2836 *Chem. Mater.* **2003,** *15,* 2836−2843

Synthesis and Characterization of Star-Shaped Poly(L-lactide)s Initiated with Hydroxyl-Terminated Poly(Amidoamine) (PAMAM-OH) Dendrimers

Youliang Zhao, Xintao Shuai, Chuanfu Chen, and Fu Xi*

State Key Laboratory of Polymer Physics and Chemistry,
Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences,
Beijing 100080, People's Republic of China

Received October 31, 2002. Revised Manuscript Received February 21, 2003

Novel biodegradable star-shaped polymers that consist of poly(L-lactide) (PLLA) arms and a starburst PAMAM dendrimer core were prepared by ring-opening polymerization of L-lactide with PAMAM-OH dendrimer (generation 1−4) initiators and a stannous octoate catalyst in bulk at 130 °C. The molecular weights of the star-shaped polymers were measured by GPC, ^{1}H NMR, and SLS. It was found that the molecular weight of the synthesized star-shaped polylactides can be controlled by variation of the generation of the dendrimer initiators and the molar ratio of monomer to initiator. Effects of molecular weight and number of arms on the thermal properties and hydrolytic degradation of the star-shaped polylactides were investigated. For polylactides initiated with the same dendrimer initiator, the melting temperature and crystallinity increased with increasing molecular weight. For star-shaped polylactides initiated with dendrimer initiators with different generations, the melting point, crystallinity, crystallization rate, and maximum decomposition temperature decreased as the number of arms increased, while the corresponding hydrolysis rate increased.

Introduction

Aliphatic polyesters such as polylactide, poly(ϵ-caprolactone), polyglycolide, and their copolymers are biodegradable and biocompatible polymers that have been successfully applied as biomaterials.[1] Until now, although poly(L-lactide) (PLLA) has been extensively used in surgical sutures, drug delivery systems, and internal bone fixation,[2] it has suffered from the lack of controlled degradation based on its high crystallinity and the induction of material defects based on lability of melt viscosity, so it is necessary to modify its physical properties. The promising approaches to overcoming these problems are the introduction of hydrophilic units to control the biodegradability and use of a branched structure to stabilize the melt viscosity and/or decrease the crystallinity of PLLA.[3] Up to this point, many branched macromolecular architectures, such as comb,[3a,4] star,[5] hyperbranched, and dendritic macromolecules[6] that contain aliphatic polyester chains have been synthesized.

As a rapidly increasing family of macromolecules, dendrimers have wide potential applications in biomedicine, materials science, and supramolecular chemistry because of their unique structures and properties.[7] Among them, the modification and functionality of poly(amidoamine) (PAMAM) dendrimers have been attracting much attention because they are safe, nonimmunogenic, commercially available, and can function as highly efficient cationic polymer vectors for delivering genetic material into cells.[8] For instance, the poly-

---

* To whom correspondence should be addressed. Tel.: ++86-10-62557907. Fax: ++86-10-62559373. E-mail: xifu@infoc3.icas.ac.cn.

(1) (a) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181. (b) Ikada, Y.; Tsuji, H. *Macromol. Rapid Commun.* **2000**, *21*, 117. (c) Griffith, L. G. *Acta Mater.* **2000**, *48*, 263. (d) Burdick, J. A.; Philpott, L. M.; Anseth, K. S. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 683. (e) Kricheldorf, H. R.; Fechner, B. *Macromolecules* **2001**, *34*, 3517. (f) Kim, J. K.; Park, D. J.; Lee, M. S.; Ihn, K. J. *Polymer* **2001**, *42*, 7429.

(2) (a) Goddard, H.; Kenneth, K. M.; Sosely, O. S. Eur. Pat. Appl. 830866 A2 25, 1988. (b) Bhardwaj, R.; Blanchard, J. *Int. J. Pharm.* **1998**, *170*, 109. (c) Winet, H.; Bao, J. Y. *J. Biomed. Mater. Res.* **1998**, *40*, 567.

(3) (a) Breitenbath, A.; Kissel, T. *Polymer* **1998**, *39*, 3261. (b) Fujiwara, T.; Miyamoto, M.; Kimura, Y.; Sakurai, S. *Polymer* **2001**, *42*, 1515. (c) D'Angelo, S.; Galletti, P.; Maglio, G.; Malinconico, M.; Morelli, P.; Palumbo, R.; Vignola, M. C. *Polymer* **2001**, *42*, 3383. (d) Lee, D.; Teraoka, I.; Fujiwara, T.; Kimura, Y. *Macromolecules* **2001**, *34*, 4949.

(4) (a) Möller, M.; Nederberg, F.; Lim, L. A.; Kånge, R.; Hawker, C. J.; Hedrick, J. L.; Gu, Y.; Shah, R.; Abbott, N. L. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 3529. (b) Lang, M.; Chu, C. C. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 4214. (c) Shinoda, H.; Matyjaszewski, K. *Macromolecules* **2001**, *34*, 6243.

(5) (a) Arvanitoyannis, I.; Nakayama, A.; Kawasaki, N.; Yamamoto, N. *Polymer* **1995**, *36*, 2947. (b) Han, D. K.; Hubbell, J. A. *Macromolecules* **1996**, *29*, 5233. (c) Arvanitoyannis, I.; Nakayama, A.; Psomiadou, E.; Kawasaki, N.; Yamamoto, N. *Polymer* **1996**, *37*, 651. (d) Li, Y.; Kissel, T. *Polymer* **1998**, *39*, 4421. (e) Choi, Y. K.; Bae, Y. H.; Kim, S. W. *Macromolecules* **1998**, *31*, 8766. (f) Heise, A.; Trollsås, M.; Magbitang, T.; Hedrick, J. L.; Frank, C. W.; Miller, R. D. *Macromolecules* **2001**, *34*, 2798. (g) Park, S. Y.; Han, D. K.; Kim, S. C. *Macromolecules* **2001**, *34*, 8821. (h) Korhonen, H.; Helminen, A.; Seppälä, J. V. *Polymer* **2001**, *42*, 7541. (i) Lee, S. H.; Kim, S. H.; Han, Y. K.; Kim, Y. H. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 973. (j) Dong, C. M.; Qiu, K. Y.; Gu, Z. W.; Feng, X. D. *Polymer* **2001**, *42*, 6891. (k) Dong, C. M.; Qiu, K. Y.; Gu, Z. W.; Feng, X. D. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 409.

(6) (a) Hedrick, J. L.; Trollsås, M.; Hawker, C. J.; Atthoff, B.; Claesson, H.; Heise, A.; Miller, B. D. *Macromolecules* **1998**, *31*, 8691. (b) Balogh, L.; de Leuze-Jallouli, A.; Dvornic, P.; Kunugi, Y.; Blumstein, A.; Tomalia, D. A. *Macromolecules* **1999**, *32*, 1036. (c)Würsch, A.; Möller, M.; Glauser, T.; Lim, L. G.; Voytek, S. B.; Hedrick, J. L.; Frank, C. W.; Hilborn, J. G. *Macromolecules* **2001**, *34*, 6601. (d) Hedrick, J. L.; Magbitang, T.; Connor, E. F.; Glauser, T.; Volksen, W.; Hawker, C. J.; Lee, V. Y.; Miller, R. D. *Chem. Eur. J.* **2002**, *8*, 3309, and references therein.

10.1021/cm0210694 CCC: $25.00

(ethylene glycol)-conjugated PAMAM dendrimer was demonstrated to be a biocompatible and highly efficient DNA delivery reagent.[8k]

To decrease the crystallinity and improve the biodegradability of polylactide, the synthesis of star-shaped polylactides initiated with starburst PAMAM-OH dendrimer (generation 3) was studied in a previous paper.[9] It is found that the molecular weight of star-shaped polylactides can be controlled by variation of molar ratios of monomer to initiator and polymerization time, and the star-shaped polylactides possess lower glass transition temperature, melting point, crystallinity, and maximum decomposition temperature than those of linear polylactide. To further investigate the effects of number of arms and molecular weight on thermal properties and hydrolysis degradation of star polylactides with various branching, PAMAM-OH dendrimers with different generations (Gn-OH, $n = 1-4$) as macroinitiator for the ring-opening polymerization of L-lactide were investigated, and star-shaped polylactides with a PAMAM dendrimer core and 5−32 arms were synthesized and characterized in this study.

Experimental Section

Materials. L-Lactide (Aldrich) was purified by recrystallization in dry toluene and dried in a vacuum overnight at room temperature. Starburst PAMAM-OH dendrimers (Gn-OH, $n = 3, 4$) were obtained from Aldrich and used as received. PAMAM-OH (generation 1 and 2) which has the ethylenediamine core, poly(amidoamine) interior, and ethanol surface group was prepared and purified according to the literature.[8a,10] Pentaerythritol (PTL) was purified by sublimation under reduced pressure. Stannous octoate (Sigma) was distilled under reduced pressure before use. Toluene was distilled from metallic sodium and benzophenone. All the other reagents were of analytical grade and used without further purification.

Synthesis of Hydroxyl-Terminated Star-Shaped Polylactides. The PAMAM-OH dendrimer initiator was injected into a dried glass ampule and evaporated under vacuum to remove the solvent completely. Then L-lactide and stannous octoate were added, and the ampule was purged three times with dry nitrogen and sealed under vacuum. Under rigorous stirring, the bulk polymerization was carried out at 130 °C for 24 h. After polymerization, the crude product was dissolved in chloroform and then microfiltered through a 0.45-μm-pore membrane filter. The polymer was purified by repeated reprecipitations from chloroform into methanol.

Characterization. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer in $CDCl_3$ at room temperature. The molecular weight and molecular weight distribution were measured on a Waters 150C gel permeation chromatograph equipped with microstyragel columns at 35 °C. Tetrahydrofuran (THF) was used as the eluent at a flow rate of 1.0 mL/min, and polystyrene standards were used as calibrations. The weight-average molecular weight was calculated on a DLS-700 light scattering photometer equipped with a RM-102 differential refractormeter at 25 °C. Differential scanning calorimetric analysis (DSC) was carried out on a Perkin-Elmer DSC7 series thermal analysis system with a heating rate of 10 °C/min under nitrogen atmosphere, relative to indium standards. Glass transition temperatures (T_g) were determined from the second run. For isothermal crystallization kinetics studies, the samples were sealed in aluminum pans, heated to a temperature 30 °C higher than the melting point, held at the final temperature for 5 min to erase thermal history, then quenched at 300 °C/min to the desired temperature. The exothermic curves as a function of time were then recorded. Thermogravimetric analysis (TGA) was carried out on a Perkin-Elmer thermogravimetric analyzer in the temperature range of 30−500 °C under nitrogen atmosphere. The wide-angle X-ray scattering (WAXS) was carried out on a Rigaku Dmax-2400 diffractometer (40 kV, 126 mA) at ambient temperature under atmospheric conditions, using high-intensity monochromatic Cu Kα radiation from 5 to 30° (in 2θ). The samples were melt-pressed into pellets and annealed at 80 °C for 8 h.

Hydrolysis. The solution-cast samples were prepared via a casting method. Hydrolysis of PLLA films was performed in 20 mL of phosphate buffer saline solution (pH 7.4) at 37 °C for predetermined periods of time. The buffer solution was replaced every 7 days. After hydrolysis, PLLA films were washed intensively with distilled water to remove the residual buffer solution, followed by drying under reduced pressure for one week. The molecular weight of the hydrolyzed samples was determined by GPC.

Results and Discussion

It is well-known that star-shaped polymers have different physicochemical properties compared to their linear counterparts as a consequence of their unique molecular architecture. To investigate the effects of chain lengths and number of arms on thermal properties and hydrolysis degradation, five kinds of star-shaped polylactides were synthesized, using stannous octoate as catalyst and Pentaerythritol and PAMAM-OH dendrimers (Gn-OH, $n = 1-4$, with functionality of 8, 16,

---

(7) For recent accounts and reviews on dendrimers, see the following. (a) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681. (b) Percec, V.; Ahn, C. H.; Ungar, G.; Yeardley, D. J. P.; Möller, M.; Sheiko, S. S. *Nature* **1998**, *391*, 161. (c) Matthews, O. A.; Shipway, A. N.; Stoddart, J. F. *Prog. Polym. Sci.* **1998**, *23*, 1. (d) Vögtle, F. *Top. Curr. Chem.* **1998**, *197*, 1. (e) Scherf, U. *Top. Curr. Chem.* **1999**, *201*, 163. (f) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 885. (g) Majoral, J. P.; Caminade, A. M. *Chem. Rev.* **1999**, *99*, 845. (h) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665. (i) Newkome, G. R.; He, E. F.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689. (j) Vögtle, F. *Top. Curr. Chem.* **2000**, *210*, 1. (k) Yeardley, D. J. P.; Ungar, G.; Percec, V.; Holerca, M. N.; Johansson, G. *J. Am. Chem. Soc.* **2000**, *122*, 1684. (l) Schlüter, A. D.; Rabe, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 864. (m) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991. (n) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819. (o) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74. (p) Vögtle, F. *Top. Curr. Chem.* **2001**, *212*, 1. (q) Fréchet, J. M. J.; Tomalia, D. A. *Dendrimers and Other Dendritic Polymers*; Wiley-VCH: Chichester, 2001. (r) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons - Concepts, Syntheses, and Applications*; Wiley-VCH: Weinheim, Germany, 2001. (s) Tomalia, D. A.; Brothers, H. M., II; Piehler, L. T.; Durst, H. D.; Swanson, D. R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5081. (t) Stiriba, S. E.; Frey, H.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 1329. (u) Twyman, L. J.; King, A. S. H.; Martin, I. K. *Chem. Soc. Rev.* **2002**, *31*, 69. (v) Romagnoli, B.; Hayes, W. *J. Mater. Chem.* **2002**, *12*, 767. (w) Percec, V.; Holerca, M. N.; Uchida, S.; Cho, W. D.; Ungar, G.; Lee, Y.; Yeardley, D. J. P. *Chem. Eur. J.* **2002**, *8*, 1106. (x) Percec, V.; Cho, W. D.; Ungar, G.; Yeardley, D. J. P. *Chem. Eur. J.* **2002**, *8*, 2011. (y) Wang, Q.; Dordick, J. S.; Linhardt, R. J. *Chem. Mater.* **2002**, *14*, 3232. (z) Kwok, C. C.; Wong, M. S. *Chem. Mater.* **2002**, *14*, 3158.

(8) (a) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117. (b) Haensler, J.; Szoka, F. C., Jr. *Bioconjugate Chem.* **1993**, *4*, 372. (c) Tang, M. X.; Redemann, C. T.; Szoka, F. C., Jr. *Bioconjugate Chem.* **1996**, *7*, 703. (d) Kukowska-Latallo, J. F.; Bielinska, A. U.; Johnson, J.; Spindler, R.; Tomalia, D. A.; Baker, J. R., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 4897. (e) Roberts, J. C.; Akhtar, M. K.; Zera, R. T. *J. Biomed. Mater. Res.* **1996**, *30*, 53. (f) Bielinska, A. U.; Chen, C. L.; Johnson, J.; Baker, J. R., Jr. *Bioconjugate Chem.* **1999**, *10*, 843. (g) Eichman, J. D.; Bielinska, A. U.; Kukowska-Latallo, J. F.; Baker, J. R., Jr. *Pharm. Sci. Technol. Today* **2000**, *3*, 232. (h) Higashi, N.; Koga, T.; Niwa, M. *Adv. Mater.* **2000**, *12*, 1373. (i) Sui, G.; Micic, M.; Huo, Q.; Leblanc, R. M. *Langmuir* **2000**, *16*, 7847. (j) Fail, C. A.; Evenson, S. A.; Ward, L. J.; Schofield, W. C. E.; Badyal, J. P. S. *Langmuir* **2002**, *18*, 264. (k) Luo, D.; Haverstick, K.; Belcheva, N.; Han, E.; Saltaman, W. M. *Macromolecules* **2002**, *35*, 3456.

(9) Zhao, Y. L.; Cai, Q.; Jiang, J.; Shuai, X. T.; Bei, J. Z.; Chen, C. F.; Xi, F. *Polymer* **2002**, *43*, 5819.

(10) Meltzer, A. D.; Tirrell, D. A.; Jones, A. A.; Inglefield, P. T.; Hedstrand, D. M.; Tomalia, D. A. *Macromolecules* **1992**, *25*, 4541.

Table 1. Molecular Weight and Molecular Weight Distribution of PLLAs Obtained Using Various Initiators[a]

sample	initiator	F^b	$[LA]_0:[OH]_0$	yield (%)	M_n(GPC)[c]	M_w/M_n[c]	DP[d]	n^d	M_n(NMR)[d]	M_w(SLS)[e]
1[f,g]		1		97.2	64000	1.78	1000	1	72000	148000
2	PTL	4	400	86.4	82370	1.36	320	4	112000	254000
3	G1-OH	8	100	95.4	26600	1.65	78.5	7.0	41000	112000
4	G1-OH	8	50	88.8	18700	1.72	63.0	6.2	29560	72000
5	G1-OH	8	25	80.7	9600	1.78	29.2	5.7	13420	35800
6	G2-OH	16	100	94.8	29480	1.56	67.0	13.2	66950	208000
7	G2-OH	16	50	88.5	23350	1.68	55.5	12.8	54420	172000
8	G2-OH	16	25	79.2	17500	1.81	40.1	11.8	37340	97000
9[g]	G3-OH	32	100	92.4	46250	1.75	76.1	20.0	116500	496000
10[g]	G3-OH	32	50	85.6	32960	1.80	49.5	18.0	71000	312000
11[g]	G3-OH	32	25	77.5	19540	1.85	31.6	17.6	47000	204000
12	G4-OH	64	100	89.6	58400	1.74	59.2	32.0	150700	756000
13	G4-OH	64	50	82.3	38240	1.72	38.3	29.7	96200	486000
14	G4-OH	64	25	78.0	22480	1.88	24.4	27.8	63100	325000

[a] Polymerization conditions: $[SnOct_2]/[LA] = 0.15:100$, 24 h at 130 °C. [b] *F* means the functionality of various initiators. [c] Determined by GPC analysis with polystyrene standards; THF was used as eluent. [d] Determined by ^{1}H NMR analysis, $M_n(\mathrm{NMR}) = 72 \times \mathrm{DP} \times n + \mathrm{MW(initiator)}$. [e] Determined by light scattering in THF. [f] Linear polylactide, prepared only using $SnOct_2$. [g] Part of results have been reported in the literature (ref 9).

32, and 64, respectively) as initiators, respectively. As a comparison, the linear polylactide (Sample 1) was also prepared (Table 1).

Synthesis of Polylactides with Different Numbers of Arms. Under rigorously anhydrous conditions, the bulk polymerization of L-lactide was conducted at 130 °C with stannous octoate as a catalyst in the presence of dendrimer initiators. The average chain length (DP) of poly(L-lactide)s was determined by ^{1}H NMR spectroscopy, using average signal intensity ratios of methine protons of PLLA (5.17 ppm) to the terminal methine protons (4.36 ppm). As for the star-shaped polymers initiated with dendrimers, the average number of arms (*n*) was calculated from the average signal intensity ratios of reacted methylene protons of the dendrimer (4.27 ppm) to the unreacted methylene protons (3.59 ppm), combined with the number of surface hydroxyl groups. On this basis, the molecular weight of the resulting polymers (M_n(NMR)) was obtained. From Table 1, it can be estimated that 5−8 arms were attached to the surface of G1-OH, 11−14 arms were attached to the surface of G2-OH, 16−21 arms were attached to the surface of G3-OH, and 25−32 arms were attached to the surface of G4-OH. It is obvious that not all of the hydroxyl groups in the dendrimer initiators were reacted, which can be attributed to the change in the density and distribution of hydroxyl groups on different dendrimer surfaces and steric hindrance of the attached polylactide chains.[11]

It is well-known that GPC analysis is not the method of choice to determine the molecular weight of star-shaped polymers due to their smaller hydrodynamic volume compared to linear polystyrene of the same molecular weight.[12] In this study, the molecular weights of various PLLAs were measured by GPC, ^{1}H NMR, and SLS and the results are listed in Table 1. For linear PLLA, the molecular weight determined by ^{1}H NMR and SLS was close to the GPC result. For star-shaped PLLAs, however, the number-average molecular weight values estimated by ^{1}H NMR (M_n(NMR)) and the weight-average molecular weights determined by SLS (M_w(SLS)) were obviously larger than the corresponding values obtained by GPC. Taking into account the polydispersities of the various polylactides, the molecular weights estimated by ^{1}H NMR were closer to those obtained by SLS, which suggests that the molecular weights of the star-shaped polylactides obtained by ^{1}H NMR may be much closer to the real values.

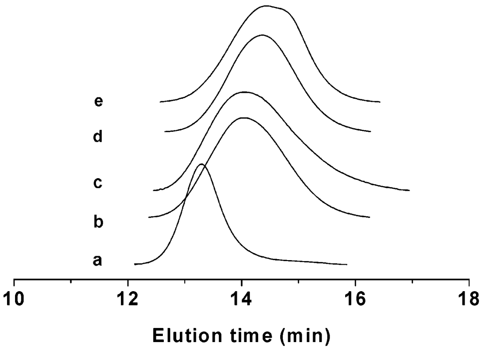

Figure 1. GPC traces of various polylactides: (a) PTL-PLLA, $M_n = 82370$, $M_w/M_n = 1.36$; (b) G4-PLLA, $M_n = 38240$, $M_w/M_n = 1.72$; (c) G3-PLLA, $M_n = 32960$, $M_w/M_n = 1.80$; (d) G2-PLLA, $M_n = 29480$, $M_w/M_n = 1.56$; (e) G1-PLLA, $M_n = 26600$, $M_w/M_n = 1.65$.

In this study, all polymers were synthesized under rigorously anhydrous conditions. As a comparison, the GPC traces of star-shaped polylactides synthesized by various initiators are shown in Figure 1. Although the polydispersities of various star polymers were relatively broad ($1.36 < M_w/M_n < 1.80$), the GPC traces were symmetrical and monomodal, suggesting that no mixture of star and linear polymers was formed.[3a] When PAMAM-OH with different generations were used as initiators, the relationship between the molecular weight and molar ratios of monomer to initiator was as outlined in Figure 2. The more hydroxyl groups present during the polymerization, the lower the molecular weight of the polymers, which indicates the role of the hydroxyl groups in dendrimer surfaces as effective propagation centers. As the molar ratios of monomer to initiator were constant, the molecular weights of star-shaped PLLAs increased with an increase in generations of dendrimer initiators. The above results demonstrate that the molecular weights of polylactides can be controlled by change of the generation of initiators and molar ratios of monomer to initiator.

---

(11) Wang, D.; Kopečková, P.; Minko, T.; Nanayakkara, V.; Kopeček, J. *Polym. Prepr.* **2000**, *41*, 994.

(12) Aoi, K.; Hatanaka, T.; Tsutsumiuchi, K.; Okada, M.; Imae, T. *Macromol. Rapid Commun.* **1999**, *20*, 378.

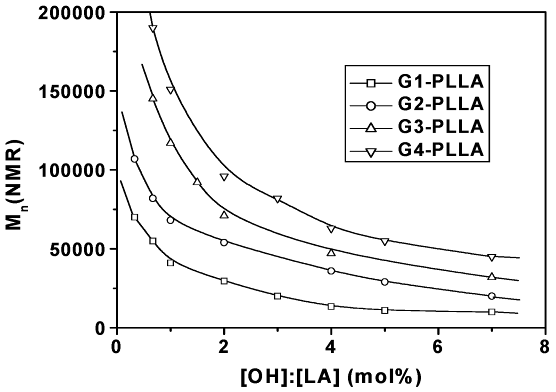

Figure 2. Effects of molar ratios of OH to monomer on molecular weight of various star-shaped polylactides. Polymerization conditions: [LA]:[$SnOct_2$] = 100:0.15, 130 °C, 24 h.

Table 2. Thermal Properties of Various Polylactides Determined by DSC and TGA

sample	n	T_g (°C)	T_m (°C)	$\Delta H_m - \Delta H_c$ (J/g)	X_c (%)	$T_{10\%}$ (°C)	T_{max} (°C)
1[a]	1	59.6	176.6	38.5	41.1	286.1	307.3
2	4	59.0	166.2	36.3	38.8	271.5	296.0
3	7.0	57.3	158.0	34.2	36.5	266.0	294.6
4	6.2	54.2	140.5	31.4	33.6	264.2	294.0
5	5.7	51.8	133.3	27.7	29.6	260.4	292.1
6	13.2	57.5	153.8	31.8	34.0	262.4	291.7
7	12.8	55.0	146.2	29.6	31.6	260.8	290.5
8	11.8	52.4	140.8	27.0	28.8	259.3	288.4
9[a]	20.0	56.9	126.0, 135.2	27.9	29.8	259.2	288.9
10[a]	18.0	54.7	122.4, 129.5	23.1	24.7	258.8	287.2
11[a]	17.6	50.8	111.5, 119.2	19.2	20.5	256.7	285.4
12	32.0	56.5	117.8, 127.0	25.4	27.1	255.4	284.5
13	29.7	53.3	110.7, 120.9	20.8	22.2	252.1	281.7
14	27.8	51.6	105.1, 116.4	19.0	20.3	250.8	278.1

[a] Part of results have been reported in the literature (ref 9).

Thermal Properties of Star-Shaped Polylactides. DSC and TGA analyses were used to determine the thermal properties of the various polylactides, and the results are listed in Table 2. From Table 2, the expected decreases in the glass transition temperatures (T_g), melting points (T_m), and degree of crystallinity (X_c) can be observed. The T_m value of PTL-PLLA (Sample 2) was determined to be 166.2 °C, the T_m values of G1-PLLA and G2-PLLA were obtained in the range of 140−160 °C, and the T_m values of G3-PLLA and G4-PLLA were obtained in the range of 100−140 °C. The melting point gradually shifted to lower temperatures as the number of arms increased, which is attributed to the crystalline imperfections due to increased free end groups and branching points in the more branched polymers.[13]

For polylactides with different numbers of arms, the DSC curves of native, melted, and annealed polylactide samples are shown in Figure 3. These curves indicate the presence of a few characteristic transitions such as glass transition, cold crystallization, and melting, which are typical for semicrystalline polylactide samples. For the star-shaped polylactides initiated with G3-OH and G4-OH, however, the cooling crystallization and melting peak in the second heating run cannot be observed, which can be attributed to the relatively slow crystallization rate. With increasing number of arms, the resulting polymers possess a similar globular structure. The existence of a globular structure will decrease the intermolecular interactions and restrict the macromolecular conformations, which considerably refine the crystallization behavior of polymers.

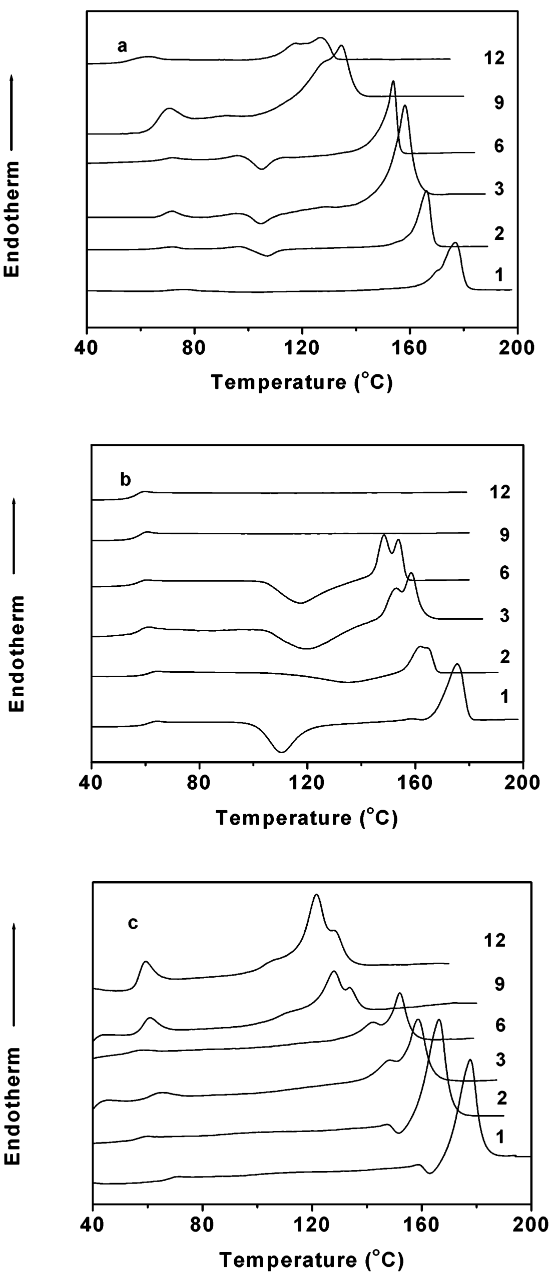

Figure 3. Comparison of DSC traces of native (a), melted (b), and annealed (c) polylactides. Numbers beside the curves indicate the samples as shown in Table 1.

From Figure 3, it is found that the melting peak broadened as the branching increased. This phenomenon was also observed by Kim et al. in the DSC curves of star-shaped poly(ether-ester) block copolymers,[13] which is ascribed to the branching effect. With increasing branches, more defects in the star-shaped PLLA will decrease the interchain cooperativity, resulting in broadening of the melting range. Moreover, it is also noted that there were always two melting signals in DSC curves of star-shaped polymers initiated with dendrimer initiators, which are derived from the crystallinities of different size and different degree of crystalline perfection.[9,14]

---

(13) Choi, Y. K.; Bae, Y. H.; Kim, S. W. *Macromolecules* **1998**, *31*, 8766.

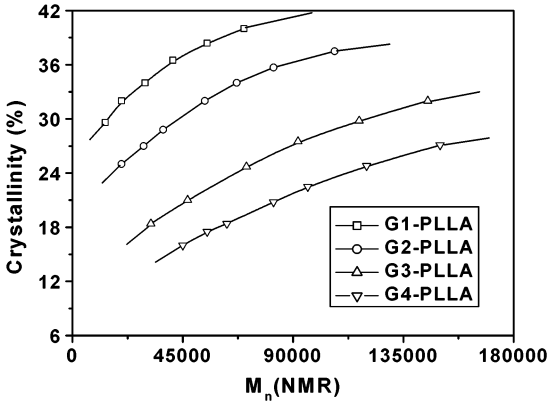

Figure 4. Effects of molecular weight on degree of crystallinity of star-shaped polylactides initiated with different hydroxyl-terminated dendrimers.

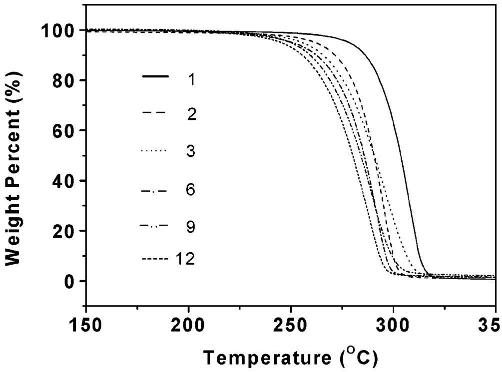

Figure 5. TGA thermograms of various polylactides. Numbers beside the curves indicate the samples as shown in Table 1.

Degree of crystallinity (X_c) of polylactides was determined from DSC measurements by the equation $X_c = (\Delta H_m - \Delta H_c)/\Delta H_m^0$, with the aid of the enthalpy of fusion of 93.6 J/g for the perfectly crystalline PLLA.[15] From Table 2, it is found that the degree of crystallinity tends to decrease with an increase in degree of branching, which can be attributed to the restricted conformation. The dependence of the crystallinity of star-shaped PLLAs on molecular weight is presented in Figure 4. It can be seen that the degree of crystallinity of star-shaped polylactides initiated with the same initiator increases with increasing molecular weight. For polylactides with the same molecular weight and different branches, however, the degree of crystallinity decreases with increasing of number of arms. The result suggests that the crystallinity of PLLAs can be controlled by variation of the molecular weight and number of arms.

Meanwhile, the thermal stability of PLLAs was also investigated. From TGA thermograms (Figure 5), it is found that all the PLLAs start to decompose at about 210 °C, but the maximum decomposition temperatures (T_{max}) of various PLLAs are different from each other. As a comparison, the temperature of 10% weight loss ($T_{10\%}$) and the maximum decomposition temperature are listed in Table 2. The results indicate that the thermal stability of polylactides slightly decreases with increasing number of arms. For instance, the values of $T_{10\%}$ and T_{max} of 7-arm polylactide (Sample 3) are 266.0 and 294.6 °C, whereas the corresponding values of 32-arm polylactide (Sample 12) are 255.4 and 284.5 °C, respectively. The relatively poor thermal stability can be ascribed to the thermally unstable nature of hydroxyl-terminated polylactides.[16]

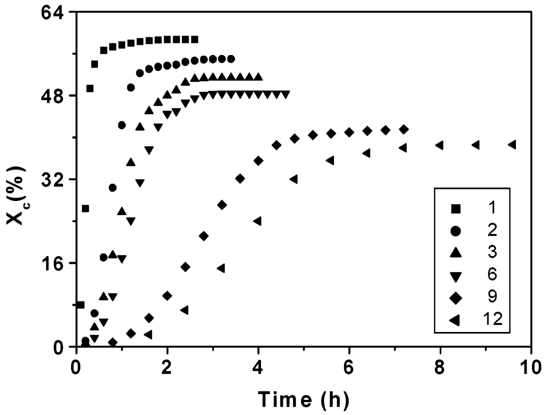

Figure 6. Effects of annealing time on crystallinity of polylactides. Numbers beside the curves indicate the samples as shown in Table 1.

Effects of Annealing on Crystallinity. Gaining control over crystallinity has attracted much attention, as the mechanical properties and degradation rates of biodegradable polymers strongly depend on their morphology or crystallinity as well as their chemical structures. For polylactide, the crystallinity is relative to many factors such as thermal history (e.g., annealing), molecular weight, copolymerization, orientation, blending, and stereosequence (e.g., S-length distribution).[1b,17] Among them, annealing of polylactide at temperatures above T_g is considered to be a promising way to achieve control over the degree of crystallinity.[14d,18] In this study, effects of annealing at 80 °C on crystallinity were investigated.

To investigate the influence of annealing time on crystallinity, several typical samples with different numbers of arms were annealed at 80 °C for various times. From curves of crystallinity vs annealing time (Figure 6), it is found that various PLLAs exhibit different crystallization behaviors. The crystallization rate decreases as the branching increases, and the crystallinity of polylactides increases with increasing annealing times. It is worth noting that for PLLAs with fewer numbers of arms, the degree of crystallinity can be controlled over a broader range. For instance, for Sample 12 with 32 arms (G4-PLLA) the proper adjustment of annealing time allowed obtention of polymers with X_c in the range from 0 to 38.4%, whereas for Sample 2 with 4 arms (PTL-PLLA) values of X_c could be regulated in the range from 0 to 54.0%. As the number of arms increased, the increased disturbance

---

(14) (a) Cohn, D.; Younes, H.; Marom, G. *Polymer* **1987**, *28*, 2018. (b) Migliaresi, C.; De Lollis, A.; Fambri, L.; Cohn, D. *Clin. Mater.* **1991**, *8*, 111. (c) Hoogsteen, W.; Postema, A. R.; Pennings, A. J.; ten Brinke, G.; Zugenmaier, P. *Macromolecules* **1990**, *23*, 634. (d) Sosnowski, S. *Polymer* **2001**, *42*, 637.

(15) Fischer, E. W.; Sterzel, H. J.; Wegner, G. K.-Z. u Z. *Polymere* **1973**, *251*, 980.

(16) Jamshidi, K.; Hyon, S. H.; Ikada, Y. *Polymer* **1988**, *29*, 2229.

(17) Thakur, K. A. M.; Kean, R. T.; Zupfer, J. M.; Buehler, N. U. *Macromolecules* **1996**, *29*, 8844.

(18) (a) Tsuji, H.; Ikada, Y. *Polymer* **1995**, *36*, 2709. (b) Cai, H.; Dave, V.; Gross, R. A.; McCarthy, S. P. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 2701.

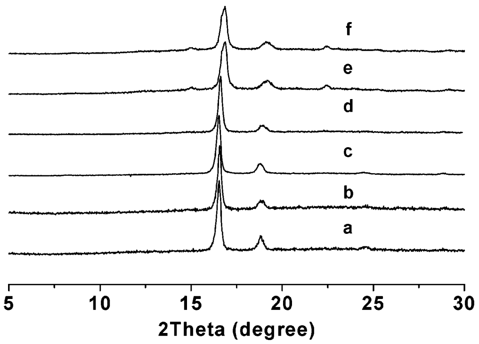

Figure 7. Plots of WAXS profiles vs scattering angle (2θ) for various PLLAs. (a) linear PLLA; (b) PTL-PLLA; (c) G1-PLLA; (d) G2-PLLA; (e) G3-PLLA; (f) G4-PLLA.

in order due to a larger number of end groups and branching results in less intermolecular interaction, which will lead to decreasing of the enthalpy of fusion.[13] Hence, the range of crystallinity varied with the number of arms of star-shaped polymers.

Wide-Angle X-ray Scattering Analysis. It is reported that there are two crystalline forms: α form (10_3-helix) and β form (3_1-helix) in crystallized PLLA.[14c,19] In general, the pure polylactides predominantly form an α crystalline form, whereas the β crystalline is formed only in stress-induced crystallinity. In this study, the WAXS measurements were used to investigate the crystal structures of various polylactides. After the specimen was quenched from 200 °C and annealed at 80 °C for 8 h, the WAXS profiles were as exhibited in Figure 7. From Figure 7, only the α crystalline form is found to exist in linear and star-shaped PLLAs, which suggests that the samples with different numbers of arms have almost the same crystal structure. Meanwhile, it is noted that the distinct diffraction located at $2\theta = 15.0°$ and 22.5° was observed in G3-PLLA and G4-PLLA, which suggests that increasing order of packing of PLLA chains may exist in crystalline domains of star-shaped PLLAs when the number of arms increases to some extent.

In addition to DSC, FTIR, and solid-state NMR techniques,[14d,17,20] WAXS is an effective approach to investigate the crystallinity of PLLA.[1f,21] From the results presented in Figure 7, the degree of crystallinity can be obtained by the peak separation of crystalline and amorphous areas. As shown in Table 3, the crystallinity results obtained by WAXS are in good agreement with DSC results. The smaller crystallinity obtained from WAXS compared with DSC results is because only appropriate crystal size and perfect crystalline region contribute to the crystalline peaks in WAXS.[1f]

Isothermal Crystallization Behavior of Various Polylactides. The isothermal crystallization of various polylactides was investigated in a wide range of temperatures, and the Avrami equation[22] was used to analyze the isothermal crystallization process. When the temperature was 90 °C (a) and 110 °C (b), the plots of $\ln(-\ln(1 - X_c(t)))$ vs $\ln t$ were as shown in Figure 8. Each curve exhibits a good linear relationship, suggesting that the isothermal crystallization kinetics is in good agreement with the Avrami equation, and the secondary crystallization is not obvious. The values of n and K determined from the line in Figure 8 are listed in Table 4. The Avrami exponent n varied in the range of 2.5 and 3.0, which means that the crystallization mode is of three-dimensional growth with a heterogeneous nucleation.

Table 3. Crystallinity and Interplanar Spacing (d) of Polylactides

sample	X_c(DSC) (%)[a]	X_c(WAXS) (%)[b]	interplanar spacing (Å)[b]
1	58.5	57.6	5.35, 4.71, 3.62
2	53.8	52.2	5.35, 4.69, 3.63
3	51.2	48.4	5.36, 4.72, 3.63
6	48.0	45.2	5.33, 4.68, 3.63
9	41.2	39.6	5.90, 5.25, 4.61, 3.95, 3.62
12	38.4	37.2	5.91, 5.26, 4.63, 3.96, 3.66

[a] Determined by DSC. [b] Calculated from WAXS.

Table 4. Isothermal Crystallization Parameters of Polylactides

sample	T_c (°C)	$t_{1/2}$ (min)	n	K (min^{-n})
1	90	3.86	2.90	0.0138
2	90	6.86	2.71	0.00375
3	90	5.06	2.50	0.0120
6	90	12.62	2.60	0.00095
9	90	7.43	2.80	0.00252
12	90	14.52	2.92	0.00028
1	110	1.47	2.86	0.230
2	110	3.05	2.69	0.0345
3	110	2.74	2.54	0.0536
6	110	7.36	2.66	0.00343

It is well-known that the crystallization rate can be described by the reciprocal of the crystallization half-time, $t_{1/2}$. As a comparison, the curves of $1/t_{1/2}$ versus crystallization temperature are shown in Figure 9. As the number of arms increased, the range of crystallization temperature obviously decreased, which can be ascribed to the relatively low melting point of higher branching polylactides. From Figure 9, it is also found the maximum crystallization temperature of different polylactides decreased with increasing number of arms. This may be attributed to the stronger restriction to polymer chain in higher branching polymer resulting from the "pseudo-cross-linking" effect in polymer structure.

Hydrolysis. The possible factors contributing to accelerated degradation are the crystallinity, the nature of the end group and the dendritic core, and the number of terminal groups.[5i,23] In this study, the hydrolysis degradation of PLLAs with different numbers of arms was investigated.

The hydrolysis behavior of the star-shaped polylactides was investigated in phosphate buffer saline solution (pH 7.4) at 37 °C and compared with that of linear PLLA. The relationships between weight loss, molecular weight reduction, and hydrolysis time are shown in Figures 10 and 11. As can be seen, the hydrolysis behavior of PLLAs was greatly improved by grafting

---

(19) (a) Eling, B.; Gogolewski, S.; Pennings, A. J. *Polymer* **1982**, *23*, 1587. (b) Kobayashi, J.; Asahi, T.; Ichiki, M.; Okikawa, A.; Suzuki, H.; Watanabe, T.; Fukada, E.; Shikinami, Y. *J. Appl. Phys.* **1995**, *77*, 2957. (c) Brizzolara, D.; Cantow, H. J.; Diederichs, K.; Keller, E.; Domb, A. J. *Macromolecules* **1996**, *29*, 191.

(20) Fujiwara, T.; Miyamoto, M.; Kimura, Y.; Sakurai, S. *Polymer* **2001**, *42*, 1515.

(21) Miyata, T.; Masuko, T. *Polymer* **1998**, *39*, 5515.

(22) (a) Avrami, M. *J. Chem. Phys.* **1939**, *7*, 1103. (b) Avrami, M. *J. Chem. Phys.* **1940**, *8*, 212.

(23) Shih, C. *J. Controlled Release* **1995**, *34*, 9.

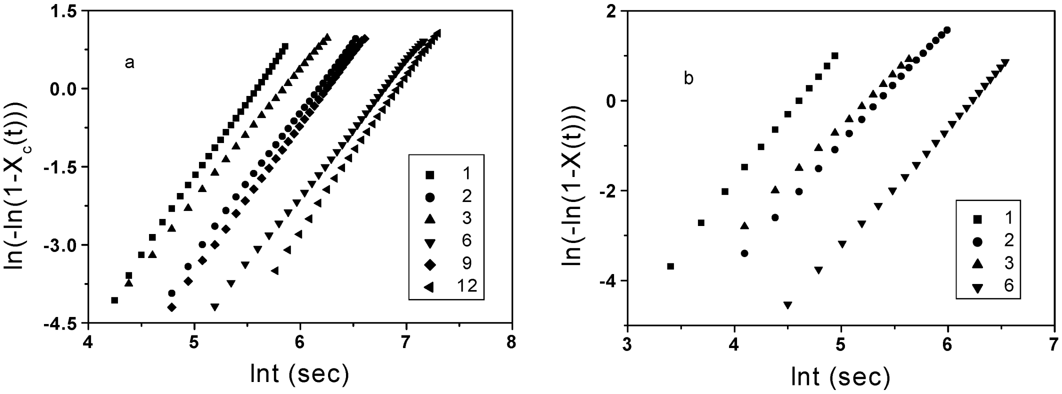

Figure 8. Isothermal crystallization kinetics curves of PLLAs in 90 °C (a) and 110 °C (b). Numbers beside the curves indicate the samples as shown in Table 1.

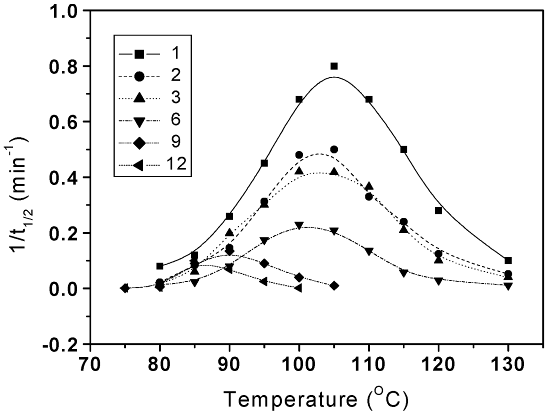

Figure 9. Effect of temperature on crystallization rate of PLLAs. Numbers beside the curves indicate the samples as shown in Table 1.

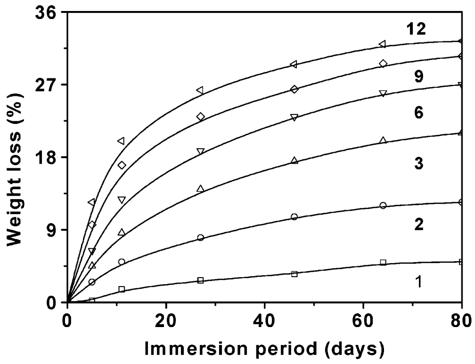

Figure 10. Weight loss after the hydrolytic degradation of various polylactides. Numbers beside the curves indicate the samples as shown in Table 1.

onto multifunctional hydrophilic dendrimers, and these characteristics are strongly dependent on the number of arms. It is obvious that the degradation rates of the star-shaped PLLAs were significantly larger than that of linear PLLA. For example, after immersion in phosphate buffer saline solution for 64 days, the weight loss of linear polylactide was 4.8%, and the remaining molecular weight was 92.4%. However, for the star-shaped polylactides with 4−32 arms, the weight loss varied from 12% to 32%, and the residual molecular weight changed from 85.2% to 50.4%, respectively. From Figure 10, the star-shaped PLLAs with more hydroxyl end groups show a faster degradation rate, which is correspondent to the result reported by Li et al. [24]

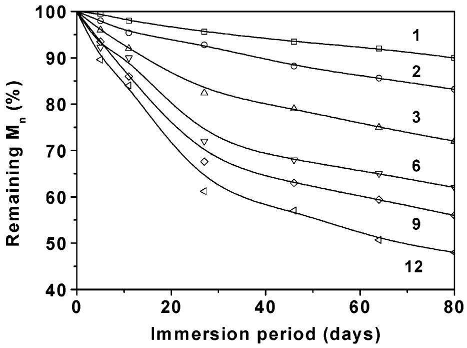

Figure 11. Remaining molecular weight after the hydrolytic degradation of various polylactides. Numbers beside the curves indicate the samples as shown in Table 1.

In addition to the number of arms, the crystal behavior also plays an important role in PLLA degradation.[5i] The major factors for crystal behavior are crystal structure, crystallinity, and crystal size. From Figure 10, it is also found that the degradation rate of PLLAs increased with decrease in the degree of crystallinity. As previously described, PLLAs with different branches, crystallinities, and crystal sizes have almost the same crystal structure. Then the distinction of degradation behavior for star-shaped PLLAs primarily derives from the different crystallinity.

It is worth noting that the stability of the dendritic core may have an obvious effect on the degradation behavior of dendrimer-like star polymers. However, the PAMAM dendrimer core used in this study was relatively stable. For instance, when PAMAM-OH (generation 4) was immersed into the solution for 27 days, the weight loss of the dendrimer initiator determined by dialysis was less than 4%, which was much lower than that of Sample 12 (26.3% of weight loss under similar conditions). Hence, the various hydrolysis behaviors of star-shaped polylactides primarily lie in the decreased crystallinity derived from the branching nature of polylactide materials.

By variation of the generation of dendrimer initiators and molar ratios of monomer to initiator, PLLAs with lower crystallinity and more branching can be prepared. Thus, the hydrolysis behavior of star-shaped PLLAs can be regulated in a wide range by manipulation of crystallinity and number of arms.

---

(24) Li, Y.; Nothnagel, J.; Kissel, T. *Polymer* **1997**, *38*, 6197.

Conclusions

Novel star-shaped polymers that consist of poly(L-lactide) (PLLA) arms and a starburst PAMAM dendrimer core were prepared by ring-opening polymerization of L-lactide in the presence of PAMAM-OH dendrimers (generation 1−4) and a catalytic amount of stannous octoate. The molecular weights of star-shaped polylactides can be controlled by changes of generations of dendrimer initiators and molar ratios of monomer to initiator. Effects of molecular weight and number of arms on the thermal properties and hydrolysis degradation of star-shaped polymers were investigated. The thermal properties showed the branching effect on polymer structure. The melting point, crystallinity, crysrallization rate, and maximum decomposition temperature decreased as the number of arms increased. As compared with linear polylactide, star-shaped PLLAs exhibited a faster hydrolysis rate due to lower crystallinity and increased branching.

Acknowledgment. The financial support to this work by the National Natural Science Foundation of China (Grants 50073026 and 50273042) is gratefully acknowledged.

CM0210694