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Molecular “Screw and Nut”: α-Cyclodextrin Recognizes Polylactide Chirality

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Cyclodextrins (CDs) are well-known to form inclusion complexes (ICs) with various polymers.[1−8] The complex formation mechanism has been recognized mainly as fitting the polymer chain width with the CD cavity through van der Waals interaction as well as the hydrophobic effect. However, chiral recognition for macromolecules by optically active CDs has not been reported. Our group has studied ICs of biodegradable polymers[9] and accidentally found that α-CD recognizes polylactide chirality: α-CD forms an IC with poly(L-lactide) (PLLA) whereas the IC formation efficiency of poly(D-lactide) (PDLA), the enantiomer of PLLA, with α-CD was extremely low (Scheme 1a). In particular, special interest should be paid to the fact that the PDLA chain was almost excluded by α-CD. This finding must be surprising to those who understand IC formation of α-CD in terms of the fitting between the polymer width and diameter of CD cavity. Our results indicate, in other words, PDLA was exceptionally excluded by α-CD, although these two enatiomeric polymers, PLLA and PDLA, have exactly the same polymer width.

Although CDs are well-known as optically active hosts,[10] their performances as enantioseparators were not so high.[11] One of the reasons may come from the almost symmetrical space of CDs’ cavity, and the majority of the previous studies for enantioselective recognition used chemically modified CDs.[12−14] There have been some reports on IC formation of CDs with stereoregular polymers.[3,15] Harada et al. reported IC formation of β-CD with stereoregular poly(propylene glycol) (PPGs) and showed that the yield of an IC of β-CD with *atactic (atac)*-PPG was significantly higher that with *isotactic (iso)*-PPG. They concluded the larger bulkiness of *atac*-PPG was favorable to

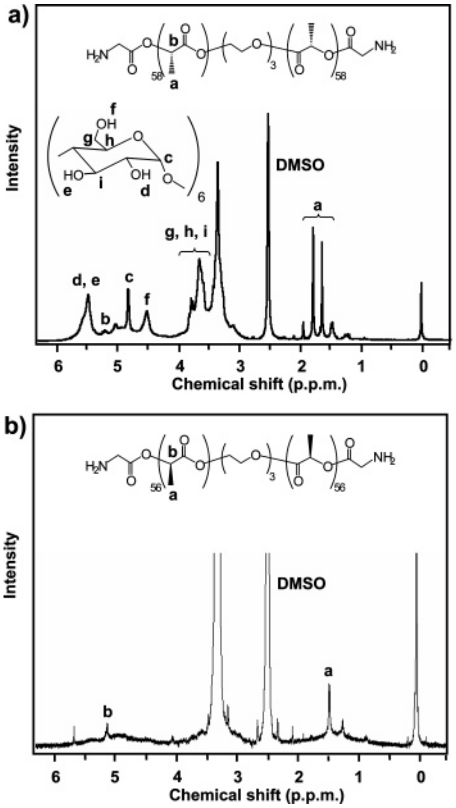

Figure 1. ^1H NMR (400 MHz) spectra of (a) PLLA/α-CD and (b) PDLA/α-CD in DMSO-d_6.

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Scheme 1. (a) Schematic Representation for the Chiral Recognition of Polylactides by α-CD and (b) Preparation of Inclusion Complex Composed of Polylactide and α-CD

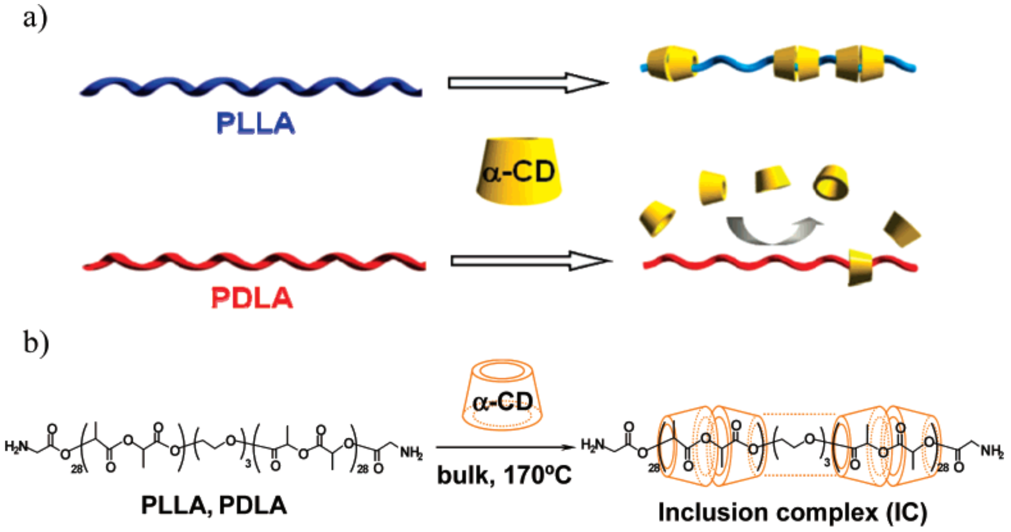

Table 1. Characterization of the ICs, the Polymers, and α-CD

sample	M_n (kDa)[a]	threaded α-CD[b] no. of α-CD per one PL(D)LA molecule	threaded α-CD[b] coverage (%)[d]	$[\alpha]_D$ (deg)[c] DMSO	$[\alpha]_D$ (deg)[c] $CHCl_3$
PLLA/α-CD	32 ± 1	24 ± 1	42 ± 2	+126	
PDLA/α-CD	12 ± 1	4 ± 1	7 ± 2	+120	
PLLA	8.4 ± 0.1			−122	−137
PDLA	8.2 ± 0.1			+117	+142
α-CD	0.970			+158	

[a] Molecular weight of PLLA/α-CD and PDLA/α-CD was estimated from the following equation: M_n of PL(D)LA/α-CD = (M_n of PL(D)LA) + (total molecular weight of threaded α-CD onto PL(D)LA). [b] The number of α-CD threaded onto PL(D)LA chains was estimated by ^{1}H NMR (10 wt % NaOD/D_2O) after hydrolysis of polylactide at RT for 24 h in 10 wt % NaOD/D_2O. [c] The specific rotation was measured in DMSO or chloroform at 10 mg mL^{-1}. [d] Calculated ratio (%) of threaded α-CD to the theoretical maximum of possible α-CD on the PLLA and PDLA, which means how much percent of the polymer chain was covered with α-CD, estimated considering one α-CD molecule should be equivalently fit to one lactide (two lactic acids) unit by the following equation: coverage (%) = 100 × (no. of α-CD threaded per PL(D)LA molecule)/(degree of polymerization of lactide).

fit the β-CD cavity.[3] Tonelli et al. studied IC formation of α-, β-, and γ-CDs with poly(3-hydroxylbutylate)s (PHB) and reported that only α-CD formed an IC with *iso*-PHB, and *atac*-PHB did not.[15] However, they discussed this difference only from the fitting of bulkiness of the polymers to the width of CD cavities and did not discuss the chirality of the polymers included in CDs as chiral hosts. PLLA is an optically active biodegradable polymer, and a few previous reports dealt with IC formation of CDs with copolymers containing PLLA.[8,9,16] However, these previous papers did not focus on the enantioselective recognition of PLLA and PDLA.

PLLA and PDLA having amino terminals were synthesized by ring-opening polymerization of L (or D)-lactide using triethylene glycol (TEG) (1,8-dihydroxy-3,6-dioxaoctane) as an initiator, coupling reaction of the polymer with hydroxyl terminals with *tert*-butoxycarbonyl (Boc)-glycine, and removal of Boc groups. The terminal amino groups were introduced for the subsequent capping reaction to obtain a polyrotaxane in the following stage. The M_n's for the PLLA and PDLA are shown in Table 1. The degrees of polymerization (DP) of lactide unit/OH group of the initiator for PLLA and PDLA were 29 and 28: total DP were 58 and 56, respectively. The specific optical rotations, $[\alpha]_D$, of the PLLA and PDLA in $CHCl_3$ were −137° and +142°, respectively. These values are very close to those of pure PLLA,[17] suggesting that the optical purity of each polymer is very high.

The preparation of an IC composed of PLLA or PDLA and α-CD was carried out in the bulk using vacuum melting at 170 °C (Scheme 1b) because PLLA and PDLA are insoluble in water, which is a common solvent for preparing ICs composed of poly(ethylene glycol) (PEG) and α-CD. The results of IC preparation are also shown in Table 1. The yield for PLLA/α-CD was relatively high (40.3%) compared with for PDLA/α-CD (16.8%). Parts a and b of Figure 1 show the ^{1}H NMR spectra for the products of PLLA/α-CD and PDLA/α-CD systems, respectively. In Figure 1a, the signals for methyl protons of lactide unit around 1.4 ppm was split into two major peaks, and broadening of the α-CD's proton signals was observed. Moreover, $[\alpha]_D$ of the PLLA/α-CD in DMSO was changed to a strong positive value (Table 1). These results strongly suggest the formation of a stable IC consisting of PLLA and α-CD. The splitting methyl signal suggests the α-CD and PLLA chain in the IC are static in the NMR time scale. On the other hand, the products of PDLA/α-CD showed almost the same ^{1}H NMR spectra as PDLA (Figure 1b), and only a small amount of α-CD was detected. The number of threaded α-CD per PLLA molecules estimated by the ^{1}H NMR spectra was 24 and significantly different from that onto PDLA, 4. Considering the stretched length of lactide unit and the depth of α-CD cavity, one α-CD molecule should be equivalently fit to two lactic acid units (one lactide unit), as reported for the case of PEG.[1,2] Estimating from these theoretical parameters, the coverage (%) for PLLA and PDLA by α-CD was 42% and 7%, respectively.

The crystalline structures of PLLA/α-CD and PDLA/α-CD were investigated by differential scanning calorimetry (DSC) and X-ray diffraction (XRD) (Figure 2a,b). Although PLLA and

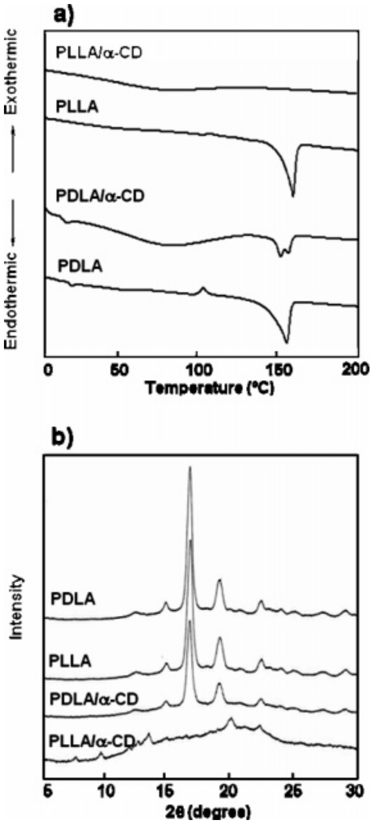

Figure 2. (a) DSC curves of PLLA, PLLA/α-CD PDLA, and PDLA/α-CD (scan rate: 10 °C/min). (b) Wide-angle X-ray diffraction patterns of PLLA, PLLA/α-CD PDLA, and PDLA/α-CD.

PDLA showed melting points around 160 °C as observed for optically pure polylactide, PLLA/α-CD did not show any obvious peak. These results indicate the PLLA/α-CD is amorphous. On the other hand, PDLA/α-CD showed a weak but obvious melting point around 160 °C, indicating the existence of crystalline nature. In Figure 2b, PLLA, PDLA, and PDLA/α-CD showed peaks at $2\theta = 17°$ and 19°, which are typical for PLLA crystal. Such diffraction peaks were not observed for the PLLA/α-CD; however, a weak but obvious peak appeared at $2\theta = 20°$, corresponding to the CD columnar structure in IC.[1,2] These results strongly suggest that α-CD recognizes PLLA to form an IC and excludes PDLA. Such a significant difference was obviously derived from the chirality of PLLA and PDLA as macromolecular guests.

To confirm such chiral recognition, we synthesized low-molecular-weight (LL)- and (DD)-lactic acid dimer methyl esters (methyl lactyl lactates, **L-1** and **D-1**) as model compounds to investigate their IC formation with α-CD. We monitored chemical shifts of methyl protons in ^{1}H NMR spectra in D_2O for **L-1** and **D-1** as a function of **L-1** (or **D-1**)/α-CD ratio (see Supporting Information). A shift of signals was observed for the combination of **L-1** and α-CD. No shift was observed for the combination of **D-1** and α-CD. These results indicate that **L-1** formed an IC with α-CD in D_2O, but **D-1** did not interact with α-CD. The dissociation constant K_d of **L-1** with α-CD was calculated to be 2.8×10^{-2} mol L^{-1} from Bergeron−Channing equation plots[18] of the ^{1}H NMR signals (see Supporting Information). These results suggest **L-1** forms a stable IC with α-CD, but **D-1** does not, and strongly support the results for the enantiomeric polymers, PLLA and PDLA.

We also succeeded in preparing ICs consisting of triblock copolymers (see Supporting Information). Both PLLA−PEG−PLLA and PDLA−PEG−PDLA triblock copolymers formed ICs having similar amounts of threaded α-CDs. From the DSC and XRD measurements, it was confirmed that α-CD existed on the PEG segment in both. These results indicate that an α-CD molecule can slide along the PDLA segment. Therefore, the reason why PDLA was excluded by α-CD is not simply due to the steric hindrance. Presumably, the difference in IC formation of α-CD with PLLA and PDLA should be derived from the thermodynamic stability of the diastereomeric ICs. PLLA was reported to fit to the crystalline urea channel having a 5.5 Å diameter,[19] which is smaller the diameter of α-CD cavity reported (4.5 Å).[1,2] However, in some reports, CDs can chirally twist to recognize chiral molecules.[20] Such chirally "twisted α-CD" may be favorable not only to strict chiral fitting with PLLA chain with CD cavity by van der Waals interaction but also to form hydrogen bonding between the α-CDs adjoining each other.

This is the first report to achieve the enantiospecific recognition of chiral macromolecules by a low-molecular-weight chiral host compound. Our results in this paper suggest the possibility of enantioselective separation of chiral macromolecules. Unidirectional molecular motors have been recently reported, and such a molecular motor system is expected to develop molecular machines in bottom-up nanotechnology.[21−24] The conformation of PLLA chain is known to be a 3_{10} helix in the crystal, and such twisted α-CD on PLLA chain may produce unidirectional rotation when it slides along the optically active and helical PLLA, looking like a "screw and nut" combination. We therefore postulate that our finding can generate a new paradigm of supramacromolecular systems for possible applications to molecular motor having unidirectional rotary movement.

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Supporting Information Available: Synthetic methods and characterizations for the products, IC formation of α-CD with **L-1**, **L-2**, and triblock copolymers, ^{1}H NMR spectra for the titration of α-CD with **L-1** or **D-1**, determination of K_d of **L-1** and α-CD, and inhibitory test of IC formation of **L-1** with α-CD. This material is available free of charge via the Internet at http://pubs.acs.org.

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