European Polymer Journal 97 (2017) 389–396

Contents lists available at ScienceDirect

European Polymer Journal

journal homepage: www.elsevier.com/locate/europolj

H-bonding binary organocatalysis promoted amine-initiated ring-opening polymerizations of lactide from polysarcosine to diblock copolymers

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ARTICLE INFO

Keywords:
Diblock copolymer
H-bonding
Organocatalysis
Polylactide
Sarcosine
Ring-opening polymerization

ABSTRACT

Alcohol-initiated ring-opening polymerization (ROP) of cyclic esters for synthesizing polyesters was well established, but amine-initiated ROP of cyclic esters was rare. A challenge is slow initiation and fast propagation in the amine-initiated ROPs. To address the difficulties, an ionic H-bond donor (iHBD) and H-bond acceptor (HBA) binary organocatalysis in amine-initiated ROP of lactide (LA) was developed. Guanidinium hexahydro-2*H*-pyrimido[1,2-*a*] pyrimidin-1-ium [$(HppH_2)^+$] and tertiary amine sparteine (SP), cooperatively played the role of iHBD/HBA binary catalysts, efficiently promoted ROP of LA from amine initiators toward polylactide (PLA) and polysarcosine-*block*-polylactide diblock copolymer (PSar-*b*-PLA). Benzyl amine and *N*-methylbenzylamine initiated ROPs of LA under mild conditions produced PLAs with predictable molecular weights ($M_{n,NMR}$ = 2.9–17.1 kg mol^{-1}) and narrow dispersities ($Đ_{M,SEC}$ = 1.13–1.23). Macroinitiator PSar copolymerized with LA under the iHBD/HBA catalysis, producing PSar-*b*-PLAs with controlled molecular weights ($M_{n,NMR}$ = 5.7–14.8 kg mol^{-1}) and low dispersities ($Đ_{M,SEC}$ = 1.16–1.21). Kinetics and chain extension experiments confirmed that the amine-initiated ROP of LA in presence of $(HppH_2)^+BF_4^-$/SP was in controlled/living manner. ^{1}H NMR, ^{13}C NMR, SEC, and MALDI-ToF MS analyses indicated that the obtained PLA was exclusively initiated from the corresponding amine with amide linkage. An iHBD/HBA binary activation mechanism was proposed.

1. Introduction

Amphiphilic block copolymers containing hydrophobic polylactide (PLA) blocks have received extensive investigations in biomedical research and development [1–3]. PLA was chosen as the hydrophobic segment due to its easy access [4], as well as its biodegradability and biocompatibility [5,6]. In preparation of PLA-containing diblock copolymers, a widely employed route was ring-opening polymerization (ROP) of lactide (LA) with poly(ethylene glycol) (PEG) as a macroinitiator. Although the PEG-*b*-PLA copolymers were approved by the US Food and Drug Administration for biomedical applications [7], the specific and nonspecific immunoresponsiveness effected by PEGs invited serious concerns recently [8–11]. Hydrophilic polypeptides [12,13] and polypeptoids [14–18] are suggested as promising alternatives to PEG. Amine groups are common in the chain ends of polypeptoid and polypeptide [12,18]. Amphiphilic block copolymers containg PLA can be synthesized by amine-initiated ROP of LA using amine-terminated hydrophilic polymers as initiators.

Amine-initiated ROP of cyclic esters for synthesizing polyesters with an amide linkage is desirable target. In fact, Saotome and Kodaira investigated primary amine-initiated ROP of valerolactone without catalyst at high temperature (> 160 °C) [19], Sporadic reports [20–24] on metal complexes catalyzed and amine initiated ROPs of LA were documented, in which metal amide formation in the initiation steps influenced the controllability and efficiency remarkably. Because the rate of inserting lactide monomer into the metal–amide bonds was slower than that into the metal–alkoxide bonds, mismatch between rates of initiation and propagation was obvious, which resulted in poor control and low efficiency [22–25]. Stannous octoate was used as catalyst for ROP of LA initiated by poly(amidoamine) dendrimers with amine end groups at 150 °C for 72 h [20]. In this case there were extensive transesterifications ($Đ_M$ = 1.5–1.8) [25]. In order to overcome the limitations, Mountford and coworkers suggested using electrophilic metal complexes as monomer activating catalyst for controlled ROP of LA using amine as an exogenous initiator [26,27]. Moreover, it is necessary to develop efficient and mild catalyst for amine-initiated

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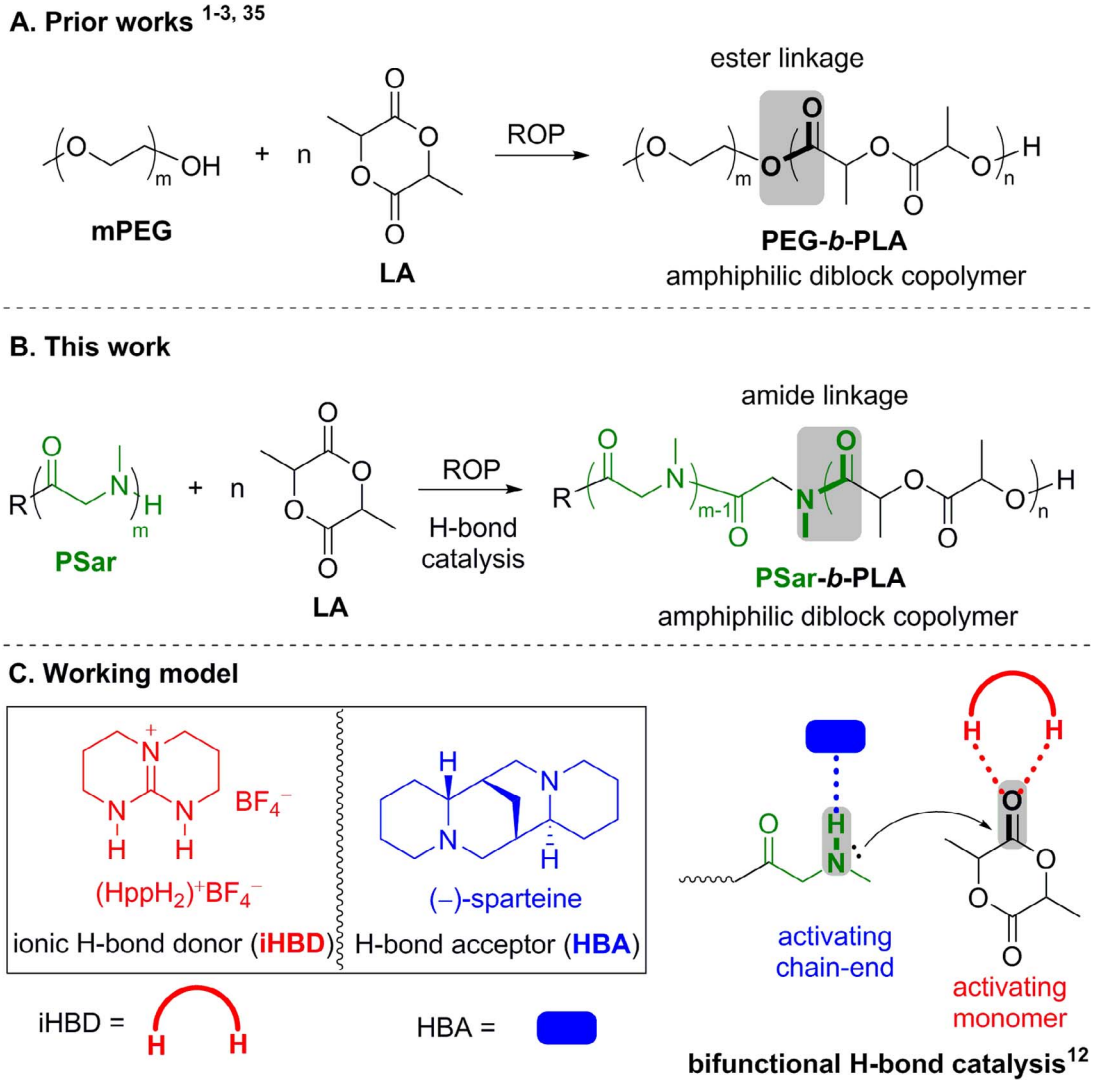
http://dx.doi.org/10.1016/j.eurpolymj.2017.10.030
Received 10 September 2017; Received in revised form 23 October 2017; Accepted 25 October 2017

controlled ROP of cyclic esters.

With the advent of organopolymerizations [28–30], the aforementioned problem of slow initiation by amine renewed interests and hopefully could be resolved. Indeed, Hedrick and coworkers reported the first *N*-heterocyclic carbene-catalyzed ROPs of LA using di-functional primary amine-terminated PEG as initiators [31]. Both primary amines and amides were activated by *N*-heterocyclic carbene catalyst to initiate ROP of LA by insertion into the N—H bonds [31,32]. H-shaped PLA polymers were obtained at 90 °C after 71 h by 85% conversion. The same group briefly mentioned a thiourea/amine binary catalysts in ROPs of LA which initiated from amino functionalized dendrimers [33]. Oligomer PLAs with low degree of polymerization (DP = 5) were obtained. Bourissou and coworkers recently reported that amide end-capped PLA oligomers were prepared by a two-step one-pot strategy using 1,8-diazabicycloundec-7-ene (DBU) as a catalyst in the second step of ROP of LA [34]. In the first step, amine reacted with one LA molecule to obtain an amine-terminated compound, and then DBU catalyzed ROPs of LA from the hydroxyl group. Indeed, DBU is a super strong base. Amine initiates ROP of LA using DBU as the catalyst in one-pot resulted in poor control of molecular weight due to side-reactions incurred by basic and nucleophilic DBU [34]. To obviate harsh reaction conditions involving the use of (super) strong bases, mild binary catalysts capable of promoting amine-initiated ROPs of esters and carbonates are necessary.

Amine-terminated polysarcosine (PSar), a polypeptoid derived from natural *N*-methyl glycine, *viz.* sarcosine [18], is a promising hydrophilic segment in functional amphiphilic diblock copolymers [14,17,18]. PSar featured with ideal water solubility, non-toxicity, biodegradability, and biocompatibility. It is recognized as a potential alternative to hydroxyl-terminated PEG [11]. Amphiphilic PEG-*b*-PLA diblock copolymers were synthesized by using hydroxyl-terminated PEG as macroinitiator, in which hydrolytically sensitive ester linkage [35] was constructed between the hydrophilic PEG segment and the hydrophobic PLA segment (Scheme 1, A). In parallel, PSar as a surrogate to PEG (Scheme 1, B) requires a direct initiation of LA form the secondary amine group of its chain end, which posed challenge to the initiating/catalysis system [14,18,36,37].

Several leading groups reported preparations of PSar-based amphiphilic block copolymers for biomedical application [37–41]. Diblock copolymers of sarcosine and cyclic esters, albeit seriously underdeveloped, attracted growing interest for their outstanding assembly properties, and biocompatibilities [36,37,42–44]. Kimura and coworkers investigated multiple step synthesis and properties of amphiphilic PLA-*b*-PSar diblock copolymers by metal complexes [37,42]. Our group firstly reported a one-pot synthesis and biomedical evaluations of PSar-*b*-PCL copolymers [43,44]. A follow up work in multi-step



Scheme 1. (A) Synthesis of amphiphilic PEG-*b*-PLA diblock copolymers from commercial PEGs. (B) Synthesis of amphiphilic PSar-*b*-PLA diblock copolymers under H-bond organocatalysis. (C) Amine-initiated ROP of LA under binary H-bonding organocatalysis.