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"Helix-in-Helix" Superstructure Formation through Encapsulation of Fullerene-Bound Helical Peptides within a Helical Poly(methyl methacrylate) Cavity

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Abstract: *A one-handed 3_{10}-helical hexapeptide is efficiently encapsulated within the helical cavity of st-PMMA when a fullerene (C_{60}) derivative is introduced at the C-terminal end of the peptide. The encapsulation is accompanied by induction of a preferred-handed helical conformation in the st-PMMA backbone with the same-handedness as that of the hexapeptide to form a crystalline st-PMMA/peptide-C_{60} inclusion complex with a unique optically active helix-in-helix structure. Although the st-PMMA is unable to encapsulate the 3_{10}-helical peptide without the terminal C_{60} unit, the helical hollow space of the st-PMMA is almost filled by the C_{60}-bound peptides. This result suggests that the C_{60} moiety can serve as a versatile molecular carrier of specific molecules and polymers in the helical cavity of the st-PMMA for the formation of an inclusion complex, thus producing unique supramolecular soft materials that cannot be prepared by other methods.*

The development of host molecules, supramolecules, and polymers that possess a unique confined nano-space suitable for encapsulating specific guests has been attracting significant attention[1] because of their broad applications toward molecular recognition, sensing, separation[1c,g,j] and catalysis,[1h,k,l,o,p] as well as electronic and optoelectronic materials.[1d] Cyclic host molecules, such as modified cyclodextrins[1a,g] and self-assembled metal–organic cages[1f,h,i,l–n] and organic nanocapsules,[1c] are among the most extensively investigated host molecules. However, owing to their rigid and distinct conformational scaffold, a limited number of guest molecules of complementary size and shape can be entrapped in their cavities. Biological helical polymers, such as amylose,[2] schizophyllan,[3] and assembled proteins,[4] are also known to form inclusion complexes with a variety of small molecules and polymers including carbon nanotubes.[2a,b,3c] Although such biopolymer-based helical host systems have been well established, it remains challenging to develop synthetic helical polymers with an efficient encapsulation capability for a broad range of guest molecules and polymers.[1p,5]

Previously, we found that syndiotactic poly(methyl methacrylate) (st-PMMA), a commodity plastic, folds into a preferred-handed helical conformation (18_1-helix) with an inner cavity of approximately 1 nm in toluene in the presence of an optically active alcohol or amine, accompanied by gelation, in which a series of achiral (C_{60} and C_{70})[6,7] and chiral fullerenes (e.g., C_{76}, C_{78}, C_{80}, C_{90}, and C_{96})[8] are size- and enantioselectively encapsulated within its helical cavity through an induced-fit mechanism to form optically active peapod-like inclusion complexes which are retained after removal of the chiral additives[6a–c,8] (helicity memory).[1p,9] We also found that a preferred-handed helical st-PMMA can serve as an optically active polymeric host to encapsulate the complementary isotactic PMMA (it-PMMA) in a helix-sense-controlled manner to produce the first optically active PMMA stereocomplex.[6b,10]

Based on these results, we envisaged that functionalization of various organic molecules and polymers with a C_{60} unit at their terminals would lead to inclusion complex formations with the st-PMMA thanks to the C_{60} moiety that could act as a molecular carrier of the C_{60}-bound molecules and polymers within the helical cavity of the st-PMMA, even if the molecules and polymers themselves do not form such an inclusion complex with the st-PMMA. Herein we report a novel strategy to construct a unique "helix-in-helix"[3a,b,5,6b,12] supramolecular structure composed of C_{60}-bound one-handed 3_{10}-helical[13] peptides (fulleropeptides)[14] (L-**1** and D-**1**) wrapped by a helical st-PMMA (Figure 1 a), and at the same time, a preferred-handed helical structure is induced in the st-PMMA backbone during the inclusion complex formation.

We designed and synthesized an N-terminal-protected hexapeptide containing strongly helix-promoting α-aminoisobutyric acid (Aib)[13,15] residues with the sequence Boc-L-Leu-Aib-L-Leu_2-Aib-Gly- (Boc = *tert*-butoxycarbonyl) and its enantiomer as a pendant of C_{60} (L-**1** or D-**1**, Figure 1 a and Scheme S1 in the Supporting Information), because of its predictable helical structure,[13,15] such as 3_{10}- and α-helices, where the C-terminal Gly residue was incorporated as a flexible spacer to reduce the structural strain during the inclusion complex formation within the st-PMMA helical cavity. The theoretical studies of L-**1** and an L-**1**/st-PMMA (72mer) inclusion complex revealed that encapsulation of the

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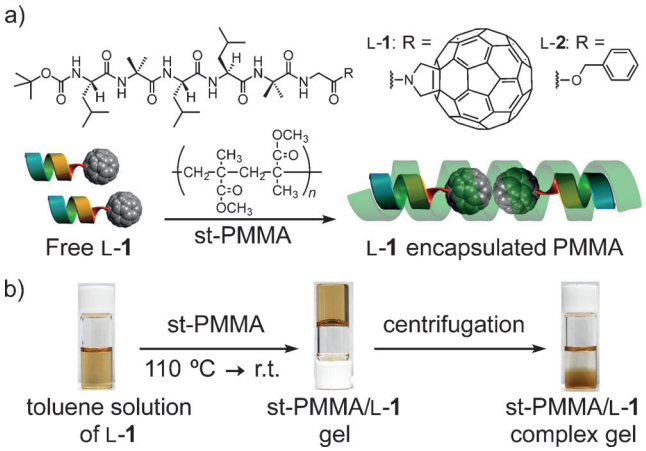

Figure 1. a) Chemical structures of the peptide-bound C_{60} (L-**1**), C_{60}-free peptide (L-**2**), and st-PMMA and a schematic illustration of the encapsulation of L-**1** in the st-PMMA helical cavity upon gelation. b) Photographs of a toluene solution of L-**1** (0.35 mg mL^{-1}, 1 mL; left), st-PMMA/L-**1** gel after the addition of st-PMMA (10 mg) with subsequent heating to 110 °C and then cooling to room temperature (middle), and the st-PMMA/L-**1** complex gel after centrifugation at 1700 *g* for 10 min (right).

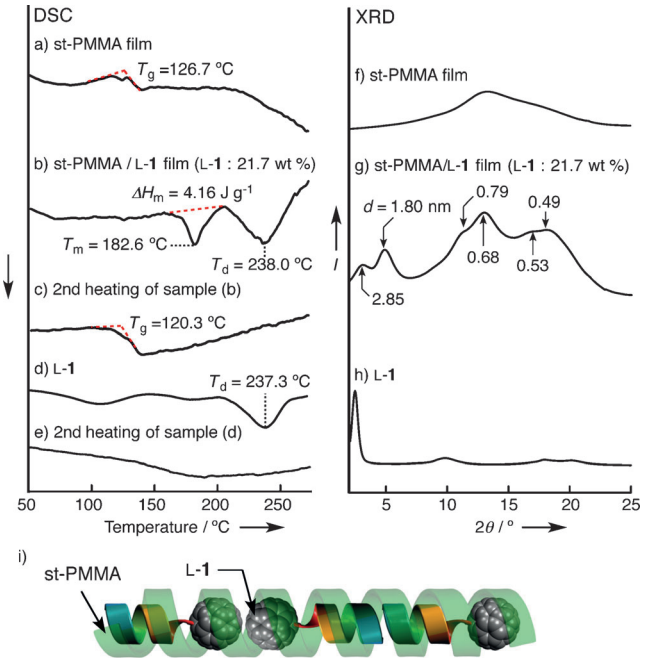

Figure 2. a)–e) DSC thermograms of: st-PMMA film (a), st-PMMA/L-**1** complex film containing 21.7 wt % of L-**1** (b), and L-**1** (d). These films were prepared by evaporating the solvents from the st-PMMA and st-PMMA/L-**1** complex gels in toluene. The DSC measurements were conducted after cooling the samples at −30 °C, followed by heating to 280 °C (10 °C min^{-1}) under nitrogen. The samples (b) and (d) were then cooled to −30 °C (40 °C min^{-1}), and then heated again ((c) and (e), respectively; 10 °C min^{-1}). The arrow to the left of the DSC data indicates the endothermic direction. f)–h) XRD profiles of: st-PMMA film (f), st-PMMA/L-**1** complex film (21.7 wt % of L-**1**) (g), and L-**1** powder (h). i) Schematic representation of a possible structure of the st-PMMA/L-**1** complex with head-to-head arrangement of the included L-**1** molecules.[19]

right-handed 3_{10}-helical L-**1** into the st-PMMA helix hardly disrupts both helical structures (Figures S1 and S2).

The enantiomeric L-**1** and D-**1** and a C_{60}-free hexapeptide model (L-**2**) bearing a C-terminal benzyl ester group instead of the fulleropyrrolidine[16] (Figure 1a) were synthesized in a stepwise manner, and their structures were fully characterized by NMR spectroscopy and high-resolution mass spectroscopy measurements (see the Supporting Information). The 3_{10}-helical conformation of L-**1** was confirmed by its ^{1}H NMR and two-dimensional NOESY spectra in $CDCl_3$ in combination with solvent-dependent chemical shift changes of the amide NH protons of L-**1** upon the addition of the hydrogen-bond accepting [D_6]DMSO (Figures S3a and S4).[17] Similar [D_6]DMSO-dependent chemical shift changes of the amide NH protons were also observed for L-**2** (Figure S3b), indicating that L-**2** possesses the identical 3_{10}-helical structure to that of L-**1**.

To confirm the st-PMMA⊃L-**1** inclusion complex formation, st-PMMA (10 mg) was dissolved in a brown-colored toluene solution of L-**1** (Figure 1b, left) by heating at 110 °C. The solution was then cooled to room temperature, resulting in gelation within 10 min (Figure 1b, middle). After centrifugation, a brown-colored condensed gel was obtained, whereas the supernatant solution was almost colorless (Figure 1b, right). Based on the difference in the absorption spectra between the feed L-**1** solution and the supernatant, it was suggested that 0.3 mg of L-**1** (2.9 wt %) was encapsulated within the st-PMMA cavities (Figure S5). The encapsulated L-**1** content gradually increased by repeatedly adding the feed L-**1** or D-**1** toluene solution to the st-PMMA/**1** gel followed by heating to 110 °C and cooling to room temperature, then centrifuging,[18] and finally reaching a plateau value (ca. 25 wt %, Figure S6). We then roughly estimated the maximum amount of **1** (25.5 wt %) that fills the st-PMMA helical hollow space in a head-to-head close packing array (Figure 2i and see below)[19] based on an 18_1-helical st-PMMA structure[6a] and a molecular length of the calculated 3_{10}-helical L-**1** structure (2.2 nm; Figure S2), which is almost identical to the observed maximum amount of the encapsulated **1** (ca. 25 wt %)[21] In sharp contrast, the C_{60}-free model peptide (L-**2**) did not form such an inclusion complex with st-PMMA at all, as revealed by the ^{1}H NMR experiments (Figure S9), indicating the indispensable role of the terminal C_{60} moiety of **1** for the inclusion complex formation with the st-PMMA.

Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) profiles of the st-PMMA⊃L-**1** film obtained from the gel provided a detailed insight into the crystalline structure of the inclusion complex that is completely different from those of the st-PMMA film and L-**1** powders (Figure 2). The DSC profile of the st-PMMA film, prepared by drying the st-PMMA gel in toluene, showed only a heat capacity change at the glass-transition temperature (T_g = 126.7 °C) being typical for amorphous st-PMMAs (Figure 2a), as supported by its featureless, and broad XRD pattern (Figure 2f).[6a] In contrast, the DSC thermogram of the st-PMMA⊃L-**1** film containing 21.7 wt % of L-**1** displayed characteristic endothermic peaks at 182.6 and 238.0 °C corresponding to the melting temperature (T_m) of the st-PMMA⊃L-**1** complex and

the decomposition temperature (T_d) of L-**1** (Figure 2b,d),[23] respectively, but then showed only the T_g during its second heating (Figure 2c). Importantly, this st-PMMA/L-**1** complex film had almost no T_g around 120–130 °C during the first heating (Figure 2b), suggesting that the st-PMMA hollow spaces may be mostly filled with the L-**1** molecules. A similar DSC profile with the T_m of 212.4 °C was also observed for the st-PMMA/C_{60} complex film (23.5 wt % of C_{60}),[6a] which also supports the inclusion complex formation between the st-PMMA and L-**1**. The XRD profile of the crystalline st-PMMA/L-**1** film (21.7 wt %) revealed a characteristic reflection at the *d*-spacing of 1.80 nm arising from the st-PMMA helix bundle structures (Figure 2g,i), which is larger than that of the st-PMMA complexed with C_{60} (1.67 nm),[6a] but smaller than that with larger fullerenes, such as C_{70} (1.92 nm) and C_{84} (2.04 nm).[6a,24]

To obtain further convincing evidence for the inclusion complex formation between the st-PMMA and L-**1**, the ^{13}C cross-polarization magic-angle spinning (CP-MAS) solid-state NMR measurements were carried out (Figure S10). The ^{13}C signals of the terminal C_{60} moieties in the st-PMMA/L-**1** complex (21.7 wt %) were slightly shifted downfield relative to those of the free L-**1**, as observed for the st-PMMA/C_{60} inclusion complex.[25] In addition, the ^1H-^{13}C heteronuclear correlation (HETCOR) spectrum of the st-PMMA/L-**1** complex exhibited apparent intermolecular correlation peaks between the ^{13}C signals of the terminal C_{60} moieties and the ^1H signals of the methylene and methoxy groups of the st-PMMA (Figure S11d).[26] Although the L-**1** powders, which may be randomly packed close to each other, showed non-specific intermolecular correlation peaks between the ^{13}C signals of the terminal C_{60} moieties and ^1H of the neighboring L-**1** molecules in addition to some intramolecular correlation peaks (Figure S11a,c), such non-specific intermolecular correlation peaks between L-**1**s could not be observed for the st-PMMA/L-**1** complex because most of the L-**1** molecules were encapsulated within the helical st-PMMA cavities. In addition, intermolecular correlation peaks between the ^{13}C signals of the C-terminal C_{60} moieties and the proton signals of the N-terminal Boc group of L-**1** would be observed if the L-**1** molecules exist in a head-to-tail close packing array in the st-PMMA helix. However, such intermolecular correlation peaks were not observed probably because the present method exceeds the detection limit (Figure S11c,d). Based on the solid-state NMR data together with the IR, DSC, and XRD results, we propose a unique "helix-in-helix" supramolecular structure for the st-PMMA/L-**1** inclusion complex composed of the one-handed 3_{10}-helical L-**1** chains entrapped in the hollow space of the helical st-PMMA (Figure 2i).[19]

As expected, the electronic CD (ECD) spectral patterns corresponding to the fulleropyrrolidine absorption regions of L-**1** and D-**1** in toluene were drastically changed once encapsulated into the st-PMMA helical cavities in a gel formed in toluene (Figure 3), probably resulting from an exciton coupling interaction between the nearest neighbor fulleropyrrolidine residues in the st-PMMA helical cavity and/or an encapsulation-induced conformational change around the C-terminal region.

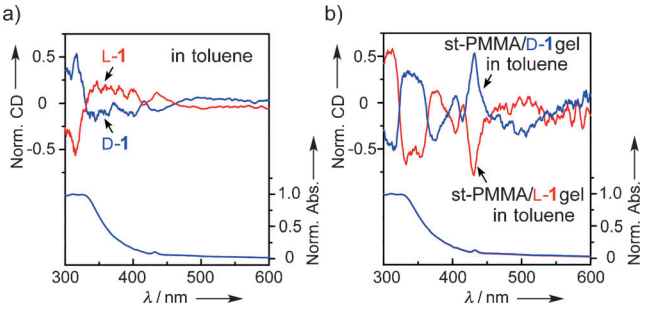

Figure 3. a) ECD (top) and absorption (bottom) spectra of L-**1** (red) and D-**1** (blue) in toluene at 25 °C: [**1**] = 3.6×10^{-4} M. b) ECD (top) and absorption (bottom) spectra of st-PMMA/L-**1** gel (10.1 wt % of L-**1**) (red) and st-PMMA/D-**1** gel (9.9 wt % of D-**1**) (blue) in toluene at 25 °C. The ECD and absorption spectra were normalized based on the corresponding absorption spectra at 25 °C. The contribution of the linear dichroism caused by the macroscopic anisotropy was negligible.

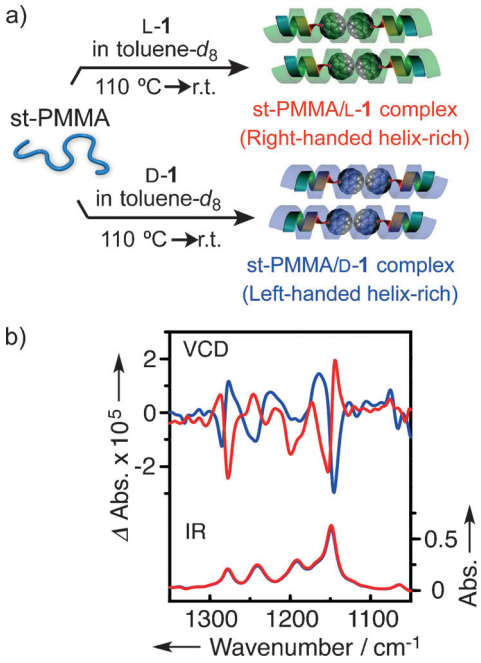

Figure 4. a) Schematic illustration of right-handed (top) and left-handed bottom) helicity induction in st-PMMA upon encapsulation of L-**1** and D-**1**, respectively. b) VCD (top) and IR (bottom) spectra of st-PMMA/L-**1** (11.3 wt % of L-**1**) (red) and st-PMMA/D-**1** (11.3 wt % of D-**1**) (blue) complex gels in [D_8]toluene at room temperature.

Interestingly, a preferred-handed helical conformation could be induced in the st-PMMA backbone once the one-handed helical L-**1** or D-**1** was encapsulated within the st-PMMA helical cavity (Figure 4a). In fact, the st-PMMA/L-**1** and st-PMMA/D-**1** complex gels (11.3 wt % of **1**) exhibited mirror-image vibrational CD (VCD) spectra in the PMMA IR regions (Figure 4b),[27] whose spectral patterns are in good agreement with the calculated VCD spectra of the right- and left-handed 18_1-helical st-PMMAs.[6a] Therefore, it is concluded that the right- and left-handed 3_{10}-helical L-**1** and D-**1** are able to induce predominantly right- and left-handed helical conformations in the st-PMMA chains, respectively,

thus producing optically active supramolecular helix-in-helix structures with the same-handedness to each other.

In summary, we have demonstrated an unprecedented approach to construct a unique supramolecular helix-in-helix structure through encapsulation of optically active helical peptides bearing a C_{60} moiety at one end within the helical st-PMMA cavity as a result of a molecular carrier (or anchor) effect driven by a strong interaction between the terminal C_{60} moiety and the hydrophobic st-PMMA helical cavity. This encapsulation process is accompanied by the preferred-handed helix formation of the st-PMMA backbone induced by the helical chirality of the encapsulated peptides. These findings will provide a rational design strategy not only for a novel helical st-PMMA-based separation system for various chiral fullerene derivatives, but also for developing a unique supramolecular nano-reactor, in which encapsulated C_{60}-based catalysts may catalyze organic and polymerization reactions in a confined helical nanospace of the st-PMMA, thus producing products with specific regio- and enantioselectivities.

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Conflict of interest

The authors declare no conflict of interest.

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[21] The encapsulated L-**1** most likely maintained its 3_{10}-helical structure, as supported by the IR spectra of the st-PMMA⊿L-**1** complex gel (10.4 wt %) in toluene and the dried film derived from the complex gel, which were similar to that of the 3_{10}-helical L-**1** in $CHCl_3$ (Figure S8).[22]
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[23] The T_d of L-**1** was assigned by its DSC and disappeared in the second heating (Figure 2d,e).
[24] The exact helical packing arrangements (hexagonal or orthogonal, for example) of the st-PMMA⊿L-**1** complex helices as well as those of the st-PMMA/fullerenes (C_{60}, C_{70}, or C_{84}) complex helices[6a] have not yet been determined because all the reflections could not be reasonably indexed owing to rather broad reflections probably resulting from the samples that were not uniaxially oriented.[6a]
[25] M. R. Kincer, R. Choudhury, M. Srinivasarao, H. W. Beckham, G. A. D. Briggs, K. Porfyrakis, D. G. Bucknall, *Polymer* **2015**, *56*, 516 – 522.
[26] This observation is consistent with the energy-minimized structure of the st-PMMA⊿L-**1** inclusion complex (Figure S2).
[27] The contribution of the encapsulated **1** within the st-PMMA (11.3 wt % of **1**) to the IR and VCD spectra (Figure 4b) was almost negligible under the present conditions.

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Communications

Supramolecular Chemistry

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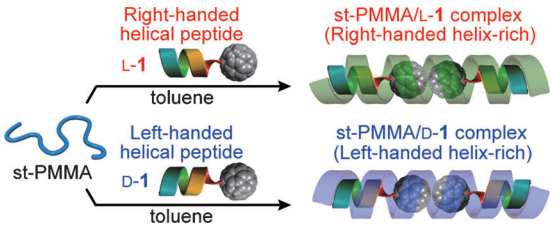
"Helix-in-Helix" Superstructure Formation through Encapsulation of Fullerene-Bound Helical Peptides within a Helical Poly(methyl methacrylate) Cavity



One hand twisting: A one-handed helical peptide bearing a C_{60} moiety at one end is encapsulated within the helical cavity of syndiotactic poly(methyl methacrylate) (st-PMMA) as a result of the C_{60} moiety which strongly interacts with the st-PMMA cavity. This encapsulation induces the st-PMMA backbone to adopt the same handedness as the encapsulated peptides.

