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Synthesis and Self-Polyaddition of Optically Active Monomers Derived from Tyrosine

Hiroto Kudo, Atsushi Nagai, Junichi Ishikawa, and Takeshi Endo*

Department of Polymer Science and Engineering, Faculty of Engineering Yamagata University, 4-3-16 Jonan, Yonezawa, Yamagata 992-8510, Japan

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Amino acids are expected not only as biocompatible materials but also as sources of chemically functional materials. We have developed amino acids based on polymers and peptides, where wide varieties of polymerization methods are employed such as fermentation, polycondensation, polyaddition, ring-opening polymerization, and so on.[1] Endo et al. have developed radical self-polyaddition of the optically active monomer derived from cysteine to afford the corresponding polymer having cysteine moieties in the main chain and heterotelechelic structure with thiol and olefin groups. Furthermore, it might be suggested the polymer had some higher order structure by the specific rotation and circular dichroism analysis.[2] Meijer et al. have reported synthesis and polyaddition of α,ω-isocyanato alcohols from α,ω-amino alcohol and di-*tert*-butyltricarbonate ($(BOC)_2CO_3$) under mild conditions.[3]

This article deals with the synthesis and self-polyaddition of optically active monomers derived from tyrosine. The tyrosine-based monomer, L-tyrosine methyl ester [I-T(L)-M] having isocyanate and hydroxyl groups was synthesized by the reaction of tyrosine methyl ester [T(L)-M] and $(BOC)_2CO_3$ in chloroform ($CHCl_3$) (Scheme 1).[4] $(BOC)_2CO_3$ was synthesized according to the reported method.[5]

The structure of the I-T(L)-M was confirmed by ^1H NMR, ^{13}C NMR, and IR spectroscopy. IR absorptions assignable to isocyanate and hydroxyl groups were observed strongly around 2267.9 and 3479.0 cm^{-1} in a $CHCl_3$ solution of I-T(L)-M, respectively. Figure 1b shows the ^1H NMR spectrum of I-T(L)-M obtained from

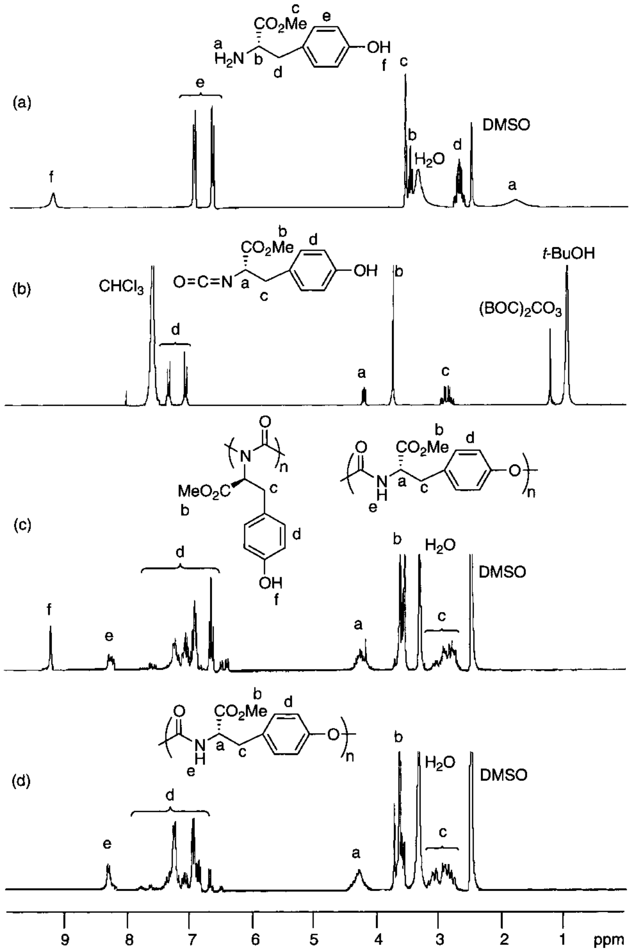

Figure 1. ^1H NMR spectra (270 MHz) of (a) L-tyrosine methyl ester [T(L)-M], (b) isocyanate of L-tyrosine methyl ester [I-T(L)-M] ($CDCl_3$), (c) the polymer obtained in polymerization with $Zr(acac)_4$ (run 4 in Table 1) (DMSO-d_6), and (d) the polymer obtained in polymerization with NEt_3 (run 6 in Table 1) (DMSO-d_6).

* To whom all correspondence should be addressed.

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Table 1. Polymerization of I-T(L)-M[a]

run	catalyst[b]	solvent	yield[c] (%)	M_n (M_w/M_n)[d]	nylon-1/linear polyurethane[e]	$[M]_D^{25}$ [f]
1	$Zr(acac)_4$	$CHCl_3$	2	633 (1.10)	36/64	*g*
2	$C_{32}H_{64}O_4Sn$	$CHCl_3$	>99	937 (1.48)	50/50	*g*
3	NEt_3	$CHCl_3$	98	2287 (1.50)	15/85	44.3
4	$Zr(acac)_4$	THF	13	1200 (1.13)	76/24	48.3
5	$C_{32}H_{64}O_4Sn$	THF	77	1900 (1.29)	35/65	108.3
6	NEt_3	THF	>99	18900 (1.55)	0/100	251.3

[a] Conditions: L-tyrosine methyl ester [T(L)-M] (1.0 mmol), $(BOC)_2CO_3$ (1.1 mmol), $CHCl_3$ or THF (2.2 mL), catalyst (0.03 mmol), at 25 °C for 24 h. [b] $Zr(acac)_4$: zirconium (IV) acetylacetonate. $C_{32}H_{64}O_4Sn$: dibutyltin dilaurate. NEt_3: triethylamine. [c] Ethyl ether-insoluble part. [d] Estimated by GPC based on polystyrene standards, eluent THF. [e] Determined by ^1H NMR. [f] $[M]_D^{25} = [\alpha]^{25}_D \times MW/100$, where MW represents the formula weight of the monomer repeating unit, $[\alpha]^{25}_D$ was measured by a polarimeter at 25 °C (c = 0.1 g/dL, THF). [g] Not observed.

the reaction of T(L)-M (spectrum in Figure 1a) with $(BOC)_2CO_3$. These results indicated that no side product could be formed and I-T(L)-M was stable at room temperature in the solution, but I-T(L)-M could not be isolated by recrystallization and distillation. A similar result was obtained in the synthesis of I-T(L)-M with $(BOC)_2CO_3$ in tetrahydrofuran (THF) (Scheme 1).

The polymerization of I-T(L)-M was carried out in situ by addition of several catalysts at 25 °C for 24 h in $CHCl_3$ and THF (Scheme 1 and Table 1). In all of the cases, the reaction mixture was consistently homogeneous with all starting materials and products remaining in the solution. The reaction mixture was poured into ethyl ether to precipitate a white powdery polymer that was soluble in common organic solvents such as dimethyl sulfoxide, dimethylformamide, $CHCl_3$, and THF. The structure of the corresponding polymers was confirmed by ^1H NMR and IR spectroscopy. No IR absorption assignable to the isocyanate group was observed at 2268 cm^{-1}. Figure 1c illustrates the ^1H NMR spectrum of the polymer obtained by the polymerization at 25 °C by zirconium(IV) acetylacetonate in $CHCl_3$ (run 1). The figure shows signals assignable to hydroxyl (OH) and amide (NH) of urethane moieties at 9.3 and 8.3 ppm, respectively. These results indicated that the corresponding polymer consisted of nylon 1 from the polymerization of isocyanate group and linear polyurethane from the self-polyaddition of isocyanate with the hydroxyl group of I-T(L)-M. The similar results were also obtained in the polymerization with dibutyltin dilaurate and triethylamine (NEt_3) (runs 2−5). On the other hand, as shown in Figure 1d of the ^1H NMR spectra of the obtained polymer by the polymerization at 25 °C by NEt_3 in THF (run 6), no assignable to hydroxyl group was observed. Furthermore, the result of the ^{13}C NMR could be supported that the obtained polymer was linear polyurethanes, poly[I-T(L)-M].[6] In addition, the number-average molecular weights (M_n), polymer yield and the degree of $[M]_D$ increased with linear polyurethane (Table 1). T_{d5}s and T_gs were observed in the ranges 360.5−380.3 and 125.3−131.2 °C, respectively.[7]

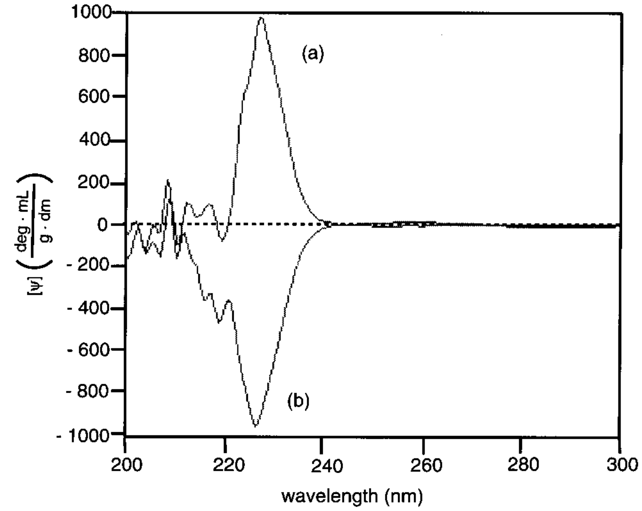
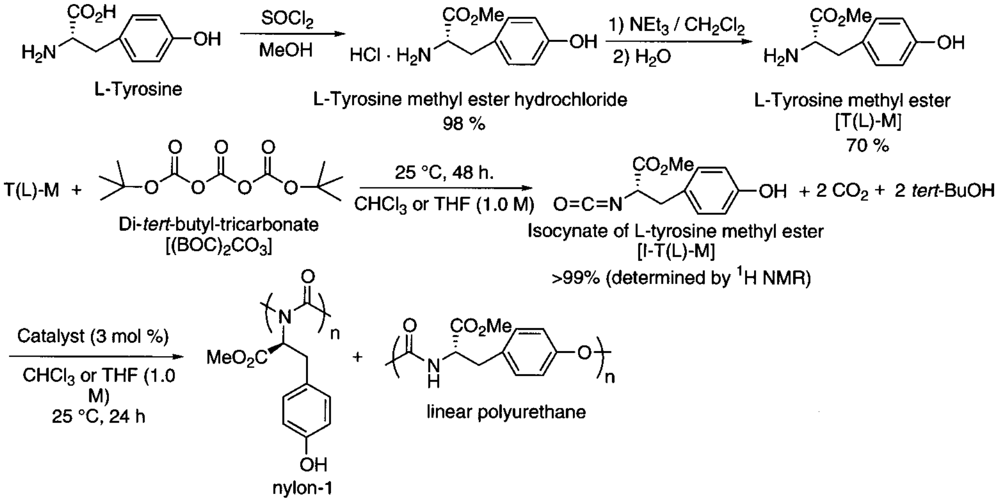


Figure 2. CD spectra (c = 0.1 g/dL, THF) of (a) poly[I-T(L)-M] (M_n 19 800, M_w/M_n 1.55) and (b) poly[I-T(D)-M] (M_n 15 000, M_w/M_n 1.55).

Furthermore, in a manner similar to that above, isocyanate of D-tyrosine methyl ester [I-T(D)-M] was also synthesized and its polymerization was carried out in the presence of NEt_3 (3 mol %) in THF (1 M) to afford the corresponding polymer, poly[I-T(D)-M] with M_n of 15 000 (M_w/M_n = 1.24) in 95% yield. Figure 2 illustrates the CD spectra of poly[I-T(L)-M] (M_n = 18 900, M_w/M_n = 1.55) and poly[I-T(D)-M] (M_n = 15 000, M_w/M_n = 1.24) measured in THF solutions (c = 0.1 g/dL). The former, poly[I-T(L)-M] ($[M]_D^{25}$ = 251.3) showed a positive Cotton effect, whereas the latter, poly[I-T(D)-M] ($[M]_D^{25}$ = −245.6), exhibited a negative one. It is noteworthy that the specific ellipticities [ψ] whose maxima exhibited

Scheme 1



good correspondence with λ_{max} values of UV were observed around 1000 deg·mL·g^{-1}·dm^{-1}. These results might suggest that the linear polyurethanes had some regulated higher order structures such as helical conformation due to its asymmetric carbon.

In summary, the synthesis and polymerization of the optically active monomers derived from tyrosine were examined. The self-polyaddition of the tyrosine-based monomers, isocyanate of L-tyrosine methyl ester [I-T(L)-M] and D-tyrosine methyl ester [I-T(D)-M] having isocyanate and hydroxyl groups proceeded satisfactorily to afford the corresponding linear polyurethanes having tyrosine moieties in the main chain, poly[I-T(L)-M] (M_n 18 900, M_w/M_n 1.55) and poly[I-T(D)-M] (M_n 15 000, M_w/M_n 1.55), respectively in good yields. The absolute value of $[M]_D^{25}$ of poly[I-T(L)-M] (251.3) almost agreed with that of poly[I-T(D)-M] (−245.6). Also, the positive Cotton effect of poly[I-T(L)-M] and the negative one of poly[I-T(D)-M] were observed, respectively. The specific rotation and CD spectrospecific analysis might suggest that the linear polyurethanes had some higher order structures.

Acknowledgment. We thank Yoshihiko Mizuno for determining the T_{d5} and T_g.

Supporting Information Available: Text giving experimental procedure and ^{1}H NMR, ^{13}C NMR, and IR data as well as depictions of the structures for T(L)-M, T(D)-M, I-T(L)-M, poly[I-T(L)-M], and poly[I-T(D)-M]. This material is available free of charge via the Internet at http:/pubs.acs.org.

References and Notes

(1) Review: Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 2651.

(2) Kudo, H.; Sanda, F.; Endo, T. *Macromolecules* **1999**, *32*, 8370.

(3) Versteegen, R. M.; Sijbesma, R. P.; Meijer, E. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 2917.

(4) Tyrosine methyl ester [T(L)-M] (195 mg, 1.0 mmol) was added to a solution of di-*tert*-butyl tricarbonate ($(BOC)_2CO_3$) (280 mg, 1.1 mmol) in THF (2.1. mL) at 25 °C. The reaction mixture was stirred at 25 °C for 48 h under an argon atmosphere. After the reaction started, the mixture became homogeneous after 24 h. This reaction is accompanied by the formation of 2 equiv of carbon dioxide and *tert*-butyl alcohol.

(5) (a) Dean. C. S.; Tarbell, D, S.; Friderang, A. W. *J. Org. Chem.* **1970**, *35*, 3393. (b) Pope, B. M.; Yamamoto, Y.; Tarbell, D. S. *Org. Synth.* **1978**, *57*, 45.

(6) Spectroscopic data of poly[I-T(L)-M] obtained in polymerization with NEt_3 (run 6 in Table 1). ^{13}C NMR (DMSO-d_6, 270 MHz): δ = 36.81 ($-CH_2-$), 51.66 ($-OCH_3$), 56.14 ($>CH-$), 115.54, 120.9, 127.16, 130.37 ($-C_6H_5-$), 156.52 ($-C$(O)NH), 173.16 ($-C$(O)OMe) ppm.

(7) Temperature (T_{d5}) with 5% weight loss were determined by thermogravimetric analysis (TGA) at a heating rate of 10 °C/min under nitrogen atmosphere. Glass transition temperatures (T_g) were taken as an inflection point on a trace at a heating rate of 10 °C/min by differential scanning calorimetry (DSC).

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