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ORIGINAL ARTICLE

Ring-opening polymerization of a five-membered lactone *trans*-fused to a cyclohexane ring

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The ring-opening polymerization behavior of five-membered lactones fused to a cyclohexane ring (that is, the *trans*- and *cis*-hexahydro-2(3*H*)-benzofuranone denoted T6L and C6L, respectively) was investigated under various conditions. The potassium *tert*-butoxide (^{t}BuOK)-initiated anionic polymerization of T6L yields polymers with number-average molecular weight (*M*n) values of 5000. However, no polymeric products were obtained via cationic and coordination polymerization. Among the anionic initiators, a base stronger than an alkoxide initiated the polymerization of T6L. In contrast, *cis*-isomer C6L did not polymerize regardless of the initiator species used, which implied an increase in the ring strain of the lactone ring by the *trans*-fused cyclohexane. The anionic polymerization of T6L was reversible, and the thermodynamic parameters characterizing the polymerization of T6L were estimated to be $\Delta H_p^\circ = -18\,\mathrm{kJ \cdot mol^{-1}}$ and $\Delta S_p^\circ = -65\,\mathrm{J \cdot K^{-1} mol^{-1}}$ on the basis of the measurement of the equilibrium monomer concentration.

INTRODUCTION

Aliphatic polyesters are attractive as biodegradable and biocompatible materials.[1,2] For their synthesis, two procedures that have been employed are (a) the polycondensation between dicarboxylic acids and diols and (b) the ring-opening polymerization of lactones.[3,4] The latter proceeds via chain polymerization and has the potential to control the molecular weight of the resulting polymer. The ring-opening behavior of the lactones depends on their ring size. γ-Butyrolactone (BL), a typical five-membered lactone, is known to undergo a positive enthalpy change during ring opening and to hardly polymerize to yield its homopolymer. Some attempts have been made to polymerize BL.[1] Most of these attempts resulted in only low-molecular weight materials and the formation of a high-molecular weight polymer that required extraordinary conditions, such as a very high pressure.

It is well known that the ring-opening polymerization of five-membered cyclic carbonates are also thermodynamically unfavorable and produce no polymeric materials or polyethers accompanied by the elimination of CO_2.[5–10] However, we have demonstrated that the five-membered cyclic carbonates (that is, methyl 2,3-*O*-carbonyl-4,6-*O*-benzylidene-α-D-glucopyranoside (MBCG)[11,12] and *trans*-cyclohexane-2,3-diyl carbonate (T6C)[13] do polymerize without any decarbonylation to yield polycarbonates containing no polyether units. Both of these monomers have five-membered cyclic carbonates fused to a six-membered ring in a *trans*- manner. The increase in the polymerizability of these monomers is most likely
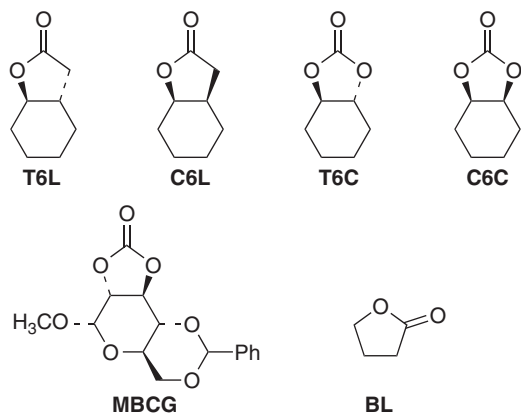
responsible for increasing the ring strain because of the *trans*-fused cycles.

To strengthen these experimental results, we became interested in the polymerization of a five-membered lactone fused to a cyclohexane ring. Newman *et al.*[14] reported the synthesis of a lactone with such a structure, *trans*-hexahydro-2(3*H*)-benzofuranone (T6L). In this compound, the ring strain of the lactone should increase enough to polymerize similar to the polymerization of the five-membered carbonates. However, Hall and Schneider[15] mentioned that the ring-opening polymerization of T6L did not proceed, but the experimental conditions were not reported in detail. In this study, we report the details of the polymerization behavior of T6L and *cis*-isomer C6L. The fundamental thermodynamic parameters characterizing the polymerization of T6L are also determined (Scheme 1).

EXPERIMENTAL PROCEDURE

Measurements

The NMR spectra were recorded using a JEOL JNM-ECX 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer (JEOL Ltd., Akishima, Tokyo, Japan). The chemical shift values were in p.p.m. downfield from tetramethylsilane (0.0 p.p.m.) and CDCl$_3$ (77.0 p.p.m.), which were employed as internal standards for the ^{1}H and ^{13}C measurements, respectively. IR spectra were recorded using a Nicolet 6700 FT-IR spectrometer (ThermoFisher Scientific, Waltham, MA, USA) equipped with a Smart Orbit attachment for the attenuated total reflectance (ATR) measurements. The number-average (*M*n)

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Scheme 1 Structures of the monomers and related compounds.

Table 1 Results from the ring-opening polymerization of T6L[a]

run	Initiator or catalyst	Temperature/ °C	Conversion[b]/ %	Yield[c]/ %	$Mn \times 10^{-3}$		
					SEC[d]	NMR[b]	PDI[d]
1	^{t}BuOK	40	73	44	5.0	2.6	1.6$_2$
2	TfOH	40	20	0	—	—	—
3	Sn(Oct)$_2$	60	0	—	—	—	—
4	nBuLi	40	69	48	5.4	2.8	1.2$_2$
5	LDA	40	72	61	6.2	2.6	1.2$_2$
6	DBU	40	0	—	—	—	—
7	Et$_3$N	40	0	—	—	—	—
8	DMAP	40	0	—	—	—	—

[a]Time 24 h, $[T6L]_0/[I]_0 = 50$.
[b]Estimated by ^{1}H NMR spectra measured in CDCl$_3$.
[c]Methanol-insoluble fraction.
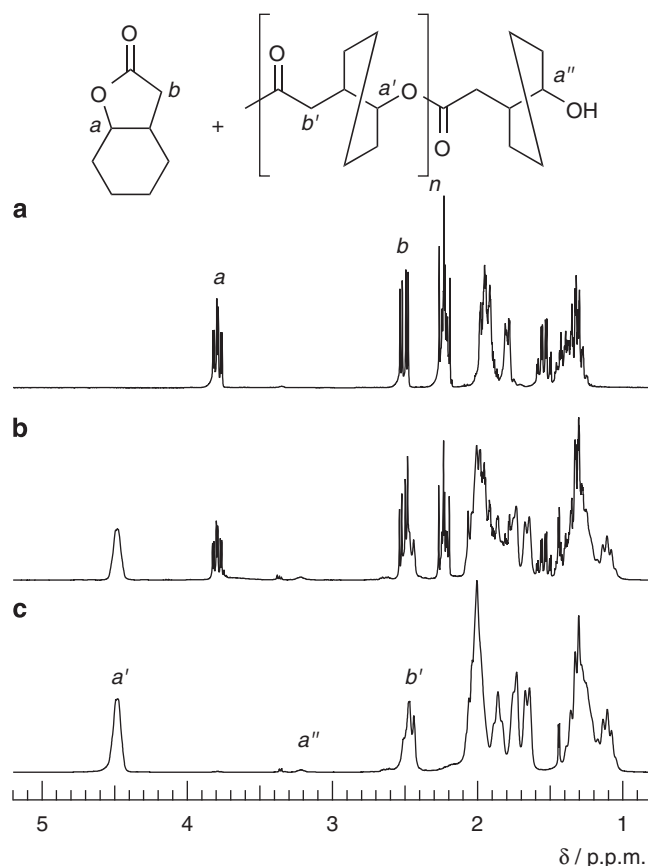[d]Calculated from SEC eluted with CHCl$_3$ on the basis of polystyrene calibration.

and weight-average (Mw) molecular weights were determined with size-exclusion chromatography (SEC) using a Tosoh HLC-8120 GPC apparatus (Tosoh Co., Tokyo, Japan) with three polystyrene gel columns (Tosoh TSK gels G-2500H$_{XL}$, G-3000H$_{XL}$ and G-4000H$_{XL}$) in CHCl$_3$ in conjunction with a calibration curve on the basis of polystyrene standards. The density measurements of T6L were performed with an Anton Paar DMA 4500 M instrument (Anton Paar GmbH, Graz, Austria). The density of T6L is 1.077 at 30 °C, 1.068 at 40 °C and 1.060 at 50 °C. The optimized conformations of the monomers were obtained using *ab initio*-restricted Hartree-Fock (RHF) calculations with the 6–31 G + + (d, p) basis set as implemented in Firefly (version 7.1.G) software (Alex A. Granovsky, http://www.classic.chem.msu.su/gran/firefly/index.html).[16] The results from the calculations were visualized using the Avogadro (version 1.1.0) software (http://avogadro.openmolecules.net/wiki/Main_Page).[17]

Materials

The lactone monomer, *trans*-hexahydro-2(3*H*)-benzofuranone (T6L), was prepared from 1,2-epoxycyclohexane and diethyl malonate according to the procedure reported by Newman and VanderWerf[14] and distilled twice before use. The *cis*-isomer, C6L, was prepared via the epimerization of T6L according to the procedure reported by Pirkle and Adams.[18] Potassium *tert*-butoxide (^{t}BuOK) was purchased as a 1.0 M solution in THF (Sigma-Aldrich Co., St Louis, MO, USA) and used as received.

Anionic polymerization of T6L

A typical procedure was as follows: T6L (0.30 g, 2.1 mmol) was added to a test tube equipped with a three-way stopcock and filled with nitrogen. The tube was heated at 40 °C followed by the addition of an initiator, which was a 1.0 M solution of ^{t}BuOK in THF (43 μl, 0.043 mmol), with a syringe. The mixture was stirred at this temperature for 24 h. Then, acetic acid (15 μl) was added to quench the reaction. The mixture was diluted with ~1 ml of CHCl$_3$ and then poured into methanol (100 ml). The white precipitate was collected by filtration, reprecipitated from CHCl$_3$ into methanol and dried *in vacuo* at room temperature. The yield was 0.13 g (44%). $Mn = 5000$, $Mw/Mn = 1.6_2$ (SEC). ^{1}H NMR (CDCl$_3$): δ (p.p.m.) = 4.6–4.4 (br, 1H, H-4), 2.4–2.2 (br 2H, H-2), 2.1–1.0 (m). IR (ATR): ν (cm^{-1}) = 2930–2860 (C–H), 1720 (C=O).

RESULTS AND DISCUSSION

The monomer T6L was prepared according to the procedure reported by Newman and VanderWerf.[14] In general, lactones produce polyesters via a ring-opening polymerization through anionic, cationic or coordination polymerization. To search for suitable polymerization systems, the polymerizations of T6L were tested using potassium *tert*-butoxide (^{t}BuOK), trifluoromethanesulfonic acid (TfOH) or tin bis(2-ethylhexanoate) (SnOct$_2$) as the anionic initiator, cationic initiator or coordination catalyst, respectively. The results are shown in Table 1 (entry 1–3). The polymerizations were

Figure 1 ^{1}H NMR spectra of (**a**) T6L, (**b**) poly(T6L), and (**c**) the crude product obtained from polymerization of T6L with ^{t}BuOK after 30 min of polymerization. See Table 1 for the detailed polymerization conditions.

performed in the bulk at 40 and 60 °C. When the anionic polymerization was performed at 40 °C (run 1), the polymerization reaction was confirmed by the ^{1}H NMR spectra of the crude product without precipitation. Figure 1 shows an example of the spectrum of the reaction mixture after 30 min of polymerization as well as those of T6L and poly(T6L) after reprecipitation into methanol. The methine signal (a) of T6L appeared at 3.8 p.p.m. and was shifted downfield to 4.5 p.p.m. (a′) in poly(T6L). The monomer conversion could be estimated from the integration ratio of these signals. In addition, the

terminal methine proton (a″) adjacent to the hydroxyl group appeared at 3.2 p.p.m., which allows us to calculate the M_n by integrating the signals at 4.5 (a′) to those at 3.2 p.p.m. (a″).

During the anionic polymerization for 24 h (run 1), T6L was consumed with 73% conversion, and a 44% yield of the methanol insoluble product was obtained. The M_n of this product was 5000 and 2600 by SEC and ¹H NMR, respectively. The polymerization homogeneously afforded a clear transparent monomer/polymer mixture melt from the liquid monomer. However, cationic polymerization (run2) resulted in no polymeric materials, but the monomer conversion reached a value of 20%. Therefore, the only low-molecular weight material was formed by the cationic initiator. T6L did not react at all with the SnOct₂ catalyst, and the unreacted monomer was quantitatively recovered (run 3). Therefore, anionic initiators, such as ᵗBuOK, are suitable for the polymerization of T6L. For comparison, the polymerization of BL was examined under the same conditions as in run 1. However, no consumption of BL was observed. Therefore, T6L can be polymerized by anionic initiators and has a superior polymerizability compared with BL, which is most likely due to the increase in the ring strain of the lactone by the *trans*-fused cyclohexane.

Next, additional five anionic initiators were examined. The results are also listed in Table 1 (runs 4–8). The initiators with a stronger basicity than ᵗBuOK (that is, n-butyl lithium (nBuLi) and lithium diisopropylamide (LDA)) produced methanol-insoluble products with nearly the same M_n in a similar yield as observed for ᵗBuOK. The weaker bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine (Et₃N), and N,N-dimethyl-4-aminopyridine (DMAP), did not initiate the polymerization, and the unreacted monomer was quantitatively recovered. The anionic polymerization of T6L requires initiators with greater basicity than the alkoxides. Therefore, ᵗBuOK was employed in subsequent experiments.

Figure 2 shows the time course of the monomer conversion for the anionic polymerization of T6L at temperatures ranging from 30 to 80 °C. At any temperature, the polymerization proceeded very rapidly after the polymerization began but apparently terminated to afford a constant amount of monomer residues. A higher polymerization temperature resulted in a higher amount of residues, which is characteristic of equilibrium polymerization. To confirm the reversibility of the polymerization of T6L, the temperature was increased to
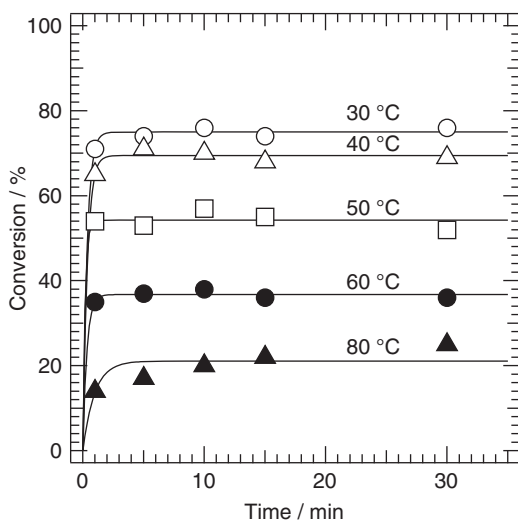
80 °C or lowered to 0 °C after the polymerization at 40 °C for 15 min. Figure 3 shows the ¹H NMR spectra of the reaction mixture 24 h after the temperature was changed. The conversion, which was 64% at 40 °C, increased to 86% at 0 °C and decreased to 23% at 80 °C, which implied that the polymerization is in an equilibrium state at the temperature examined.

To evaluate the polymerizability of T6L, the standard enthalpy change (ΔH_p°) and entropy change (ΔS_p°) in the polymerization may be determined according to Dainton's equation[19,20] (1):

$$\ln [M]_e = \frac{\Delta H_p^\circ}{RT} - \frac{\Delta S_p^\circ}{R} \tag{1}$$

where $[M]_e$ and R are the equilibrium monomer concentration and the gas constant, respectively. Figure 4 is a plot of the logarithm of $[M]_e$, which was calculated from the monomer conversion in equilibrium, as shown in Figure 2, and the density measurements of the monomer assuming the volume of the polymerization mixture is constant as a function of the inverse of the temperature. Moderately
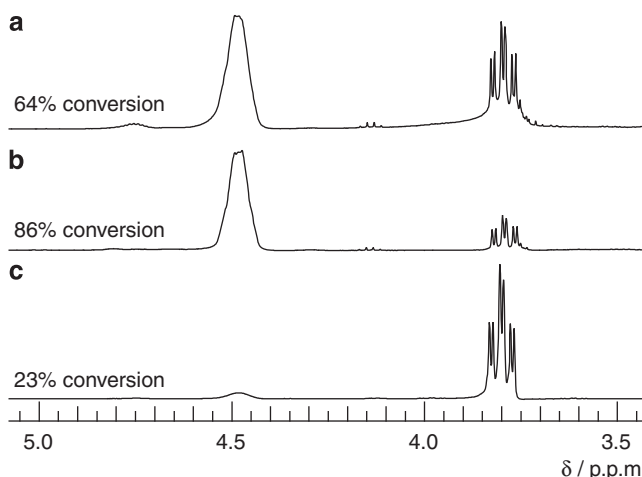
Figure 3 ¹H NMR spectra of the polymerization mixture after the polymerization (**a**) at 40 °C for 15 min, (**b**) at 40 °C for 15 min, then at 0 °C for 24 h and (**c**) at 40 °C for 15 min, then at 80 °C for 24 h.

Figure 2 The time course of the conversion of T6L for the anionic polymerization with ᵗBuOK at (○) 30, (△) 40, (□) 50, (●) 60 and (▲) 80 °C.
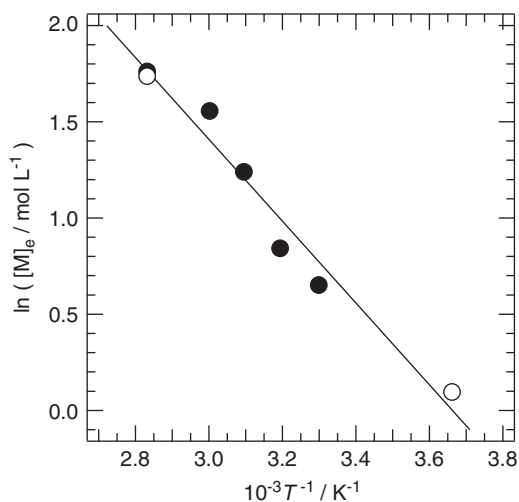
Figure 4 Dainton's plot for the anionic polymerization of T6L with ᵗBuOK. The closed circles were obtained from the polymerization at various temperatures (Figure 2). The open circles were obtained from the experiment when the temperature was varied after reaching equilibrium (Figure 3).

good linearity is obtained in this plot and allows for the determination of $\Delta H_p° = -18$ kJ mol^{-1} and $\Delta S_p° = -65$ J (mol K)$^{-1}$, from the slope and y-intercept of the line, respectively. The enthalpy value is negative despite the positive value of BL[20] ($+5.1$ kJ mol^{-1}) and is comparable to that of some polymerizable cyclic compounds, such as tetrahydrofuran[20,21] (-19.1 kJ mol^{-1}) and 1,4-dioxane-2-one[20,22] (-13.8 kJ mol^{-1}). Therefore, the unusually good polymerizability of T6L for a five-membered lactone has been clearly demonstrated.

The *cis*-isomer of T6L, C6L, was prepared according to the procedure reported by Pirkle and Adams.[18] However, all of our attempts to polymerize C6L with any of the anionic initiators at any temperature failed. Therefore, the high polymerizability of T6L might be attributed to the *trans*-fused cyclic structure to the cyclohexane ring similar to MBCG and T6C.
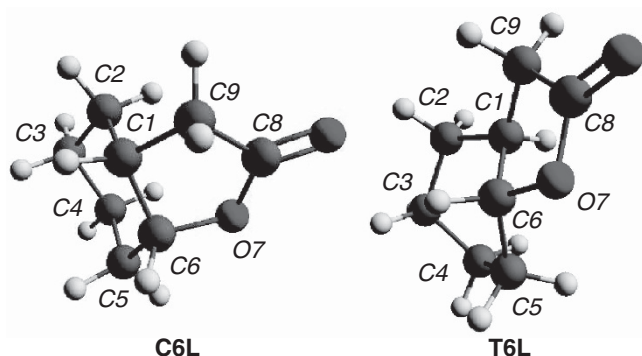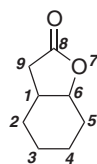

Figure 5 Optimized structure of the monomers obtained using *ab initio* RHF/6-31G + + (d,p) calculations. A full color version of this figure is available at *Polymer Journal* online.

Table 2 Dihedral angles in the optimized structure of the monomers

	Dihedral angle, ψ[a]/degree	
Bonds	C6L	T6L
Lactone ring		
O7-C6-C1-C9	−36.0	−35.8
C6-C1-C9-C8	32.4	31.7
C1-C9-C8-O7	−18.7	−18.1
C9-C8-C7-C6	−5.0	−5.1
C8-C7-C6-C1	26.7	26.4
Cyclohexane ring		
C6-C5-C4-C3	−52.1	−26.5
C5-C4-C3-C2	59.8	60.5
C4-C3-C2-C1	−57.8	−26.1
C3-C2-C1-C6	46.6	−35.3
C2-C1-C6-C5	−39.1	71.3
C1-C6-C5-C4	42.5	−36.0

[a]Estimated from the optimized structure obtained by the *ab initio* RHF/6-31G + + (d,p) calculation.

To elucidate the origin of the difference in the polymerizability of the monomers, we performed *ab initio* RHF calculations to obtain the optimized conformation of the monomers (that is, T6L and C6L). The results are shown in Figure 5, and the dihedral angle (ψ) between each of the bonds is summarized in Table 2. The lactone ring in both monomers is in nearly the same conformation and has a similar ψ for all of the bonds. However, a significant difference was observed in the conformation of the cyclohexane ring. The cyclohexane in C6L exists in a pseudo chair conformation with ψ close to 55°, which is observed in the chair form of cyclohexane,[23] except for those between C3-C2-C1-C6, C2-C1-C6-C5 and C1-C6-C5-C4, which are close to 40°, because of strain caused by sharing C4 and C9 with the lactone ring. In contrast, the cyclohexane ring in T6L appears to be in a twist-boat conformation with a much smaller ψ ranging from 20 to 35° except ψ between C5-C4-C3-C2 and C2-C1-C6-C5. It is known that the stable twist-boat conformer forms exist with bulky substituents[24–26] or in fused-[27–30] and bridged[31] ring systems as well as in the carbocation.[32] The difference in the standard enthalpy between the chair and the twist-boat conformations in cyclohexane has been reported to be −23 kJ mol^{-1},[33] which is in good agreement with the $\Delta H_p°$ of T6L (-18 kJ mol^{-1}). Therefore, the polymerizability of T6L is primarily controlled by the release of the ring strain in the cyclohexane ring from the twist-boat to the chair conformations, that is, the strained cyclohexane assists the non-strained five-membered lactone in the ring-opening reaction.

SUMMARY

The polymerizations of the five-membered lactone *trans*-fused to the cyclohexane ring, T6L, were examined. The anionic initiators, which have a higher basicity than an alkoxide, initiated the polymerization of T6L and produced a polyester with $Mn > 2000$. The anionic polymerization of T6L was reversible, and the thermodynamic parameters were estimated to be $\Delta H_p° = -18$ kJ mol^{-1} and $\Delta S_p° = -65$ J (mol K)$^{-1}$. The negative $\Delta H_p°$ clearly indicated the high ring strain in T6L, which might be caused by the ring strain in the cyclohexane fused to the five-membered lactone.

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