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Citation for published version:

Perry, MR & Shaver, MP 2011, 'Flexible and rigid core molecules in the synthesis of poly(lactic acid) star polymers', *Canadian Journal of Chemistry*, vol. 89, no. 4, pp. 499-505. <https://doi.org/10.1139/V11-002>

Digital Object Identifier (DOI):

[10.1139/V11-002](https://doi.org/10.1139/V11-002)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Canadian Journal of Chemistry

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Published article available at: <http://dx.doi.org/10.1139/V11-002>

Cite as:

Perry, M. R., & Shaver, M. P. (2011). Flexible and rigid core molecules in the synthesis of poly(lactic acid) star polymers. *Canadian Journal of Chemistry – Revue Canadienne De Chimie*, 89(4), 499-505.

Manuscript received: 19/10/2010; Accepted: 06/12/2010; Article published: 19/03/2011

Flexible and rigid core molecules in the synthesis of poly(lactic acid) star polymers**

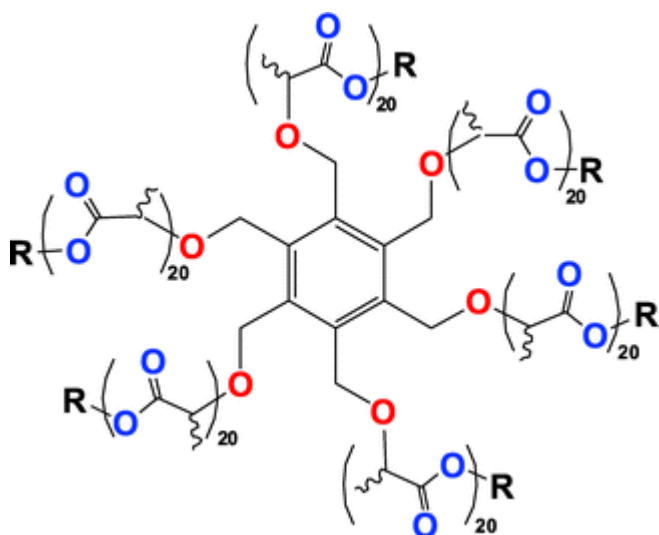
Mitchell R. Perry¹ and Michael P. Shaver¹

^[1]Department of Chemistry, University of Prince Edward Island, 550 University Avenue, Charlottetown, PE C1A 4P3, Canada.

^[*]Corresponding author; (current address): Michael.Shaver@ed.ac.uk, EaStCHEM, School of Chemistry, Joseph Black Building, University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK.

^[**]We thank the Natural Sciences and Engineering Research Council of Canada and the University of Prince Edward Island for financial support, the Canada Foundation for Innovation and the Atlantic Canada Opportunities Agency for infrastructure and Dr. Rabin Bissessur, UPEI, for access to TGA and DSC instrumentation.

Graphical abstract:



Keywords:

Polymer star; lactide; poly(lactic acid); ring opening polymerization

Abstract

This study presents the synthesis and physical characterization of a series of structurally well-defined star-shaped poly(lactic acids). Polymer stars are prepared from a series of multifunctional alcohol cores including flexible polyols pentaerythritol and dipentaerythritol (four-armed and six-armed cores, respectively) and rigid substituted arenes tri(hydroxymethyl)benzene and hexa(hydroxymethyl)benzene. Utilizing a tin(II) octanoate catalyst, arms of 10 monomer units long are built from *rac*-lactide and L-lactide to form atactic and isotactic star polymers. Polymers were subsequently characterized by means of NMR spectroscopy, gel permeation chromatography, differential scanning calorimetry, and thermogravimetric analysis. Our results support previous work that suggests that the length of the individual arms, not the total molecular weight, correlates to physical characteristics including glass, melt, crystallization, and decomposition temperatures. In addition, differences between core molecules suggest that the chemical nature of the core can significantly alter the physical properties of the star polymer. Trends in crystallization and glass transition temperatures relative to the core used merit further study and correlate closest to the molecular weight and the number of arms emanating from the star core. It is also clear that the rigidity provided by aromatic cores has a significant effect on the melting temperatures of these macromolecules.

Introduction

Poly(lactic acid), PLA, has become an essential green material as it is derived from renewable feedstocks, is biodegradable and bioassimilable, and has found many niche applications across a broad sweep of commercial fields.^[1] Of particular interest is the role these and other aliphatic polyesters have to play in the biomedical industry.^[2] While linear PLA homo- and co-polymers have been used in sutures and stents since 1960,^[3] the physical properties of the macromolecules can be refined by incorporating PLA into more complex macrostructures like polymer stars^[4] and brushes.^[5] In particular, PLA polymer stars have found utility as matrices for controlled-release drug delivery and other biomedical applications.^[6]

The core-first approach dominates star polymer synthesis for PLA, where a multifunctional initiator promotes the ring-opening polymerization of the lactide monomer from alcohol or amine functionalities. When catalyzed by tin(II) octanoate, Sn(Oct)₂, the reaction transforms *rac*- or L-lactide into atactic PLA, a-PLA, and isotactic PLA, L-PLA, stars respectively. Previous studies have focused on the role of molecular weight^[7] or polymer tacticity^[8] in shaping polymer properties while others have examined the incorporation of PLA stars into miktoarm^[9-11] and dendritic frameworks^[12-14] or examined the application of these materials in self assembly and drug delivery.^[15,16] The initiator is also a key differentiator between polymer stars. A diverse array of simple multifunctional polyols have been used as initiators for PLA polymer stars including 3-armed stars prepared from trimethylolpropane and glycerol, 4-armed stars from pentaerythritol, ditrimethylolpropane and erythritol, 5-armed stars from xylitol, 6-armed stars from dipentaerythritol, inositol and sorbitol and 8-

armed stars from tripentaerythritol. Less clear is the effect of these cores on polymer star synthesis or properties, but some key trends have been observed. The macromolecular structure dependence of thermal properties were investigated for 3- to 6-armed L-PLA stars.^[17] Increasing molecular weights of 6-armed sorbitol polymers correlated to concomitant increases in thermal decomposition, T_d , and melting, T_m , temperatures, a trend exacerbated by the different reactivities between primary and secondary alcohol functionalities in the sorbitol core. For polymer stars with similar theoretical absolute molecular weights, $M_{n,th}$, structures with fewer arms exhibited higher T_m values suggesting that physical properties correlate with the length of the polymer arm emanating from the star core rather than the absolute molecular weight of the star.^[17]

There is a surprising lack of chemical diversity in the choice of simple, discrete initiators for this ring opening polymerization due to an expected focus on flexible sugar alcohols. Cores with more rigidity include β -cyclodextrins,^[18] modified perylenes,^[19] hexahydroxytriphenylene^[20] and dibenzoylmethane and bipyridine ligated metal complexes.^[21] While these cores impart photochemical, spectroscopic and supramolecular properties to the stars, no correlation between core structure and properties has been made.

In this vein we endeavoured to develop synthetic methodologies to prepare three, four and six armed star polymers of *rac*- and L-lactide with variable core structures with a focus on simple, rigid cores. Specifically we targeted PLA stars built from 1,3,5-tri(hydroxymethyl)benzene (THMB, **1**), hexa(hydroxymethyl)benzene (HHMB, **2**), pentaerythritol (PE, **3**) and dipentaerythritol (DPE, **4**) (Figure 1) and characterized the star polymers with gel permeation chromatography (GPC), ^1H NMR spectroscopy, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).

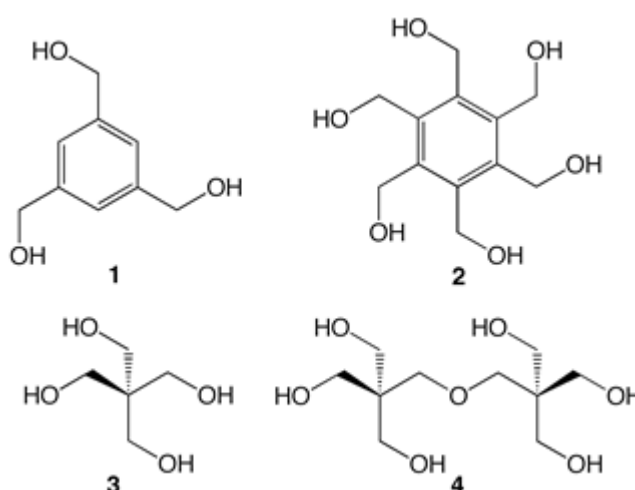


Figure 1. Core molecules for poly(lactic acid) star polymers.

Experimental

Materials. HPLC-grade toluene, THF, methanol and dichloromethane were purchased from Fisher Scientific while deuterated solvents were purchased from Cambridge Isotopes. Anhydrous toluene was obtained by passing the solvent through an Innovative Technologies solvent purification system consisting of columns of alumina and a copper catalyst. Anhydrous solvents were tested with addition of a toluene solution of sodium benzophenone ketyl prior to use. Tin(II) octanoate, $\text{Sn}(\text{Oct})_2$, was purchased from Aldrich Chemical Co. and distilled prior to use. Dipentaerythritol and pentaerythritol were purchased from Aldrich Chemical Co. and purified by recrystallization from methanol and vacuum sublimation three times, respectively before being dried *in vacuo* for 48 h prior to use. 1,4-dioxane was dried over CaH_2 and distilled prior to use. Benzene-1,3,5-tricarboxylic acid, 98% was purchased from Aldrich Chemical Co. and used as received. The monomers *rac*- and L-lactide were purchased from PURAC Biomaterials and purified by three successive vacuum sublimations of the material prior to use.

General Considerations. All experiments involving moisture and air sensitive compounds and catalysts were performed under a nitrogen atmosphere using an MBraun LABmaster sp glovebox system equipped with a -35°C freezer and $[\text{H}_2\text{O}]$ and $[\text{O}_2]$ analyzers. Gel permeation chromatography (GPC) was carried out in THF (flow rate: 1 mL min⁻¹) at 50°C with a Polymer Labs PL-GPC 50 Plus integrated GPC system using three 300×7.5 mm Resipore columns. Polystyrene standards were used for calibration and corrected for PLA.^[22] ¹H-NMR spectra were recorded with a Bruker Avance Spectrometer (300 MHz) in CDCl_3 or D_2O . Thermogravimetric analysis (TGA) was performed on a TA instruments TGA Q500 under an inert nitrogen atmosphere with a flow rate of 60 mL min⁻¹ and a heating rate of 10°C min⁻¹. Differential scanning calorimetry (DSC) was performed on a TA instruments DSC Q100 using a heating rate of 5°C min⁻¹ and a flow rate of 50 mL min⁻¹. Guelph Analytical Laboratories conducted CHN elemental analyses.

Core Syntheses. *1,3,5-tri(hydroxymethyl)benzene*: This procedure was modified from an existing literature procedure.^[23] In a glovebox, lithium aluminum hydride (2.505 g, 6.60 mmol) was added to a 250 mL round bottom Schlenk flask and suspended in 10 mL anhydrous THF. The vessel was sealed and removed from the glovebox. Trimethyl 1,3,5-benzene-tricarboxylate (5.002 g, 1.98 mmol) was dissolved in 50 mL anhydrous THF in a 250 mL Schlenk tube. The carboxylate solution was added via cannula dropwise to the LiAlH_4 and the dark grey lithium suspension turned to a deep orange colour which quickly dissipated. Upon completion of the carboxylate addition, the mixture was a deep green colour. The mixture was allowed to reflux for five hours after which the vessel was cooled in an ice-water bath and stirred. Three solutions: 5 mL H_2O , 5 mL 15%(w/w) NaOH in H_2O , and 15 mL H_2O , were sequentially added in a dropwise fashion to quench any remaining LiAlH_4 and hydrolyze the Al salts. Filtration and washing with three 20 mL portions of THF provided a colourless filtrate. Organics were removed under reduced pressure, yielding a colourless, crude oil in 92% yield. Purification of this material by recrystallization from ethyl acetate and column chromatography gave an analytically pure white powder collected (0.934 g, 0.56 mol, 28.2%). Improved yields are obtained by

forgoing recrystallization and purifying the material by silica gel column chromatography. ^1H NMR data (300 MHz, MeOD, 298 K): δ 7.25 (s, 3H, ArH), 4.60 (s, 6H, ArCH₂). ^{13}C NMR data (75 MHz, MeOD, 298 K): δ 141.41 (s, Ar-CH₂), 126.00 (s, Ar-H), 64.04 (s, CH₂). EA data: C 65.41%, H 7.22%, N 0.00%. Expected: C 65.27%, H 7.19%, N 0.00%.

Hexa(hydroxymethyl)benzene: This synthesis was modified from an existing literature procedure.^[24] In a glovebox, 2-butyne-1,4-diol (6.008 g, 6.98 mmol) was dissolved using 50 mL anhydrous dioxane in a 250 mL round bottom flask. Cyclopentadienylcobalt dicarbonyl (2.06 g, 1.05 mmol) was added, along with 50 mL dioxane, to a 250 mL round bottom flask. The cobalt mixture was transferred to a 500 mL Strauss flask, to which the alkyne solution was added in a dropwise fashion. The vessel was sealed and removed from the glovebox where it was left to react in a 130 °C oil bath for four days. The formation of an orange precipitate was evident after one day. After the allotted reaction time, the mixture was filtered using a fine glass filter frit, the solid was collected, washed three times using 25 mL THF and dried *in vacuo* (3.73 g, 1.44 mmol, 62.0%). ^1H NMR data (300 MHz, *d*₆-DMSO, 298 K) δ 4.86 (s, 6H, ArCH₂), 4.69 (s, 12H, OH). ^{13}C NMR data (75 MHz, *d*₆-DMSO, 298 K): δ 138.79 (s, Ar), 56.75 (s, CH₂). EA data: C 56.06%, H 6.88%, N 0.00%. Expected: C 55.81%, H 7.02%, N 0.00%.

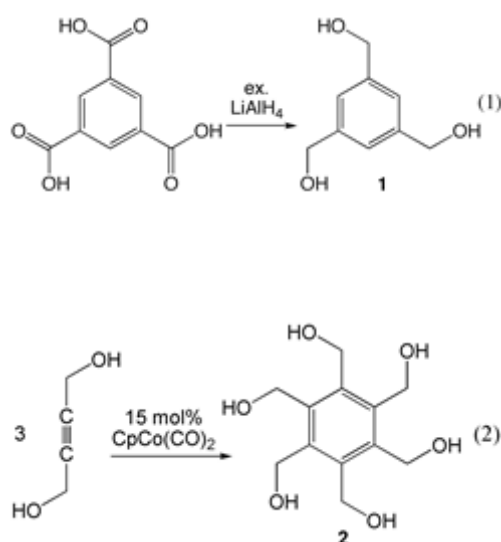
Polymerization Experiments. Polymerization procedures were modified from previously reported protocols.^[25] All polymerization reactions were performed in sealed 25 mL round bottom ampoules under an inert atmosphere, at 125 °C, with a molar ratio of monomer:alcohol functionality:catalyst of 10:1:0.04. The catalyst employed in each instance was Sn(Oct)₂. Monomers employed included *rac*-lactide and L-lactide and core initiators **1-4**. Experiments were also conducted with a benzyl alcohol initiator to prepare a standard material for comparative purposes. The reaction proceeded for approximately 8 hours and was then quenched with 10 mL of a 9:1 v/v solution of CH₂Cl₂/MeOH for 30 min at room temperature. The resulting mixture was precipitated from cold methanol, collected via filtration, washed with 50 mL H₂O and 50 mL MeOH, and dried *in vacuo* prior to analysis.

For example, *rac*-lactide (0.545 g, 3.86 mmol) and hexa(hydroxymethyl)benzene (0.0162 g, 6.83 mmol) were added to a dry 25 mL round bottom ampoule equipped with a magnetic stirring bar. The ampoule was connected to a Schlenk line, sealed and evacuated for ten minutes before being filled with N₂. This evacuation/refill procedure was repeated three times. 2.1 mL of 7.33 mM (6.24 mg, 0.0154 mmol) Sn(Oct)₂ solution in toluene was syringed into the vessel which was then sealed and put under vacuum to remove the toluene. The ampoule was then placed into a preheated oil bath at 125 °C for eight hours. After the allotted time, the vessel was cooled to room temperature, opened to the atmosphere and quenched with 10 mL of a 10:1 v/v solution of CH₂Cl₂ and methanol. The solution was stirred for 30 minutes and then added dropwise to 100 mL of cold methanol to precipitate the polymer. The resultant white polymer was collected via filtration, washed with 50 mL MeOH and 50 mL H₂O, and dried *in vacuo* for 12 hours. Monomer conversion was determined gravimetrically to be 89.7% (0.5033 g).

Results and Discussion

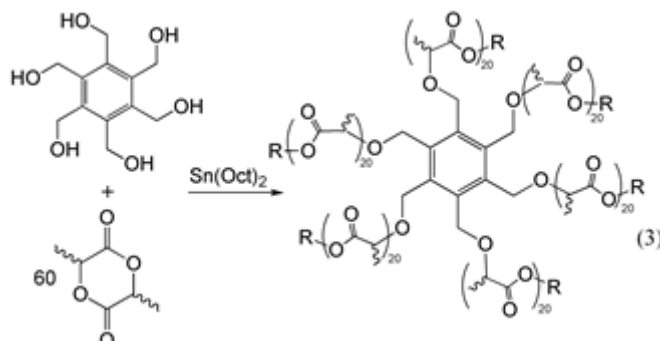
Core and Polymer Synthesis

While PE and DPE are commercially available polyols, the rigid THMB and HHMB cores had to be synthesized. The reduction of 1,3,5-benzene-tricarboxylate with excess lithium aluminum hydride provided the crude desired aromatic **1** in high yields. Purification substantially lowered yields, but enough product was isolated from this effort that optimization of this step was not pursued. For the hexasubstituted core initiator, the $\text{CpCo}(\text{CO})_2$ catalyzed cyclotrimerization of 2-butyne-1,4-diol afforded **2** in moderate yields. Attempts to synthesize **1** via a cobaltcatalyzed cyclotrimerization of 1-propyn-3-ol were unsuccessful, accessing a mixture of aromatic isomers with various substitution patterns arising from head-to-tail additions and an insoluble polymeric material resulting from thermal polymerization of the propargyl alcohol. These reactions are shown in Equations 1 and 2 respectively.



PLA stars with ten monomer units per alcohol functionality were synthesized. Oligomeric arm lengths were chosen because their low overall molecular weights accentuate the structural differences.^[4] A molar ratio corresponding to 0.04 $\text{Sn}(\text{Oct})_2$ units and 10 lactide monomer units per alcohol functionality was used (ie. 0.25:1:60 using one DPE molecule). Higher catalyst loadings, up to the one catalyst unit per growing arm expected for living ring opening polymerizations, gave consistent bimodal product distributions. This suggests self-initiation behavior by the $\text{Sn}(\text{Oct})_2$ or a reaction impurity while also increasing the propensity for transesterification reactions leading to reduced molecular weights for long reaction times. Additionally, the efficacy of low catalyst loadings suggests some immortal behavior for the tin catalyst under these reaction

conditions.^[26] As an example, the synthesis of the resultant star polymer for an HHMB core is shown in Equation 3.



¹H NMR analysis in CDCl₃ of the resultant PLA macromolecules shows that all alcohol functionalities associated with the parent core molecules disappear, suggesting activation of all arms in the formation of the star polymers. In addition, each sample exhibits a shift in the methylene (CH₂) resonances towards higher ppm due to the deshielded environment of the polymer chain. For example, HHMB-initiated PLA displays the loss of the OH peak present at 4.86 ppm and shifts the CH₂ peak from 4.69 ppm to 5.16 ppm. Due to peak overlap, end group analysis of the terminal alcohol functionalities after polymer isolation could not assist in further polymer characterization although the uniformity of the spectral resonances is suggestive of arms of similar lengths. Characterization by gel permeation chromatography is collected in Table 1. Percent conversions, measured gravimetrically, are shown along with the determined polydispersity and molecular weight values calculated relative to polystyrene standards and corrected for linear PLA, but remain uncorrected for the differences in star hydrodynamic volumes. Polymerization times of 8 h were chosen as shorter reaction times led to inefficient initiation and broadened polydispersities while reaction times of 24 h led to significant transesterification.

Table 1. Polymer data for atactic and isotactic PLA stars.

| Initiator | Monomer | % Conv. | M _{n, GPC} | M _{n, th} | PDI |
|-----------|----------------|---------|---------------------|--------------------|------|
| 1 | <i>rac</i> -LA | 68.4 | 5023 | 4488 | 1.23 |
| 1 | L-LA | 76.9 | 3490 | 4506 | 1.32 |
| 2 | <i>rac</i> -LA | 89.7 | 13787 | 8030 | 1.22 |
| 2 | L-LA | 98.8 | 8944 | 8845 | 1.51 |
| 3 | <i>rac</i> -LA | 78.2 | 4642 | 5707 | 1.20 |
| 3 | L-LA | 86.3 | 5920 | 5905 | 1.16 |
| 4 | <i>rac</i> -LA | 86.7 | 9899 | 7723 | 1.21 |
| 4 | L-LA | 78.7 | 8452 | 7011 | 1.18 |

Low to moderate polydispersities imply good control over the polymerization reactions. Slightly higher PDIs for aromatic initiators **1** and **2** may be due to longer initiation times, as expected from comparative benzyl alcohol and isopropanol initiations of linear PLA.^[1] Deviations from expected molecular weights are likely due to significant differences in effective hydrodynamic volume between linear and star-shaped polymers affecting size exclusion chromatographic techniques,^[4] with six-armed stars built from **2** and **4** showing, as expected, the highest M_n deviations.

Physical Properties of Polymer Stars

The six polymer stars in question were then characterized by thermogravimetric analysis and differential scanning calorimetry to assess the effect of core initiator on polymer properties. These data are collected in Table 2. T_g , T_c and T_m values refer to glass, crystallization and melting transitions respectively, while T_d refers to the onset temperature for polymer decomposition and X_c refers to the percent crystallinity of the star samples.

Table 2. DSC and TGA thermal data for PLA stars.

| Star | T_g (°C) | T_c (°C) | T_m (°C) | T_d (°C) | X_c (%) |
|------------|------------|------------|----------------|------------|-----------|
| 1-r | 42.14 | - | - | 228.39 | - |
| 1-L | 41.16 | 86.99 | 130.60, 138.43 | 235.35 | 29.1 |
| 2-r | 45.25 | - | - | 234.35 | - |
| 2-L | 49.72 | 93.33 | 148.14, 159.25 | 242.35 | 27.0 |
| 3-r | 40.48 | - | - | 218.14 | - |
| 3-L | 43.67 | 99.63 | 121.10, 135.42 | 232.39 | 17.5 |
| 4-r | 45.72 | - | - | 227.75 | - |
| 4-L | 49.21 | 84.38 | 125.41, 139.35 | 256.16 | 27.3 |

The variation of core initiator was shown to influence the chemical properties of the resulting polymeric material, in both atactic and isotactic PLA. Differences in glass transition temperature depended predominantly on the number of polymer arms, not the core molecule. Additionally, differences in T_g may also be due to changes in molecular weight between the different samples.^[25] In the case of initiators **2**, **3** and **4**, the isotactic samples exhibited higher T_g values than their atactic partners. Due to the lower molecular weights ($M_{n,th}$ = 4.5 kDa vs. 5.8-8.8 kDa), the stars formed from initiator **1** do not follow this trend. For samples of the same or similar molecular weight and number of arms little difference is observed in comparing rigid to flexible cores. While we expected the rigidity present in the aromatic initiator to restrict the movement of the polymer arms and potentially prevent energy distribution throughout the macromolecule, the low energy process associated with the glass transition is unaffected. Similarly, crystallization characteristics observed for

stereoregular stars derived from L-lactide (T_c , X_c) are unaffected by core rigidity. Crystallization temperatures appear to have an inverse relationship to percent crystallinity, with THMB-derived samples exhibiting a low T_c and the highest X_c while PE-derived samples had the highest T_c and the lowest X_c .

As expected, melting signals were only observed for isotactic polymer stars.^[4] In agreement with previous work, the presence of two melting points is characteristic of semicrystalline PLA.^[27] Here, clear differences exist between rigid and flexible core initiators: THMB, **1**, and HHMB, **2**, possess the two highest T_m values, suggesting increased order and rigidity throughout the star. The thermal stability imparted by the rigid core is especially apparent when comparing two six-armed polymer stars of similar molecular weights, with an increase of ~ 20 °C in the T_m for the hexa-substituted benzene versus the flexible dipentaerythritol. Comparing **1** to **2** and **3** to **4** also shows that a greater number of arms in PLA star polymers may induce higher melting temperatures, but this trend may be an artifact of molecular weight differences between the samples. A representative DSC profile for sample **2-L** is shown in Figure 2.

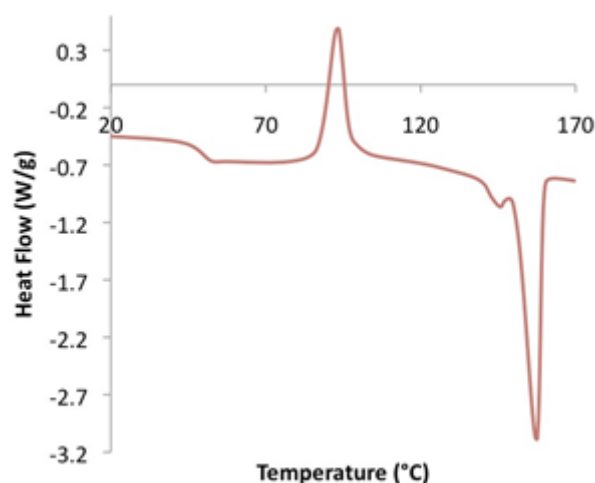


Figure 2. DSC profile for HHMB PLA star **2-L**.

Finally, thermal stability was measured by TGA and reported as the onset temperature (T_d) of rapid thermal decomposition. In each case, the isotactic samples showed higher thermal stability, as high as a 25 °C difference for DPE stars. Six-armed stars also possessed higher decomposition points, but few obvious trends existed between the nature of the initiating core and the thermal stability. For aromatic, rigid cores, drawn out decomposition profiles are observed, with larger decomposition ranges noted in both isotactic and atactic samples with cores **1** and **2**. Two representative TGA profiles are shown in Figure 3 for HHMB-initiated atactic (red) and isotactic (blue) star polymers. Small weight percentages which remain intact in each case may be due to persistence of the HHMB core, as pure HHMB has a T_d of ~ 320 °C.

Current efforts are focused on expanding the range of rigid and flexible polymer cores to other numbers of arms, including 3-armed flexible, 4-armed rigid and 5-armed flexible and rigid cores based upon hydroxybenzyl and polyol frameworks.

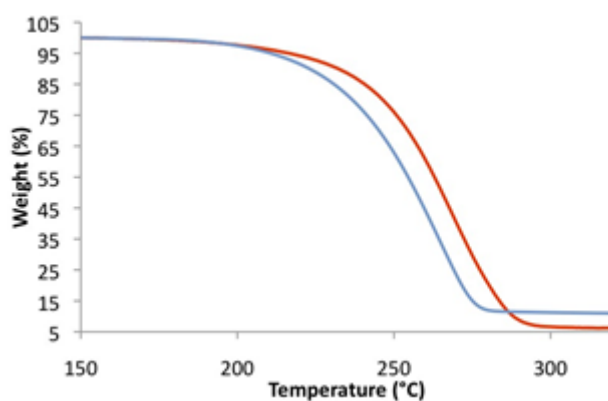


Figure 3. TGA profile for **2-r** (blue) and **2-L** (red).

Conclusions

Eight poly(lactic acid) polymer stars have been prepared from four multi-functional core initiators. While good control over the reaction, in general, is offered by the $\text{Sn}(\text{Oct})_2$ catalyst, the benzyl functionalities in hexa- and tri-(hydroxymethyl)benzene initiators are more challenging to initiate and lead to minor deviations from ideal living characteristics. Physical properties of the stars correlate well with established markers including molecular weight and the number of polymer arms. A striking effect of the rigidity of the core was noted in the melting temperatures of the star polymers, with increased core rigidity correlating with higher T_m values. Efforts to examine whether the core initiator has an effect on polymer degradation and to expand the range of core initiators accessible for star polymer synthesis continue.

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