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Homochiral Supramolecular Polymerization of an "*S*"-Shaped Chiral Monomer: Translation of Optical Purity into Molecular Weight Distribution

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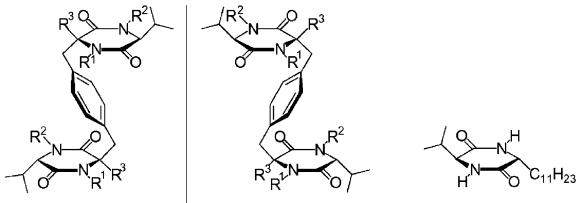
Supramolecular polymers, formed via noncovalent interactions, have attracted increasing attention as a new class of environment-responsive polymeric materials because of their reversible polymerization/depolymerization characteristics.[1] For example, those via quadruple hydrogen-bonding interactions[2] have been demonstrated to cope with both a sufficient thermodynamic stability (comparable to that of covalent polymers) and stimuli-responsive depolymerization characteristics.[3] We report here the first example of "homochiral supramolecular polymerization", where a racemic cyclic

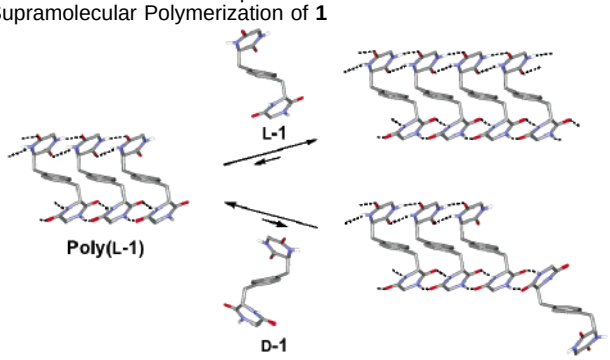


1: $R^1 = R^2 = H$, $R^3 = CH_2CH(OC_{18}H_{37})_2$
2: $R^1 = R^2 = CH_2C_6H_4$-4-OCH_3, $R^3 = CH_2CH(OC_{18}H_{37})_2$
3: $R^1 = R^2 = R^3 = H$
5: $R^2 = R^3 = H$, $R^1 = CH_2C_6H_5$
6: $R^1 = R^3 = H$, $R^2 = CH_2C_6H_5$

dipeptide derivative (**1**) in solution forms two enantiomeric supramolecular polymers of individual optical antipodes, poly(L-**1**) and poly(D-**1**), via enantioselective hydrogen-bonding interactions (Scheme 1). As the result of this unique chiral association event, "optical purity of monomer **1**" is translated into "molecular weight distribution of the resulting polymer". Homochiral supramolecular polymers can be regarded as *discrete one-dimensional conglomerates*. Over the past 150 years since the discovery of Pasteur,[4] successful examples of spontaneous optical segregation have been limited to crystalline states[5] and more recently extended to liquid crystalline states.[6] However, no examples have been reported for the formation of large homochiral assemblies in solution.

A xylylene-bridged bis(cyclic dipeptide) (**1**), which was chosen as the monomer for supramolecular polymerization, exhibited an extremely high enantioselectivity in hydrogen-bonding interactions. Conformational studies on cyclic dipeptides with benzylic side chains have indicated that the aromatic groups most likely "hover over" the diketopiperadine ring, due to a dipole−dipole interaction.[7] Hence, **1** having a *p*-xylylene bridge should adopt an "*S*"-shaped conformation with the aromatic ring stacked by the two diketopiperadine units. According to molecular models, monomers L-**1**

Scheme 1. Schematic Representation of Homochiral Supramolecular Polymerization of **1**



and D-**1** composed of L- and D-valine units, respectively, are expected to possess "*S*" and "anti-*S*"-shaped (NH ⇒ CO) ⇒ (CO ⇒ NH) sequences. Such a conformational preference results in an antiparallel arrangement of the two hydrogen-bonding amide functionalities on each side of the "*S*" (or "anti-*S*") shape, thereby enhancing the steric requisites for the complementary hydrogen-bonding interactions (Scheme 1).

L-**1** and D-**1** were synthesized by diastereoselective alkylation of 1,4-bis(4-methoxybenzyl)-3-(1-methylethyl)piperazine-2,5-dione,[8] followed by oxidative removal of the N-protecting groups.[9] We succeeded in obtaining a crystal structure of L-**3** (Figure 1), a slightly modified version of **1** for an enhanced crystallinity, which clearly displayed an "*S*"-shaped conformation, as expected for 1,4-xylylene-bridged bis(diketopiperadine) derivatives. Furthermore, L-**3** in the crystalline state forms a columnar assembly via complementary hydrogen bonds at every amide functionality, suggesting that **1** could form a one-dimensional supramolecular polymer in solution.[10,11]

Size-exclusion chromatography (SEC) indicated that **1** in aprotic solvents forms a supramolecular polymer,[12] whose average molecular weight is dependent on the concentration of **1**. For example,

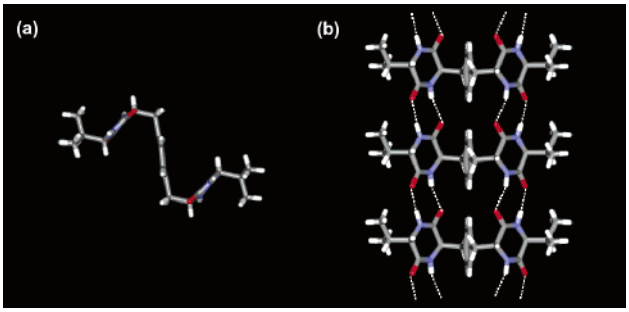


Figure 1. Crystal structure of L-**3** viewed along (a) the *c*-axis and (b) the *a*-axis. The dotted lines represent hydrogen bonds. Solvent molecules are omitted for clarity.

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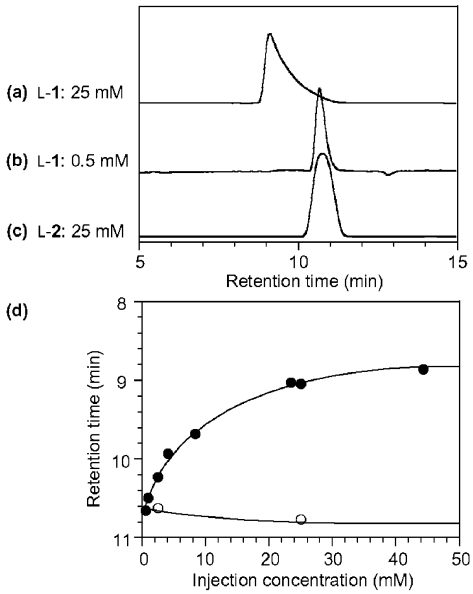


Figure 2. Size-exclusion chromatography (SEC) traces of L-**1** and L-**2** with freshly distilled $CHCl_3$ as eluent on a JAIGEL-2.5H-A column, monitored by a UV detector at 250 and 290 nm, respectively. Loading concentrations: (a) $[\text{L-}\mathbf{1}]_{\text{loaded}} = 25$ mM, (b) $[\text{L-}\mathbf{1}]_{\text{loaded}} = 0.5$ mM, and (c) $[\text{L-}\mathbf{2}]_{\text{loaded}} = 25$ mM. (d) Concentration dependence of retention time (L-**1**; filled circles, L-**2**; open circles).

SEC trace of L-**1** (loading concentration: $[\text{L-}\mathbf{1}]_{\text{loaded}} = 25$ mM) with $CHCl_3$ as eluent displayed a monodisperse chromatogram with a broad tail (Figure 2a), typical of noncovalent polymeric aggregates, whereas that of N-protected L-**2** without hydrogen-bonding capability showed a less broad elution peak with a longer retention time (Figure 2c).[13] Since supramolecular polymerization has a dynamic character, loading of a lower concentration of L-**1** to SEC obviously resulted in a longer elution time (lower molecular weight) of the resulting polymer (Figure 2b).

^{1}H NMR spectroscopy at 20 °C of a $CDCl_3$ solution of L-**1** at 2.0 mM showed one set of very broad signals due to hydrogen-bonded amide-N**H** with significant downfield shifts at δ 9.4 and 9.8 ppm, which turned to ordinary, sharp signals upon addition of trifluoroacetic acid (2.5%) to break the hydrogen bonds among L-**1**.[11] Since L-**4** with only a single diketopiperadine ring (4.0 mM), under similar conditions, did not show any sign of hydrogen-bonding interactions (amide-N**H**: δ 5.9 ppm),[11] a high association tendency of L-**1** is most likely due to the simultaneous participation of the two diketopiperadine units, to allow the formation of four double-hydrogen bonds (Scheme 1). The ^{1}H NMR spectrum also showed that L-**1** adopts an "*S*"-shaped conformation in solution, where a notable ring current effect from the xylylene unit was observed for the C*-**H** resonance (δ 2.85 ppm; for reference, C*-**H** in L-**4**: δ 3.80 ppm).[11] As described in the introductory part, the homochiral association is strongly favored by the "*S*"-shaped conformation of **1**, since the two diketopiperadine units can simultaneously participate in hydrogen-bonding interactions. On the other hand, the heterochiral association of **1** must be unlikely to occur, since a possible mismatch of the hydrogen-donor/acceptor arrays would allow only one of the two diketopiperadine units to participate in hydrogen-bonding interactions (Scheme 1). In fact, **5** and **6**, half-protected analogues of **1**, formed a stable dimeric complex only when they were homochiral; the amide-N**H** signal of L-**6**, upon mixing with L-**5**, showed a 1-ppm downfield shift due to the hydrogen-bonding interactions (Figure 3a), but the signal remained totally intact with the addition of D-**5** (Figure 3b).

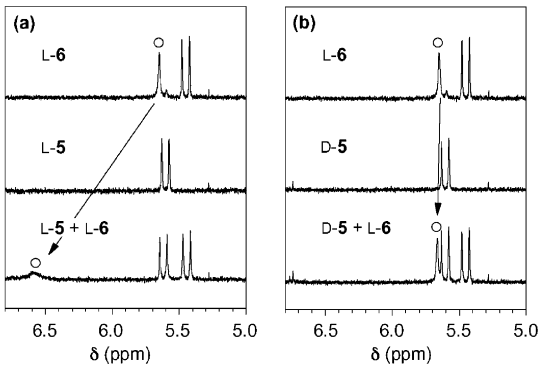
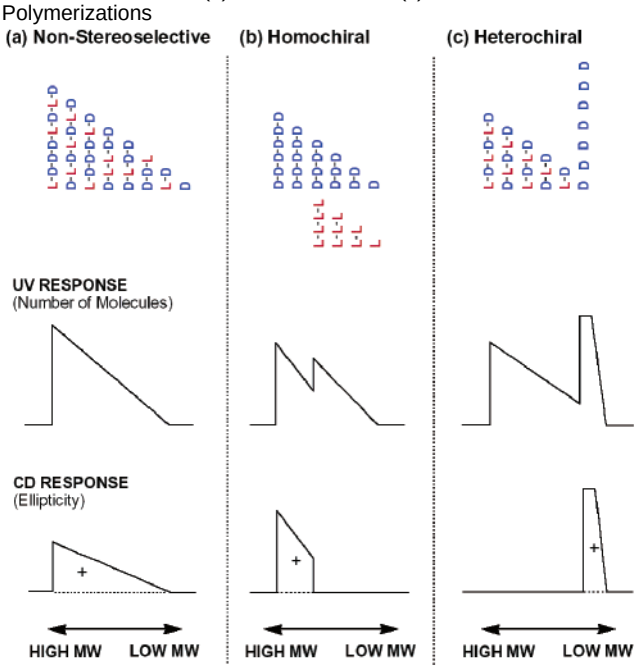


Figure 3. ^{1}H NMR spectral changes of an amide-NH signal of L-**6** (1.0 mM) upon mixing with (a) L-**5** (1.0 mM) and (b) D-**5** (1.0 mM) in freshly distilled $CDCl_3$ at 20 °C.

Scheme 2. Schematic Representations of Size-Exclusion Chromatographic (SEC) Profiles of an Enantiomerically Unbalanced (D-enriched) Monomer, as Expected for (a) Non-stereoselective, (b) Homochiral, and (c) Heterochiral Polymerizations



In supramolecular polymerization of the chiral monomer, the molecular weight of polymer and its distribution (MWD) are generally affected by the stereoselectivity of the association event as well as the optical purity of the monomer. Scheme 2 shows three extreme cases of supramolecular polymerization of an enantiomerically unbalanced monomer (e.g., [D] > [L]). For nonstereoselective supramolecular polymerization, SEC profiles (monitored by absorption [UV] and circular dichroism [CD] detectors) shown in Scheme 2a are expected, where MWD is unimodal as in the case of the polymerization of optically pure monomers and should not change with [L]/[D], whereas the CD intensity response should just reflect enantiomeric purity of the monomer. Scheme 2b shows SEC profiles, as expected for perfect homochiral supramolecular polymerization, where a bimodal MWD should result due to the formation of poly(L) and poly(D) with different molecular weights, depending on chiral monomer concentrations [L] and [D], respectively. According to a theoretical prediction,[14] the CD response should initially be positive (or negative) but display a sudden drop to the baseline level at the beginning of the second peak, due to partial cancellation in ellipticity of poly(D) by lower-molecular-

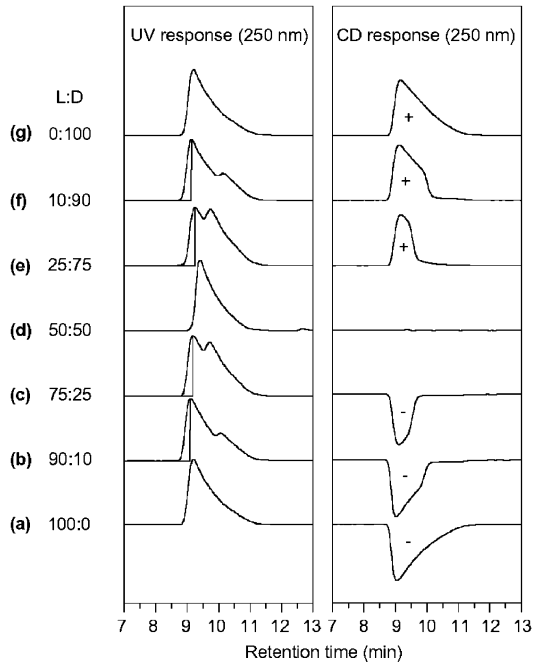


Figure 4. UV (left) and CD (right) responses at 250 nm in size-exclusion chromatography (SEC) traces of mixtures of L-**1** and D-**1** (loading concentration; [L-**1** + D-**1**] = 25 mM] with freshly distilled $CHCl_3$ as eluent on a JAIGEL-2.5H-A column at L:D molar ratios of (a) 100:0, (b) 90:10, (c) 75:25, (d) 50:50, (e) 25:75, (f) 10:90, and (g) 0:100. The shaded parts were fractionated for the evaluation of optical purity of **1**.

weight poly(L) ([D] > [L]).[15] On the other hand, Scheme 2c shows SEC characteristics, as expected for perfect heterochiral supramolecular polymerization, in which a CD-silent copolymer with an alternating sequence of L- and D-monomers should be formed. In the SEC profile, the D-monomer, which exists in excess with respect to the L-monomer, should be observed as a CD-active, sharp peak at the end of the chromatogram.

The SEC profile of the supramolecular polymerization of **1** is what we have expected for the homochiral supramolecular polymerization (Scheme 2b). Similarly to enantiomerically pure L-**1** and D-**1** (Figure 4, a and g), **1** in racemic form (*rac*-**1**) displayed a unimodal SEC profile (Figure 4d). In contrast, when **1** was not racemic but enriched in either of the two enantiomers, the SEC trace was clearly bimodal, as poly(L-**1**) and poly(D-**1**) possess different chain lengths from one another. When the mole ratio [L]:[D] was gradually changed from 100:0 to 0:100 at a constant concentration of **1** ($[\text{L-}\mathbf{1} + \text{D-}\mathbf{1}]_{\text{loaded}}$ = 25 mM) (Figure 4, a−g), the two peak tops once merged at [L]:[D] = 50:50 (Figure 4d), and then they were separated once again. The CD profiles of the chromatograms, thus observed, were exactly what we had expected for the homochiral supramolecular polymerization of enantiomerically unbalanced **1** (Scheme 2b). When the SEC trace of a mixture of L-**1** and D-**1** at a mol ratio of, for example, 10:90 was monitored by a CD detector at 250 nm, the chromatogram, initially with a positive sign, displayed a steep drop to the baseline level at the beginning of the second peak and remained almost unchanged thereafter (Figure 4f). By virtue of this homochiral supramolecular polymerization, enantiomerically pure L-**1** and D-**1** could be isolated from the fractions corresponding to the shaded parts of the chromatograms, b, c, e, and f, in Figure 4.[11]

In conclusion, we demonstrated the first example of spontaneous optical segregation of a chiral compound *in solution*, through studies on supramolecular polymerization of "*S*"-shaped bis(cyclic dipeptide) **1**. Here, the optical purity of **1** is translated into molecular weight distribution, thereby enabling isolation of enantiomers by means of size-exclusion chromatography. Chiral motifs with "*S*"-shaped hydrogen-bonding arrays such as **1**, **5**, and **6** would also allow exploration of nonlinear phenomena in asymmetric transformations.

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Supporting Information Available: Experimental details for synthesis of **1**−**6**, details of crystal structure determination of L-**3** and its diastereoisomer, ^{1}H NMR spectra of L-**1** and L-**4**, and experimental details for the measurements of SEC and VPO of L-**1**, theoretical calculation of molecular weight distribution expected for supramolecular polymerization (PDF). X-ray crystallographic data for L-**3** and its diastereoisomer (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Irrespective of the molar ratio [L-**1**]/[D-**1**], the low-molecular weight region (poly(L-**1**) + poly(D-**1**)) should not show a CD sign opposite to that in the higher-molecular weight region (poly(D-**1**) or poly(L-**1**)). See Supporting Information.

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