Macromolecules

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Drug-Initiated, Controlled Ring-Opening Polymerization for the Synthesis of Polymer–Drug Conjugates

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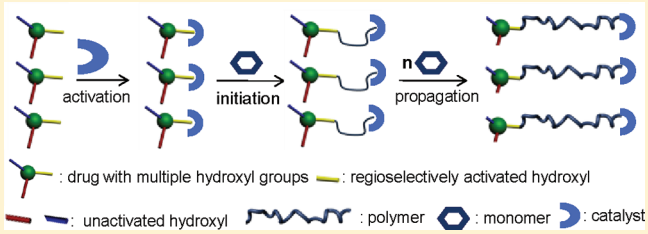
Supporting Information

ABSTRACT: Paclitaxel, a polyol chemotherapeutic agent, was covalently conjugated through its 2′-OH to polylactide with 100% regioselectivity via controlled polymerization of lactide mediated by paclitaxel/(BDI-II)ZnN(TMS)$_2$ (BDI-II = 2-((2,6-diisopropylphenyl)amino)-4-((2,6-diisopropylphenyl)-imino)-2-pentene). The steric bulk of the substituents on the *N*-aryl groups of the BDI ligand drastically affected the regiochemistry of coordination of the metal catalysts to paclitaxel and the subsequent ring-opening polymerization of lactide. The drug-initiated, controlled polymerization of lactide was extended, again with 100% regioselectivity, to docetaxel, a chemotherapeutic agent that is even more structurally complex than paclitaxel. Regioselective incorporation of paclitaxel (or docetaxel) to other biopolymers (i.e., poly(δ-valerolactone), poly(trimethylene carbonate), and poly(ε-caprolactone)) was also achieved through drug/(BDI-II)ZnN(TMS)$_2$-mediated controlled polymerization. These drug–polylactide conjugates with precisely controlled structures are expected to be excellent building blocks for drug delivery, coating, and controlled-release applications.



INTRODUCTION

Research on the use of drug-containing polymeric nanoparticles for improved cancer treatments is an emerging field.[1] Chemotherapeutic agents incorporated in polymeric nanoparticulate delivery vehicles typically have improved water solubility,[2] prolonged retention in circulation,[3] and reduced drug resistance[4] relative to conventional chemotherapeutics. Therefore, polymeric nanomedicines are expected to have reduced toxicity and improved efficacy.[5] A handful of polymeric nanomedicines have been developed for clinical cancer treatment in the past 2–3 decades;[6] among these, polymer–drug conjugates have been one of the most intensively investigated delivery platforms.[7]

The preparation of polymer–drug conjugates with well-defined structures and compositions is extremely important for their in vivo applications, but this task can be difficult. Polymer–drug conjugates usually exhibit heterogeneous structures. Heterogeneities may result from (1) molecular weight distributions (MWDs) of the polymers (Scheme 1A), (2) lack of control of the drug conjugation site on the polymer backbone (Scheme 1B), and (3) lack of regioselectivity with regard to the conjugation site on drugs with multiple conjugation-amenable functional groups. These heterogeneities, which are not easily addressed, may present bottlenecks in the clinical translation of polymer–drug conjugates.[6d] In the past several decades, there have been numerous efforts to minimize these heterogeneities, including the development of polymers with low MWDs (e.g., dendrimer),[8] the conjugation of therapeutic agents to specific sites along the polymer backbone (e.g., the termini),[2,9] and the activation of specific functional groups on the therapeutic agents by means of protection/deprotection chemistry.[10]

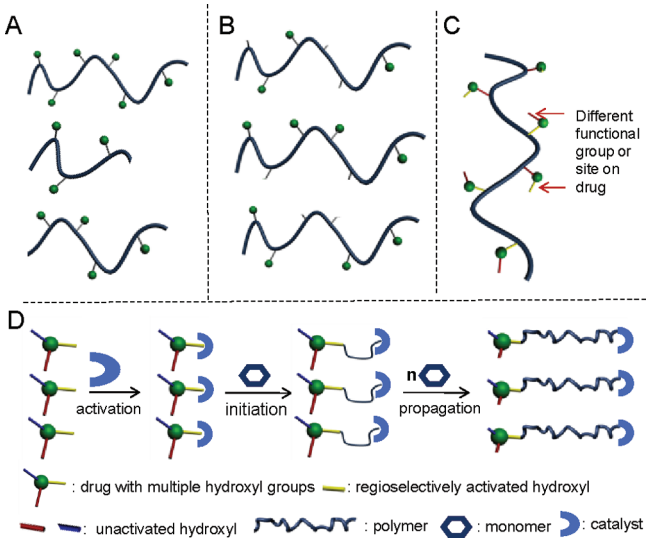
We have been interested in controlling the conjugation of drugs to polymers with reduced heterogeneity via a controlled ring-opening polymerization (ROP) strategy. In our initial attempt, we used a complex of paclitaxel (Ptxl), a mitotic inhibitor with three hydroxyl groups, and a Zn catalyst to initiate the ROP of lactide (LA), which results in efficient conjugation of Ptxl molecules to the termini of polylactide (PLA) chains.[11] In ROP studies conducted by the chemistry community, the focus is on control of the molecular weights (MWs), MWDs, and structures of the polymer products (that is, the chain propagation step),[12] whereas the focus of our studies on drug-initiated ROP has been more on the initiation step. We are particularly interested in controlling the regioselective coordination of a structurally complex drug molecule (the initiator) bearing multiple hydroxyl groups with the metal catalyst. In the Ptxl/Zn polymerization system specifically, investigation of Zn catalysts that interact with Ptxl to afford regioselective initiation and controlled polymerization is imperative. Exploring whether this chemistry is widely applicable for the synthesis of drug–polymer conjugates with various hydroxyl-containing therapeutics and with various polymer backbones is also important.

Here, we report the rationale design of metal catalysts that allow for regioselective conjugation of PLA to Ptxl via its 2′-OH

Received: November 27, 2011
Revised: February 3, 2012
Published: February 27, 2012

 © 2012 American Chemical Society dx.doi.org/10.1021/ma202581d | *Macromolecules* 2012, 45, 2225–2232

Scheme 1. (A) Polymer−Drug Conjugates with a Broad Distribution of Polymer Chain Lengths; (B) Polymer−Drug Conjugates in Which the Conjugation Site on the Polymer Backbone Is Uncontrolled; (C) Polymer−Drug Conjugates in Which a Multifunctional Therapeutic Agent Is Conjugated without Regioselectivity; (D) Drug-Initiated, Controlled Polymerization for the Synthesis of Polymer−Drug Conjugates with Low MWDs[a]



[a]The drug molecules are conjugated regioselectively to the polymer chain termini.

to afford Ptxl−PLA conjugates with precisely controlled MWs, predefined drug loading, and narrow MWDs (Scheme 1D). We found that this chemistry could be extended to the ROP of cyclic esters and carbonates to prepare a large variety of drug−polyester and drug−polycarbonate conjugates. Docetaxel−PLA conjugates were also prepared with remarkably controlled MWs and low MWDs. These materials are expected to be excellent building blocks for the design of systems for drug delivery, coating, and controlled release applications.

RESULTS AND DISCUSSION

(BDI-EE)Zn/Ptxl-Mediated LA Polymerization. Metal oxides (M-ORs) are well-known initiators for living ROP of cyclic esters such as LA (Figure 1).[12c] By judicious design, labile M-ORs prepared in situ by mixing a hydroxyl-containing compound with an active metal complex[12a] can initiate the controlled living ROP of LA, resulting in quantitative incorporation of the initiating alcohol group at the PLA terminals with nearly 100% monomer conversion.[12c] The use of various hydroxyl-containing cholesterol derivatives coordinated with an Al(III) or a Sn(II) complex as co-initiators for cyclic ester polymerization has been reported previously.[13] Because Ptxl has hydroxyl groups, we attempted to use it to initiate the ROP of LA in the presence of (BDI-X)ZnN(TMS)$_2$ (BDI = 2-((2,6-dialkylphenyl)amino)-4-((2,6-dialkylphenyl)imino)-2-pentene, Table 1),[11] a class of catalysts developed by Coates and co-workers for controlled ROP of LA. (BDI-EE)ZnN(TMS)$_2$ (Table 1) was synthesized and mixed with Ptxl, instantly resulting in (BDI-EE)Zn/Ptxl; this active complex subsequently initiated LA polymerization at a LA/Ptxl/(BDI-EE)ZnN(TMS)$_2$ ratio of 200:1:1.01. Ptxl was quantitatively conjugated to PLA to afford Ptxl-LA$_n$ (in this paper, PLA is denoted as LA$_n$, where n = M/I) as indicated by HPLC and ^{1}H NMR analysis (entry 1, Table 2). The drug loadings could be

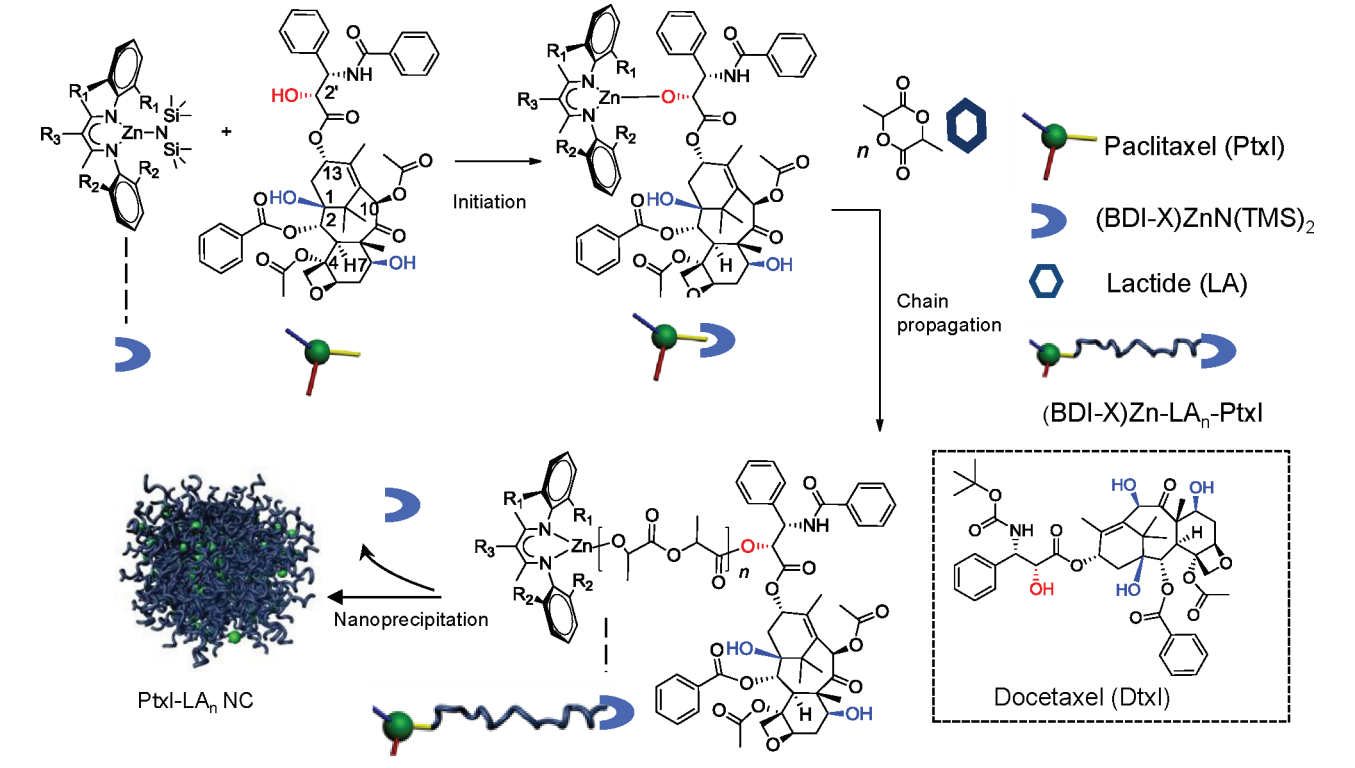
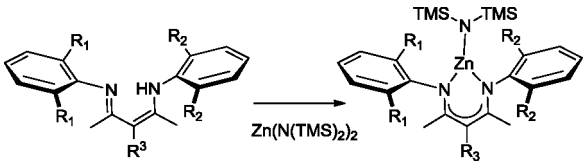


Figure 1. Preparation of PEGylated Ptxl−PLA nanoconjugates (NCs) via Ptxl-initiated LA polymerization in the presence of (BDI-X)ZnN(TMS)$_2$ (X = II, EE, EI, IICN; see Table 1), followed by nanoprecipitation and noncovalent surface modification[11,19] with poly(lactide-*co*-glycolide)-methoxy poly(ethylene glycol) (PLGA-mPEG) or poly(lactide)-methoxy poly(ethylene glycol) (PLA-mPEG).

dx.doi.org/10.1021/ma202581d | *Macromolecules* 2012, 45, 2225−2232

Table 1. Synthesis of (BDI-X)ZnN(TMS)$_2$[a]



BDI-X	R_1	R_2	R_3
BDI-II	^{i}Pr	^{i}Pr	H
BDI-EE	Et	Et	H
BDI-EI	Et	^{i}Pr	H
BDI-IICN	^{i}Pr	^{i}Pr	CN

[a]Abbreviations: ^{i}Pr, isopropyl; Et, ethyl.

precisely controlled by adjusting the LA/Ptxl ratio. The M_n value was 30.2 × 10^3 g/mol, which is in excellent agreement with the expected value (29.7 × 10^3 g/mol). However, the MWD was fairly broad (M_w/M_n = 1.30).

Use of Reductive Reaction To Determine Regioselectivity of Ptxl-LA$_5$ Formation. Ptxl has three hydroxyl groups, at the C-2′, C-1, and C-7 positions (Figure 1). All three can potentially initiate LA polymerization, resulting in Ptxl-PLA conjugates with one to three PLA chains attached to Ptxl. The tertiary 1-OH is least accessible and is typically inactive,[14] but both the 2′-OH and 7-OH are active, with the 2′-OH being sterically more accessible.[15] We next evaluated the regioselectivity of polymerization initiation in the presence of (BDI-EE)ZnN(TMS)$_2$.

Tetrabutylammonium borohydride (Bu_4NBH_4) has been used for selectively and quantitatively reducing the C13-ester bond of Ptxl to afford baccatin III (BAC) and (1*S*,2*R*)-*N*-1-(1-phenyl-2,3-dihydroxypropyl)benzamide (PDB; Figure 2A).[16] We attempted to use this reductive reaction to disassemble Ptxl-LA$_5$ obtained from (BDI-EE)ZnN(TMS)$_2$/Ptxl-mediated polymerization and then determine whether PLA was attached only to the 2′-OH or to both the 2′-OH and 7-OH (Figure 2B). If the initiation occurred regioselectively at the 2′-OH, no BAC-PLA should have been observed. However, analysis of the fragments obtained from the reductive cleavage of the C13-ester bond of Ptxl-LA$_5$ clearly showed the presence of both PDB−PLA and BAC−PLA, indicating that the (BDI-EE)ZnN(TMS)$_2$/Ptxl-mediated polymerization exhibited poor regioselectivity (Figure 2C), which may explain the relatively broad MWD of the Ptxl-LA$_{200}$ synthesized with (BDI-EE)ZnN(TMS)$_2$/Ptxl (entry 1, Table 2).

The substituents on the *N*-aryl groups (R_1 and R_2) and at the *β*-position (R_3) of the BDI ligand drastically affect its ability to control the ROP of LA.[12a,17] By varying the steric bulk of the *N*-aryl substituents and the electronic properties of R_3, we studied the effects of the BDI substituents on the initiation regioselectivity and the LA polymerization mediated by

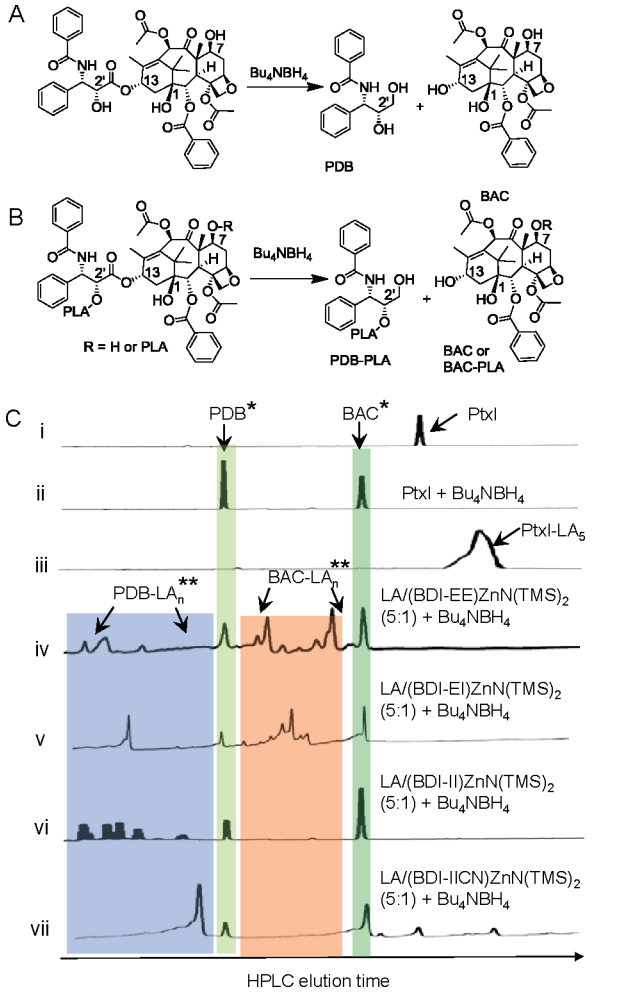


Figure 2. (A) Bu_4NBH_4-induced site-specific degradation of Ptxl to form PDB and BAC. (B) Reductive degradation of C13-ester of Ptxl-PLA. (C) HPLC traces for (i) Ptxl, (ii) Ptxl treated with Bu_4NBH_4, (iii) Ptxl-LA$_5$, and (iv−vii) Ptxl-LA$_5$ prepared using (BDI-X)ZnN(TMS)$_2$ (X = EE, EI, II, and IICN; see Table 1) and subsequent treatment with Bu_4NBH_4. *The PDB and partial BAC detected in (iv−vii) were produced from free Ptxl not completely consumed during the polymerization at low [LA]/[Ptxl] (i.e., ≤5). Separation of Ptxl was not attempted. Comparison of the patterns of BAC and PDB in (vi) and (ii) clearly indicates that the BAC in (vi) was produced partially by degradation of unreacted Ptxl and partially by reduction of Ptxl-PLA with the PLA being attached to the 2′-OH of Ptxl. **Peaks were verified by mass spectrometry.

Table 2. Effect of Ligand Substituents on LA ROP Mediated by Ptxl/(BDI-X)ZnN(TMS)$_2$[a]

entry	ligand (BDI-X)	[LA]/[Ptxl]	LA conv (%)	incorp eff (%)	M_{exp} (×10^3 g/mol)	M_n (×10^3 g/mol)	MWD (M_w/M_n)
1	BDI-EE	200	>99	>99	29.7	30.2	1.30
2	BDI-EI	200	>99	>99	29.7	31.4	1.17
3	BDI-II	200	>99	>99	29.7	28.1	1.02
4	BDI-IICN	200	>99	>99	29.7	27.4	1.04
5	BDI-II	50	>99	>99	8.1	7.8	1.04
6	BDI-II	100	>99	>99	15.3	12.7	1.03

[a]All reactions were performed with [Ptxl]/[(BDI-X)ZnN(TMS)$_2$] = 1:1.01 in anhydrous THF with $[LA]_0$ = 0.69 M at room temperature for 12 h. Abbreviations: LA, lactide; Ptxl, paclitaxel; conv, conversion; incorp eff, incorporation efficiency; M_{exp}: expected MW; MWD, molecular weight distribution. LA conversion was measured by monitoring the disappearance of the LA peak (1772 cm^{-1}) in the FT-IR spectrum. Incorporation efficiency was determined by reversed-phase HPLC analysis of unincorporated Ptxl. M_n and MWD were measured by GPC.

dx.doi.org/10.1021/ma202581d | *Macromolecules* 2012, 45, 2225−2232

(BDI-X)Zn(TMS)$_2$/Ptxl (Table 1).[18] When one of the ethyl groups in BDI-EE was replaced with the more bulky isopropyl (^{i}Pr) group (BDI-EI), the polymerization reaction afforded Ptxl-LA$_{200}$ with a much narrower MWD (M_w/M_n = 1.17, LA/Ptxl/(BDI-EI)ZnN(TMS)$_2$ = 200:1:1.01, entry 2, Table 2). When both the ethyl groups were replaced with ^{i}Pr groups, remarkably well controlled polymerization was observed: Ptxl-LA$_{200}$ was obtained with the expected MW (M_n = 28.1 × 10^3 g/mol) and an extremely narrow MWD (M_w/M_n = 1.02, entry 3).

Interestingly, the regioselectivities obtained with these catalysts followed a similar trend as the polymerization results. Analysis of the fragments of the reductive cleavage of Ptxl-LA$_5$ prepared from (BDI-EI)ZnN(TMS)$_2$/Ptxl showed reduced amounts of BAC-PLA relative to the amount observed with (BDI-EE)ZnN(TMS)$_2$/Ptxl. When Ptxl-LA$_5$ prepared from (BDI-II)ZnN(TMS)$_2$/Ptxl was treated with Bu_4NBH_4 and analyzed similarly, no BAC-PLA peaks were identified, indicating that (BDI-II)ZnN(TMS)$_2$/Ptxl-mediated polymerization was highly regioselective (Figure 2). The steric bulk of the substituents at the 2- and 6-positions of the *N*-aryl group clearly had a strong effect on the regioselectivity and controlled polymerization. The bulky ^{i}Pr groups on the BDI ligand may have hindered metal complexation with the 7-OH of Ptxl, thereby minimizing undesired chain initiation and propagation via this hydroxyl group. To determine whether R_3 also affected initiation regioselectivity and polymerization, we prepared BDI-IICN, an analogue of BDI-II with an additional CN group on R_3. (BDI-IICN)ZnN(TMS)$_2$ behaved similarly to (BDI-II)ZnN(TMS)$_2$ (entry 4).

Controlled polymerizations of PLA were observed when (BDI-II)ZnN(TMS)$_2$/Ptxl was used at various [LA]/[Ptxl] ratios (50:1−300:1; Figure 3A): the obtained MWs were in excellent agreement with the expected MWs (Table S1); the MWDs were in a range of 1.02−1.09. Monomodal gel permeation chromatography (GPC) curves were observed in all cases (Figure 3B).

Regioselectivity of Ptxl/Anhydride Reaction. We next investigated whether the regioselectivity observed at the initiation step for the formation of Ptxl-LA$_n$ could be achieved with other substrates besides LA. Previous studies showed that (BDI-II)-ZnO^{i}Pr (or other Zn-alkoxides) can mediate controlled ROP of LA via a coordination−insertion mechanism (Scheme 2A). In addition, the same catalyst can also mediate ROP of anhydrides and epoxides by a similar mechanism.[20] These results suggested that succinic anhydride (SA) could be used as a model monomer and that ROP reactions mediated by (BDI-X)ZnN(TMS)$_2$/Ptxl could terminate after the initiation step (*O*-acylation, Scheme 2B). Such reactions would afford not a polymer but the small molecule Ptxl-succinic acid (Ptxl-SA), whose structure could be easily and precisely determined by routine characterization methods.

To perform the acylation, we prepared various (BDI-X)ZnN-(TMS)$_2$/Ptxl complexes in situ and mixed them with SA for 4 h at 40 °C at a Ptxl/SA ratio of 1:1.1 (Table 3). The reaction mixtures were quenched and analyzed by HPLC. The structures of the acylation products were determined by NMR after separation by TLC or HPLC (^{1}H NMR shown in Figure 4). The chemical shift of the C2′-H of Ptxl-2′-SA was shifted downfield relative to that of Ptxl (from 4.78 to 5.53 ppm), whereas the chemical shifts of C7-H were nearly the same (δ = 4.40 ppm, Figure 4). For Ptxl-2′,7-diSA, both C2′-H and C7-H were shifted downfield relative to the corresponding protons of Ptxl (δ (C2′-H) from 4.78 to 5.53 ppm; δ(C7-H) from 4.40 to 5.64 ppm). By measuring the yields of Ptxl-2′-SA and Ptxl-2′,7-diSA (Table 3), we found that the 2′-OH regioselectivity obtained with the various catalysts followed exactly

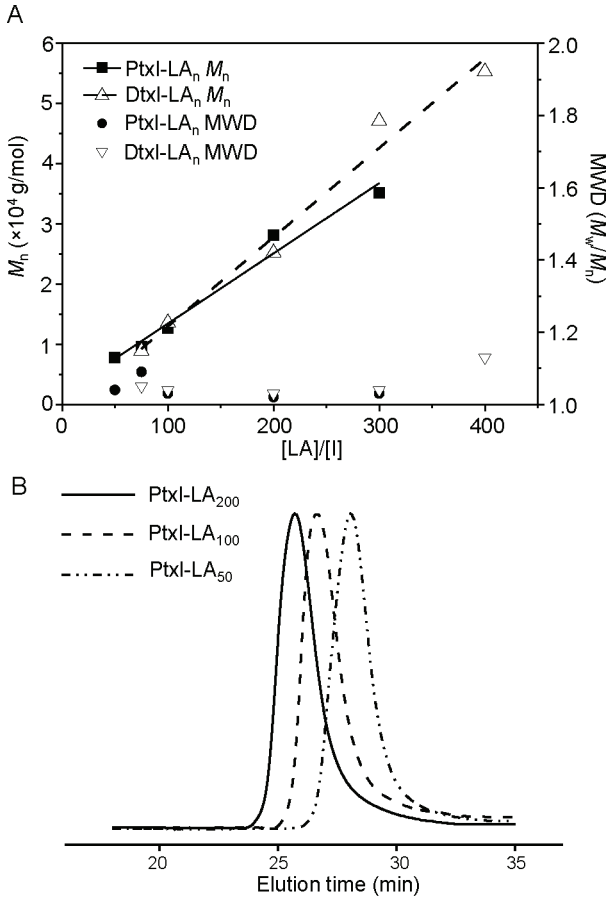
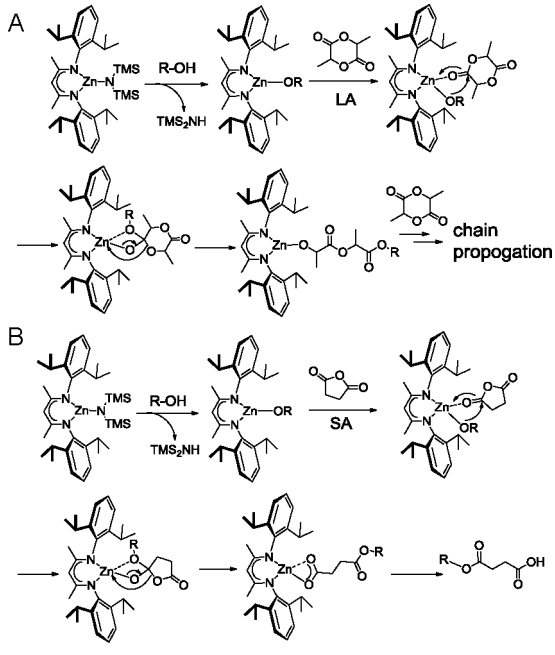


Figure 3. (A) Plots of M_n and MWD versus [LA]/[I] (I = Ptxl or Dtxl) for LA polymerization initiated by Ptxl/(BDI-II)ZnN(TMS)$_2$ and Dtxl/(BDI-II)ZnN(TMS)$_2$. (B) Overlay of GPC chromatograms for Ptxl-LA$_{200}$, Ptxl-LA$_{100}$, and Ptxl-LA$_{50}$ obtained by (BDI-II)ZnN-(TMS)$_2$-mediated polymerization.

Scheme 2. (BDI-II)ZnN(TMS)$_2$-Mediated Ring-Opening of (A) LA and (B) SA via a Coordination−Insertion Mechanism



dx.doi.org/10.1021/ma202581d | *Macromolecules* 2012, 45, 2225−2232

Table 3. Ring-Opening Reactions of SA Mediated by Ptxl (or Dtxl)/(BDI-X)ZnN(TMS)$_2$[a]

entry	initiator (R)	catalyst ligand (BDI-X)	yield of R-2′-SA (%)	yield of R-2′,7-diSA and other R-SA (%)	total yield of R-SA (%)	regioselectivity for 2′-OH (%)
1	Ptxl	BDI-EE	29.6	55.4	85	34.8
2	Ptxl	BDI-EI	45	13.4	58.4	77.1
3	Ptxl	BDI-II	39.7	0	39.7	100
4	Ptxl	BDI-IICN	53.6	0	53.6	100
5	Dtxl	BDI-II	71.5	0	71.5	100

[a]All reactions were performed with [Ptxl]/[(BDI-X)ZnN(TMS)$_2$]/[SA] = 1/1.01/1.1 in anhydrous THF with [SA]$_0$ = 0.011 M at 40 °C for 4 h. Abbreviations: SA, succinic anhydride; Ptxl, paclitaxel; Dtxl, docetaxel. Yields were determined by reversed-phase HPLC analysis. SA derivatives were confirmed by NMR and MS.

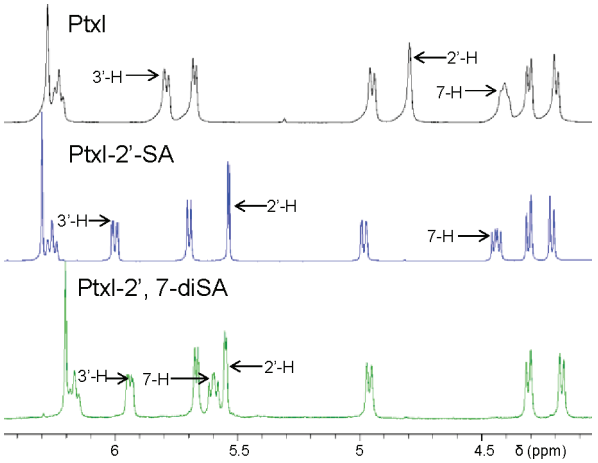
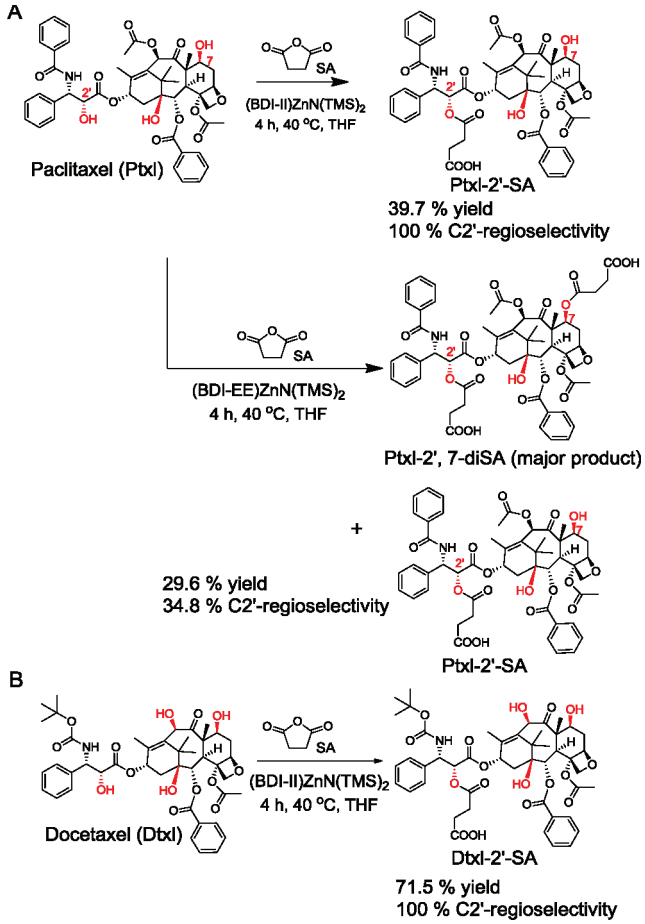


Figure 4. ^{1}H NMR spectrum of Ptxl, Ptxl-2′-SA, and Ptxl-2′,7-diSA.

Scheme 3. Regioselective Acylation of (A) Ptxl and (B) Dtxl with SA



the same trend observed for the reactions with LA, as determined by Bu_4NBH_4-mediated reductive cleavage (Figure 2). That is, the regioselectivity of the Ptxl/SA reaction increased as the sizes of R_1 and R_2 increased; (BDI-II)ZnN(TMS)$_2$ showed the best regioselectivity and (BDI-EE)ZnN(TMS)$_2$ the worst (Scheme 3A).

Specifically, the (BDI-EE)ZnN(TMS)$_2$/Ptxl-mediated ring-opening acylation with SA showed poor regioselectivity (34.8%, entry 1, Table 3). Only 29.6% of the Ptxl was converted to Ptxl-2′-SA), whereas 55.4% was converted to Ptxl-2′,7-diSA, the undesired byproduct. In contrast, with (BDI-EI)ZnN(TMS)$_2$/Ptxl, the regioselectivity of the acylation was 77.1% (entry 2). When Ptxl/(BDI-II)ZnN(TMS)$_2$ was used, the regioselectivity of the reaction was 100%: Ptxl-2′-SA was the only acylation product (entry 3). Although the reactions of Ptxl with SA and LA showed similar regioselectivity trends, the overall reactivity of (BDI-X)ZnN(TMS)$_2$ was inversely correlated with the sizes of R_1 and R_2, as indicated by the overall yields of the Ptxl/SA reactions (entries 1−3). Changing R_3 from −H (BDI-II) to the electron-withdrawing −CN group (BDI-IICN) did not change the regioselectivity of the Ptxl/SA reaction. However, additional of the CN group enhanced the reactivity of the resulting catalyst ((BDI-IICN)ZnN(TMS)$_2$), leading to a higher yield of Ptxl-2′-SA (entry 4).

Regioselective (BDI-II)ZnN(TMS)$_2$/Docetaxel-Initiated Ring-Opening of LA and SA. After demonstrating the regioselectivity of the Ptxl ring-opening reactions with LA and SA in the presence of (BDI-II)ZnN(TMS)$_2$, we determined whether this catalyst could be used for regioselective ROP of LA and for ring-opening acylation of SA with a more structurally complex therapeutic agent. We chose docetaxel (Dtxl), which is an important clinical therapeutic for the treatment of prostate cancer and which has four hydroxyl groups, at C-2′, C-1, C-7, and C-10 (Figure 1). When complexed with (BDI-II)ZnN(TMS)$_2$, Dtxl reacted with SA to yield Dtxl-2′-SA with 100% regioselectivity and 71.5% yield (entry 5, Table 3; Scheme 3B). In addition, (BDI-II)ZnN(TMS)$_2$/Dtxl showed excellent control for the ROP of LA, affording Dtxl-PLA with predictable MWs and very narrow MWDs (Figure 3A and Supporting Information Table S2).

Ptxl-Initiated Controlled Polymerization of δ-Valerolactone, Trimethylene Carbonate, and ε-Caprolactone. Poly(δ-valerolactone) (PVL), poly(trimethylene carbonate) (PTMC), and poly(ε-caprolactone) (PCL) have been extensively used as alternatives to PLA in suturing, drug delivery, and tissue engineering applications. We next studied whether the Ptxl (or Dtxl)/(BDI-II)ZnN(TMS)2-mediated controlled ROP of LA could be extended to the synthesis of Ptxl-PCL, Ptxl-PVL, and Ptxl-PTMC conjugates from the corresponding monomers. Ptxl/(BDI-II)ZnN(TMS)$_2$ showed excellent control over the polymerization of δ-valerolactone (VL), trimethylene carbonate (TMC), and ε-caprolactone (CL) (Table 4; for comprehensive polymerization results, see Supporting Information Table S3). All the polymerization reactions gave drug−polymer conjugates with the expected MWs and narrow MWDs (M_w/M_n < 1.2); Ptxl (or Dtxl) was quantitatively conjugated to the termini of the polymers via ester bonds. The

dx.doi.org/10.1021/ma202581d | Macromolecules 2012, 45, 2225−2232

Table 4. Ptxl (or Dtxl)/(BDI-II)ZnN(TMS)$_2$-Mediated ROP of VL, TMC, and CL[a]

entry	initiator (R)	monomer	[M]/[R]	time (h)	temp (°C)	conv (%)	incorp eff (%)	M_n/M_{exp} (× 10^3 g/mol)	MWD (M_w/M_n)
1	Ptxl	VL	100	12	rt	>99	>99	15.1/10.8	1.17
2	Ptxl	VL	200	12	rt	>99	>99	23.1/20.8	1.18
3	Ptxl	VL	300	12	rt	>99	>99	31.2/30.8	1.18
4	Ptxl	CL	200	10	rt	>99	>99	20.3/23.7	1.07
5	Dtxl	CL	100	10	rt	>99	>99	11.2/12.2	1.05
6	Ptxl	TMC	100	6	50	>99	>99	14.7/11.1	1.10

[a]All reactions were performed in anhydrous THF with $[monomer]_0$ = 0.69 M. Abbreviations: conv = conversion; Dtxl = docetaxel; incorp eff = incorporation efficiency; M_{exp}, expected MW; MWD = molecular weight distribution; Ptxl = paclitaxel; rt = room temperature. Monomer conversion was measured by FT-IR. Incorporation efficiency was determined by reversed-phase HPLC analysis of unreacted Ptxl (or Dtxl). M_n and MWD were determined by GPC.

polymerizations of VL and CL proceeded at room temperature, and the monomer conversions were quantitative (entries 1−5, Table 4). However, the polymerization of TMC required a slightly elevated reaction temperature; quantitative TMC conversation took place in 6 h at 50 °C (entry 6).

CONCLUSION

When complexed with hydroxyl-containing therapeutics, Zn catalysts mediated the polymerization of LA and afforded PLA chains with drugs incorporated at the chain termini through ester linkages.[6a,11,21] Our previous work showed that the resulting drug−polymer conjugates could be nanoprecipitated to formulate nanoparticles with high drug loadings, nearly quantitative loading efficiencies, controlled release profiles without burst release effects, and narrow particle size distributions.[11,19] We systemically investigated the effects of BDI ligand substituents on the initiation and chain propagation during LA polymerization. The steric bulk of the *N*-aryl substituents of the BDI ligand drastically affected the regioselectivity of the coordination of the metal catalysts with the drugs. (BDI-II)ZnN(TMS)$_2$, which bears bulky ^{i}Pr groups at the 2- and 6-positions of the *N*-aryl rings, formed coordination complexes with Ptxl only via the 2′-OH of Ptxl and yielded Ptxl-2′-PLA and Ptxl-2′-SA with 100% regioselectivity. This strategy for the controlled polymerization of LA (and acylation with SA) was extended to Dtxl, which has a more complex structure, with 100% regioselectivity. We also demonstrated that the scope of the Ptxl (or Dtxl)/(BDI-II)ZnN(TMS)$_2$-mediated controlled polymerization could be expanded to three other biopolymers, poly(δ-valerolactone, poly(trimethylene carbonate), and poly(ε-caprolactone). Importantly, the heterogeneity of the resulting polyester−drug conjugates was substantially reduced by means of this unprecedented controlled chemistry. Particularly noteworthy is that the extension of the reaction to various monomers may have benefits for drug delivery: drugs could be entrapped within separate populations of particles with different release kinetics because different polyesters degrade at different rates.[22]

EXPERIMENTAL SECTION

Materials and Methods. *General.* BDI ligands and the corresponding metal catalysts (BDI-X)ZnN(TMS)$_2$ were prepared by following the published procedure[12a] and were stored at −30 °C in a glovebox. All anhydrous solvents were purified through alumina columns and kept anhydrous over molecular sieves. Paclitaxel (Ptxl) and docetaxel (Dtxl) were purchased from LC Laboratories (Woburn, MA) and used as received. All other chemicals were purchased from Sigma-Aldrich (St. Louis, MO) and used as received unless otherwise noted. The molecular weights of polymer−drug conjugates were determined by gel permeation chromatography (GPC) on a system equipped with an isocratic pump (Model 1100, Agilent Technology, Santa Clara, CA), a DAWN HELEOS 18-angle laser light scattering detector (MALLS), and an Optilab rEX refractive index detector (Wyatt Technology, Santa Barbara, CA). The wavelength of the HELEOS detector was set at 658 nm. Size-exclusion columns used for the separation of PLA or drug−PLA conjugates were connected in series to the GPC system (Phenogel columns 100, 500, 10^3, and 10^4 Å, 5 μm, 300 × 7.8 mm, Phenomenex, Torrance, CA). THF (HPLC grade) was used as the mobile phase for PLA. DMF containing 0.1 M LiBr at 60 °C was used as the mobile phase for PVL, PCL, and PTMC. Low-resolution electrospray ionization mass spectrometry (LR-ESI-MS) experiments were conducted on a Waters Quattro II mass spectrometer. HPLC analysis was performed on a System Gold system (Beckman Coulter, Fullerton, CA) equipped with a 126P solvent module, a System Gold 128 UV detector, and an analytical pentafluorophenyl column (Curosil-PFP or Luna C18(2), both 250 × 4.6 mm, 5 μ, Phenomenex, Torrance, CA). The UV wavelengths for Ptxl and Dtxl were set at 227 nm; the mobile phase was acetonitrile/water containing 0.1 wt % trifluoroacetic acid. NMR analyses were conducted on a Varian U500, VXR500, or UI500NB (500 MHz).

Monomer. DL-Lactide (LA) was purchased from TCI America (Portland, OR). It was recrystallized three times from toluene and stored in a glovebox. ε-Caprolactone (CL) was purchased from Sigma-Aldrich, dried over CaH_2 for 48 h, and fractionally distilled under reduced pressure. δ-Valerolactone (VL) was purchased from Sigma-Aldrich, dried over CaH_2 overnight, and fractionally distilled under reduced pressure. The whole process was repeated. Trimethyl carbonate (TMC) was synthesized according to published procedures.[23] The monomer was recrystallized from ether twice, dried, and stored in a glovebox. All monomers were stored in the freezer of a glovebox at −30 °C before use.

Ptxl-Mediated Ring-Opening Polymerization of LA in the Presence of a Zn Catalyst. In a glovebox, Ptxl (8.5 mg, 0.01 mmol) was dissolved in anhydrous THF (2 mL). (BDI-II)ZnN(TMS)$_2$[12a] (6.4 mg, 0.01 mmol) was added and allowed to react with Ptxl for 15−20 min. LA (144.0 mg, 1.0 mmol) in THF (1 mL) was added dropwise to the mixture of Ptxl and (BDI-II)ZnN(TMS)$_2$ with vigorous stirring. The polymerization was monitored using FT-IR by following the lactone band at 1772 cm^{-1} or using ^{1}H NMR by checking the methine (−C*H*−) peak of LA around 5.2−5.0 ppm. After the polymerization was complete, an aliquot of the polymerization solution was analyzed using HPLC to quantify the unreacted Ptxl to determine the efficiency of Ptxl incorporation into Ptxl-LA$_{100}$. One drop of water was added to the polymerization solution to hydrolyze the Zn-Ptxl oxide. The resulting Ptxl-LA$_{100}$ was precipitated from ethyl ether (10 mL), and the precipitate was washed with ether and toluene to remove the BDI ligand, dried under vacuum, and characterized by GPC. Complete removal of BDI from Ptxl-PLA was verified by TLC.

Reductive Degradation of Ptxl-PLA Using Bu_4NBH_4. The reductive degradation of Ptxl at C-13 was achieved by following the literature reported procedure.[16] Ptxl (5 mg, 5.8 mmol) in anhydrous dichloromethane (1 mL) was allowed to react with Bu_4NBH_4 (2.5 mg, 10 mmol) for 1.5 h in a glovebox. Acetic acid (∼100 μL) was added to the reaction mixture to terminate the reaction. The reaction solution was stirred for 20 min, and then the solvent was completely removed. The residual solid was redissolved in acetonitrile. An aliquot of the solution was analyzed on an HPLC equipped with a Curosil RP

column (250 × 4.6 mm, 5 μm; Phenomenex, Torrance, CA). The desired fractions were collected and analyzed by LR-ESI-MS. The Ptxl-PLA conjugate was reductively degraded and analyzed similarly.

Reaction of Ptxl with SA in the Presence of a Zn Catalyst. In a glovebox, Ptxl (8.5 mg, 0.01 mmol) was dissolved in anhydrous THF (400 μL). (BDI-II)ZnN(TMS)$_2$ (6.5 mg, 0.01 mmol) was added and allowed to react with Ptxl for 15−20 min. SA (1.1 mg, 0.011 mmol) in THF (600 μL) was added dropwise to the mixture of Ptxl and (BDI-II)ZnN(TMS)$_2$ with vigorous stirring ([SA] = 0.011 M). The reaction vial was tightly sealed and heated at 40 °C outside the glovebox. The reaction was allowed to proceed for 4 h and quenched with 1 mL of ice-cold methanol. The resulting solution was immediately analyzed by HPLC.

Pure Ptxl-2′-SA (or Dtxl-2′-SA) for NMR analysis was obtained by preparative TLC on a silica gel matrix (UV254, 1500 μm thickness, Sigma-Aldrich). Silica gel containing the desired compounds was scraped from the glass plate and extracted with methanol (2 × 30 mL). The resulting solution was evaporated under vacuum for NMR analysis.

Ptxl-2′-SA. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 7.28 Hz, 2H), 7.77 (d, J = 7.36 Hz, 2H), 7.61−7.36 (m, 15H), 7.26−7.24 (m, 6H), 7.03 (d, J = 9.16 Hz, 1H), 6.25 (s, 1H), 6.22 (d, J = 8.9 Hz, 1H), 5.97, 5.95 (dd, J = 2.84 Hz, 2.76 Hz, 1H), 5.67 (d, J = 7.08 Hz, 1H), 5.56 (d, 1H), 5.47 (d, J = 2.96 Hz, 1H), 4.96 (d, J = 9.36 Hz, 1H), 4.85−4.79 (m, 3H), 4.65 (d, J = 11.9 Hz, 1H), 4.41 (s, 1H), 4.31 −4.27 (m, 2H), 4.19 (d, J = 8.44 Hz, 1H), 3.99 (t, J = 9.20 Hz, 1H), 3.81−3.73 (m,3H), 3.64 (t, J = 9.20 Hz, 1H), 3.31 (s, 3H), 2.72−2.51 (m, 4H), 2.42 (s, 3H), 2.40−2.30 (m, 1H), 2.21 (s, 3H), 1.89 (s, 3H), 1.66 (s, 6H), 1.64 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 171.5, 171.2, 171.1, 169.8, 167.9, 167.3, 167.0, 142.6, 138.4,137.2, 136.9, 133.7, 133.6, 132.8, 132.0, 130.2, 129.2, 129.1, 129.0, 128.7, 128.5, 128.3, 127.7, 127.6, 127.2, 126.6, 126.0, 101.4, 97.5, 84.4, 82.1, 81.0, 79.0, 76.4, 75.6, 75.1, 74.3, 73.1,72.1, 71.9, 58.5, 52.8, 49.1, 45.6, 43.2,35.6, 33.9, 29.7, 29.0, 28.9, 26.8, 25.6, 24.9, 22.7, 22.1, 20.8, 14.8, 9.6. ESI-MS (low resolution, positive mode): calculated for $C_{52}H_{57}NO_{16}$, m/z 954.3 $[M + H]^+$; found 954.8 $[M + H]^+$.

Ptxl-2′-7-diSA. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, 2H), 7.77 (d, 2H), 7.61−7.36 (m, 15H), 7.26−7.24 (m, 6H), 6.21(s, 1H), 6.16 (s, 1H), 6.09 (d, 1H), 5.95 (dd, 1H), 5.86 (dd, 1H), 5.64 (m, 1H), 5.58 (d, 1H), 4.91 (d, 1H), 4.85−4.79 (m, 3H), 4.65 (d, J = 11.9 Hz, 1H), 4.41 (s, 1H), 4.31 −4.27 (m, 2H), 4.17 (d, 1H), 3.99 (t, 1H), 3.86 (m, 3H), 3.64 (t, J = 9.20 Hz, 1H), 3.31 (s, 3H), 2.8−2.5 (m, 8H), 2.39 (s, 3H), 2.40−2.30 (m, 1H), 2.13 (s, 3H), 1.88 (s, 3H), 1.79 (s, 6H), 1.64 (s, 3H), 1.19 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 171.6, 169.8, 169.1, 168.3, 167.5, 166.8, 162.7, 141.2, 138.0, 136.8, 133.7, 133.5, 132.4, 132.0, 130.2, 129.1, 129.0, 128.7, 128.5, 128.2, 127.2, 126.7, 127.2, 126.6, 103.6, 100.2, 99.3, 83.9, 80.8, 78.5, 76.4, 75.8, 75.3, 74.4, 74.1, 71.7, 71.9, 65.8, 55.9, 53.1, 46.9, 43.2, 36.6, 35.2, 33.1, 31.5, 29.0, 28.8, 27.3, 26.4, 24.7, 22.6, 21.1, 20.7, 15.2, 14.5, 10.8. ESI-MS (low resolution, positive mode): calculated for $C_{55}H_{59}NO_{20}$, m/z 1054.4 $[M + H]^+$; found 1054.8 $[M + H]^+$.

Dtxl-2′-SA. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, 2H), 7.66 (t, 1H), 7.54 (t, 2H), 7.40 (m, 2H), 7.37 (m, 3H), 6.20 (s, 1H), 5.71 (d, 1H), 5.50 (s, 1H), 5.26 (s, 1H), 4.40−4.20 (m, 3H), 3.94 (s, 1H), 2.85 (m, 1H), 2.6 (m, 4H), 2.45−2.35 (m, 2H), 1.98 (s, 3H), 1.87 (t, 1H), 1.79 (s, 3H), 1.54 (s, 3H), 1.38 (s, 9H), 1.29 (s, 3H), 1.25 (s, 3H). ESI-MS (low resolution, positive mode): calculated for $C_{47}H_{57}NO_{17}$, m/z 907.4 $[M + H]^+$; found 907.4 $[M + H]^+$.

Synthesis of Ptxl-VL$_n$ (or Ptxl-CL$_n$) Polymer. In a glovebox, Ptxl (8.6 mg, 0.010 mmol) and (BDI-II)ZnN(TMS)$_2$ (6.5 mg, 0.01 mmol) were dissolved in 300 μL of THF. The mixture was stirred for 20 min. δ-Valerolactone (VL, 92.6 μL, 100 mg, 1.0 mmol) in THF (0.5 mL) was added to the mixture of Ptxl and (BDI-II)ZnN(TMS)$_2$. The polymerization was monitored by FT-IR; the 1739 cm^{-1} peak of the lactone bond in VL shifted to 1728 cm^{-1} for the ester bond in poly(δ-valerolactone) (PVL). The reaction solution was quenched with 1 mL of ice-cold methanol. The conversion of VL was determined by ^{1}H NMR. The polymer was precipitated with ethyl ether (10 mL), and the precipitate was washed with ether and toluene to remove BDI ligand, dried under vacuum, and characterized by GPC. Complete removal of BDI from Ptxl-PVL was verified by TLC. Similar procedures were used for Ptxl-PCL synthesis. The ^{1}H NMR spectra of Ptxl-VL$_{100}$ and Ptxl-CL$_{100}$ are shown in Figures S4 and S5.

Synthesis of Ptxl-TMC$_n$ Polymer. In a glovebox, Ptxl (8.6 mg, 0.010 mmol) and (BDI-II)ZnN(TMS)$_2$ (6.6 mg, 0.011 mmol) were mixed in 300 μL of THF. The mixture stirred was stirred for 20 min. TMC (102 mg, 1.0 mmol) in toluene (300 μL) was added into the mixture. The reaction vessel was tightly sealed and heated at 50 °C for 5 h out of the box. The reaction solution was quenched with 5 mL of ice-cold methanol. The conversion of TMC was determined by ^{1}H NMR. The polymer was precipitated with ethyl ether (10 mL), and the precipitate was washed with ether and toluene to remove the BDI ligand, dried under vacuum, and characterized by GPC. The ^{1}H NMR spectrum of Ptxl-TMC$_{100}$ is shown in Figure S6.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Polymerization data; characterization of polymer−drug conjugates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.C. acknowledges support from the NSF (DMR-0748834), the NIH (NIH Director's New Innovator Award 1DP2OD007246-01), and the Midwest Cancer Nanotechnology Training Center, University of Illinois at Urbana−Champaign (UIUC). R.T. acknowledges a student fellowship (2007−2010) from the Siteman Center for Cancer Nanotechnology Excellence (SCCNE, Washington University)−Center for Nanoscale Science and Technology (CNST, UIUC).

■ REFERENCES

(1) Some recent reviews about nanomedicine: (a) Alexis, F.; Rhee, J. W.; Richie, J. P.; Radovic-Moreno, A. F.; Langer, R.; Farokhzad, O. C. *Urol. Oncol: Semin. Orig. Invest.* **2008**, *26*, 74. (b) Peer, D.; Karp, J. M.; Hong, S.; FaroKhzad, O. C.; Margalit, R.; Langer, R. *Nature Nanotechnol.* **2007**, *2*, 751. (c) Farokhzad, O. C.; Langer, R. *Adv. Drug Delivery Rev.* **2006**, *58*, 1456. (d) Pun, S. H.; Tack, F.; Bellocq, N. C.; Cheng, J. J.; Grubbs, B. H.; Jensen, G. S.; Davis, M. E.; Brewster, M.; Janicot, M.; Janssens, B.; Floren, W.; Bakker, A. *Cancer Biol. Ther.* **2004**, *3*, 641. (e) Pack, D. W.; Hoffman, A. S.; Pun, S.; Stayton, P. S. *Nat. Rev. Drug Discovery* **2005**, *4*, 581. (f) Zhang, L.; Gu, F. X.; Chan, J. M.; Wang, A. Z.; Langer, R. S.; Farokhzad, O. C. *Clin. Pharmacol. Ther.* **2008**, *83*, 761.

(2) (a) Cheng, J. J.; Khin, K. T.; Jensen, G. S.; Liu, A. J.; Davis, M. E. *Bioconjugate Chem.* **2003**, *14*, 1007. (b) Cheng, J.; Khin, K. T.; Davis, M. E. *Mol. Pharmaceutics* **2004**, *1*, 183.

(3) Schluep, T.; Cheng, J.; Khin, K. T.; Davis, M. E. *Cancer Chemother. Pharmacol.* **2006**, *57*, 654.

(4) (a) Schluep, T.; Hwang, J.; Cheng, J.; Heidel, J. D.; Bartlett, D. W.; Hollister, B.; Davis, M. E. *Clin. Cancer Res.* **2006**, *12*, 1606. (b) Duncan, R. *Nat. Rev. Cancer* **2006**, *6*, 688. (c) Bagalkot, V.; Farokhzad, O. C.; Langer, R.; Jon, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8149.

(5) Ferrari, M. *Nat. Rev. Cancer* **2005**, *5*, 161.
(6) Examples: (a) Chan, J. M.; Zhang, L. F.; Tong, R.; Ghosh, D.; Gao, W. W.; Liao, G.; Yuet, K. P.; Gray, D.; Rhee, J. W.; Cheng, J. J.; Golomb, G.; Libby, P.; Langer, R.; Farokhzad, O. C. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 2213. (b) Farokhzad, O. C.; Cheng, J. J.; Teply, B. A.; Sherifi, I.; Jon, S.; Kantoff, P. W.; Richie, J. P.; Langer, R. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 6315. (c) Tong, R.; Christian, D. A.; Tang, L.; Cabral, H.; Baker, J. R.; Kataoka, K.; Discher, D. E.; Cheng, J. J. *MRS Bull.* **2009**, *34*, 422. (d) Tong, R.; Cheng, J. J. *Polym. Rev.* **2007**, *47*, 345. (e) Almutairi, A.; Rossin, R.; Shokeen, M.; Hagooly, A.; Ananth, A.; Capoccia, B.; Guillaudeu, S.; Abendschein, D.; Anderson, C. J.; Welch, M. J.; Frechet, J. M. J. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 685. (f) Kwon, Y. J.; James, E.; Shastri, N.; Frechet, J. M. J. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 18264. (g) Murthy, N.; Xu, M. C.; Schuck, S.; Kunisawa, J.; Shastri, N.; Frechet, J. M. J. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 4995. (h) Davis, M. E. *Mol. Pharmaceutics* **2009**, *6*, 659. (i) Davis, M. E. *Adv. Drug Delivery Rev.* **2009**, *61*, 1189. (j) Davis, M. E.; Zuckerman, J. E.; Choi, C. H. J.; Seligson, D.; Tolcher, A.; Alabi, C. A.; Yen, Y.; Heidel, J. D.; Ribas, A. *Nature* **2010**, *464*, 1067.
(7) Some recent reviews about polymer−drug conjugates: (a) Wagner, V.; Dullaart, A.; Bock, A. K.; Zweck, A. *Nat. Biotechnol.* **2006**, *24*, 1211. (b) Li, C.; Wallace, S. *Adv. Drug Delivery Rev.* **2008**, *60*, 886. (c) Li, C. *Adv. Drug Delivery Rev.* **2002**, *54*, 695. (d) Nori, A.; Kopeček, J. *Adv. Drug Delivery Rev.* **2005**, *57*, 609. (e) Duncan, R. *Curr. Opin. Biotechnol.* **2011**, *22*, 492. (f) Joralemon, M. J.; McRae, S.; Emrick, T. *Chem. Commun.* **2010**, *46*, 1377. (g) Duncan, R.; Vicent, M. J. *Adv. Drug Delivery Rev.* **2010**, *62*, 272. (h) Khandare, J.; Minko, T. *Prog. Polym. Sci.* **2006**, *31*, 359. (i) Greco, F.; Vicent, M. J. *Adv. Drug Delivery Rev.* **2009**, *61*, 1203.
(8) Examples: (a) Lee, C. C.; MacKay, J. A.; Frechet, J. M. J.; Szoka, F. C. *Nat. Biotechnol.* **2005**, *23*, 1517. (b) Srinivasachari, S.; Fichter, K. M.; Reineke, T. M. *J. Am. Chem. Soc.* **2008**, *130*, 4618. (c) Lu, H.; Cheng, J. *J. Am. Chem. Soc.* **2008**, *130*, 12562. (d) Lu, H.; Cheng, J. J. *J. Am. Chem. Soc.* **2007**, *129*, 14114. (e) Cheng, J. J.; Deming, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 9457. (f) Medina, S. H.; El-Sayed, M. E. H. *Chem. Rev.* **2009**, *109*, 3141. (g) Gillies, E. R.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2002**, *124*, 14137. (h) Lee, C. C.; Gillies, E. R.; Fox, M. E.; Guillaudeu, S. J.; Frechet, J. M. J.; Dy, E. E.; Szoka, F. C. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 16649. (i) Liu, G.; Jia, L. *J. Am. Chem. Soc.* **2004**, *126*, 14716.
(9) Examples: (a) Zhang, X. F.; Li, Y. X.; Chen, X. S.; Wang, X. H.; Xu, X. Y.; Liang, Q. Z.; Hu, J. L.; Jing, X. B. *Biomaterials* **2005**, *26*, 2121. (b) Shen, Y. Q.; Jin, E. L.; Zhang, B.; Murphy, C. J.; Sui, M. H.; Zhao, J.; Wang, J. Q.; Tang, J. B.; Fan, M. H.; Van Kirk, E.; Murdoch, W. J. *J. Am. Chem. Soc.* **2010**, *132*, 4259. (c) Kim, S. C.; Kim, D. W.; Shim, Y. H.; Bang, J. S.; Oh, H. S.; Kim, S. W.; Seo, M. H. *J. Controlled Release* **2001**, *72*, 191. (d) Benny, O.; Fainaru, O.; Adini, A.; Cassiola, F.; Bazinet, L.; Adini, I.; Pravda, E.; Nahmias, Y.; Koirala, S.; Corfas, G.; D'Amato, R. J.; Folkman, J. *Nat. Biotechnol.* **2008**, *26*, 799. (e) Lee, S. H.; Zhang, Z. P.; Feng, S. S. *Biomaterials* **2007**, *28*, 2041. (f) Zhang, Z. P.; Feng, S. S. *Biomaterials* **2006**, *27*, 262.
(10) Examples: (a) Sengupta, S.; Eavarone, D.; Capila, I.; Zhao, G. L.; Watson, N.; Kiziltepe, T.; Sasisekharan, R. *Nature* **2005**, *436*, 568. (b) Yoo, H. S.; Lee, K. H.; Oh, J. E.; Park, T. G. *J. Controlled Release* **2000**, *68*, 419.
(11) Tong, R.; Cheng, J. *J. Angew. Chem., Int. Ed.* **2008**, *47*, 4830.
(12) (a) Chamberlain, B. M.; Cheng, M.; Moore, D. R.; Ovitt, T. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2001**, *123*, 3229. (b) du Boullay, O. T.; Marchal, E.; Martin-Vaca, B.; Cossio, F. P.; Bourissou, D. *J. Am. Chem. Soc.* **2006**, *128*, 16442. (c) Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D. *Chem. Rev.* **2004**, *104*, 6147.
(13) Kricheldorf, H. R.; Kreisersaunders, I. *Polymer* **1994**, *35*, 4175.
(14) Mastropaolo, D.; Camerman, A.; Luo, Y. G.; Brayer, G. D.; Camerman, N. *Proc. Natl. Acad. Sci. U. S. A.* **1995**, *92*, 6920.
(15) Mathew, A. E.; Mejillano, M. R.; Nath, J. P.; Himes, R. H.; Stella, V. J. *J. Med. Chem.* **1992**, *35*, 145.
(16) Magri, N. F.; Kingston, D. G. I.; Jitrangsri, C.; Piccariello, T. J. *Org. Chem.* **1986**, *51*, 3239.
(17) Moore, D. R.; Cheng, M.; Lobkovsky, E. B.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2599.
(18) (a) Moore, D. R.; Cheng, M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2003**, *125*, 11911. (b) Cheng, M.; Moore, D. R.; Reczek, J. J.; Chamberlain, B. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2001**, *123*, 8738.
(19) Tong, R.; Yala, L.; Fan, T. M.; Cheng, J. *Biomaterials* **2010**, *31*, 3043.
(20) (a) Jeske, R. C.; DiCiccio, A. M.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 11330. (b) Jeske, R. C.; Rowley, J. M.; Coates, G. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 6041.
(21) (a) Tong, R.; Cheng, J. *J. Bioconjugate Chem.* **2010**, *21*, 111. (b) Tong, R.; Yala, L. D.; Fan, T. M.; Cheng, J. *J. Biomaterials* **2010**, *31*, 3043. (c) Tong, R.; Cheng, J. J. *J. Am. Chem. Soc.* **2009**, *131*, 4744.
(22) (a) Grayson, A. C. R.; Choi, I. S.; Tyler, B. M.; Wang, P. P.; Brem, H.; Cima, M. J.; Langer, R. *Nature Mater.* **2003**, *2*, 767. (b) Grayson, A. C. R.; Voskerician, G.; Lynn, A.; Anderson, J. M.; Cima, M. J.; Langer, R. *J. Biomater. Sci., Polym. Ed.* **2004**, *15*, 1281.
(23) Helou, M.; Miserque, O.; Brusson, J. M.; Carpentier, J. F.; Guillaume, S. M. *Chem.—Eur. J.* **2008**, *14*, 8772.