Published in final edited form as:
Macromolecules. 2011 April 26; 44(8): 2660–2667. doi:10.1021/ma200021m.

A Versatile Monomer for Preparing Well-Defined Functional Polycarbonates and Poly(ester-carbonates)

Jianwen Xu, **Fioleda Prifti**, and **Jie Song***
Department of Orthopedics and Physical Rehabilitation, Department of Cell Biology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA

Abstract

Despite the increasing demands for functional degradable biomaterials, strategies for generating materials with modular compositions and well-defined functionalities from common building blocks are still lacking. Here we report an azido-functionalized cyclic carbonate monomer, AzDXO, that exhibited controlled/"living" ring-opening polymerization kinetics under the catalysis of 1,8-diazabicyclo[5.4.0]-undec-7-ene. Homopolymerization of AzDXO and copolymerization of AzDXO with lactide resulted in polycarbonate and poly(ester-carbonates) with well-defined composition and narrow polydispersity. Further side-chain functionalizations of these polymers were accomplished under facile conditions via copper-catalyzed or copper-free strain-promoted azido-alkyne cyclcoaddition. This versatile monomer building block, obtainable in two steps without tedious purifications, provides a practical solution to the preparation of well-defined functional polycarbonates and poly(ester-carbonates).

Keywords

Polycarbonate; Poly(carbonate-ester); Ring-Opening Polymerization; Click chemistry; Degradable Materials

Introduction

Biodegradable polymers that share core structural features while exhibiting incremental variations in chemical functionalities and physical properties are valuable for screening optimal drug delivery vehicles and tissue engineering scaffolds.[1,2] By tuning macromolecular architectures, compositions and molecular weights, degradable materials with a broad range of mechanical properties and degradation profiles have been developed.[3,4] Among them, aliphatic polycarbonates have attracted increasing interest due to their non-acidic degradation products and potential to introduce properties complementary to those obtainable by other degradable polymers.[5-10] The hydrophobic nature and the lack of side chain functionalities of polycarbonates, however, have limited their biomedical applications.[11] Indeed, such limitations are shared by synthetic biodegradable polymers in general, including the more extensively studied polyesters, polyanhydrides, and polyorthoesters.[12-14]

Current methods for imparting functionalities and improving the hydrophilicity of biodegradable polymers include post-polymerization surface irradiation grafting,[15] post-

* Jie.Song@umassmed.edu .

Supporting Information Supporting figures and tables of detailed NMR, DSC, FTIR characterizations of polymerization kinetics, copolymer compositions, microstructures, and the side-chain functionalziations by CuAAC could be found in the supporting information. This information is available free of charge via the Internet at http://pubs.acs.org/.

polymerization end-group modification,[16] polymerization initiated by hydrophilic/functional polymer precursors,[17,18] and (co)polymerization of functional monomers.[19-32] Among them, (co)polymerization of functional monomers provides a straightforward way to introduce functionalities and hydrophilicity with better-controlled polymer compositions and structures given that suitable monomers could be designed.[21,23] However, due to the incompatibility of most reactive groups (e.g. hydroxyls,[21,24,33-35] amines,[26,36] carboxyls,[37-39] and thiols) with the polymerization conditions, cumbersome protection and post-polymerization deprotection involving heavy metal catalysts and lowering overall yields are often required. The degradable nature of the backbone of these polymers also imposes additional challenges to the preparation of well-defined functional derivatives. A monomer functionalized with reactive groups orthogonal to polymerization conditions and could enable facile post-polymerization functionalization without tedious protection/deprotection is highly desired.[40,41] Towards this end, several monomers with "clickable" functionalities including alkyne-[42-46] and (methyl)acrylate-containing[47] lactones or carbonates have been prepared. Here we reported the preparation of an azido-substituted cyclic trimethylene carbonate monomer, its controlled homopolymerization and copolymerization with lactide, and the facile functionalization of the resulting polycarbonates and poly(ester-carbonates) via copper-catalyzed (CuAAC)[48] and strain-promoted (SPAAC)[49] azido-alkyne cycloaddition "click" chemistries.

Results and Discussions

Monomer Design and Preparation

High molecular weight polyesters and polycarbonates are usually prepared by ring-opening polymerization (ROP) of cyclic monomers.[50] Conventional catalysts and polymerization conditions employed in ROP could result in relatively broad molecular weight distributions and unexpected ether formations.[7,51] Recent developments on organic catalysts for ROP [52,53] have made it possible to prepare well-defined polyesters and polycarbonates (PDI <1.1) under mild conditions.[52-59] A general method for preparing functional poly(ester-carbonates) with well-defined compositions and structures, however, is yet to be developed. Our goal is to develop an azido-functionalized cyclic carbonate monomer that exhibits ROP kinetics similar to that of the ROP of lactides under the same mild conditions enabled by organic catalyst 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). Such an approximation of polymerization kinetics could enable poly(ester-carbonates) with both random and block architectures be prepared with well-defined compositions and narrow polydispersity. The choice of the azido functionality [60] over alkyne or acrylate as a "clickable" group of the monomer is mainly inspired by its ability to withstand most basic and acidic conditions as well as temperatures up to 130 °C where alkynes and acrylates tended to self-crosslink or participate in free radical polymerizations.[61,62] In addition, the availability of many commercialized alkyne and cyclooctyne derivatives [63] makes the post-polymerization functionalization with or without copper catalyst straightforward. Finally, the azido groups could also enable functionalizations via Staudinger ligation, which could be useful for certain biological investigations both *in vitro* and *in vivo*.[64]

Specifically, we designed 5,5-bis(azidomethyl)-1,3-dioxan-2-one (AzDXO, Figure 1a) as the functional monomer. AzDXO was synthesized from 2,2-bis(bromomethyl)propane-1,3-diol [65-68] in 2 steps with an overall yield of 45.6% . High purity (>99%) product was obtained by recrystallization purification. Despite its high azido content, the monomer was safe to handle during room temperature. No decomposition or explosion was observed when it was vacuum-dried at 90 °C for 2 days, although like all azido compounds, this monomer should always be handled with precaution.

Polymerization Kinetics

AzDXO could be polymerized with both conventional transition metal catalyst stannous octoate and organocatalysts such as 1,5,7-triazabicylco[4.4.0]dec-1-ene (TBD) and DBU, with DBU exhibiting the best control over the polydispersity (PDI<1.1) among the three, thus of particular interest to us. Comparing to TBD, DBU is a less basic organocatalyst with lower catalytic activity, yet demonstrated better control over PDI in the polymerization of trimethylene carbonate.[52] Here we focus the ROP of AzDXO using DBU as a catalyst. ROP of AzDXO was carried out at room temperature in deuterated chloroform with DBU (0.01M) as the catalyst. The polymerization kinetics was studied using benzyl alcohol (Bz) as an initiator (Figure 1a) and monitored by gel permeation chromatography (GPC) and ^{1}H NMR spectroscopy. The polymerization occurred instantly upon the addition of DBU, as supported by the decrease of the intensity of the GPC signal of the monomer (at 19.35 min) and the appearance of a new, earlier-eluting peak (around 18.10 min) as early as at 20 sec (Figure 1b). The polymerization was almost completed by 60 min as supported by the disappearance of the monomer peak. ^{1}H NMR monitoring (Figure S1) revealed similar polymerization kinetics. The number-averaged molecular weight (M_n) of Bz-P(AzDXO$_n$) determined from GPC exhibited a linear positive correlation with the monomer conversion, with the low polydispersity index (PDI <1.1) maintained as the M_n increased (Figure 1c), supporting that the initiating sites remained active during the polymerization. The minimal increase of PDI at very high conversion (PDI still well below 1.1) was likely due to decreased solubility of the higher molecular weight active species and led to some chain termination. It was previously shown that under the catalysis of DBU, cyclic carbonate and lactone could be polymerized in controlled/"living" anionic ROP, with a presumed hydrogen-bonding interaction between the initiating alcohol and the nucleophilic nitrogen of DBU.[58,69] Our results indicate that the ROP of AzDXO proceeded in a similar fashion. The plot of ln([M]$_0$/[M]) versus time revealed a linear first-order polymerization kinetics (Figure 1d), indicating that the concentration of the growing end remained constant during polymerization and further supporting the living polymerization mechanism. The ROP rate constants of AzDXO and L-lactide (L-LA) under identical reaction conditions were determined as 0.084 min^{-1} and 0.116 min^{-1}, respectively. These relatively close rate constants make it possible to prepare copolymers of L-LA and AzDXO in a controlled manner without significantly changing the polymerization conditions.

Thermal Properties of Homopolymers

The thermal properties of homopolymer Bz-P(AzDXO$_n$) (n = 20, 40 or 80) were analyzed by differential scanning calorimetry (DSC). All homopolymers exhibited large endothermic melting peaks around 50-100 °C (Figure 2), with melting point (T_m) increased from 86.31 to 98.43 °C while melting enthalpy (ΔH_m) remained constant around −52.0 J/g as the chain length increased from 20 to 80 repeating units (Table S1). After quenching the melts to −50 °C, a glass transition slightly below 0 °C was detected from the second heating scan in all homopolymers, with the T_g slightly increasing as the chain length increased. In comparison, the most studied aliphatic polycarbonate poly(trimethylene carbonate) of comparable molecular weights exhibited T_g's ranging from −26 to −15 °C, a T_m of 36 °C and ΔH_m of −4.5 to 10 J/g.[10]

Copolymerization of AzDXO and L-LA

The comparable DBU-catalyzed homopolymerization rates observed with AzDXO and L-LA make the preparation of copolymers of AzDXO and L-LA straightforward (Figure 3a). To investigate the copolymerization behavior of AzDXO with L-LA, equal concentration of the monomers (1.0 M) were polymerized in $CDCl_3$ using 1-pyrnenbutanol as initiator at a monomer/initiator/catalyst ratio of [AzDXO] : [L-LA] : [1-pyrenebutanol] : [DBU] = 50 : 50 : 1 : 0.5. Both monomers began being incorporated into the polymer chains at as early as

30 sec with 5.0% conversion for AzDXO and 16.8% conversion for L-LA (Figure 3b). Both monomers reached near complete conversion (~97%) after 1 h, with the M_n of the copolymer steadily increasing with higher monomer conversions while the PDI remaining low (PDI<1.10) during the copolymerization. The respective polymerization rate constants (k) for the two monomers, determined by fitting the $\ln([M]_0/[M])$ versus time plots (Figure 3b), revealed a faster polymerization rate for AzDXO ($k = 0.061\ min^{-1}$) than for L-LA ($k = 0.171\ min^{-1}$) during the one-step copolymerization. By contrast, homopolymerization rate constants for L-LA and AzDXO determined at the same monomer concentration and catalyst-to-initiator ratio (Fig. 1d) were $0.116\ min^{-1}$ and $0.084\ min^{-1}$, respectively. The higher rate constant observed for L-LA during its copolymerization with AzDXO than during its homopolymerization may be explained by the fact that alternating primary alcohol (higher reactivity) and secondary alcohol (lower reactivity) chain ends were generated during the former whereas only secondary alcohol chain ends were produced during the latter. A copolymer with a gradient composition favoring higher L-LA content at one end and higher AzDXO at the other is likely. Overall, these rate constants suggest that although the compositions of the copolymers of AzDXO and L-LA generated by this one-step monomer feeding method would not be perfectly alternating, the formation of polymer domains extensively enriched for one monomer (thus causing phase separation) would not occur as supported by subsequent DSC characterizations.

Using ethylene glycol as an initiator, random copolymers with varying compositions and narrow PDI (~1.1, Table S2) were successfully prepared by simultaneous addition of the two monomers (Figure 3a). By changing the monomer feed ratios during the one-step random copolymerization, materials with altered crystallinity and thermal properties could be prepared. The T_m's and ΔH_m's of the random copolymers decreased with the increase of AzDXO content (Figure S2, Table S2) while their physical appearance changed from crystalline white powders to semi-crystalline translucent solids to amorphous transparent resins. Although homopolymers EG-P(LLA_{100}) and EG-P($AzDXO_{100}$) are both highly crystalline materials with a ΔH_m of −50.0 J/g and −47.8 J/g, respectively, their equal molar ratio random copolymer EG-P(LLA_{50}-co-$AzDXO_{50}$) was amorphous as indicated by the lack of melting peaks (Figure S2d), supporting a random distribution of AzDXO and L-LA along the copolymer chains.

Block copolymers tethered by two or more distinct chain segments can exhibit unique properties distinctive from those of the corresponding homopolymers and random copolymers.[70] Block copolymers can be prepared by sequentially growing the blocks using different polymerization techniques following proper end-group manipulations.[71-74] Alternatively, they can be prepared using the same polymerization technique (e.g. Atom Transfer Radical Polymerization [75] and Reversible Addition–Fragmentation Chain Transfer Polymerization[76]) under identical reaction conditions by feeding monomers of interest in batches. The latter strategy eliminates the need for end group functionalization and is potentially far more efficient during scale-ups. The incompatibility of many organic functional groups with ROP conditions, however, has made it difficult to broadly apply such a strategy to the preparation of functional biodegradable block copolymers. Compatible with ROP conditions and with a ROP rate constant comparable to that of L-LA, AzDXO offers a unique opportunity to the efficient preparation of functional poly(ester-carbonate) block copolymers.

To test our hypothesis, we prepared block copolymer Pyrene-P(LLA_x)-b-P($AzDXO_y$) with fixed L-LA block length (x = 100) and varying AzDXO block lengths (y = 5, 10, 20, 35) by DBU-catalyzed ROP at room temperature using 1-pyrenebutanol as the initiator. 1-Pyrenebutanol was chosen for easy monitoring of the polymerization by GPC and NMR due to its strong UV-vis absorption and distinct down-field ^1H NMR signals away from those of

the polymeric units. The rapid polymerization (<1 h) and high conversion of monomers (>99%) under the employed conditions enabled the sequential feed of monomers without the need for purification of the first polymer block. All block copolymers were prepared in quantitative yield with narrow polydispersity (Table 1).

Representative GPC traces for Pyrene-P(LLA_{100}) and Pyrene-P(LLA_{100})-b-P($AzDXO_{35}$) (Figure 4a) show that both ELS and UV-vis peaks shifted to an earlier elution upon feeding the second monomer AzDXO while the peak shapes remained unchanged. The drop in intensity of UV-vis signal upon the polymerization of the P($AzDXO_{35}$) block supports that the polymerization of AzDXO was initiated by the Pyrene-P(LLA_{100}) block. ^{1}H and ^{13}C NMR (Figures S3 and S4) showed two distinct groups of peaks correlating to the two functional blocks in the block copolymer whereas broader and more scattered peaks for the random copolymer. The microstructural difference of the copolymers also translated into distinctive thermal properties. As the AzDXO block grew longer after the L-LA block, the appearance of two distinct melting peaks and two distinct glass transitions in the block copolymer became apparent (Figure S5). For instance, Pyrene-P(LLA_{100})-b-P($AzDXO_{20}$) exhibited two melting peaks (T_m^1 = 80.6 °C; T_m^2 = 143.6 °C) and two glass transitions (T_g^1 = −1.5 °C; T_g^2 = 48.7 °C) that resembled the respective transitions for the homopolymers Pyrene-P(LLA_{100}) and P($AzDXO_{100}$) (Figure 4b), supporting the block microstructure. By contrast, the random copolymer Pyrene-P(LLA_{100}-*co*-$AzDXO_{20}$) only exhibited one small broad melting peak around 117.8 °C and a single glass transition around 39.2 °C, consistent with its more randomly distributed compositions and less ordered microstructure.

Functionalization of Block Copolymers via Copper-catalyzed Azido-Alkyne Cycloaddtion (CuAAC)

To demonstrate the facile post-polymerization conversions of the azido functionality, copper-catalyzed azido-alkyne cycloaddtion (CuAAC) reaction[48,77] was carried out at room temperature in DMF to attach 5-hexyn-1-ol (HX) to the block and random copolymers (Figure 5a). Nearly all azido groups were converted by 24 h, as supported by FTIR (Figure S6) and ^{1}H NMR spectra (Figure S7). The GPC traces, however, revealed complex elution profiles for HX-modified block and random copolymers (Figure 5b&c). The apparent M_n calculated from the main peaks showed lower value than the original polymers, indicating the decrease of hydrodynamic radii of the polymers upon CuAAC, likely as a result of the collapse of the hydrophilic HX side chains due to either poor solvation[44] or complexation with residue Cu^{2+}. The extra shoulder peaks at earlier elution time may have derived from copolymer aggregates formed via the triazole-Cu^{2+} complexation. After intensive dialysis against Cu^{2+} sequestrant 2,2′-bipyridine, these shoulder peaks was reduced although never completely removed.

Functionalization of Block Copolymers via Strain-Promoted Azido-Alkyne Cyclcoaddtion (SPAAC)

To avoid the potential toxicity of residual copper catalyst in CuAAC, copper-free, strain-promoted azido-alkyne cyclcoaddtion (SPAAC) [63,78] was carried out to modify the block and random copolymers (Figure 6a) using aza-dibenzocyclooctyne NHS ester (DBCO-NHS). Near complete conversion (>95%) of azido groups was achieved in 4 h when 1 eq. DBCO-NHS was added in DMF. Complete conversion was achieved when the DBCO-NHS to azide ratio was increased by 3 folds. GPC traces revealed the expected increase of molecular weight upon the modification of either block (Figure 6b) or random copolymer (Figure 6c) with the narrow polydispersity retained. ^{1}H NMR (Figure 6d) confirmed the complete disappearance of proton resonance for $-CH_2N_3$ at 3.50 ppm (Figure S3) and the appearance of proton resonances associated with the covalently attached DBCO-NHS. The resonance around 4.40 ppm corresponding to the AzDXO unit was more readily detected in

Pyrene-P(LLA_{100}-*co*-$AzDXO_{20}$)-DN than in Pyrene-P(LLA_{100}-*b*-$AzDXO_{20}$)-DN, supporting the random distribution of the bulky DN rings and consequently the less profound shielding effect in the former. Consistent with this observation, higher peak intensities were also detected for the resonances corresponding to the LLA protons in the random copolymers.

Conclusions

In conclusion, we synthesized an azido-functionalized cyclic carbonate monomer in 2 steps without tedious chromatographic purifications. The compatibility of the azido groups with the ROP conditions, its pseudo-living polymerization kinetics, and the versatile "click" chemistry that it enables, make this monomer uniquely suited for preparing functional degradable polycarbonates and poly(ester-carbonates). This methodology could be extended for the preparation of chemically defined functional biodegradable materials with diverse architectures and for screening suitable biomaterials for drug delivery and tissue engineering applications. The mechanical properties and *in vitro* and *in vivo* degradation profiles of these polymers are being investigated and can be tuned by polymer structures, compositions and molecular weights for specific biomedical applications.

Experimental Section

Materials and Instrumentation

Aza-dibenzocyclooctyne NHS ester (DBCO-NHS) was purchased from Click Chemistry Tools Inc. (Macon, GA, USA). All other chemicals were purchased from Sigma-Aldrich (St. Louis, MO) and used as received unless otherwise specified. Chloroform and deuterated chloroform used for reactions were pre-dried by refluxing with phosphorus pentoxide overnight and then distilled under argon. Triethyl amine (TEA, >99%) was dried by refluxing with calcium hydride and distilled under argon. (3S)-Cis-3,6-dimethyl-1,4-dioxane-2,5-dione (L-lactide, 98%) was further purified prior to use by repeated (3×) recrystallization from anhydrous toluene. 1,8-Diazabicyclo[5.4.0]-undec-7-ene (DBU, 98%) was freshly distilled under vacuum prior to use.

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian INOVA-400 spectrometer in deuterated chloroform ($CDCl_3$, 99.8 atom% D with 0.03% v/v TMS) or dimethyl sulfoxide-d6 (99.9 atom% D with 0.03% v/v TMS). High resolution mass spectroscopy (HRMS) spectra were recorded on a Waters Q-Tof Premier mass spectrometer using electro spray ionization (ESI) with W-mode and a spray voltage of 3500V. Samples (0.1 or 10 mg/mL) in methanol or methanol/water mixture (50:50) were infused at a rate of 5 μl/min. Fourier transformed infrared spectroscopy (FTIR) spectra were taken on a Thermo Electron Nicolet IR100 spectrometer with 2-cm^{-1} spectral resolution. Liquid samples were coated on a NaCl salt window and solid samples were mold-pressed into thin transparent discs with KBr, respectively.

Gel permeation chromatrography (GPC) measurements were taken on a Varian Prostar HPLC system equipped with two 5-mm PLGel MiniMIX-D columns (Polymer Laboratory, Amherst, MA), a UV-vis detector and a PL-ELS2100 evaporative light scattering detector (Polymer Laboratory, Amherst, MA). For characterization of azido-functionalized polycarbonates and poly(ester-carbonates), THF was used as an eluent at a flow rate of 0.3 mL/min at rt. The number-averaged molecular weight (M_n) and the polydispersity index (PDI) were calculated by a Cirrus AIA GPC Software using narrowly dispersed polystyrenes (ReadyCal kits, PSS Polymer Standards Service Inc. Germany) as calibration standards. For characterization of the more polar functional polymers following "click" chemistry, DMF was used as an eluent at a flow rate of 0.3 ml/min at 50°C. The M_n and PDI were calculated

by using narrowly dispersed poly(methyl methacrylates) (EasiVial, Polymer Laboratory, Amherst, MA) as standards.

The thermal properties of polymers were determined on a TA Instruments Q200 Differential Scanning Calorimeter (DSC). The enthalpy (cell constant) and temperatures are calibrated by running a high-purity indium standard under the conditions identical to those used for sample measurements. To determine the crystallinity and glass transitions of the polymer samples, each specimen (around 5 mg) was subject to two scanning cycles: (1) cooling from 40 °C (standby temperature) to −50 °C at −10 °C/min, equilibrating for 2 min before being heated to 175 °C at a heating rate of 10 °C/min; (2) cooling to −50°C at −10 °C/min, equilibrating for 2 min, and then being heated to 175 °C at a rate of 10 °C/min. The endothermic peak maximum in the first heating cycle was recorded as the melting temperature (T_m), and its associated peak integration was calculated as melting enthalpy (ΔH). The midpoint of the first endothermic transition from the second heating cycle was identified as the glass transition temperature (T_g).

Monomer Synthesis and Polymerizations

2,2-bis(azidomethyl)propane-1,3-diol—2,2-Bis(azidomethyl)propane-1,3-diol was prepared according to literature procedure[65-68] with minor modifications. Briefly, 2,2-bis(bromomethyl)propane-1,3-diol (98%, 104.7 g, 0.40 mol) was dissolved in DMSO (300 mL) in a 1000-mL 3-neck flack equipped with a reflux condenser, to which sodium azide (65.0 g, 1.0 mol) was added under argon. The suspension was heated to 110 °C and stirred for 16 h. After being cooled to rt, 150-mL water was added and the mixture was transferred to a 2-L separatory funnel and extracted with 800-mL ethyl acetate 3 times. The combined organic phase was washed by 200-mL saturated brine 3 times and dried with sodium sulfate. Pale yellow oil (71.0 g, 95.3% yield) was obtained after removing the volatiles under vacuum. ^{1}H NMR ($CDCl_3$, 400 MHz, 20 °C): δ 3.629-3.616 (d, 4H, J = 5.1 Hz), 3.420 (s, 4H), 2.473-2.446 (t, 2H, J = 5.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 20 °C): δ 63.841, 51.907, 45.020 ppm. ESI-HRMS (m/z): $C_5H_{10}N_6O_2Na^+$ $[M+Na]^+$, calculated 209.0763, found 209.0754.

5,5-bis(azidomethyl)-1,3-dioxane-2-one (AzDXO)—To a solution of ethyl chloroformate (97%, 47.8 g, 0.44 mol) in anhydrous THF (300 mL) was added a THF solution (40 mL) of 2,2-bis(azidomethyl)propane-1,3-diol (34.0 g, 0.18 mol) over 10 min at 0 °C under argon. Dry TEA (50.0 g, 0.50 mol) was added slowly over 30 min. The reaction was continued in ice bath for 4 h and then at rt overnight. After removing the white precipitate by filtration, the volatile was removed under vacuum. The crude product was dissolved in dichloromethane and passed through a short silica gel pad (230-400 mesh size) to remove salts. After removing the solvent by rotovapping, ethyl ether (250 mL) was added to dissolve the product and refluxed for 10 min. Upon cooling, crystalline solid product was collected by filtration. The recrystallization was repeated once. After dried under vacuum for 48h, spectroscopically pure product (18.3 g) was obtained in 47.9% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, 20 °C): δ 4.251(s, 4H), 3.550(s, 4H) ppm. 13C NMR ($CDCl_3$, 100 MHz, 20 °C): δ 147.33, 70.41, 50.34, 36.61 ppm.^{1}H NMR (DMSO-D6, 400MHz, 40 °C): δ 3.59 (s, 4 H) 4.27 (s, 4 H) ppm; ^{13}C NMR (DMSO-D6, 100 MHz, 40 °C): δ 147.94, 70.90, 51.20, 36.87 ppm. ESI-HRMS (m/z): $C_6H_8N_6O_3Na^+$ $[M+Na]^+$, calculated 235.0556, found 235.0556.

Typical procedures for the homopolymerization of AzDXO—AzDXO (0.848 g, 4.0 mmol) and 800-μL benzyl alcohol solution (0.1M in chloroform) were mixed in a 6-mL reaction vessel under argon, to which 3.0-mL chloroform was added to completely dissolve the monomer. The polymerization was initiated by the injection of 200-μL DBU solution

(0.2 M in chloroform). The reaction was terminated after 2 h by adding benzoic acid (≥99.5%, 12.2 mg, 0.1 mmol). The polymer was precipitated by 50-mL methanol, redissolved in 4-mL chloroform and reprecipitated in methanol. The precipitation purification was repeated twice to remove residue catalyst and benzoic acid. The final precipitate was further washed by ethyl ether and dried in vacuum oven at 60 °C for at least 48 h prior to any thermal analysis. Around 0.820g white powder product resulted (97% yield)

Typical procedures for the random copolymerization of AzDXO with L-LA—L-LA and AzDXO were polymerized in one-pot using $CHCl_3$ as solvent, ethylene glycol (EG) as the initiator, DBU (0.01M) as the catalyst, and with the total monomer concentration kept at 1.0 M. The molar ratio of AzDXO and L-LA was varied to prepare random block copolymers with different AzDXO contents. For example, to prepared EG-P(LLA_{90}-co-$AzDXO_{10}$), chemicals at the molar ratio of $[L\text{-}LA]_0$: $[AzDXO]_0$: [EG]:[DBU] = 90 : 10 : 1 : 0.01 were added. AzDXO (0.085 g, 0.4 mmol), recrystalized L-LA (0.519 g, 3.6 mmol), and 400-μL ethylene glycol solution (0.1 M in chloroform) were mixed in a 6-mL reaction vessel under argon, to which 3.4-mL chloroform was added to completely dissolve the monomer. The polymerization was initiated by the injection of 200-μL DBU solution (0.2 M in chloroform). The reaction was terminated after 2 h by adding benzoic acid, and the copolymer EG-P(LLA_{90}-co-$AzDXO_{10}$) was purified as described above and resulted in 0.59 g white powder (98% yield)

Typical procedures for the sequential copolymerization of AzDXO with L-LA—L-LA and AzDXO were polymerized sequentially using $CHCl_3$ as solvent, 1-pyrenbutanol as the initiator, DBU (0.01 M) as the catalyst, and with $[L\text{-}LA]_0$ = 1.0 M. The amount of AzDXO added next was varied to prepare block copolymers with different AzDXO block lengths. For example, to prepared Pyrene-P(LLA_{100})-b-P($AzDXO_{20}$), chemicals at the molar ratio of $[L\text{-}LA]_0$: $[AzDXO]_0$: [1-pyrenebutanol] : [DBU] = 100 : 20 : 1 : 0.01 were added in the first step. Rrecrystalized L-LA (0.577 g, 4.0 mmol) and 1-pyrenebutanol (99%, 10.9 mg, 0.040 mmol) were dissolved in 3.8-mL chloroform under argon. The polymerization was initiated by the injection of 200-μL DBU solution (0.2 M in chloroform). After 2 h, AzDXO (0.169 g, 0.80 mmol) was added under argon and reacted for another 2 h before benzoic acid (≥99.5%, 12.2 mg, 0.1 mmol) was added to terminate the polymerization. The product was purified as described above and the copolymer Pyrene-P(LLA_{100})-b-P($AzDXO_{20}$) was obtained in the white powder form (0.72g, 97% yield)

Side-chain Functionalization by “Click” Chemistry

Typical Procedures for the Functionalization of Poly(ester-carbonates) by Copper-catalyzed Azido-Alkyne Cycloaddtion (CuAAC)—The copolymers were functionalized in DMF at rt under inert atmosphere with varying amounts of 5-hexyn-1-ol by CuAAC. For example, Pyrene-P(LLA_{100})-*b*-($AzDXO_{20}$) or Pyrene-P(LLA_{100}-*co*-$AzDXO_{20}$) (30.0 mg, ~70 μmol of azido groups) and 5-hexyn-1-ol (96%, 120 mg, 1.23 mmol) were dissolved in 2.0 mL DMF, and degassed with argon for 30 min before CuBr (99.999%, 5 mg) was added. The reaction was allowed to continue at rt for 24 h. The product was transferred to a 4-mL regenerated cellulose dialysis tubing (MWCO = 3500 Dalton) and dialyzed against 400-mL DMF in the presence of 0.1-g 2,2′-bipyridine to remove the copper catalyst. The DMF solution was changed every two days for 7 days. After additional dialysis against fresh DMF without 2,2′-bipyridine for another 2 days, the polymer solution in the dialysis tubing was dropped into 50-mL ethyl ether for precipitation. Light green powder (32.0 mg, yield ≈ 88%) was obtained after drying in vacuum oven at rt for 48 h.

Typical Procedures for the Functionalization of Poly(ester-carbonates) by Copper-free Strain-Promoted Azido-Alkyne Cyclcoaddtion (SPAAC)—The copolymers were functionalized in DMF at rt with varying amounts of DBCO-NHS by SPAAC. For example, Pyrene-P(LLA_{100})-*b*-P($AzDXO_{20}$) or Pyrene-P(LLA_{100}-*co*-$AzDXO_{20}$) (30.0 mg, ~70 μmol of azido groups) and DBCO-NHS (101.0 mg, 210 μmol) were dissolved in 2.0-mL DMF, and reacted at rt for 12 h before being precipitated in 50-mL ethyl ether. The precipitate was redissovled in DMF and reprecipitated in ethyl ether. Off-white powder (~60.0 mg, yield ≈ 93%) was obtained after drying in vacuum oven at rt for 48 h.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institute of Health (R01AR055615 and R01GM088678).

References

(1). Hook AL, Anderson DG, Langer R, Williams P, Davies MC, Alexander MR. Biomaterials. 2010; 31:187–198. [PubMed: 19815273]

(2). Hubbell JA. Nat. Biotechnol. 2004; 22:828–829. [PubMed: 15229544]

(3). Nair LS, Laurencin CT. Prog. Polym. Sci. 2007; 32:762–798.

(4). Sodergard A, Stolt M. Prog. Polym. Sci. 2002; 27:1123–1163.

(5). Pego AP, Poot AA, Grijpma DW, Feijen J. J. Biomater. Sci., Polym. Ed. 2001; 12:35–53. [PubMed: 11334188]

(6). Pego AP, Poot AA, Grijpma DW, Feijen J. Macromol. Biosci. 2002; 2:411–419.

(7). Rokicki G. Prog. Polym. Sci. 2000; 25:259–342.

(8). Bat E, Kothman BHM, Higuera GA, van Blitterswijk CA, Feijen J, Grijpma DW. Biomaterials. 2010; 31:8696–8705. [PubMed: 20739060]

(9). Dankers PYW, Zhang Z, Wisse E, Grijpma DW, Sijbesma RP, Feijen J, Meijer EW. Macromolecules. 2006; 39:8763–8771.

(10). Zhu KJ, Hendren RW, Jensen K, Pitt CG. Macromolecules. 1991; 24:1736–1740.

(11). Zelikin AN, Zawaneh PN, Putnam D. Biomacromolecules. 2006; 7:3239–3244. [PubMed: 17096556]

(12). Vert M. Biomacromolecules. 2005; 6:538–546. [PubMed: 15762610]

(13). Rasal RM, Janorkar AV, Hirt DE. Prog. Polym. Sci. 2010; 35:338–356.

(14). Kumar N, Langer RS, Domb AJ. Adv. Drug Delivery Rev. 2002; 54:889–910.

(15). Edlund U, Kallrot M, Albertsson AC. J. Am. Chem. Soc. 2005; 127:8865–8871. [PubMed: 15954795]

(16). Suriano F, Coulembier O, Dubois P. J. Polym. Sci., Part A: Polym. Chem. 2010; 48:3271–3280.

(17). He CL, Sun JR, Zhao T, Hong ZK, Zhuang XL, Chen XS, Jing XB. Biomacromolecules. 2006; 7:252–258. [PubMed: 16398522]

(18). Zhang Z, Grijpma DW, Feijen J. J. Controlled Release. 2006; 112:57–63.

(19). Gautier S, D'Aloia V, Halleux O, Mazza M, Lecomte P, Jerome R. J. Biomater. Sci., Polym. Ed. 2003; 14:63–85. [PubMed: 12635771]

(20). Lu J, Shoichet MS. Macromolecules. 2010; 43:4943–4953.

(21). Trollsas M, Lee VY, Mecerreyes D, Lowenhielm P, Moller M, Miller RD, Hedrick JL. Macromolecules. 2000; 33:4619–4627.

(22). Jiang XW, Horton JM, Baker GL, Smith MR. Abstr. Papers Am. Chem. Soc. 2005; 230:U4073–U4073.

(23). Gerhardt WW, Noga DE, Hardcastle KI, Garcia AJ, Collard DM, Weck M. Biomacromolecules. 2006; 7:1735–1742. [PubMed: 16768392]

(24). Hu XL, Liu S, Chen XS, Mo GJ, Xie ZG, Jing XB. Biomacromolecules. 2008; 9:553–560. [PubMed: 18208317]

(25). Pratt RC, Nederberg F, Waymouth RM, Hedrick JL. Chem. Commun. 2008:114–116.

(26). Hu XL, Chen XS, Xie ZG, Cheng HB, Jing XB. J. Polym. Sci., Part A: Polym. Chem. 2008; 46:7022–7032.

(27). Hu XL, Chen XS, Xie ZG, Liu S, Jing XB. J. Polym. Sci., Part A: Polym. Chem. 2007; 45:5518–5528.

(28). Xie ZG, Lu CH, Chen XS, Chen L, Wang Y, Hu XL, Shi Q, Jing XB. J. Polym. Sci., Part A: Polym. Chem. 2007; 45:1737–1745.

(29). Lou XD, Detrembleur C, Jerome R. Macromol. Rapid Commun. 2003; 24:161–172.

(30). Detrembleur C, Mazza M, Halleux O, Lecomte P, Mecerreyes D, Hedrick JL, Jerome R. Macromolecules. 2000; 33:14–18.

(31). Rieger J, Bernaerts KV, Du Prez FE, Jerome R, Jerome C. Macromolecules. 2004; 37:9738–9745.

(32). Yin M, Baker GL. Macromolecules. 1999; 32:7711–7718.

(33). Vandenberg EJ, Tian D. Macromolecules. 1999; 32:3613–3619.

(34). Zhang XJ, Mei HJ, Hu C, Zhong ZL, Zhuo RX. Macromolecules. 2009; 42:1010–1016.

(35). Noga DE, Petrie TA, Kumar A, Weck M, Garcia AJ, Collard DM. Biomacromolecules. 2008; 9:2056–2062. [PubMed: 18576683]

(36). Sanda F, Kamatani J, Endo T. Macromolecules. 2001; 34:1564–1569.

(37). Kimura Y, Shirotani K, Yamane H, Kitao T. Macromolecules. 1988; 21:3338–3340.

(38). Al-Azemi TF, Bisht KS. Macromolecules. 1999; 32:6536–6540.

(39). Pounder RJ, Dove AP. Biomacromolecules. 2010; 11:1930–1939. [PubMed: 20690706]

(40). Iha RK, Wooley KL, Nystrom AM, Burke DJ, Kade MJ, Hawker CJ. Chem. Rev. 2009; 109:5620–5686. [PubMed: 19905010]

(41). Sumerlin BS, Vogt AP. Macromolecules. 2010; 43:1–13.

(42). Parrish B, Breitenkamp RB, Emrick T. J. Am. Chem. Soc. 2005; 127:7404–7410. [PubMed: 15898789]

(43). Han YD, Shi Q, Hu JL, Du Q, Chen XS, Jing XB. Macromol. Biosci. 2008; 8:638–644. [PubMed: 18401865]

(44). Jiang X, Vogel EB, Smith MR, Baker GL. Macromolecules. 2008; 41:1937–1944.

(45). Darcos V, El Habnouni S, Nottelet B, El Ghzaoui A, Coudane J. Polymer Chemistry. 2010; 1:280–282.

(46). van der Ende AE, Harrell J, Sathiyakumar V, Meschievitz M, Katz J, Adcock K, Harth E. Macromolecules. 2010; 43:5665–5671.

(47). Chen W, Yang HC, Wang R, Cheng R, Meng FH, Wei WX, Zhong ZY. Macromolecules. 2010; 43:201–207.

(48). Kolb HC, Finn MG, Sharpless KB. Angew. Chem., Int. Ed. 2001; 40:2004–2021.

(49). Agard NJ, Prescher JA, Bertozzi CR. J. Am. Chem. Soc. 2004; 126:15046–15047. [PubMed: 15547999]

(50). Dechy-Cabaret O, Martin-Vaca B, Bourissou D. Chem. Rev. 2004; 104:6147–6176. [PubMed: 15584698]

(51). Ariga T, Takata T, Endo T. Macromolecules. 1997; 30:737–744.

(52). Nederberg F, Lohmeijer BGG, Leibfarth F, Pratt RC, Choi J, Dove AP, Waymouth RM, Hedrick JL. Biomacromolecules. 2007; 8:153–160. [PubMed: 17206801]

(53). Kamber NE, Jeong W, Waymouth RM, Pratt RC, Lohmeijer BGG, Hedrick JL. Chem. Rev. 2007; 107:5813–5840. [PubMed: 17988157]

(54). Dove AP, Pratt RC, Lohmeijer BGG, Culkin DA, Hagberg EC, Nyce GW, Waymouth RM, Hedrick JL. Polymer. 2006; 47:4018–4025.

(55). Lohmeijer BGG, Pratt RC, Leibfarth F, Logan JW, Long DA, Dove AP, Nederberg F, Choi J, Wade C, Waymouth RM, Hedrick JL. Macromolecules. 2006; 39:8574–8583.

(56). Chuma A, Horn HW, Swope WC, Pratt RC, Zhang L, Lohmeijer BGG, Wade CG, Waymouth RM, Hedrick JL, Rice JE. J. Am. Chem. Soc. 2008; 130:6749–6754. [PubMed: 18454532]

(57). Kiesewetter MK, Scholten MD, Kirn N, Weber RL, Hedrick JL, Waymouth RM. J. Org. Chem. 2009; 74:9490–9496. [PubMed: 19928812]

(58). Kiesewetter MK, Shin EJ, Hedrick JL, Waymouth RM. Macromolecules. 2010; 43:2093–2107.

(59). Zhang L, Pratt RC, Nederberg F, Horn HW, Rice JE, Waymouth RM, Wade CG, Hedrick JL. Macromolecules. 2010; 43:1660–1664.

(60). Brase S, Gil C, Knepper K, Zimmermann V. Angew. Chem., Int. Ed. 2005; 44:5188–5240.

(61). Kuhling S, Keul H, Hocker H. Macromolecules. 1990; 23:4192–4195.

(62). Sumerlin BS, Tsarevsky NV, Louche G, Lee RY, Matyjaszewski K. Macromolecules. 2005; 38:7540–7545.

(63). Baskin JM, Bertozzi CR. Aldrichimica Acta. 2010; 43:15–23.

(64). Saxon E, Bertozzi CR. Science. 2000; 287:2007–2010. [PubMed: 10720325]

(65). Kolar, CK.; Hans Peter; Dehmel; Konrad Office. E., P., editors. Vol. DE3432320. Behringwerke AG; German: 1986. p. 1-30.

(66). Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. Angew. Chem., Int. Ed. 2002; 41:2596–2599.

(67). Liu XM, Thakur A, Wang D. Biomacromolecules. 2007; 8:2653–2658. [PubMed: 17688321]

(68). Diaz DD, Punna S, Holzer P, Mcpherson AK, Sharpless KB, Fokin VV, Finn MG. J. Polym. Sci., Part A: Polym. Chem. 2004; 42:4392–4403.

(69). Endo T, Kakimoto K, Ochiai B, Nagai D. Macromolecules. 2005; 38:8177–8182.

(70). Hadjichristidis, N.; Pispas, S.; Floudas, G. Block copolymers: synthetic strategies, physical properties, and applications. John Wiley and Sons; 2002.

(71). Hedrick JL, Trollsas M, Hawker CJ, Atthoff B, Claesson H, Heise A, Miller RD, Mecerreyes D, Jerome R, Dubois P. Macromolecules. 1998; 31:8691–8705.

(72). Feng XS, Pan CY. Macromolecules. 2002; 35:2084–2089.

(73). Hawker CJ, Hedrick JL, Malmstrom EE, Trollsas M, Mecerreyes D, Moineau G, Dubois P, Jerome R. Macromolecules. 1998; 31:213–219.

(74). Matyjaszewski K. Macromol. Symp. 1998; 132:85–101.

(75). Matyjaszewski K, Xia JH. Chem. Rev. 2001; 101:2921–2990. [PubMed: 11749397]

(76). Chong YK, Le TPT, Moad G, Rizzardo E, Thang SH. Macromolecules. 1999; 32:2071–2074.

(77). Hawker CJ, Fokin VV, Finn MG, Sharpless KB. Aust. J. Chem. 2007; 60:381–383.

(78). Agard NJ, Prescher JA, Bertozzi CR. J. Am. Chem. Soc. 2005; 127:11196–11196.

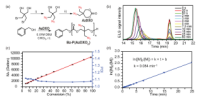

Figure 1.

Synthesis and polymerization kinetics of azido-functionalized cyclic carbonate monomer AzDXO. (a) AzDXO was synthesized in 2 steps in 45.6% overall yield: i) NaN_3, DMSO, 110°C, 16h; ii) ethyl chloroformate, THF, ice bath 4h, rt 12h. Ring opening polymerization of AzDXO was carried out in $CDCl_3$ at rt using benzyl alcohol (Bz) as an initiator and 1,8-Diazabicyclo[5.4.0]-undec-7-ene (DBU) as a catalyst. $[AzDXO]_0$ = 1.0 M; $[AzDXO]_0$: [Bz]: [DBU] = 50: 1 : 0.5. (b) GPC monitoring of polymerization by evaporative light scattering (ELS) detector over time; (c) Polymerization kinetics determined from GPC showing linear increase of number-average molecular weight (M_n) and consistent low polydispersity (PDI) with the increase of monomer conversion, respectively. (d) Plot of $\ln([M]_0/[M])$ vs time (t) showing a linear first-order kinetics for the ROP of AzDXO, supporting a controlled/"living" polymerization mechanism. $[M]_0$ and [M] are the monomer concentrations at time zero and time t, respectively, and t is the reaction time in minutes.

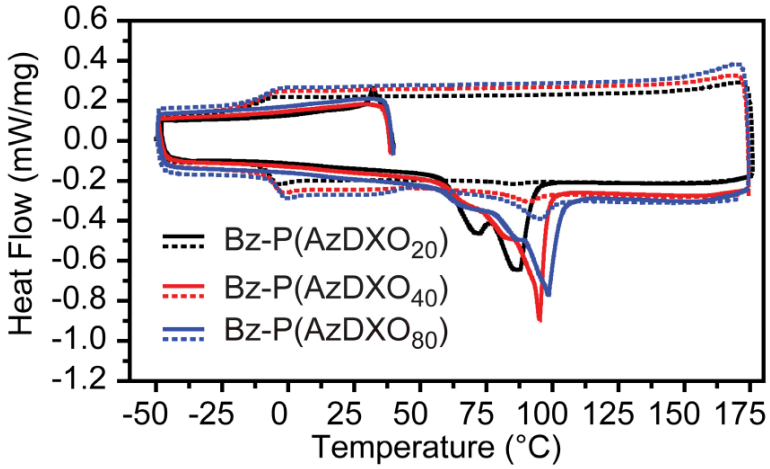

Figure 2.
Differential scanning calorimetry of homopolymers of AzDXO with different molecular weights. The solid and dotted curves denote the first and the second DSC cycles, respectively.

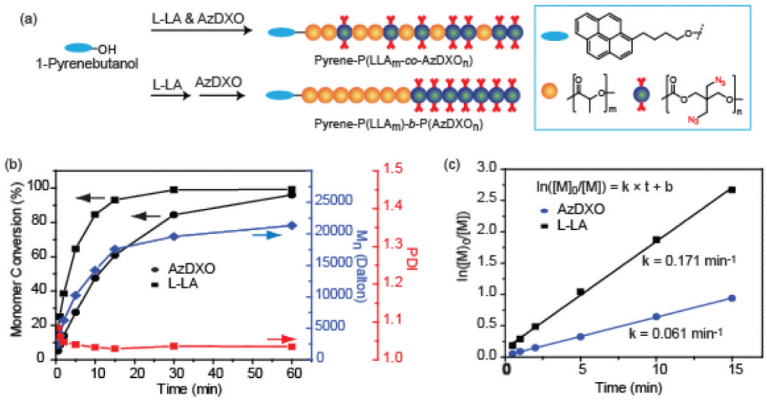

Figure 3.

Copolymerization of L-LA and AzDXO to prepare random and block copolymers by one-step and sequential polymerizations, respectively. (a) Random and block copolymerization schemes. (b) Monomer conversion, M_n and PDI as a function of time during the one-step copolymerization of L-LA and AzDXO. The copolymerization was carried out in $CDCl_3$ at rt. $[AzDXO]_0 = [L\text{-}LA]_0 = 1.0$ M. [DBU] = 0.01 M, [AzDXO] : [L-LA] : [1-pyrenebutanol] : [DBU] = 50 : 50 : 1 : 0.5. (c) Polymerization rate constants for L-LA and AzDXO determined by curve fitting of $\ln([M]_0/[M])$ vs. time for the respective monomers.

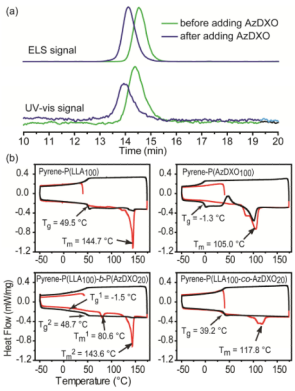

Figure 4.

GPC traces and DSC scans confirming the successful preparation of block and random copolymers of L-LA and AzDXO. (a) Representative GPC traces for Pyrene-P(LLA_{100})-*b*-P($AzDXO_{35}$) before and after feeding AzDXO; (b) DSC curves of homopolymers, and block and random copolymers of L-LA and AzDXO.

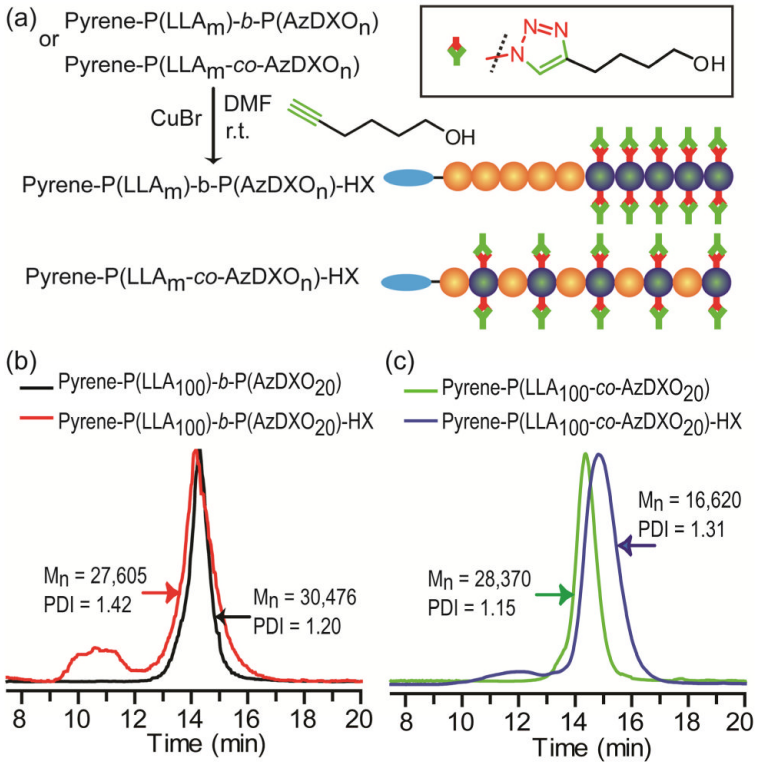

Figure 5.

Functionalization of block and random copolymers with 5-hexyn-1-ol (HX) via copper-catalyzed azido-alkyne cycloaddtion (CuAAC). (a) Reaction scheme; (b) GPC traces (DMF, 50°C), M_n and PDI of block copolymer P(LLA$_{100}$)-*b*-P(AzDXO$_{20}$) before and after CuAAC; (c) GPC traces (DMF, 50°C), M_n and PDI of random copolymer P(LLA$_{100}$)-*co*-P(AzDXO$_{20}$) before and after CuAAC.

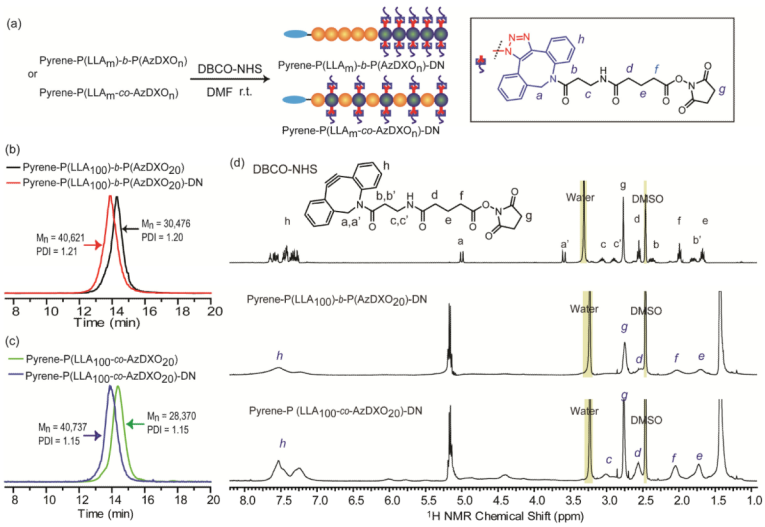

Figure 6.

GPC traces and ^{1}H NMR spectra indicated the successful modification of block and random copolymers by strain-promoted azido-alkyne cycloaddition (SPAAC). (a) reaction scheme; (b) GPC traces (ELS detector) of block copolymer Pyrene-P(LLA$_{100}$)-*b*-P(AzDXO$_{20}$) before and after SPAAC; (c) GPC traces (ELS detector) of random copolymer Pyrene-P(LLA$_{100}$-*co*-AzDXO$_{20}$) before and after SPAAC; (d) ^{1}H NMR of DBCO-NHS (DN) (top), Pyrene-P(LLA$_{100}$)-*b*-P(AzDXO$_{20}$)-DN (middle) and Pyrene-P(LLA$_{100}$-*co*-AzDXO$_{20}$)-DN (bottom).

Table 1

Block and random copolymers of L-LA and AzDXO

Name[a]	L-LA: AzDXO[b]	M_n[c]	PDI[c]
Pyrene-P(LLA_{100})	97.0 : 0	19392	1.06
Pyrene-P(LLA_{100})-b-P($AzDXO_5$)	116.6 : 3.2	22356	1.06
Pyrene-P(LLA_{100})-b-P($AzDXO_{10}$)	106.8 : 9.2	23487	1.06
Pyrene-P(LLA_{100})-b-P($AzDXO_{20}$)	110.8 : 18.3	27362	1.11
Pyrene-P(LLA_{100})-b-P(AzDXO35)	98.8 : 33.1	31030	1.07
Pyrene-P($AzDXO_{100}$)	0 : 106.0	19888	1.14
Pyrene-P(LLA_{100}-co-$AzDXO_{20}$)[d]	98.0 : 18.6	25524	1.07

[a] The naming of the samples reflect the theoretical copolymer compositions

[b] copolymer compositions determined from ^{1}H NMR

[c] number-averaged molecular weight and polydispersity index determined from GPC using an ELS detector

[d] two monomers were added in one-step for the preparation of random copolymer.