulted in the simultaneous and independent formation of two different foldecture morphologies, indicating the intermolecular interactions between different enantiomers are more favorable in the solid state. Synchrotron PXRD analysis of racemic foldecture **FRS1** revealed a large monoclinic unit cell consistent with the parallelogram plate shaped morphology (Figure 2). This study demonstrates that there are fundamental differences between self-assembling organic materials composed of enantiopure and racemic mixtures of synthons and hints at the complexity possible with racemic building blocks. Further studies are underway to explore the relationship between enantiomer

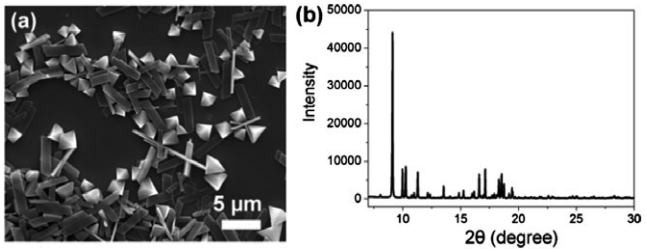

Figure 2. (a) SEM image of self-assembled foldecture morphologies from a 2:1 molar ratio mixture (THF stock solution) of **R** and **S** showing the presence of both **FR1** and **FRS1**. (b) Synchrotron PXRD peak pattern of **FRS1**.

stoichiometry and morphology selection, and also to determine the relative rates of self-assembly for **FS1** and **FRS1**.

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