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Linear and cyclic poly(2-isopropyl-2-oxazoline)s for fine control of thermoresponsiveness

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ABSTRACT

Linear and cyclic poly(2-isopropyl-2-oxazoline)s (**POx**)s with the same average molar mass and molar mass distribution were synthesized by living cationic ring-opening polymerization of 2-isopropyl-2-oxazoline (**Ox**) and a successive intramolecular Cu(I)-catalyzed click reaction. The synthesis of linear poly(2-isopropyl-2-oxazoline) (*l*-**POx**) and cyclic poly(2-isopropyl-2-oxazoline) (*c*-**POx**) was characterized by ^{1}H NMR, FT-IR, MALDI-TOF-MS and analytical SEC. Both **POx**s exhibited a sharp thermal transition upon temperature changes in physiological saline (150 mM NaCl) phosphate buffered solution (PBS, 10 mM, pH 7.4). Interestingly, the thermal transition temperature of the *c*-**POx** was much higher than that of the *l*-**POx**. The large difference of thermal transition temperatures between *c*-**POx** and *l*-**POx** was utilized for the fine tuning of the thermal transition temperature. By adjusting the mixing ratio of the two polymers, the thermal transition temperatures were varied from 44 to 57 °C.

1. Introduction

Stimuli-responsive polymeric materials are essential for the design of smart functional devices that can actively change their properties in response to variations in their external environment [1–5]. Various external forces, such as mechanical stress, moisture, temperature, pH, and electric and magnetic fields, have been utilized as major stimuli for controlling the chemical and physical properties of stimuli-responsive polymers [6–13]. Among various stimuli-responsive materials, thermoresponsive polymers are collecting interests in a variety of applications ranging from drug delivery, sensors, and supports for catalysts [14–16]. Especially, poly(2-isopropyl-2-oxazoline) (**POx**) has attracted attention in the biomedical fields because the lower critical solution temperature (LCST) of **POx** is very close to body temperature and excellent biocompatibility [17,18]. **POx** can be obtained by cationic ring-opening polymerization of 2-isopropyl-2-oxazoline (**Ox**) monomer [19]. Through the living cationic polymerization, fine control of average molar mass with narrow molar mass distribution can be possible. The thermoresponsiveness of **POx** relies on several structural parameters [20,21]. Generally, the LCST of **POx** decreases by increasing chain length. If the chain lengths are not sufficiently long, every **POx** chains may have slightly different thermal transition temperatures. Therefore, the control of molar mass distribution is significantly important for the fine control of thermoresponsiveness. Several attempts at achieving precise control of the thermal transition temperature of **POx** have thus far been conducted [17,22–24]. The thermal transition temperature of **POx** is influenced by the concentration

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of the polymer itself and additives such as salts or surfactants [25,26]. Terminal functional group also influences on the thermal transition temperature of **POx** [27].

Macrocyclic polymers are very interesting objects because they have no end functional group and distinguishable characteristics when they are compared to linear polymers [28]. For example, the density, viscosity, hydrodynamic volume and surface property of macrocyclic polymer differ from those of linear polymer counterparts [29–31]. Due to these distinguishable properties, macrocyclic polymers were continuously researched by chemists. Winnik et al. evaluated thermoresponsiveness of cyclic and linear poly(*N*-isopropylacrylamide) (PNIPAM) [32,33]. In this experiment, cyclic PNIPAM exhibited slightly higher thermal transition temperature than linear PNIPAM having similar molar mass. Grayson et al. prepared cyclic poly(2-ethyl-2-oxazoline)s as the precursor for the preparation of cyclic polyethyleneimines (PEI) [34]. Compare to linear PEI, the cyclic PEI exhibited improved cell viability and transfection efficacy upon in vitro DNA delivery. Although the poly(2-ethyl-2-oxazoline)s were used as the precursor of PEI, the thermoresponsiveness of poly(2-ethyl-2-oxazoline)s was not investigated at all.

In this study, we synthesized linear and cyclic **POx**s with the same average molar mass and molar mass distribution by living cationic ring-opening polymerization of **Ox** and a successive intramolecular Cu(I)-catalyzed click reaction. The thermoresponsiveness of linear and cyclic **POx**s has been investigated.

2. Experimental section

2.1. Materials and measurements

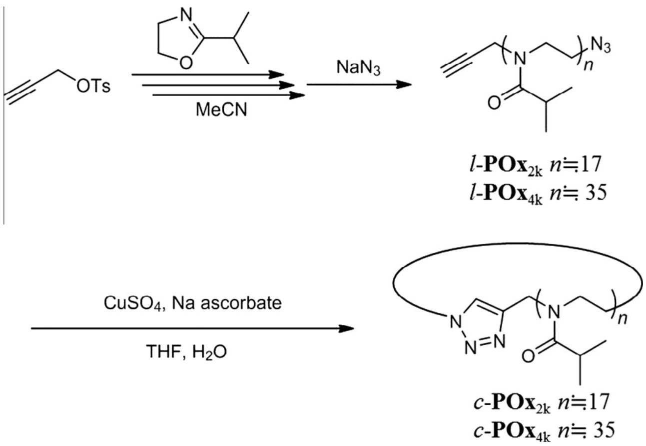
All commercially available reagents were reagent grade and were used without further purification. Tetrahydrofuran (THF) and acetonitrile were freshly distilled before each use. Dialysis membranes were used Spectra/Por® Dialysis Membrane that has 1 kD cut-off pore size. Recycling preparative size exclusion chromatography (SEC) was performed on a LC-9201 (JAI, Tokyo, Japan) instrument equipped with JAIGEL-1H, JAIGEL-2H and JAIGEL-3H columns using $CHCl_3$ as the eluent. UV–vis absorption spectra were measured using a V-660 (JASCO, Tokyo, Japan) spectrophotometer equipped with a thermostatic cell holder coupled with a controller (ETCS-761, JASCO, Tokyo, Japan). ^1H NMR spectra were recorded using a Bruker DPX 400 (400 MHz) spectrometer in $CDCl_3$. Analytical SEC was performed on a JASCO HPLC equipped with HF-403HQ and HF-404HQ columns (Shodex, Tokyo, Japan) using THF as eluent. MALDI-TOF-MS measurements were performed on a Bruker model LRF20 using dithranol (1,8,9-trihydroxyantracene) or CHCA (α-Cyano-4-hydroxycinnamic acid) as the matrix.

2.2. Determination of cloud point

The transmittance of the solution at 700 nm was measured using a V-660 spectrophotometer equipped with a thermostatic cell holder coupled with a controller (ETCS-761, JASCO). The heating rate of the sample cells was adjusted to 0.5 or 1.0 °C/min. The cloud points (CP) were taken as the temperature at which the transmittance reached 50% in the resulting transmittance versus temperature curves.

2.3. Synthesis

The synthetic procedures of *l*-**POx**s and *c*-**POx**s are outlined in Scheme 1. **Ox** was synthesized according to literature procedure [35].



Scheme 1. Synthesis of *l*-**POx**s and *c*-**POx**s.

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