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A method for preparing water soluble cyclic polymers

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ABSTRACT

A novel ring-closure method was developed to specifically focus on the preparation of water soluble cyclic polymers. The well-defined linear polymers were synthesized by a standard RAFT polymerization using a functional RAFT agent **1**. The cyclic polymers were then obtained by virtue of an efficient bromomaleimide-thiol substitution reaction to ring-close the linear precursors. This technique is unique in that it not only produces various well-defined water soluble cyclic polymers with high efficiency and topology purity, but also employs the environmentally benign solvent, water, as the ring-closure reaction media.

1. Introduction

Cyclic polymers, as one of the oldest topological polymers, have rejuvenated recently due to the significant achievements in cyclic polymer synthesis [1–6]. With the endless molecular topology, cyclic polymers have markedly different characteristics than their linear counterparts, such as a smaller radius of gyration and hydrodynamic volume, lower melt viscosity, and higher thermostability. To date, the known synthesis methods for cyclic polymers can be generalized into two categories: the ring-expansion and ring-closure strategies.

In the ring-expansion approach, the cyclic polymers are formed by a continuous insertion of monomer units into the activated cyclic chains. Because the cyclic polymers remain intact during the whole ring expansion process, this strategy can produce pure cyclic polymers with high molecular weight at concentrated solution and even in bulk. However, the ring-expansion approach is hardly to control the molecular weight and polydispersity of the resultant cyclic polymers [7–11]. In addition, it is difficult to produce the topological polymers derived from monocyclic polymers, such as the theta, eight, and tadpole shape polymers.

In the ring-closure method, cyclic polymers are prepared by applying highly efficient coupling chemistry to end-functionalized linear telechelic polymers. Especially when click chemistry is combined with controlled polymerization, this approach has demonstrated its power in the preparation of varied cyclic polymers with controlled molecular weight and low polydispersity [12–14]. In addition to the simple monocyclic topology, the ring-closure strategy can produce the cyclic polymer derivatives with complex architectures, such as theta and eight shapes conveniently [15–18]. However, the disadvantages are also obvious in this approach.

One of the main problems lies in the requirement of highly diluted coupling reaction condition to avoid the intermolecular reaction. Usually, this concentration goes to 10^{-5} M, which means that the preparation of 100 mg cyclic polymers needs around 1 L solvent [12,14,19]. As the environmental pollution becomes a very heavy topic nowadays, the utilization of huge amount of toxic organic solvents should be viewed as a significant limitation for producing cyclic polymers. Nearly all of the current ring-closure methods, however, are developed using the hazardous organic solvents as reaction media. Resultantly, the unique ring-closure techniques are urgently needed to produce cyclic polymer in the environmentally benign reaction media, such as water. In addition, since the natural bioorganic transformations are all carried out in water, the water solubility is a fundamental prerequisite for cyclic polymers when used in biology fields. From this point, it is again necessary to develop efficient ring-closuring techniques specifically focusing on the preparation of water soluble cyclic polymers.

The critical issue for producing cyclic polymers in water is to choose the right coupling reaction which has a high efficiency using water as reaction media. In 2009, Baker and co-workers discovered that bromomaleimides undergo rapid and highly efficient substitution reaction with thiol group in aqueous solution [20]. Subsequently, they demonstrated that this reaction can be utilized to prepare protein-polymer conjugates with high efficiency [21–23]. Just recently, this chemistry was extended into polymer synthesis field [24,25]. Robin et al. designed a novel dibromomaleimide reversible addition-fragmentation chain transfer (RAFT) agent, various well-defined polymers with dibromomaleimide end group were then produced by RAFT polymerization. The high

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reactivity of the end dibromomaleimide was demonstrated by reacting with a model thiophenol chemical [24].

Inspired by this, we developed a unique ring-closure method for the preparation of water soluble cyclic polymers by combining RAFT polymerization and bromomaleimide-thiol substitution reaction herein. Fig. 1 shows the main process. In the first step, the well-defined water soluble linear polymers were synthesized by RAFT polymerization using a functional RAFT agent **1**. As the second step, in the linear precursor water solution, the reducing agent $NaBH_4$ was used to cut the thiocarbonylthio group and release the thiol group, the cyclic polymers were then obtained in situ by virtue of thebromomaleimide-thiol substitution reaction.

2. Experimental

2.1. Materials

Bromobenzene, carbon disulfide (CS_2), maleimide, bromine, 4,4′-azobis(4-cyano-1-pentanol), 1-propanethiol, triphenylphosphine (PPh_3), diisopropylazodicarboxylate (DIAD), and sodium borohydride were purchased as regent grade from Aldrich, Acros, Alfa Aesar and used as received. Ethyl acetate, diethyl ether, methanol, chloroform, dichloromethane (DCM), tetrahydrofuran (THF) were purchased as regent grade from Beijing Chemical Reagent Co. and used as received unless otherwise noted. *N*-isopropylacrylamide (NIPAM) was purified by recrystallization in a mixture of n-hexane and toluene. *N,N*-dimethylacrylamide (DMAM) was dried over CaH_2 and distilled before use. 2,2′-Azoisobutyronitrile (AIBN) was recrystallized from ethanol and stored at 4 °C. 2,3-Dibromomaleimide [26], 2-bromomaleimide [27], and 4-Cyano-4-((thiobenzoyl)sulfanyl)pentanol (**a**in Fig. 2) [28] were synthesized according to the previous literature.

2.2. Preparation of 2-dibromo-3-propylsulfanyl-maleimide (b in Fig. 2)

A methanol solution (20 mL) of sodium acetate (360 mg, 4.39 mmol) and propanethiol (304 mg, 4.00 mmol) was dropwised into a methanol solution (16 mL) of 2,3-dibromomaleimide (2.04 g, 8 mmol)over 1 h. On completion of addition, the solution was stirred at room temperature for another 3 h. After that, the solution was concentrated and the crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/1) to produce the yellow solid product (520 mg) with a yield of 52%.

2.3. Preparation of RAFT agent 1

4-Cyano-4-((thiobenzoyl)sulfanyl)pentanol (**a**) (661 mg, 2.49 mmol), 2-dibromo-3-propylsulfanyl-maleimide (**b**) (520 mg, 2.08 mmol), and PPh_3 (654 mg, 2.49 mmol) were dissolved in anhydrous THF (10 mL). After cooled the mixture to 0 °C in an ice/water bath, DIAD (502 mg, 2.49 mmol) was dropwised into the solution and left it to stir for 30 min. The solution was then warmed to room temperature and kept stirring for another 12 h. After that, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 9/1) to afford the red oil product (486 mg) with a yield of 47%.

2.4. Preparation of Linear PDMAM

A mixed solution of DMAM (1.1 g, 11.11 mmol), RAFT agent 1 (53 mg, 0.11 mmol), and AIBN (3.5 mg, 0.02 mmol) was degassed via three freeze–thaw–pump cycles. After stirring for 5.5 h at 60 °C, the reaction was terminated by exposing system to air. The polymer was precipitated from an excess of mixture of ether and petroleum ether (v/v = 1/3) three times. After drying overnight in a vacuum oven at room temperature, the light red product was obtained with a yield of 22.11%. The monomer conversion was obtained from ^{1}H NMR with 23.94%.

2.5. Preparation of cyclic PDMAM

After dissolving linear PDMAM (20 mg) in water (100 mL) 1 h, $NaBH_4$ (80 mg, 2 mmol) was added and the solution was kept stirring for 24 h at room temperature. After that, the reaction solution was concentrated by vacuum evaporation to produce the cyclic PDMAM.

2.6. Preparation of linear PNIPAM

A mixed solution of N-isopropylacrylamide (4 g, 35.34 mmol), RAFT agent (176 mg, 0.35 mmol), AIBN (12 mg, 0.07 mmol), and DMF (4 g) was degassed via three freeze–thaw–pump cycles. After stirring for 24 h at 60 °C, the reaction was terminated by exposing system to air. The polymer was precipitated from an excess mixture of ether and petroleum ether (v/v = 1/3). After drying overnight in a vacuum oven at room temperature, the light red product was obtained with a yield of 17.21%. The monomer conversion was obtained from ^{1}H NMR with 19.74%.

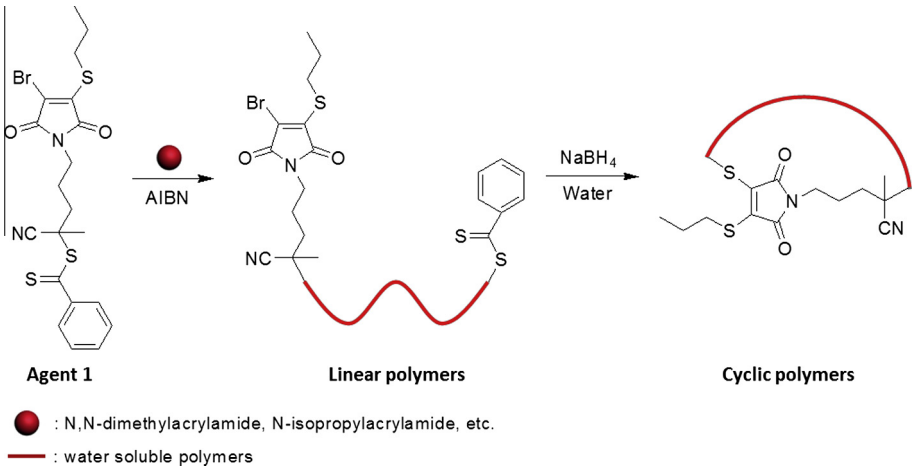

Fig. 1. The preparation of linear water soluble polymers by RAFT polymerization and the corresponding cyclic polymers by bromomaleimide-thiol substitution reaction.