Supporting Information

Biodegradable, multi-layered coatings for controlled release of small molecules

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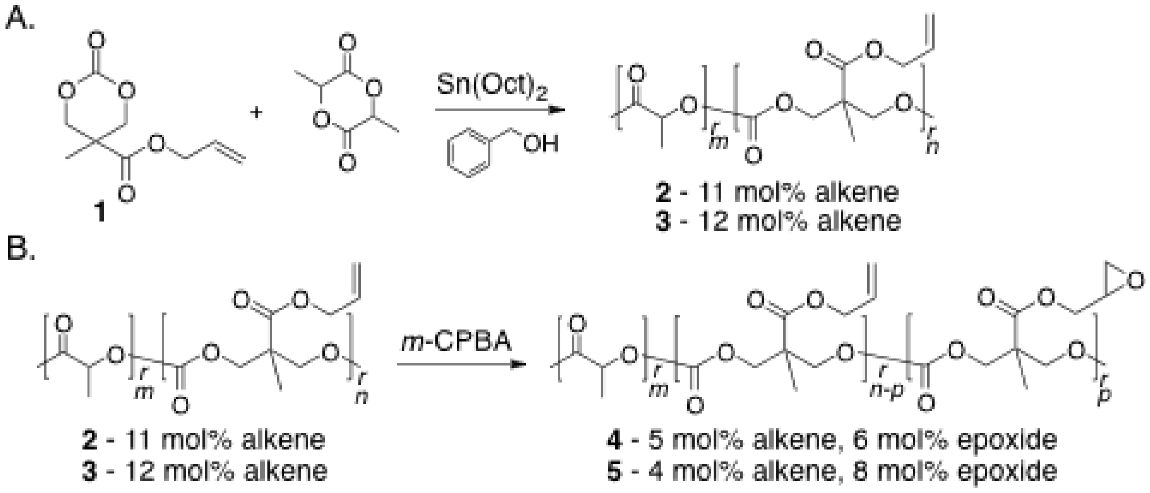
General

Chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. All materials were characterized by nuclear magnetic resonance (NMR) spectroscopy using Varian 400 and Varian 600 MHz spectrometers as indicated. Chemical shifts are reported in ppm and referenced to the solvent (proton and carbon). Fluorescence spectra were recorded on Varian Cary Eclipse Fluorescence Spectrometer using quartz cuvettes. Gel permeation chromatography (GPC) was performed in THF on a Waters system (Millford, MA, USA) equipped with four 5-mm Waters columns (300 × 7.7 mm) connected in series with increasing pore size (10^2, 10^3, 10^4, and 10^6 Å). Waters 410 differential refractometer index and Waters 996 photodiode array detectors were employed. The molecular weights of the polymers were calculated relative to linear PS standards. Scanning electron microscope (SEM) images were obtained at 5 kV and spot size value of 3, using a FEI XL30 Sirion FEG Digital Scanning Microscope. Since the samples were loaded having the cross-section perpendicular to the imaging detector, the SEM images of the face of the film were obtained at a tilt angle of 14°. The sample was immobilized on the sample holder using double-sided copper tape and a small drop of silver paste was cast at an edge to make contact between the face of the sample and the mount. A thin layer of gold was sputtered to avoid charge build-up in the non-conductive areas of the polymeric material.

Synthesis of dual-functionalized PLA

Alkene functional monomer **1** was synthesized from commercially available 2,2-bis(hydroxymethyl)propionic acid following literature procedure.[1] This compound can be synthesized in multi gram scale in only two steps that did not require any type of column chromatography. The pure carbonate product, **1**, was obtained as translucent crystals after recrystallization from hexanes. Next, ring-opening polymerization of **1** and D,L-lactide was carried out using benzyl alcohol as an initiator and stannous octoate as a catalyst. The reaction proceeded for 12 hours in hot toluene, followed by purification by several precipitations into hexanes to remove unreacted monomer and the catalyst. Two alkene-functionalized polymers, **2** and **3**, were synthesized having molecular weights of 27 and 35 kDa with polydispersity index of 1.6 and 1.5 respectively (Scheme 1A). These materials contained comparable degree of alkene functionality - 11% (polymer **2**) and 12% (polymer **3**), which was estimated from ^{1}H-NMR. Epoxidation of the double bonds in polymers **2** and **3** was carried out using *m*-chloroperbenzoic acid (*m*-CPBA) at room temperature (Scheme 1B). Reaction progress was monitored by ^{1}H-NMR and it was quenched after the desired ratio between epoxide and alkene groups was achieved. Polymer **4** contained 6% of epoxides and 5% of alkenes, whereas polymer **5** contained 8% of the epoxide groups and 4% of alkenes. After purification by several precipitations in hexanes both batches were isolated in nearly quantitative yield affording 3.0 grams of **4** (M_n = 27 kDa) and 7.0 grams of **5** (M_n = 35 kDa).

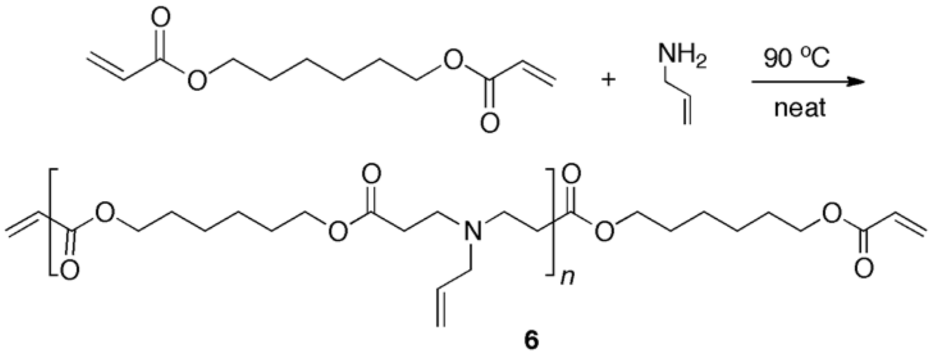


Scheme 1. Synthesis of epoxide and alkene-functionalized polymers **4** and **5**.

Polymer 4 was prepared in 93% yield by oxidation of the alkene-functionalized polymer **2**[1] using *m*-CPBA. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 5.94 - 5.82 (1H, m), 5.26 - 5.00 (24H, m), 4.59 (3H, s), 4.43 - 4.29 (16H, m), 3.97 - 3.90 (1H, m), 3.15 (1H, br s), 2.78 - 2.76 (1H, m), 2.58 (1H, br s), 1.54 - 1.45 (99H, m), 1.24 (12H, d, J = 5 Hz). ^{13}C NMR (150 MHz, $CDCl_3$, ppm): δ 171.79, 171.78, 171.76, 171.73, 171.70, 171.66, 171.63, 171.62, 171.60, 169.59, 169.57, 169.55, 169.51, 169.37, 169.30, 169.27, 169.25, 169.09, 154.28, 154.00, 131.49, 118.77, 118.73, 118.68, 118.49, 118.45, 71.55, 71.50, 69.14, 68.95, 68.92, 65.97, 65.93, 65.92, 65.89, 65.87, 65.82, 65.78, 65.75, 65.68, 65.61, 48.98, 48.93, 46.58, 46.48, 44.49, 44.45, 34.62, 31.54, 29.01, 25.23, 22.61, 18.70, 17.55, 17.49, 17.47, 17.41, 16.74, 16.71, 16.70, 16.63, 16.61, 16.59, 16.57, 14.08, 11.39.

Synthesis of alkene functional poly-β-aminoester 6

In order to obtain ene-functionalized poly-β-aminoester (**6**), polymerization was accomplished by mixing 1,6-hexane diacrylate and allyl amine without using a solvent or any additional reagents. The monomers were added to a round-bottomed flask in a 1:1.2 molar ratio having allylamine in excess and the reaction proceeded at 90°C for 24 hours, yielding viscous liquid of polymer **6** (Scheme 2). Polymer **6** was used without purification.



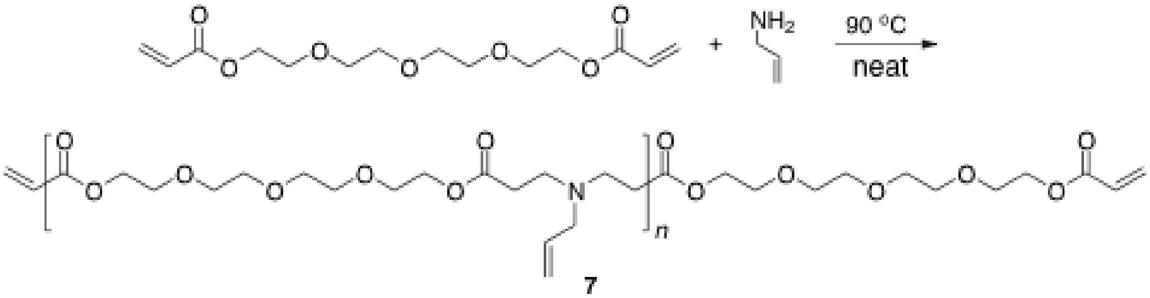
6

Scheme 2. Synthesis of poly-β-aminoester **6**.

Poly-β-aminoester 6 was synthesized from 1,6-hexane diacrylate and allylamine in 98% yield (M_n = 3 kDa, PDI = 1.8). ^{1}H NMR (600 MHz, $CDCl_3$, ppm): δ 6.33 (2H, dd, J_1 = 17 Hz, J_2 = 1 Hz), 6.05 (2H, dd, J_1 = 17 Hz, J_2 = 10 Hz), 5.77 - 5.70 (6H, m), 5.13 - 5.05 (9H, m), 4.09 (4H, t, J = 7 Hz), 3.99 (20H, t, J = 7 Hz), 3.03 (10H, d, J = 6 Hz), 2.72 (20H, t, J = 7 Hz), 2.38 (20H, t, J = 7 Hz), 1.63 - 1.55 (25H, m), 1.34 - 1.30 (25H, m). ^{13}C NMR (150 MHz, $CDCl_3$, ppm): δ 172.49, 166.15, 135.31, 130.45, 128.49, 117.40, 64.36, 64.23, 56.86, 48.86, 32.56, 32.55, 32.54, 28.44, 28.43, 25.53.

Synthesis of alkene functional poly-β-aminoester 7

Poly-β-aminoester (**7**) was synthesized from tetra(ethylene glycol) diacrylate and allyl amine as described above (Scheme 3). Polymer **7** was used without purification.



Scheme 3. Synthesis of poly-β-aminoester **7**.

Poly-β-aminoester 7 was synthesized from tetra(ethylene glycol) diacrylate and allylamine in 97% yield (Mn = 4 kDa, PDI = 1.7). ^{1}H NMR (600 MHz, $CDCl_3$, ppm): δ 6.38 (1H, dd, J_1 = 17 Hz, J_2 = 1 Hz), 6.11 (1H, dd, J_1 = 17 Hz, J_2 = 10 Hz), 5.81 - 5.72 (5H, m), 5.15 - 5.06 (8H, m), 4.27 (2H, t, J = 5 Hz), 4.18 (15H, t, J = 5 Hz), 3.71 - 3.60 (62H, m), 3.05 (8H, d, J = 7 Hz), 2.74 (15H, t, J = 7 Hz), 2.43 (15H, t, J = 7 Hz). ^{13}C NMR (150 MHz, $CDCl_3$, ppm): δ 172.38, 135.28, 130.95, 128.21, 117.46, 70.56, 70.55, 70.54, 70.49, 70.47, 69.07, 69.05, 63.61, 63.44, 63.43, 56.85, 48.80, 32.44.

Adhesion studies

Silicon wafers with a native oxide layer were used to optimize various parameters for the adhesion. These flat substrates were chosen as models for facile processability and characterization techniques. In order to expose free hydroxyl groups on the substrate surface we performed oxygen plasma treatment of the silicon wafers or glass slides for two minutes. Polymers **4** and **5** containing 6 and 8% of the epoxide groups respectively were subjected to the adhesion studies as well as non-functional PLA. Adhesion test were performed using a universal materials tester (CETR, Campbell, CA). A 1/8” borosilicate bead, cleaned with ethanol and water followed by plasma cleaning for 5 min, was used as the probe. The polymers, dissolved in chlorobenzene (10 g/ml), were spin coated onto 1 cm x 1 cm silicon wafers at 2000 rpm for 45 seconds. The polymer-coated wafer was then placed in an oven at 70 °C for 10 min to evaporate the solvent. In a typical adhesion test, the probe was brought into contact to the polymer film and a preload of 0.2 g was maintained for 30 s. The probe was then pulled off at a rate of 0.05 mm/s. The normal force F_z was recorded throughout the process. Adhesion tests were performed 50 times for each sample at different locations under ambient temperature and humidity.

Compound	**% Epoxide**	**Adhesion force (mN)**
PLA (control)	0	none
Polymer **4**	6	1.14 (±0.09)
Polymer **5**	8	1.53 (±0.08)

General procedure for fabrication of bilayer films

Formation of mono and bilayers was tested on SiO_2 surface as our model substrate. Rhodamine B was used as a model chromofore for the preparation of dye-loaded thin polymer films. 4,5-Dimethoxy-2-nitrobenzyl 2,4,6-trimethylbenzenesulfonate (DMNB) was used as thermal acid generator as it was shown that in solid state it decomposes to form acid after 1 hour at 135 ^{o}C.[2] Polymer **4** (200 mg) was dissolved in hexafluoroisopropanol (HFIP) to achieve 15 wt% solution. Rhodamine B was then added to the polymer solution giving a polymer/dye system containing 28 wt% dye, followed by the addition of catalytic amount of DMNB. Silicon wafers were cleaned by ultrasonication in acetone (twice at 15 min. each time) and iso-propanol (twice at 15 min. each time), and then treated with oxygen plasma for 2 minutes in order to expose hydroxyl groups on top of the surface. Films were spin coated onto the silicon wafers at

2000 rpm for 45 seconds and left to cure at 135°C for 1 hour. After the crosslinking, the excess of dye was removed by subsequent washing of the films with ethyl acetate. In order to introduce the second polymer coating, a solution of ene-functional poly-β-aminoester **6** in ethyl acetate (50 vol%) was prepared. To this solution pentaerythritol tetrakis(3-mercaptopropionate) (PTMP) was added in a 1:2 weight ratio with respect to polymer **6**, followed by the addition of catalytic amount of 2,2-dimethoxy-2-phenylacetophenon (DMPA). After spin coating the solution on top of the PLA-based coating, the curing of the second layer was conducted under exposure to UV-radiation at 365 nm for 2 minutes. SEM was used to determine the film thickness (Figure 1).

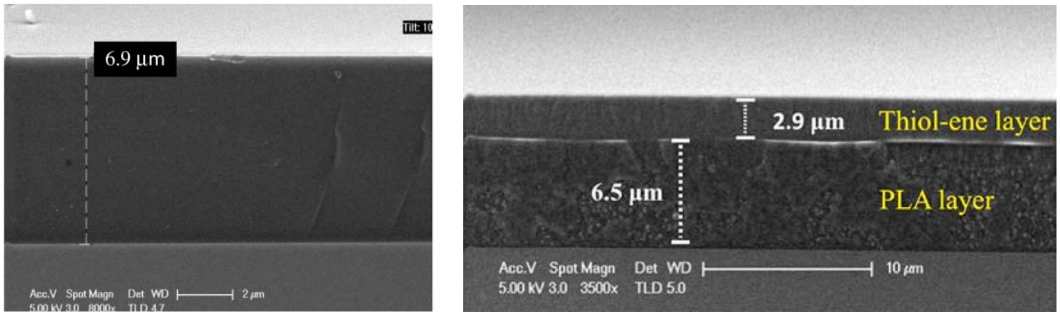


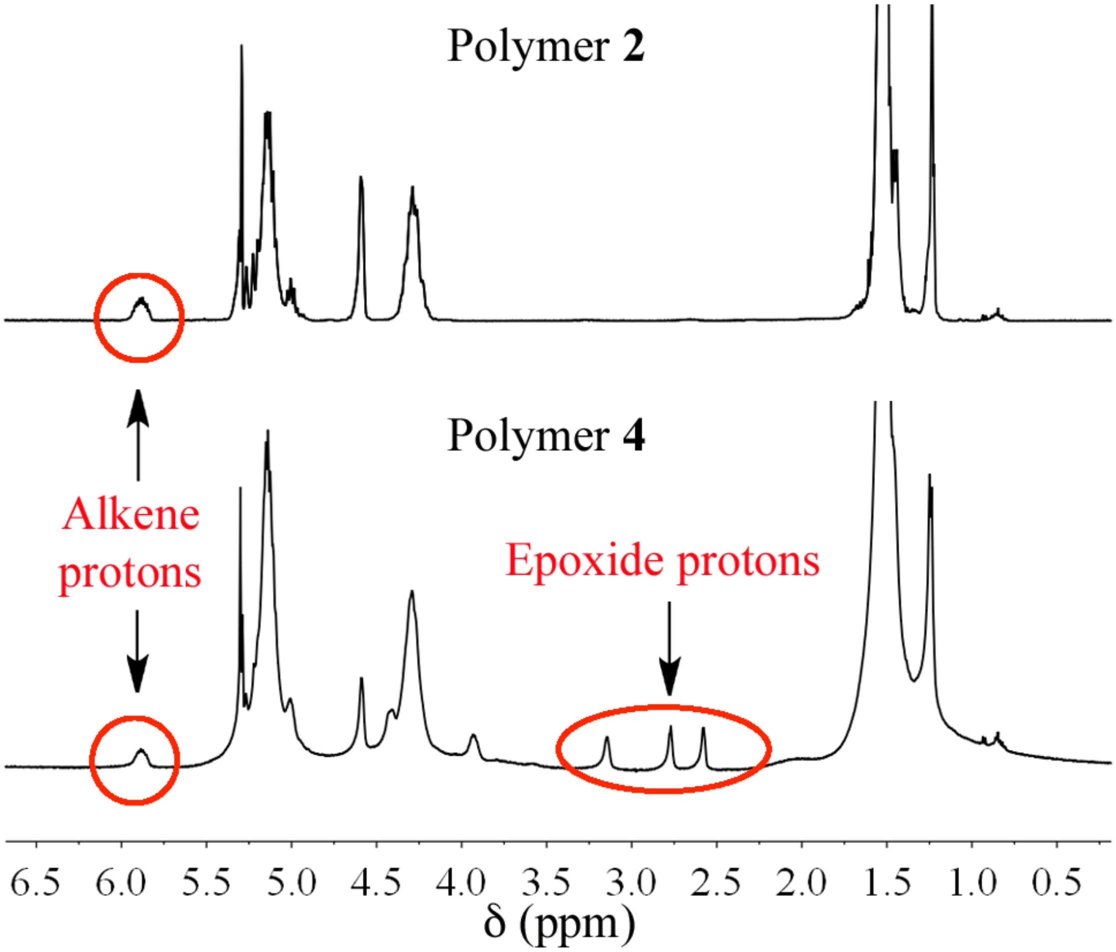
Figure 1. Left column) Monolayer of crosslinked polymer **4** with incorporated rhodamine B. Right column) Bilayer system consisted of the dye-loaded PLA-based layer and thiol-ene layer.

General procedure for dye-release experiment

Dye-release experiment was setup as follows: thin films containing rhodamine B were placed in vials containing 5 ml buffered saline (PBS, pH 7.4). The vials were kept at 37°C while monitoring the release of rhodamine B using fluorescence over a period of 25 days. This was done by collecting the dye containing PBS solution and then replacing it with 5 ml of fresh PBS solution every 24 hours.

References:

1. X. Hu, X. Chen, Z. Xie, S. Liu and X. Jing, *J. Polym. Sci. Part A*, 2007, **45**, 5518-5528.
2. J. Oberlander, S. Wanat, D. Mckenzie and E. Kokinda, *Proceedings of SPIE*, 2000, **3999**, 655-664.


Polymer **2**
Polymer **4**
Alkene protons
Epoxide protons
6.5
6.0
5.5
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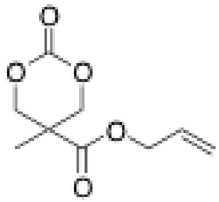
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
δ (ppm)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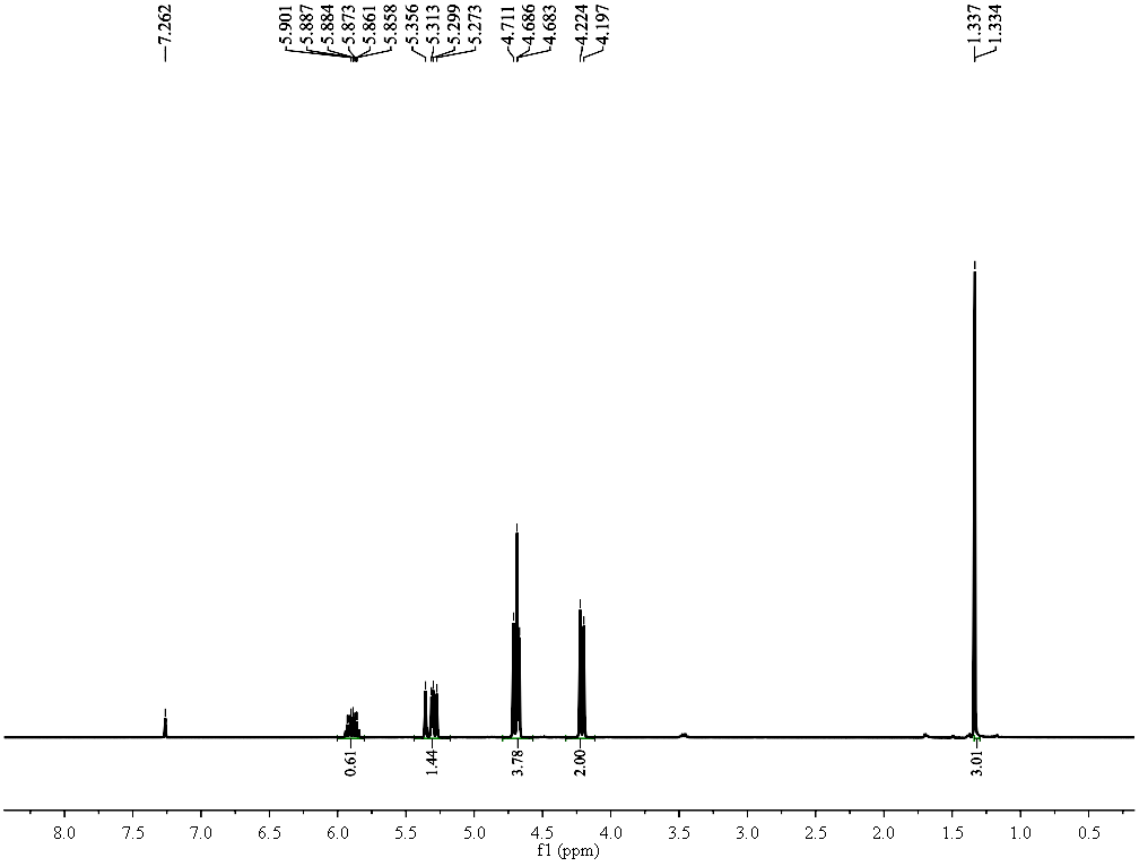
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4.683
4.224
4.197
1.337
1.334
0.61
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3.78
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7.5
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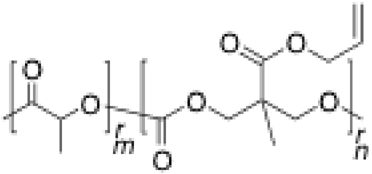
f1 (ppm)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m
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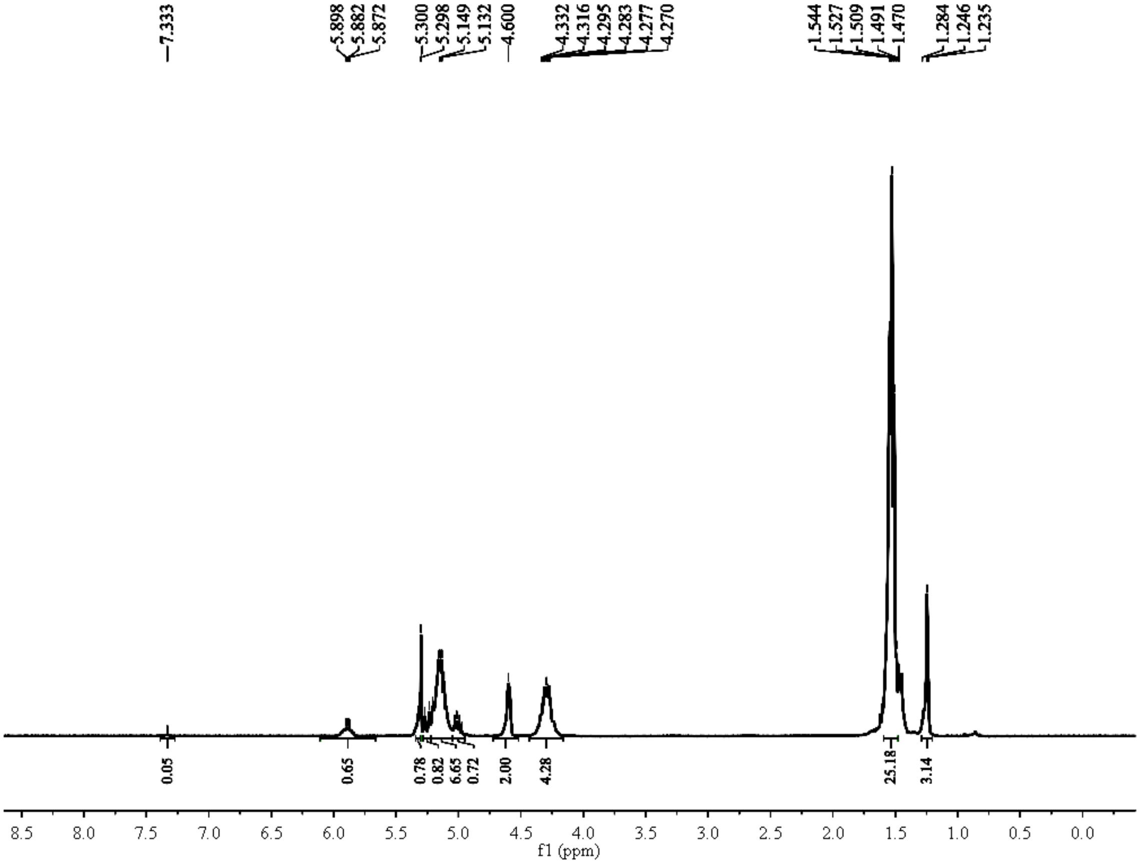
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0.78
0.82
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7.0
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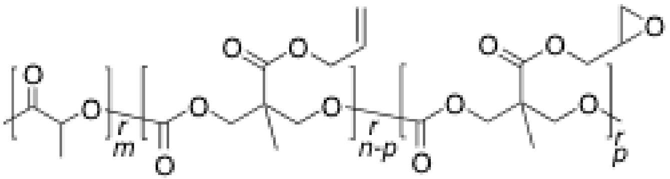
f1 (ppm)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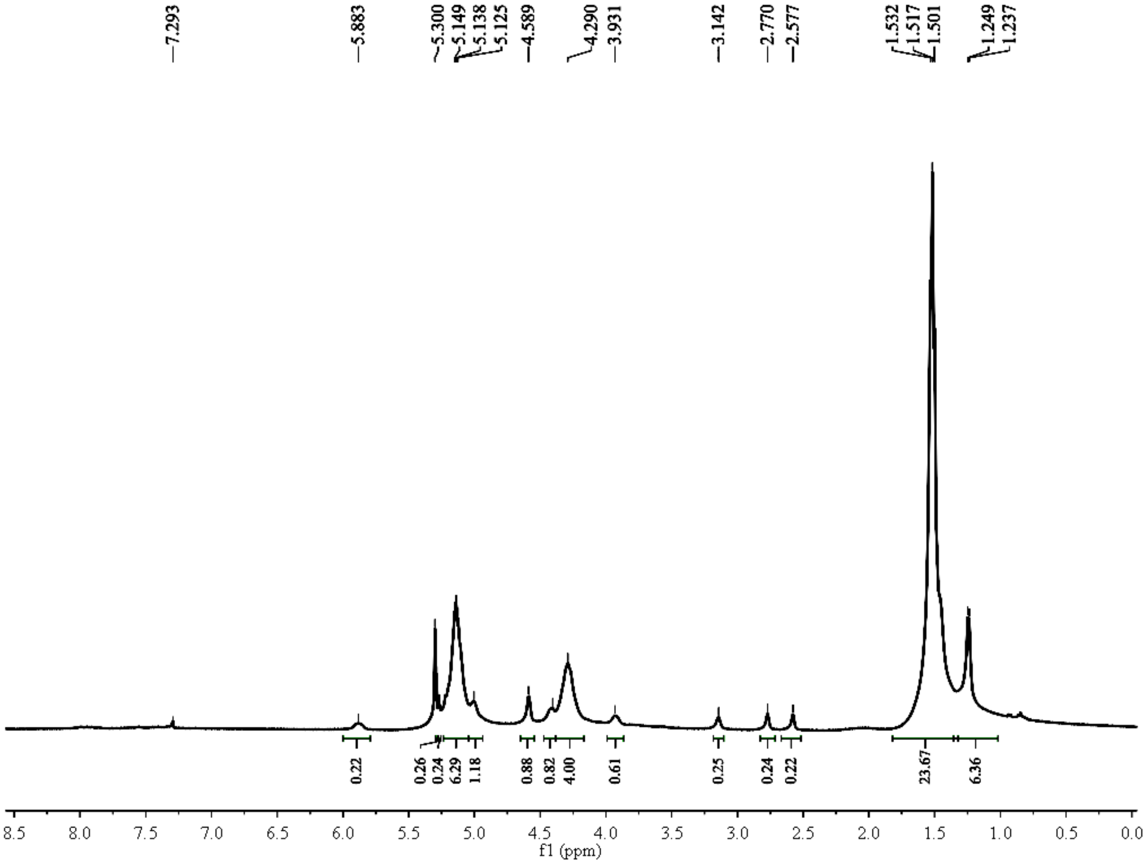
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