Synthesis and Characterization of Linear, Homopolyester, Benzoyl Protected Bis-MPA

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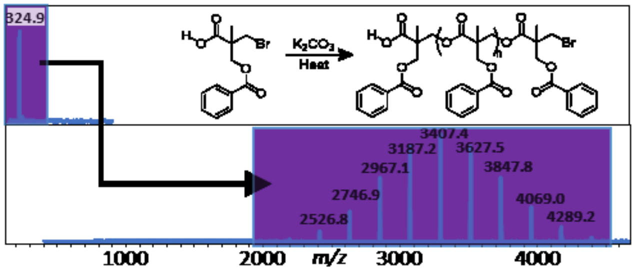


KEYWORDS: bis-MPA, Benzoate Ester, Chain-Addition, Hanessian-Hullar, Homopolyester, MALDI-TOF MS

ABSTRACT

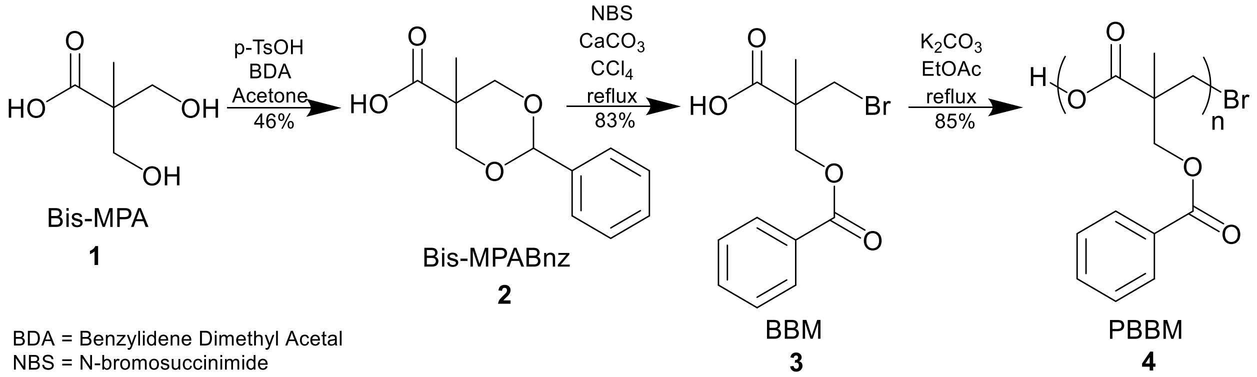
Because of the growing interest in bis-MPA dendrimers and hyperbranched polymers, a linear, polyester equivalent is of great importance in understanding how this commercially viable family of branched polymers behaves when compared to their linear analogs. Herein, we describe the first synthesis and characterization of a novel, linear, chain-growth bis-MPA homopolyester that can be used for such an investigation. Linear benzoyl bis-MPA or poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM) was synthesized efficiently using a small molecule brominated bis-MPA derivative followed by a chain-addition polymerization using potassium carbonate (K_2CO_3). This polymerization can take place in a range of solvents with low dispersity values (<1.2). The polymerization mechanism and the post-functionalization of PBBM are discussed. A preliminary solution size comparison using gel permeation chromatography (GPC) was also conducted with respect to benzylidene-protected bis-MPA dendrimers.

INTRODUCTION

Dendrimers are monodisperse, polymeric materials that are composed of branched "arms" or "wedges" that emanate from a central "core". Their branched arms are made up of an AB_x-monomer that allows for growth of the dendrimer through successive iterative steps, increasing functionality exponentially. This growth strategy affords a polymer that is well-defined in nature and thus leads to a tighter correlation of structure-property relationships. Since their inception, various dendrimers have been synthesized with different properties and architectures expanding into numerous subcategories of dendritic materials.[1,2] This has led to the use of dendrimers as drug delivery vectors, as building blocks for three-dimensional networks, and as mass calibrants.[2–7] However, the potential for application of some of these dendrimers has often been limited due to their perceived synthetic difficulty and expensive reagents.[8] Therefore, a dendritic material that can be synthesized on a multigram scale while maintaining high purity and use of inexpensive, benign reagents has huge potential for commercial applications. Despite the perception of dendrimers being synthetically demanding, in recent years, there have been a few publications that have shown this synthetic reputation is no longer valid.[2,9–12] Bis-MPA based dendrimers avoid many of the complications of some early dendrimers since they can be synthesized cleanly on multigram scale using a fluoride activated divergent synthesis published by Malkoch and coworkers.[8]

Understanding how structure may influence the behavior of dendrimers is something that has been investigated in detail. Jean Fréchet found in his studies of aromatic polyesters and polyethers, that the architecture of dendrimers, when compared to their hyperbranched and linear analogues, not only influenced physical properties like solubility and glass transition temperatures, but even the reactivity of their terminal hydroxyl groups.[13] Some have tried to relate these properties to the fact that the functional groups on dendrimers are localized at the periphery.[14–17] However, this assumption is highly debated, and there are multiple examples of studies that demonstrate that dendrimer arms may fold and extend depending on generation size, solvent quality, or distance between branch points.[18–20] It is unlikely all dendritic materials follow one rule set and for that reason it is important to understand how each dendritic system behaves.

In recent decades, the adoption of bis-MPA branched materials has greatly increased such that they can be purchased from commercial vendors such as Perstorp and Millipore-Sigma under trademarked names such as Boltorn™ and SpheriCal®. As the use of these dendritic materials increases, there is a growing need to understand how their architecture may affect their behavior or reactivity. Though multiple branched architectures based on bis-MPA have been reported or are commercially available, a linear equivalent has remained elusive. A bis-MPA linear polycarbonate was firstly described by Bisht and coworker synthesized through a ring opening polymerization (ROP) of cyclic carbonate bis-MPA derivatives, “MBC” and “MCC”.[21,22] However, this polycarbonate, and its derivatives, are not a good analogue for bis-MPA dendritic materials. These linear polycarbonates contain carbonate linkages which are not seen in either the dendrimer or hyperbranched bis-MPA analogues. These polycarbonate examples contain a pendent carboxylic acid that can be later modified for biological applications. Some groups have even taken this initial synthesis and used these polycarbonates as scaffolds for several block copolymers or functionalized polycarbonate derivatives.[23–25] Even though these polycarbonates are biodegradable and can be synthesized to high mass ranges, a linear bis-MPA homopolyester analogous to the dendrimer or the hyperbranched polymer is more desirable for this type of comparison.



Scheme 1. Synthetic scheme of poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM).

Herein, we describe the first synthesis of a linear, benzoyl-protected, bis-MPA homopolyester (PBBM). This was accomplished using the Hanessian-Hullar[26] ring opening procedure of benzylidene acetals using N-bromosuccinimide. Previously, this reaction was used predominately in carbohydrate chemistry by providing an avenue for further functionalization of complex carbohydrates.[26,27] However, this procedure proved problematic since it utilized barium carbonate ($BaCO_3$), a toxic reagent, as an "acid scavenger". To avoid this, Chrétien *et al.*[27] described an alternative acid scavenger in calcium carbonate ($CaCO_3$) that still works as efficiently while avoiding issues of toxicity. The procedure described in this report uses a similar synthetic methodology for ring opening benzylidene acetals as reported by Chrétien *et al.* (**Scheme 1**). This synthetic approach was used to synthesize BBM, which was subsequently used to produce a linear benzoyl-protected bis-MPA homopolyester (PBBM): both of these for the first time. PBBM is later compared to its dendritic analogs through a preliminary size comparison study.

EXPERIMENTAL SECTION

Benzylidene-protected bis-MPA (5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid).[28] A round bottom flask was charged with a stir bar and acetone (1925 ml). While stirring, bis-MPA (345.55 g, 258 mmol) was added slowly to prevent the stir bar from seizing since the solution is a suspension. Then benzaldehyde dimethyl acetal (588.12 g, 386 mmol, 580 ml) was added, followed by *para*-toluene sulfonic acid (*p*-TsOH, 4.19 g, 25 mmol). The reaction mixture was stirred for 16 hours under inert atmosphere (N_2) as a suspension of white solid. The solution was then filtered to isolate the white solid, and the white solid was washed several times with cold acetone. The white solid was then dried under high vacuum to remove residual acetone (266.168 g, 46.4%). ^1H NMR (**Figure S1**) ($CDCl_3$, 300 MHz) δ 1.11 (s, 3H, CH_3), 3.70 (d, J = 11.7 Hz, 2H, CH_2), 4.63 (d, J = 11.7 Hz, 2H, CH_2), 5.49 (s, 1H, CH_{acetal}), 7.41 (m, 5H, ArH). ^{13}C NMR (**Figure S2**) ($CD_3S(O)CD_3$, 75 MHz) δ 17.6 (CH_3), 41.5 ($C_{quaternary}$), 72.6 (CH_2), 100.3 (CH_{acetal}), 126.1 ($CH_{\textit{ortho}\ \text{Ar-H}}$), 128.0 ($CH_{\textit{meta}\ \text{Ar-H}}$), 128.7 ($CH_{\textit{para}\ \text{Ar-H}}$), 138.4 ($C_{\text{quaternary Ar-H}}$), 173.9 (C(O)).

3-(Benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid (BBM). To a round bottom flask, benzylidene-protected bis-MPA (10.0 g, 45 mmol), N-bromosuccinimide (NBS, 8.81 g, 49 mmol), and $CaCO_3$ (5.45 g, 54 mmol) was added. The flask was charged with a stir bar and placed under a reflux condenser. Carbon tetrachloride (CCl_4, 50 ml) was added to the flask and the reaction was stirred at 85 °C for 3 hours. The reaction mixture started as a white slurry and then turned to a red-orange slurry approximately 15 minutes after heating. After reacting, the red-orange slurry was then allowed to cool to room temperature and filtered to remove $CaCO_3$. The resulting red-orange translucent solution was then washed with sodium sulfite (Na_2SO_3), sodium hydrogen sulfate ($NaHSO_4$), and deionized H_2O. The red-orange solution turned orange after all the washes and was then dried with magnesium sulfate ($MgSO_4$), filtered, and the solvent was removed via rotary evaporator. After concentration, the orange solution turned to a red viscous oil. The resulting red oil was dried under high vacuum and set aside for polymerization. (11.2 g, 82.7%). MALDI-ToF MS (**Figure S4**) calcd. m/z + Na^+ [322.99 m/z] obs. m/z + Na^+ [322.94 m/z]. ^1H NMR (**Figure 1**) ($CDCl_3$, 300 MHz) δ 1.48 (s, 3H, CH_3), 3.69 (d, J = 10.4 Hz, 1H, CH_2-Br), 3.74 (d, J = 10.4 Hz, 1H, CH_2-Br), 4.52 (d, J = 11.2 Hz, 1H, CH_2-OBz), 4.57 (d, J = 11.2 Hz, 1H, CH_2-OBz), 7.43 (t, J = 7.4 Hz, 2H, $CH_{\textit{meta}\ \text{Ar-H}}$), 7.57 (t, J = 7.4, 1.6 Hz, 1H, $CH_{\textit{para}\ \text{Ar-H}}$), 8.00 (t, J = 7.4, 1.6 Hz, 2H, $CCH_{\textit{ortho}\ \text{Ar-H}}$). ^{13}C & ^{13}C DEPT 135 NMR (**Figure S3**) ($CD_3S(O)CD_3$, 75 MHz) δ 19.85 (CH_3), 38.03 (CH_2-Br), 47.24 ($C_{\text{quaternary}}$), 67.37 (CH_2-O-C(O)), 129.32 ($CH_{\textit{ortho}\ \text{Ar-H}}$), 129.67 ($C_{\text{quaternary Ar-H}}$), 129.72 ($CH_{\textit{meta}\ \text{Ar-H}}$), 134.05 ($CH_{\textit{para}\ \text{Ar-H}}$), 165.69 (C(O)Bz), 173.89 ($C(O)_{\text{backbone}}$). Elemental Analysis Calcd for $C_{12}H_{13}BrO_4$: C, 47.9%; H, 4.4%. Found: C, 48.9%; H, 4.5%. IR Stretches (**Figure S5**) 1650-1800 cm^{-1} C=OBz & C=OOH, 2350-2800 cm^{-1} C=OOH, 2800-3100 cm^{-1} Ar-H, 3100-3700 cm^{-1} O-H.

Poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM). A round bottom flask was charged with a stir bar, BBM (8.00 g, 27 mmol), and K_2CO_3 (14.7 g, 106 mmol). Ethyl acetate (266 ml) was then added, and the reaction mixture was stirred under reflux for 16 hours. The resulting mixture was then acidified with $NaHSO_4$ to quench the reaction. The product was extracted out with several washes of $CHCl_3$. This organic layer was then washed with DI water, dried with $MgSO_4$, and then excess solvent was removed using a rotary evaporator producing a brown solid. This solid was then re-dissolved in $CHCl_3$ then precipitated into cold hexanes (1:10) to produce a white powder (4.91 g, 84.7%, M_n 2200). MALDI-ToF MS (**Figure 3**) calcd. m/z + Na^+ [2085.92 m/z] obs. m/z + Na^+ [2085.62 m/z]. ^1H NMR (**Figure 4**) ($CDCl_3$, 300 MHz) δ 1.24 (m, $CH_{3\text{ backbone}}$), 1.33 (s, $CH_{3\text{ endgroup}}$), 3.62 (m, CH_2-Br), 4.35 (m, $CH_{2\text{ backbone}}$), 7.37, (m, $CH_{meta\text{ Ar-H}, para\text{ Ar-H}}$), 7.85 (m, $CH_{ortho\text{ Ar-H}}$). ^{13}C NMR (**Figure 4**) (75 MHz, $CDCl_3$) δ 17.7 (CH_3), 46.7 ($C_{\text{quatenary}}$), 65.70 (CH_2), 128.39 ($CH_{meta\text{ Ar-C}}$), 129.36 ($CH_{ortho\text{ Ar-C}}$), 129.54 ($C_{\text{quaternary Ar-C}}$),133.15 ($CH_{para\text{ Ar-C}}$), 165.55 (C(O)Bz), 171.75 ($C(O)_{\text{backbone}}$). GPC (**Figure 3**) (THF, RI): M_n (*Đ*) = 1800 g mol^{-1} (1.02) Elemental Analysis Calcd for 10-mer $C_{120}H_{121}BrO_{40}$: C, 63.1%; H, 5.3%. Found: C, 63.5%; H, 5.4%. IR Stretches (**Figure S5**) 1670-1820 cm^{-1} C=OBz & C=O, 2800-3100 cm^{-1} Ar-H, 3100-3700 cm^{-1} O-H.

Characterization. Nuclear Magnetic Resonance (NMR) spectroscopy was performed on a Bruker AVANCE 300 MHz spectrometer (**Figures 1, 4, S1-3, S15-22, S25-27, S33**). ^1H (300 MHz) experiments were performed at 298 K at a concentration of 3 mg/mL in chloroform-d ($CDCl_3$) or methanol-d_4 (MeOD), purchased from Cambridge Isotope Laboratories (Andover, MA, USA). ^{13}C and ^{13}C DEPT 135 (75 MHz) experiments were performed at 298 K at a concentration of 10 mg/mL in chloroform-d ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO). HSQC-NMR was performed at 298 K at a concentration of 20 mg/ml in dimethyl sulfoxide-d_6 (DMSO). Enough scans were collected to generate sufficient signal to noise with a relaxation delay of 3-6 seconds depending on sample.

A Bruker Autoflex III MALDI-ToF Mass Spectrometer (Bruker Daltonics, Billerica, MA) was used to collect **Figures 3, 5, 8, S4, S6-11, S13, S24, S28-29, S31.** Mass spectra data were collected in positive reflectron ion detection mode. Typical sample preparation for MALDI-ToF MS data was performed using 2 types of sample preparation. Stock solutions of matrix (20 mg/mL), polymer analyte (1 mg/mL), and a cation source (1 mg/mL) in tetrahydrofuran (THF) (VWR) were made. The stock solutions were combined in a 5/1/1 μL ratio (v/v/v) (matrix/analyte/cation) and plated via the dried droplet method. Sodium trifluoroacetate was used as the cation source and *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) (TCI) was used as the matrix in the first sample preparation method. The second method involved applying graphite from a #2 Ticonderoga pencil to the plate as the matrix, and then addition of 1 μL of polymer analyte stock solution and 1 μL of cation stock solution via the dried droplet method. MALDI-TOF MS spectra were calibrated against SpheriCal® dendritic calibrants (Polymer Factory, Sweden).

Gel permeation chromatography (GPC) was performed on a Waters Model 1515 isocratic pump and a Waters Model 2414 differential refractometer detector (Waters Corp., Milford, MA) with three PSS SDV analytical 500 Å (8 × 300 mm) columns in series; (Polymer Laboratories Inc., Amherst, MA). Data (**Figure 5, 8, S7, S12, S14, S30, S32 and Table 1**) were collected in THF at a flow rate of 1 mL/min at 30 °C. Samples for size comparison study were collected by fractionation using a Waters Model 1515 isocratic pump and a Waters Model 2414 differential refractometer detector (Waters Corp., Milford, MA) with one PSS SDV Prep 1000 Å (40 ×

250mm); (Polymer Laboratories Inc., Amherst, MA). This was done in THF at a flow rate of 8 mL/min at 30 °C.

Attenuated total reflection Fourier-transform infrared (ATR-FTIR) measurements were performed on a Nicolet iS50R spectrometer. Data (**Figure S5 and S23)** were recorded at room temperature between 4000 cm^{-1} and 400 cm^{-1} at a resolution of 4 cm^{-1} and 32 scans were averaged for each spectrum.

Thermogravimetric analysis (TGA) (**Figure 6**) was performed on a Q500 thermogravimetric analyzer (TA Instruments Inc.) at a 10 mg scale under a flowing nitrogen atmosphere at a heating rate of 10 °C/min from 25 °C to 600 °C. Temperature is reproducible to ±1 °C and mass to ± 0.2%.

Thermal behavior was investigated by differential scanning calorimetry (DSC) using a TA Instruments DSC Q-100 (**Figure 7**). The calibration was carried out using indium and sapphire standards. All samples were first equilibrated at -60 °C, and heated to 250 °C at a rate of 10 °C/min to erase thermal history, and then subjected to 3 cycles of cooling to -60 °C at 5 °C/min and heating back to 250 °C at a rate of 10 °C/min. All 3 cooling and heating scans are reported.

RESULTS AND DISCUSSION

Synthesis of Monomer and Monomer Characterization

Anders Hult and coworkers first reported the bis-MPA class of polyester dendrimer in 1993, and its related hyperbranched polymer at about the same time.[29–31] Although dendrimer and hyperbranched bis-MPA polymers have been studied and eventually commercialized, the exact linear bis-MPA polymer class has yet to be studied. Bisht and coworker were the first to describe the use of related bis-MPA cyclic carbonates to synthesize linear bis-MPA polycarbonate materials.[21,22] These polycarbonates incorporate the diol of bis-MPA in their backbone and contain a pendent carboxylic acid moiety which can be used as a vector for further functionality as demonstrated by Tempelaar *et al.,* Olsson *et al.,* and Sanders *et al.* [23–25] Though these linear bis-MPA polycarbonates are biodegradable and can be synthesized upwards of ~M_n 13,000, they are not the best linear equivalent to bis-MPA based dendrimers because they contain a carbonate linkage that are not seen in any dendrimer or hyperbranched bis-MPA materials. As a result, a true linear analogue for the purpose of comparison to bis-MPA dendrimers has remained elusive. Therefore, the work shown here is the first example of a linear, benzoyl-protected, bis-MPA polyester.

Annby *et al.*[32] were the first to use benzylidene protected bis-MPA and Trollsås *et al.*[28] used this bis-MPA derivative for a hyperbranched poly(caprolactone) system. Since then, it has been used in the synthesis of numerous benzylidene-protected bis-MPA dendritic materials.[7,9,33–35] Though typically used as a protecting group, the aforementioned benzylidene acetal can be transformed using the Hanessian-Hullar[27,36] reaction to yield 3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid (BBM) (**Scheme 1**). This novel bis-MPA derivative (**3**) can be synthesized efficiently on a multigram scale (~10 grams) and contains a pendant benzoate ester and primary bromine, the latter of which provides a direct and efficient avenue for polymerization under basic conditions in a range of solvents.

MALDI-ToF MS data (**Figure S4**) shows the expected *m/z* for **3** at 322.94 (theoretical: 322.99) with Na^+ counterion for the ^{79}Br product and at nearly the same peak intensity at $[M+2]^+$=324.94 (theoretical: 324.99) for the ^{81}Br product giving the expected isotopic distribution. This spectrum also shows the di-sodiated ^{79}Br adduct at 344.93 m/z (theoretical:

344.97) and the di-sodiated ^{81}Br adduct at 344.93 m/z (theoretical: 344.97) which is due to the proton of the carboxylic acid being exchanged for a sodium counterion. ^{1}H NMR (**Figure 1**) shows BBM has two sets of diastereotopic protons due to the chirality of the neighboring quaternary carbon. The first set is located on the brominated carbon shown at 3.71 ppm followed by the second set at 4.54 ppm which is the **CH_2**-O-C(O) carbon. Additionally, the shift of the *ortho* protons on the benzoyl ring to 7.98 ppm in BBM (**Figure 1**) from 7.33 ppm in the starting material (**Figure S1**) confirms completion of the ring-opening reaction. ^{13}C NMR shows the anticipated carbon signals and ^{13}C DEPT 135 (**Figure S3**) and confirms the proper CH_2 peaks and disappearance of the quaternary carbonyl carbons at 165.6 ppm and 173.8 ppm corresponding to the benzoyl and carboxylic acid carbons, respectively.

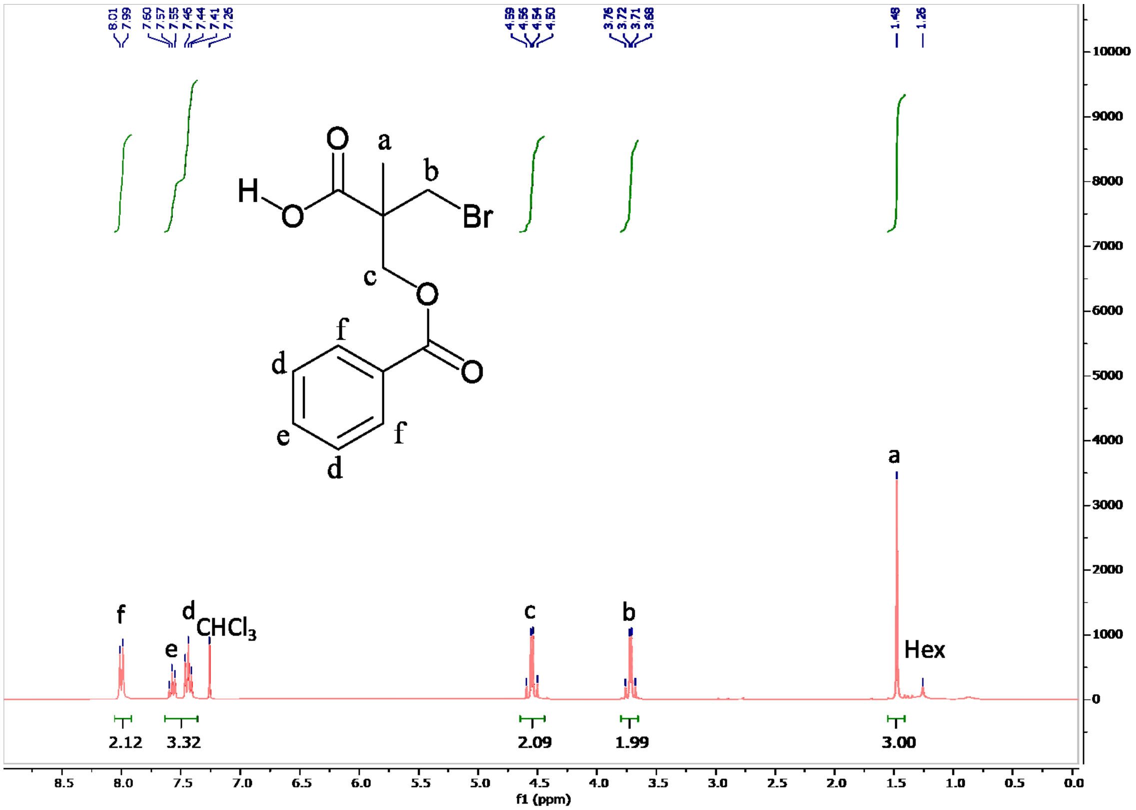


Figure 1. ^{1}H NMR (300 MHz, $CDCl_3$) of 3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid (BBM).

Polymerization of PBBM and Mechanism

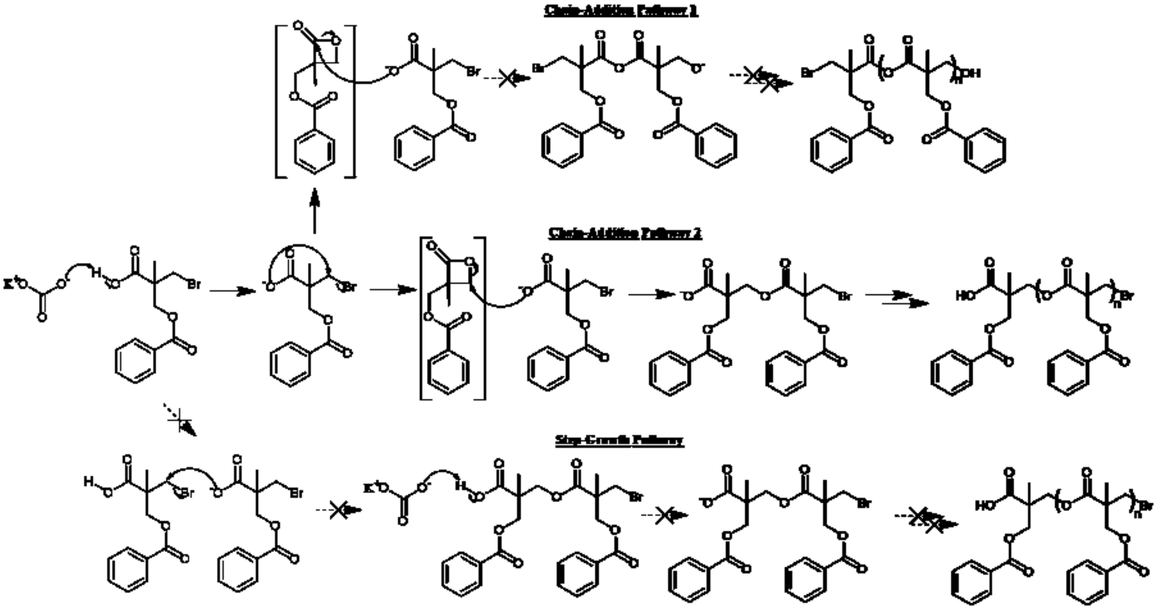


Figure 2. Possible polymerization mechanisms of PBBM.

The polymerization of BBM is accomplished via its carboxylic acid and bromine moieties using K_2CO_3. At the inception of the proposed synthetic scheme, the polymerization was expected to take place through a self-initiated, step-growth condensation polymerization. This would be due to deprotonation of the carboxylic acid to form the resulting carboxylate, which then attacks the brominated carbon of another BBM molecule (**Figure2**). Initial trials showed polymerization occurs in several solvents (**Figures S6**), though ethyl acetate, which has poor miscibility with water, was selected due to low observed dispersity values and minimal formation of side products. Ethyl acetate may seem to be a poor choice of solvent due to possible transesterification. However, though PBBM is a polyester, its ester linkages are not formed by attack of a carboxylic acid by an alcohol or alkoxide, but rather attack of the β-carbon of a propiolactone (discussed later) by a carboxylate.

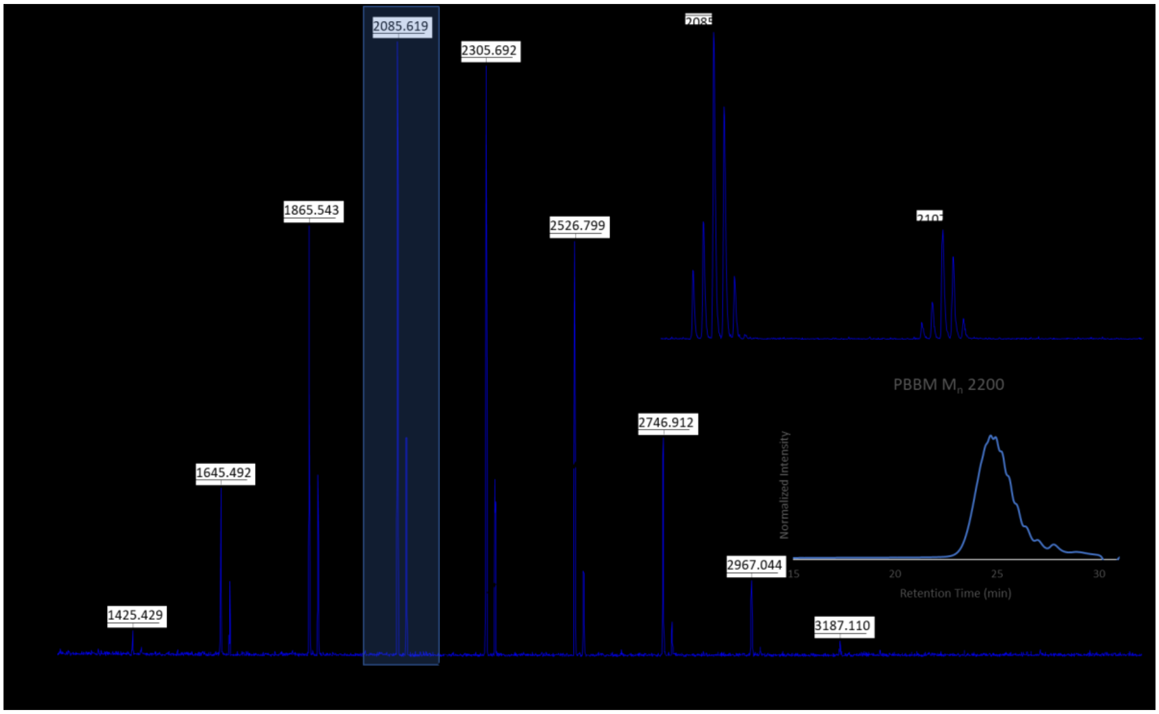


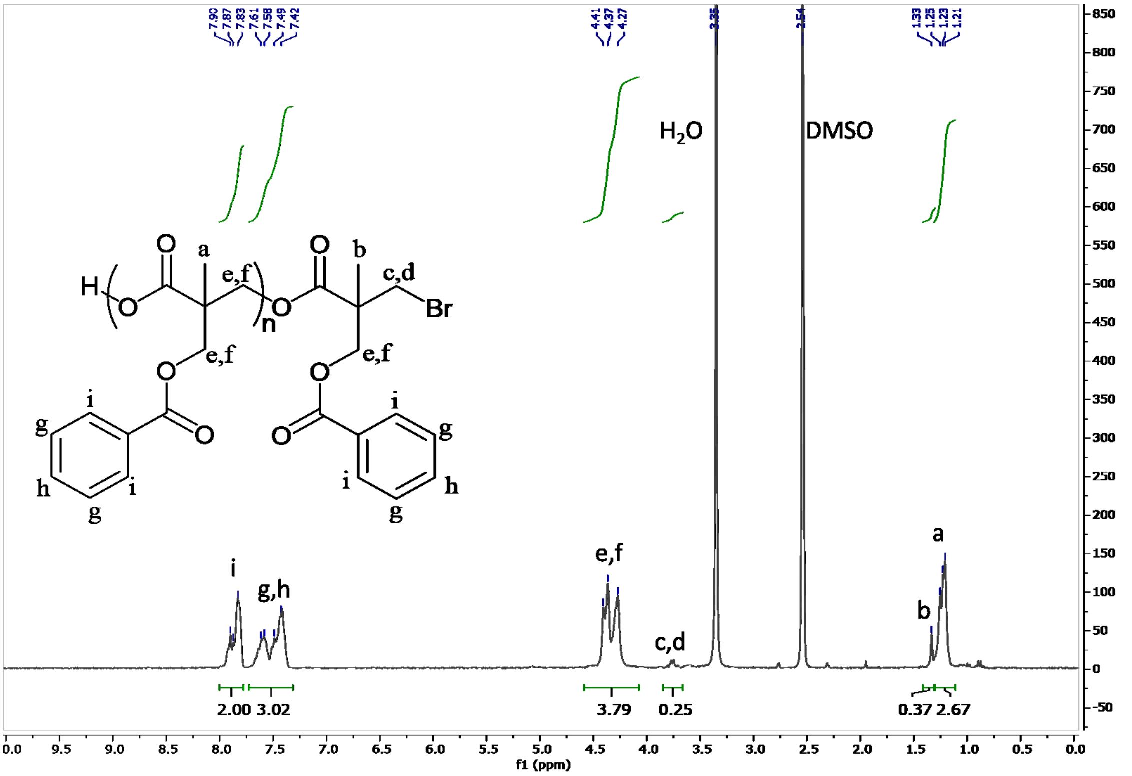
Figure 3. MALDI-ToF MS spectrum of M_n 2200 PBBM in ethyl acetate. Spectrum was obtained using Na^+ as the counterion with DCTB as the matrix. GPC trace is of M_n 2200 PBBM in THF.

MALDI-ToF MS data (Figure 3) shows that initial MALDI-ToF MS and GPC analysis reported very narrow dispersity values of less than 1.2. This was unexpected based upon the proposed synthetic scheme (**Scheme 1**) which would suggest a step-growth polymerization mechanism (**Figure 2**). This step-growth mechanism should result in a dispersity closer to 2.0 which is not what is observed. To test the initial step-growth hypothesis, poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid (PBBM) (M_n 2200) was allowed to react for 96 hours under basic conditions and no significant M_n increase was observed (**Figure S7**). In other polymerization trials, additional potassium carbonate without additional monomer was added and little polymer growth was observed. Subsequent polymerization trials where the types of base, the equivalents of base, and the initial monomer concentration were varied (**Table 1**) showed the limit of achieved molecular weight. It was always under ~7 kDa using the same starting amount of monomer. Due to this behavior, and low dispersity values, it is suspected this monomer may polymerize using a chain-reaction polymerization, possibly through a fleeting propiolactone intermediate (**Figure 2 and S28**). This suggests that polymerization requires more available monomer, or monomer intermediate, rather than the polymer for the carboxylate nucleophile to attack. This supports the idea of polymerization being limited by low concentration of the proposed lactone intermediate or increasing steric bulk around the brominated carbon hindering the step-growth pathway.

Base	Eq of Base	Int. [M]	Obs. $M_{n\ \mathrm{MALDI}}$	MALDI Đ	Obs. $M_{n\ \mathrm{GPC\ (PS)}}$	GPC Đ
K_2CO_3	2	1 M	3600	1.02	3300	1.21
K_2CO_3	2	0.5 M	3800	1.02	3100	1.22
K_2CO_3	2	0.1 M	7100	1.01	5970	1.11
K_2CO_3	2	0.05 M	5200	1.01	4000	1.12
K_2CO_3	2	0.01 M	4300	1.01	3400	1.07
K_2CO_3	1	0.1 M	7100	1.01	6100	1.12
K_2CO_3	4	0.1 M	7300	1.02	6400	1.11
K_2CO_3	8	0.1 M	7000	1.01	5900	1.11
TEA	1	0.1 M	900	1.03	1000	1.03
TEA	2	0.1 M	900	1.03	1000	1.04
TEA	4	0.1 M	900	1.04	1000	1.03
TEA	8	0.1 M	800	1.04	1000	1.02

Table 1. Polymerization trials of PBBM varying initial monomer concentration and types/equivalents of base in ethyl acetate at 70°C under reflux for 24 hours. MALDI-ToF M_n and *Đ* values were obtained using Na^+ as the counterion. GPC M_n and *Đ* (calibrated with polystyrene (PS)) values for each trial are also reported.

Mechanistically, a lactone pathway (**Figure 2**) could result in either a hydroxyl-terminated polyester with a hydroxyl on one end and a bromine on the other or a carboxylic acid on one end and a bromine on the other. Though both lactone mechanisms are plausible, there is previous work that shows attack at the β-position is preferred in the case of carboxylate nucleophiles.[37] Based upon chain-addition pathway 1, the expected resulting polymer is not observed according to MALDI-ToF MS due to existence of the di-sodiated adduct (**Figure 3**) of the carboxylic acid and lack of a carbonate signal in the ^{13}C NMR spectrum (**Figure 4**). Though a cyclic structure would also lack a carbonate signal, a cyclic structure would have, both, a different *m/z* than what is observed, due to the loss of the bromine end group, and a di-sodiated adduct would not be observed by MALDI ToF-MS. Not only does the MALDI-ToF MS *m/z* match what is expected (**Figure 3**), but the isotopic distribution also matches the expected pattern for a bromine-containing product for both the mono-sodiated and di-sodiated adducts (**Figure S24**).


7.90
7.87
7.83
7.61
7.58
7.49
7.42
4.41
4.37
4.27
3.35
2.54
1.33
1.25
1.23
1.21
H_2O
DMSO
H
O
O
a
e,f
n
O
b
c,d
Br
e,f
e,f
O
O
O
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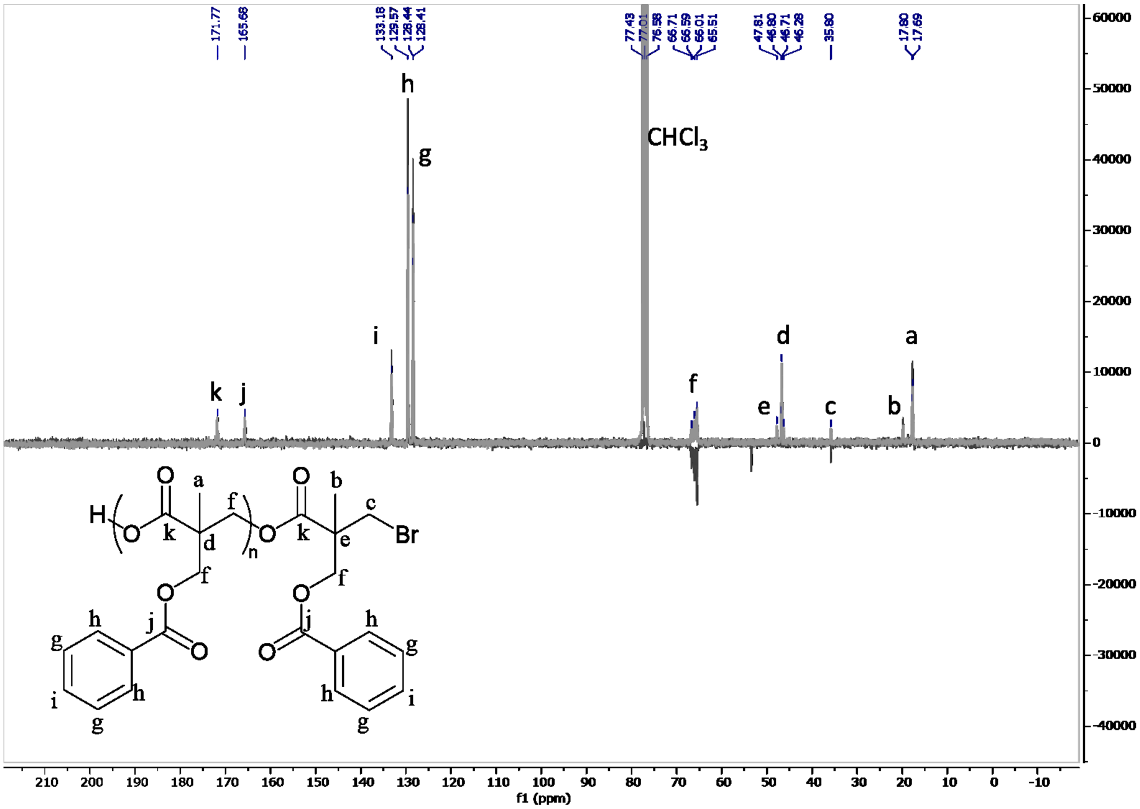
171.77
165.68
133.18
129.57
128.44
128.41
77.43
77.01
76.58
66.71
66.59
66.01
65.51
47.81
46.80
46.71
46.28
35.80
17.80
17.69
h
g
$CHCl_3$
i
d
a
k
j
f
e
c
b
H
O
a
f
O
b
c
Br
k
d
n
k
e
f
f
O
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g
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O
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i
h
h
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g
g
f1 (ppm)

Figure 4. ^{1}H NMR poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM) in DMSO at 3 mg/ml. ^{13}C NMR and ^{13}C DEPT 135 NMR of poly(3-(benzoyloxy)-2-(bromomethyl)-2-methylpropanoic acid) (PBBM) in $CDCl_3$ at 10 mg/ml.

It is possible that the step-growth pathway is inhibited due to use of a weak nucleophile in the carboxylate and increasing steric bulk around the terminal bromine. To test this notion of accessibility, PBBM was reacted with BnBr and 1-bromododecane under the same conditions after the polymerization and both were added to the polymer end group (**Figure S8, S26-27**). Though the reaction is slow (16-48 hours), it demonstrates the nucleophilicity of the carboxylic acid at the end of the polymer chain. Additionally, NaN_3 can also replace the bromine at the end of the polymer chain (**Figure S9, S25**). This further supports the assertion of the mechanism proceeding through a monomer intermediate since both the carboxylic acid appears to be a sufficient nucleophile and the bromine appears to be accessible. These observations, as well as no growth observed after 96 hours, support the unlikelihood of a step-growth polymerization. Therefore, earlier polymerization trials were likely stunted due a low concentration of available monomer. Finally, isopropoxy-BBM (2-(bromomethyl)-3-isopropoxy-2-methyl-3-oxopropyl benzoate) was added to the polymerization of BBM at a 10% molar ratio and no incorporation of this monomer derivative was observed according to MALDI-ToF MS data which was not expected if this proceeded through a step-growth polymerization (**Figure S10**). The isopropoxy group would prevent formation of the lactone, which may be the reason why it is not incorporated in the polymer chain.

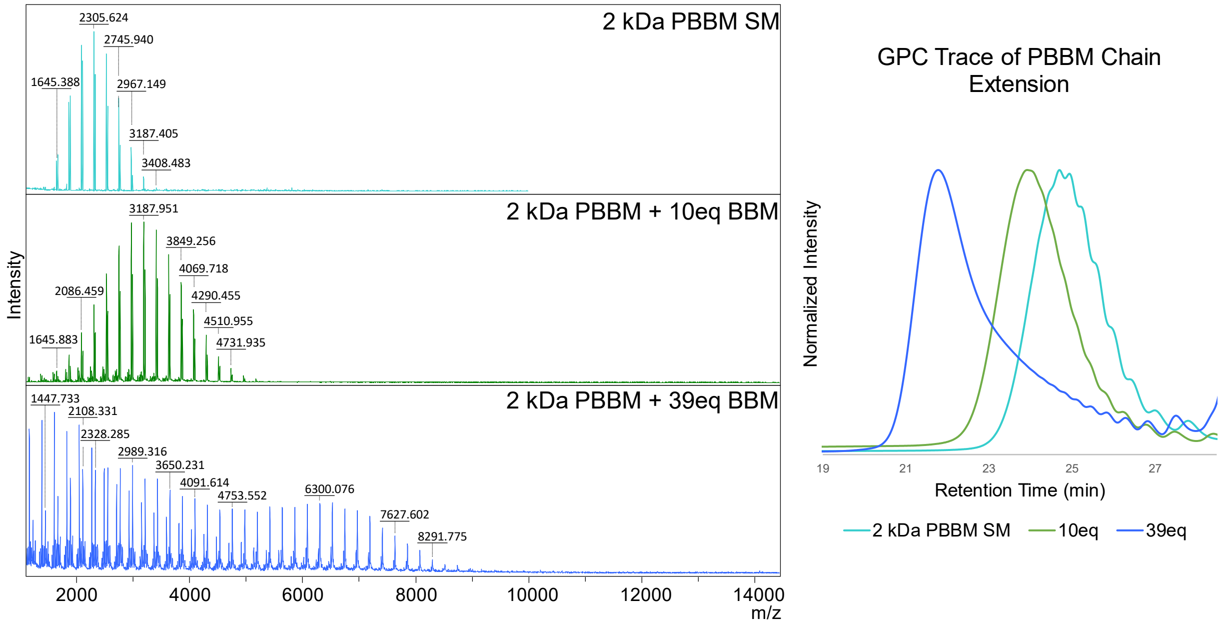


Figure 5. MALDI-ToF MS and GPC of PBBM chain extension trials. Starting with M_n 2200 PBBM, 10 eq followed by an additional 39 eq of 0.1 M BBM were added to the reaction flask at 1 ml/min.

Finally, if the polymerization proceeded through a chain-addition mechanism, then it should be possible to perform a chain extension on this polymer. A 0.1 M solution of BBM was added at 1 ml/hr to a flask of 0.1 M PBBM (M_n 2200) and K_2CO_3 at 70 °C. This resulted in an increase in polymer molecular weight but it also increased the dispersity (**Figure 5**). Increased dispersity is likely due to the addition of monomer diluting the solution to a level where formation of new chains was faster than addition to previously formed chains. To avoid this, another polymerization with a highly pure batch of BBM was done where BBM would be added neat. This BBM was added dropwise in 100 mg fractions every hour over a 6-hour period. Even in this polymerization trial, where dispersity would be artificially broadened due to monomer being added as the polymerization proceeded, dispersity never exceeded 1.3 by GPC or MALDI-ToF MS (**Figures S29 and S30**). However, measurement of early time points in the reaction was needed to see if the low observed dispersity values (<1.2) were a product of reaction times being too long in earlier trials such as in **Table 1**. To investigate this, a 300 mg scale polymerization of this highly pure BBM was analyzed using crude time aliquots from 0-18 hours. These time aliquots were analyzed using MALDI-ToF MS and GPC (**Figures S31 and S32**) to determine if a dispersity of 2 (characteristic of step-growth polymerizations) would be observed earlier in the reaction. According to this data, dispersity remains below 1.04 by MALDI-ToF MS and 1.10 by GPC throughout the reaction. As a result of all these observations, we believe this polymer is synthesized through a self-initiated, chain-addition polymerization

Thermal Properties of BBM and PBBM

The melting point of the BBM was determined to be ~73-79 °C. This is significantly lower than unprotected bis-MPA (181-190 °C)[38] and bis-MPABnz (197-198 °C)[28]. TGA analysis of 2 kDa PBBM and Tetra[G2]Bnz$_8$ demonstrates the increased stability of the branched architecture within a dendrimer (**Figure 6**). The midpoint of thermal degradation of PBBM is ~316 °C while Tetra[G2]Bnz$_8$ is ~405 °C according to TGA analysis. Since the polyester linkages in 2 kDa PBBM and Tetra[G2]Bnz$_8$ should be similar and they are of similar molecular weight, the differences in thermal degradation is likely due to architecture. The increased stability of Tetra[G2]Bnz$_8$ is due to degradation of the dendrimer subunits involving scission of three bonds versus two bond scissions in PBBM. The TGA spectrum of PBBM exhibits one degradation event which shows homogeneity among its backbone esters. This lends credence to the structure uniformity of PBBM. Tetra[G2]Bnz$_8$ also exhibits one thermal degradation event. Since this molecule is made up of largely the same bis-MPA ester linkages, this thermal event corresponds to the degradation of these esters.

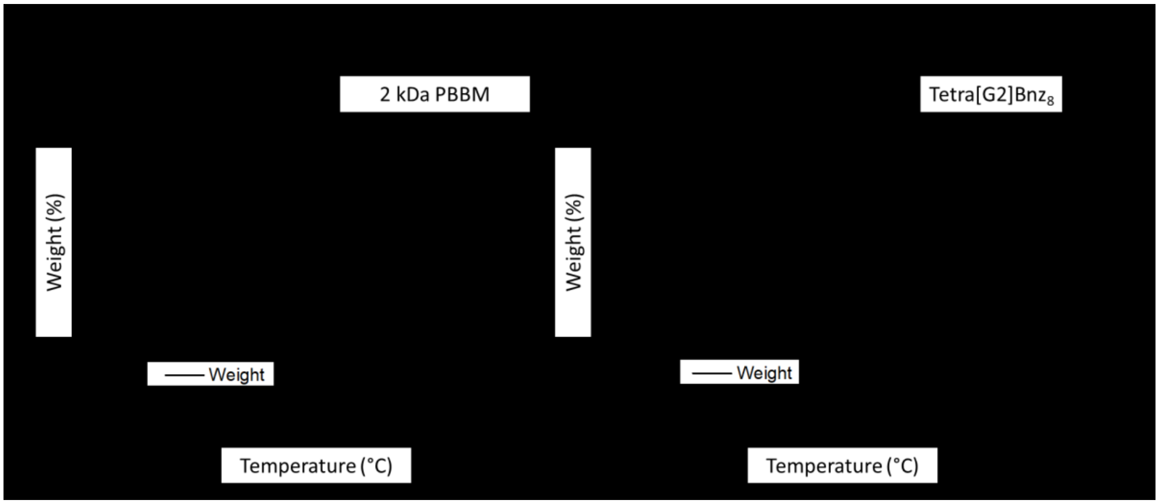


Figure 6. TGA analysis of 2 kDa PBBM and Tetra[G2]Bnz$_8$.

Tetra[G2]Bnz$_8$ and 2 kDa PBBM were also analyzed by DSC (**Figure 7**). Both samples were analyzed using three heat and cool cycles to ensure repeatability of thermal transitions. According to DSC, 2 kDa PBBM exhibits three thermal transitions: a glass transition temperature (T_g), a crystallization temperature (T_c), and a melting temperature (T_m). Existence of these transitions suggest PBBM is at least semi-crystalline most likely due to the aromatic rings of the pendant benzoate group. The T_g, T_c, and T_m are observed in the heating cycles of PBBM with transitions at ~30 °C, ~95 °C, and ~124 °C, respectively. 2 kDa PBBM and Tetra[G2]Bnz$_8$ appear to have similar glass transition temperatures as can be seen in the zoom of each set of curves. This may be attributed to the 2 kDa molecular weight or the difference in functional groups between the benzylidene acetal terminated dendrimer and the pendant benzoate ester of PBBM.[39–41] Also, there is no observed T_c of Tetra[G2]Bnz$_8$ which supports the expected amorphous nature of dendritic materials.

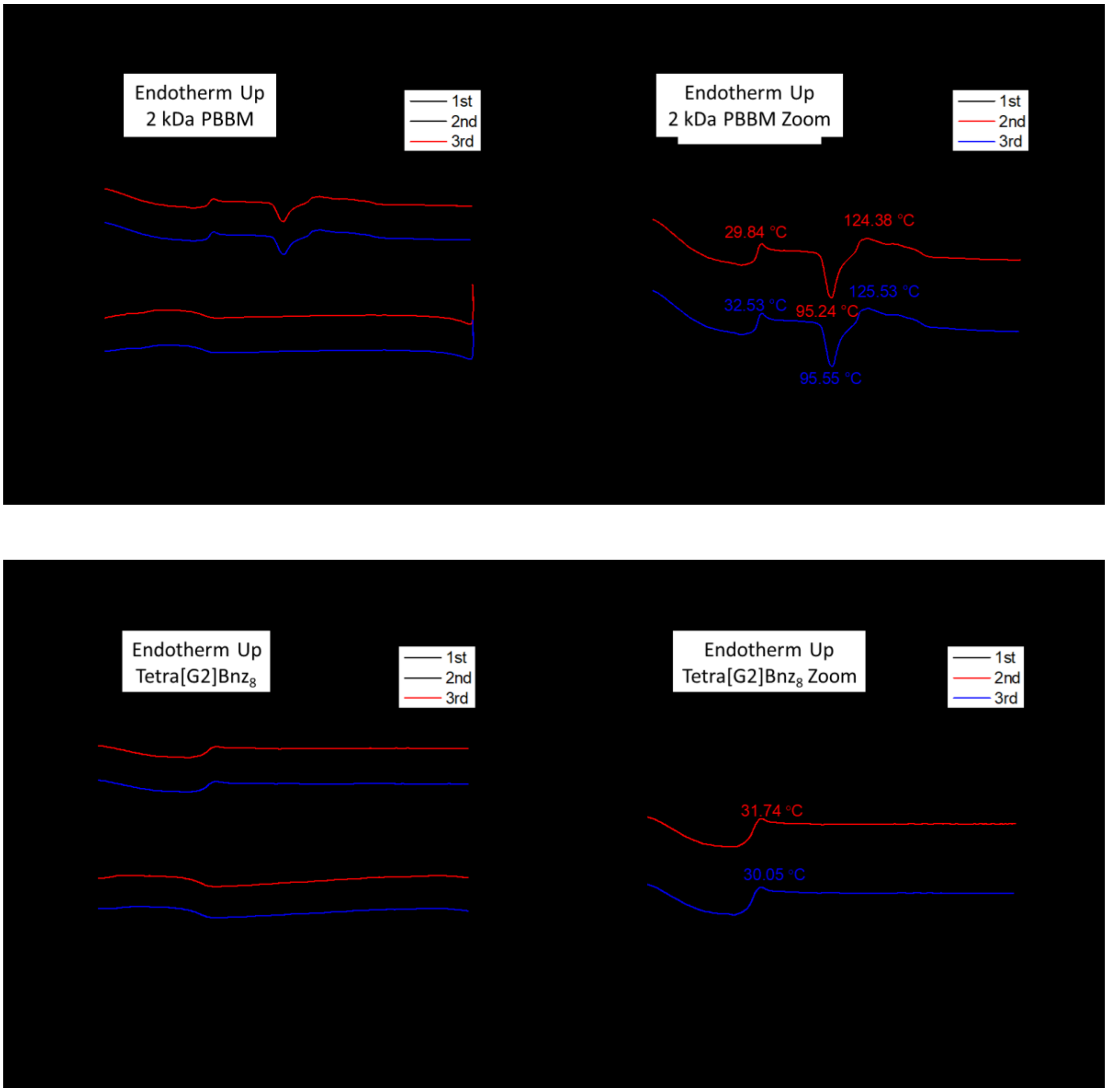
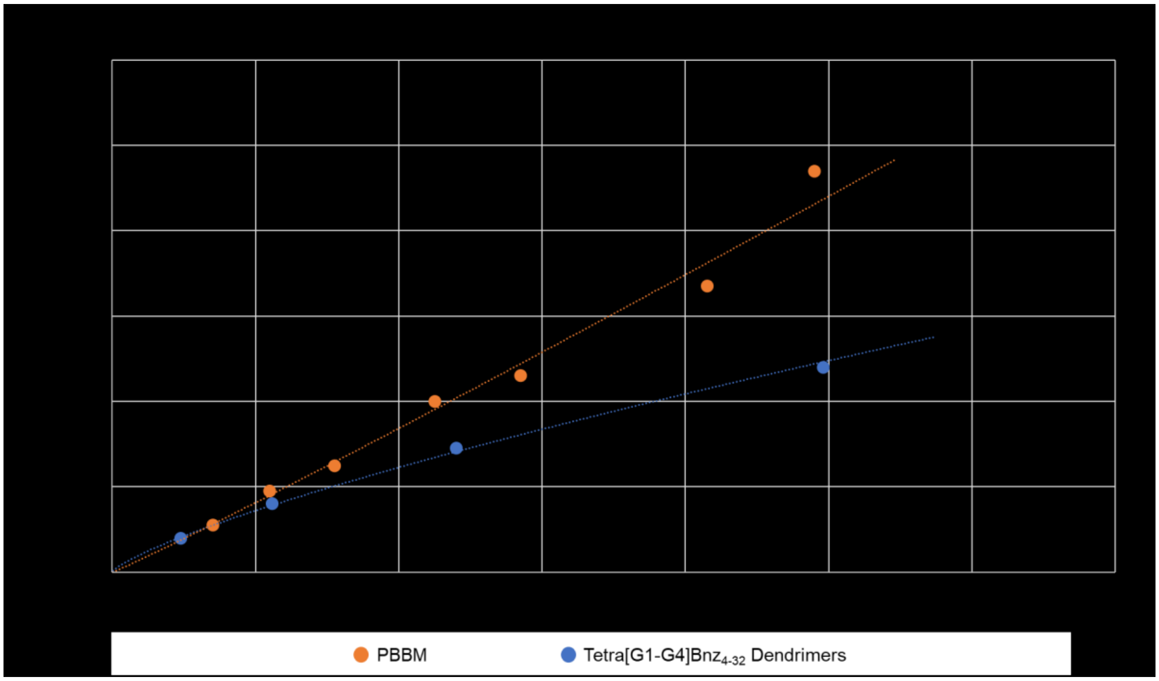


Figure 7. DSC analysis of 2 kDa PBBM and Tetra[G2]Bnz$_8$. A zoom in of the three heat cycles of each material is provided to better show thermal transitions.

Preliminary Apparent Size Comparison

A linear equivalent to bis-MPA based dendrimers helps to increase the understanding of how architecture affects polymer physical properties within the bis-MPA family. A preliminary investigation into the effect of architecture on the apparent solution size of PBBM and its dendrimer analogue was conducted using gel permeation chromatography (GPC) and MALDI-

ToF MS analysis (**Figure 8**). PBBM was fractionated using preparative GPC to separate different molecular weight distributions within the same sample (**Figures S13-S14**). All fractions were analyzed by MALDI-ToF MS and fractions within a 10% mass range of the corresponding [G1-G4] pentaerythritol-core dendrimers were selected for size comparison (**Figures S11,12**). Additional molecular weight fractions of PBBM were also examined to allow for a better trendline fit.



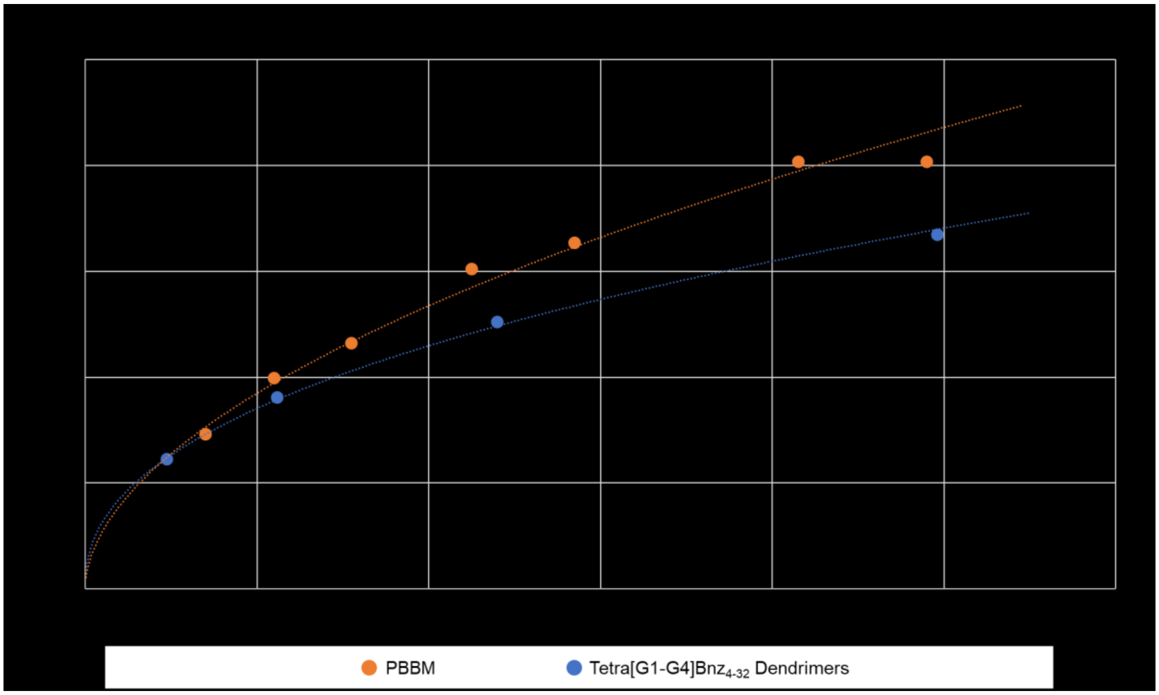


Figure 8. PBBM vs. Tetra[G1-G4] dendrimers M_n values acquired by MALDI-ToF MS and GPC in THF. GPC M_n values were used to calculate hydrodynamic radius values using an equation for polystyrene (PS) in THF from Mays and coworkers.[42]

As expected, the dendrimers appear to be "smaller" in hydrodynamic radius than their corresponding PBBM analogue despite similar molecular weights above ~M_n 2000. This is due to the branched nature of the dendrimer, meaning its molecular weight is spread out radially and not in a linear fashion as in the case of PBBM. At lower molecular weights, PBBM and the dendrimers appear to be similar in terms of apparent hydrodynamic volume, but as molecular weight increases the difference between them is as expected with the dendrimer appearing increasingly smaller by comparison despite similar M_n. Though this size analysis is preliminary, PBBM does appear to behave as we would expect a linear bis-MPA analogue would.

CONCLUSION

The synthesis of a linear, benzoyl-protected bis-MPA homopolyester, PBBM, is reported. This polymer can be synthesized on multigram scale in a range of solvents under basic conditions. Post-functionalization of this polymer has also been demonstrated on both the carboxylic acid and bromine ends. This novel polyester undergoes a chain-growth polymerization, possibly through a ring opening mechanism involving a propiolactone. Thermal analysis showed BBM has a lower melting point than its benzylidene-protected precursor. The glass transition temperature of 2 kDa PBBM was found to be about the same as the T_g of the corresponding Tetra[G2]Bnz_8 but has a lower degradation temperature according to TGA. Investigation of higher molecular weight analogues is necessary to confirm these thermal observations. Finally, preliminary size analysis shows PBBM is consistently larger than the pentaerythritol-core dendrimers in THF above M_n ~2000 despite similar molecular weights.

PBBM has been shown to be a good analogue for benzylidene-protected bis-MPA dendrimers due to its similar atom economy with the dendrimer benzylidene end group. Initial size data shows that high generation dendrimers have a lower size than their linear analogs, but a deeper investigation into how solvent may affect these results is required. In the future, we would like to look at how solvent affects the apparent size of PBBM when compared to the pentaerythritol-core dendrimers.

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SUPPORTING INFORMATION

The Supporting Information is available free of charge at ____. Synthetic procedures for benzylidene bis-MPA, and the synthesis of BBM; FTIR data for PBBM and MALDI-ToF MS data for PBBM; MALDI ToF MS and ^{1}H NMRs of the end group functionalizations for PBBM with azide terminal end group, and the dodecanoxy and benzyl ester end groups; the benzylidene protected bis-MPA dendrimers; the isolated fractions of PBBM; the bromine isotopic ratio of PBBM;; additional PBBM characterizations, and the HSQC NMR of the end groups.

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