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Functional polyesters derived from alternating copolymerization of norbornene anhydride and epoxides†

Ryan Baumgartner,[a] Ziyuan Song,[b] Yanfeng Zhang[b] and Jianjun Cheng*[a,b]

Herein, we report the synthesis of polyesters *via* the alternating copolymerization of epoxides and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (NB). The polymers are demonstrated to be of perfectly alternating structure with monomodal peak distributions and low polydispersity indexes. We demonstrate that these polyesters can be functionalized using thiol–ene and tetrazine click chemistry to form polymers with alternating functionality. Furthermore, we show that these polymers can be made thermally responsive, and can even be crosslinked when mixed with Grubbs' catalyst.

The ability to functionalize polymers and macromolecular materials is essential for the creation of architecturally versatile and tunable systems for applications ranging from drug delivery[1–3] and gene therapy,[4–7] to biomaterials[8,9] and self-assembly.[10,11] To obtain these materials functional groups are often incorporated post-polymerization for the subsequent attachment of ligands, dyes, or other groups that may modify the physicochemical properties of the material.[12] Copolymer systems, in particular, are advantageous in developing highly tunable systems, as their chemical or physical properties can be further modified by varying the co-monomers. Most copolymer systems, however, have no sequence control and result in a random distribution of monomers.[13] The ability to control the sequence of monomer addition is highly desired as one can functionalize the polymer at specific monomers located in an ordered sequence along the polymer backbone giving rise to a wide variety of new polymeric architectures.[14,15] Relatively few examples exist in which highly functional, sequence controlled polymers with low polydispersity indexes (PDIs) can be synthesized in high yields with minimal post-polymerization modification reactions from simple precursors.[16–20]

Most functionalized polymer systems are limited to polymers containing an all-carbon backbone. This precludes their degradation in biological applications and limits their potential. Polyesters have long since been used in biological applications due to their biodegradability and biocompatibility. With regard to the synthesis of polyesters, the most commonly employed methods involve ring-opening polymerization (ROP) and polycondensation.[21] While the polycondensation strategy provides for a wide range of commercially available monomers, the PDIs of these polymers can be broad, and conditions necessary for their formation are often harsh.[21–23] The ROP of lactones, on the other hand, avoids these setbacks, yet lacks structural diversity, sequence control, and often requires lengthy multistep syntheses to achieve functional monomers.[24–26] The synthesis of polyesters through the alternating copolymerization between epoxides and anhydrides may overcome many of these setbacks, as monomers are commercially available, reaction conditions are mild, and resulting polymers have low PDIs. While previous transition metal catalysts for this polymerization have given low yields and/or relatively high PDIs,[27,28] recently, several catalyst systems based on complexes of Al(III),[29–31] Zn(II),[32–34] and Cr(III)[29,30,35] have been shown to be highly active and selective for the alternating incorporation of a variety of monomers which give polymers with low PDIs and high yields.

Several combinations of epoxides and anhydrides have been demonstrated to undergo alternating polymerization to form polyesters with modest to high molecular weights (MWs).[29,32,35–41] Of these monomers, limited functional handles have been incorporated, of which, none have been utilized in post-polymerization modification reactions. Unsaturated bicyclic based monomers are largely underutilized in polyesters, despite the favorable properties they impart into the resulting polymers such as high glass transition temperatures (T_g)[26,39] and, often, a uniquely reactive olefin. In this article we demonstrate that *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (NB) can be used as a new versatile co-monomer in the alternating polymerization with a variety of epoxides to make low to medium MW alternating polyesters.

[a]Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA. E-mail: jianjunc@illinois.edu
[b]Department of Materials Science and Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

Using tetrazine[42] and thiol–ene[43] click chemistry, we also demonstrate the ability to spatially functionalize the polyesters in a perfectly alternating manner. Lastly, we show the ability of these NB incorporated alternating polyesters to be used as macromolecular precursors to form cross-linked or thermo-responsive materials.

Using NB as a functional monomer, we first investigated its ability to undergo alternating polymerization with various model epoxides to form polyesters. While $Al(OiPr)_3$ and $Mg(OEt)_2$ were shown to be viable catalysts for this polymerization (Table S1, ESI†), the PDIs were higher and the conversions much lower than those obtained from the chromium(III) salen catalyst using DMAP as a co-catalyst. Thus, using the chromium(III) catalyst system we were able to control the polymerization of NB to proceed with high conversions in a perfectly alternating manner with a variety of epoxides (Scheme 1). Under these conditions we obtained well-defined polymers with modest MWs, ranging from 3.0 kDa for polymer **5** from styrene oxide (NB-*alt*-SO) to 5.8 kDa for polymer **1** containing epichlorohydrin (NB-*alt*-ECH) (Table 1). ECH required low

temperatures to achieve controlled polymerization, as polymerization at 110 °C resulted in polymer with a large molecular weight distribution. Other polymers derived from monomers such as the sterically hindered cyclohexene oxide (NB-*alt*-CHO) and phenyl glycidyl ether (NB-*alt*-PGE) also formed well defined polymers **3** and **4**, respectively, with higher MWs. High conversions were found for all polymers under these conditions except for polymer **6** from butylene oxide (NB-*alt*-BO) which is likely due to evaporative losses during the longer polymerization times near the boiling point of BO. All of the polymerizations are found to have MWs much lower than expected based upon the [M] : [I] ratio. Water or trace hydrolyzed anhydrides are known to act as chain transfer agents in this polymerization and since water was not rigorously removed from the NB monomer, this causes the lower MWs.[37,44] From entry **7** performed with rigorously dried NB, we observe over a five-fold increase in MW, demonstrating the importance of dry, pure monomers. In addition, a bimodal peak shape appears in the higher MW samples, similar to results from other groups (Fig. S1, ESI†).[30,34–36,39] It is likely a small amount of hydrolyzed anhydride remains in the monomer, or is formed during the reaction leading to bi-metallic catalytically active species which form the higher MW polymer distribution. We elected to use the lower MW polymers for further study as functionalization would be easier to determine *via* matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF).

The alkene functional groups in the allyl and norbornene groups were found to be tolerant to polymerization conditions. The ^1H NMR spectra for all polymers showed resonances at δ 6.25 ppm corresponding to the intact olefin of norbornene (Fig. S2–S9, ESI†). Additionally, resonances near δ 4.2 ppm for all samples confirmed the formation of a polyester resulting from the alternating incorporation of epoxides and anhydrides into the polymer backbone. PDIs of polymerizations were usually less than 1.2, with monomodal molecular weight distributions for the low MW polymers.

Due to the rigidity of the norbornene molecules, we expected to observe high glass transition temperatures (T_g) for many of these polymers, depending upon the epoxide used. Thermal analysis of the polymers with differential scanning calorimetry (DSC) showed a wide range of T_g's (Table 1). Polymer **2** derived from allyl glycidyl ether (NB-*alt*-AGE) showed the lowest T_g due to the long aliphatic side chains, while rigid molecules such as CHO gave a polymer with a high T_g of 117 °C. Since many of these polymers are of low MW (<3 kDa), further increasing the MW should further increase the T_g's, and indeed they do. Comparison of NB-*alt*-PGE at low (**3**) and high MW (**7**) show an increase in T_g from 56 °C to 62 °C.

To determine whether other norbornene analogs would survive the polymerization conditions we also conducted polymerizations of *cis*-5-norbornene-*exo*-2,3-dicarboxylic anhydride, *cis-endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride, and methyl-5-norbornene-2,3-dicarboxylic anhydride with AGE as a model epoxide (Table S1, ESI†). These polymers
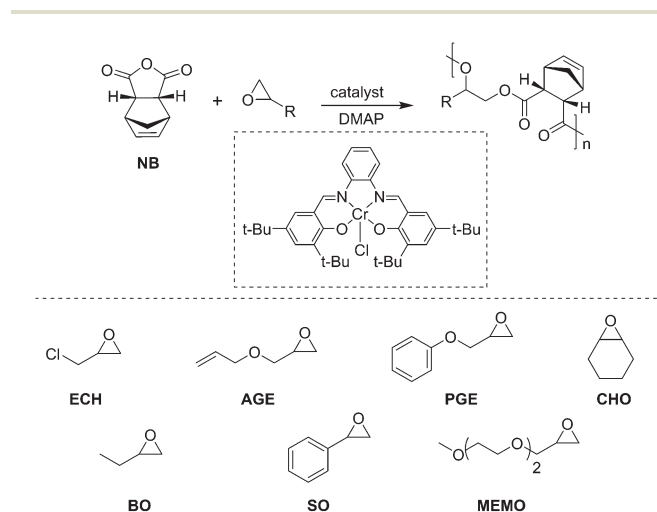
Scheme 1 Polymerization of NB with various epoxides mediated by a chromium(III) based salen catalyst and DMAP as a co-catalyst.

Table 1 Polymerization of NB with various epoxides[a]

Entry	Epoxide	% Conv.[e]	M_n[f] (kDa)	M_w/M_n[f]	T_g (°C)
1[b]	ECH	89	5.8	1.11	47
2	AGE	95	3.3	1.04	9
3	PGE	98	3.1	1.02	56
4	CHO	97	3.0	1.02	117
5	SO	94	3.0	1.12	87
6[c]	BO	67	3.0	1.04	18
7[d]	PGE	>99	17.0	1.24	62
8	MEMO	93	3.4	1.14	14

[a] Reaction conditions: [NB] : [epoxide] : [cat] : [DMAP] = 250 : 250 : 1 : 1 in toluene, 110 °C, 5 h. [b] Performed at 50 °C for 20 h. [c] Performed at 60 °C for 20 h. [d] Polymerization performed with NB dried over CaH_2. [e] Conversion NB (%) determined from ^1H NMR. [f] Determined from GPC-RI analysis in THF.
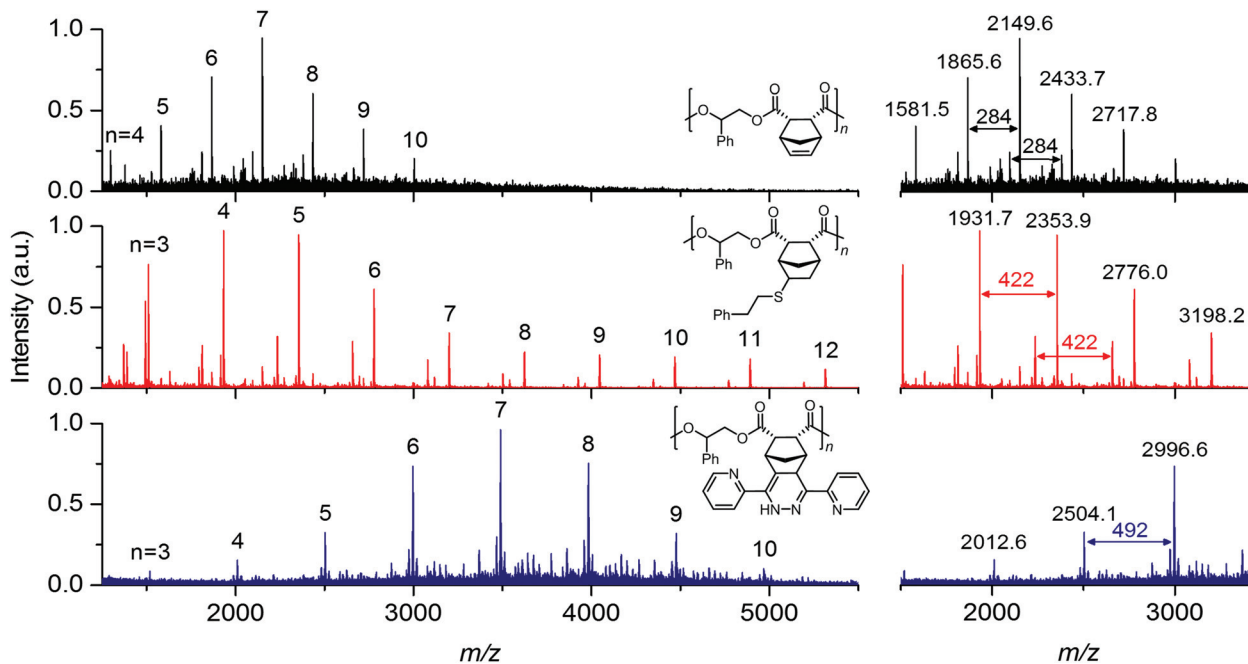
Fig. 1 MALDI-TOF of polymer **5** (a) before functionalization, (b) after thiol–ene click with 2-phenylethanethiol, (c) after iEDDA click with 3,6-di-2-pyridyl-1,2,4,5-tetrazine.

were successfully polymerized to high conversion with MWs of up to 12.6 kDa. PDIs for these polymers were slightly higher and peak distributions were partially bimodal, however, according to ^{1}H NMR the alkenes remained intact for all of these polymers (Table S1, Fig. S10–S13, ESI†).

Using MALDI-TOF, the alternating structure of the polymers was confirmed. From the MALDI-TOF spectrum of **5** (Fig. 1a), we observe the perfectly alternating structure with regular spacing of the repeat unit (m/z = 284) with no peaks corresponding to ether bond formation which would result from sequential epoxide addition into the polymer backbone. The main sequence of peaks is comprised of the SO terminated polymer, evidenced by the smaller distribution of peaks with equivalent repeating unit shifted to a lower molecular weight by m/z = 120, the mass of the SO monomer. This minor distribution of peaks corresponds to that of the NB terminated polymer.

With well-defined polymer distributions arising from copolymers of NB and retention of the reactive alkene groups spaced periodically along the backbone, we utilized both thiol–ene and tetrazine based click chemistry, to functionalize polymers on alternating residues (Scheme 2). We first treated polymer **5** with 2-phenylethanethiol and DMPA under UV light in THF for 1 hour yielding the desired polymer **5a** as a yellow solid after precipitation from hexanes. From the ^{1}H NMR of the polymer, we observe the complete disappearance of the alkene peaks of NB which appear at δ 6.25 ppm and appearance of several other aliphatic peaks corresponding to the attached thiol (Fig. S14, ESI†). The appearance of additional resonances in the aromatic region further confirm the attach-
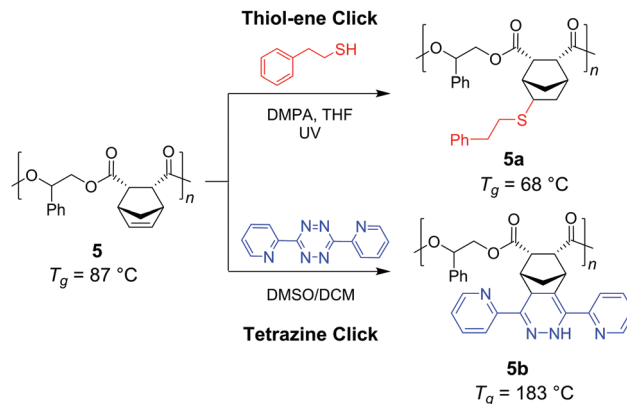
Scheme 2 Periodic functionalization of NB-*alt*-SO (**5**) using thiol–ene click chemistry or tetrazine click chemistry.

ment of 2-phenylethanethiol. Analysis of **5a** carried out using MALDI-TOF confirmed the perfectly alternating functionalization of **5** (Fig. 1b). Upon reaction of the norbornene residues with 2-phenylethanethiol, a larger repeating unit is observed with a spacing of m/z = 422, consistent with the addition of 2-phenylethanethiol across the double bond. The spacing between repeating units is consistent with addition to only the alkene of norbornene with no transesterification occurring. As was observed in the MALDI-TOF of **5**, we see the identical minor distribution of NB terminated polymer shifted 120 m/z units below that of the major distribution, further confirming no additional extraneous reactions. The spacing between

peaks in this minor distribution remains 422 m/z. In addition, we observe a change in the T_g of the polymer, decreasing slightly to 68 °C. The added flexibility of the ethyl spacer of 2-phenylethanethiol leads to this shift.

Tetrazine based click chemistry has also been reported as an efficient method for installing functional groups onto norbornene based polymers.[45,46] We reasoned that the inverse electron-demand Diels–Alder reaction (iEDDA) between tetrazine and NB would allow efficient functionalization of the polyesters on alternating residues. The reaction of model compound 3,6-di-2-pyridyl-1,2,4,5-tetrazine with **5** proceeded at room temperature in a DMSO/DCM mixture to yield the final functionalized polymer **5b** in good yield. The ^{1}H NMR spectrum confirmed the disappearance of the alkene peaks of NB at δ 6.25 ppm, with the concurrent appearance of many new aromatic peaks arising from the incorporated pyridine groups (Fig. S15, ESI†). Additionally, the reaction with the rigid, aromatic tetrazine unit significantly altered the T_g of the polymer, raising it from 87 °C to 183 °C demonstrating how post-polymerization modification can drastically modify the physical properties of the polymer. Analysis of **5b** using MALDI-TOF again confirmed the perfectly alternating functionalization of the polymer (Fig. 1c). The reaction with tetrazine shows an increase in the mass of the repeating unit, with a difference of m/z = 492, which agrees perfectly with the addition of tetrazine across the double bond with the concomitant loss of nitrogen. Both of the click reactions maintain the perfectly alternating structure of the polymer with no side reactions. The MW distribution of polymers also remain monomodal after functionalization, as observed by GPC (Fig. S16, ESI†).

Having demonstrated the utility of the olefin of NB and the specificity to which the functionalization reactions take place, we also desired to utilize the ability of norbornene to undergo ring-opening metathesis polymerization (ROMP) to create crosslinked materials. Utilizing the pendent norbornene groups along the polymer, we were able to crosslink the polymer using Grubbs' 3rd generation catalyst in a DCM solution (Fig. 2a). A solution of **5** was crosslinked in under 3 hours upon the addition of Grubbs' 3rd generation catalyst to form a soft organogel. While Grubbs' 3rd generation catalyst is known to be very active,[47] it is likely that residual DMAP in the

polymer acts to suppress its activity leading to the extended time for gelation.[48] The ability to substitute various epoxides in the alternating polymerization with NB may allow for fine tuning of the structural properties of the gels as well as for the incorporation of functional groups through the preserved olefin, as ROMP retains its functionality. In addition to forming crosslinked materials, the functional handle of norbornene would also lend itself useful in thermoresponsive materials. Deng and coworkers have previously demonstrated the utility of oligoethylene glycol pendent side chain alternating polyesters to make thermoresponsive materials for biomedical applications.[49–51] Incorporating functional monomers such as NB into thermoresponsive materials should further broaden their applications. Copolymerization between NB and 2-((2-(2-methoxyethoxy)-ethoxy)methyl)oxirane (MEMO) resulted in temperature responsive polymer **8** (NB-*alt*-MEMO) having a lower critical solution temperature (LCST) of 17 °C (Fig. 2b). While the LCST of this polymer is significantly lower than analogues based off of succinic anhydride (LCST = 49 °C),[50] the transition remains sharp, being essentially complete in a temperature change of 6 °C. The lower LCST is likely due to the larger and more hydrophobic NB monomer which decreases the ability of water to solvate the polymer. This polymer still contains the functional double bonds of the norbornene and, as such, is able to undergo further modifications to introduce functionality to this temperature responsive material.

Conclusions

In summary, we utilized the alternating ring opening polymerization between NB and various epoxides to form polyesters which contained low PDIs. The T_g's for these polymers ranged from 9 °C to 117 °C for un-substituted NB's, increasing to up to 183 °C for tetrazine reacted polymer **5b**. The functionalization of the NB incorporated polyesters proceeded in a highly efficient and well-controlled manner, modifying only the NB residues producing polyesters with functional groups incorporated on alternating residues. The reactive olefin of NB within the polyesters reacted with both thiol and tetrazine containing molecules using thiol–ene and tetrazine based click reactions, respectively. In addition, we synthesized thermoresponsive polymers using MEMO as an epoxide imparting LCST behavior with a transition occurring at 17 °C. The NB functionality in the polyester was also employed in ROMP based crosslinking reactions to create organogels. Using these crosslinked polyesters, we are currently investigating the feasibility of creating ROMP based, thermosetting resins. In addition to this application, we expect that the functionality of these NB containing polyesters holds potential for creating a wide variety of new functional biomaterials.
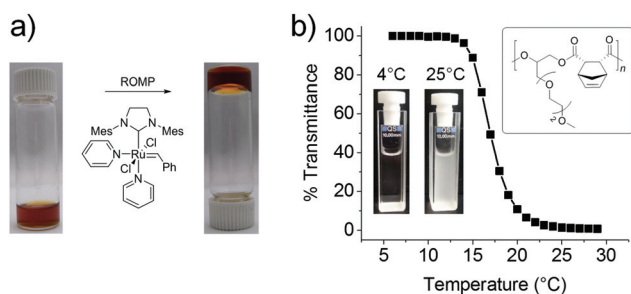
Fig. 2 (a) Organogel formed after crosslinking of **5** with Grubbs' 3rd generation catalyst (b) LCST transition for **8** (NB-*alt*-MEMO) (LCST = 17.0 °C).

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