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Topology effects of cyclic polymers: Controlling the topology for innovative functionalities

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ABSTRACT

Since polymers of cyclic topology have no main chain terminus, and the conformation is limited, they show physical and chemical properties different from those of linear polymers even the composition and molecular weight are the same. In order to pursue functions based on the topology of polymers, we have developed synthetic methods for cyclic polymers and constructed nanostructures by self-assembly. As a result, it was found that micelles and vesicles formed by cyclic polymers exhibit characteristics, which were greatly changed as compared with those of linear polymers. Based on cyclic-to-linear transformation, a gelling agent was developed, and furthermore, the reversible and repeatable topological conversion was achieved. Moreover, monolayer assemblies such as self-assembled monolayers on a gold surface and Langmuir–Blodgett films were constructed from cyclic macromolecules.

1. Introduction

"Topology" is one of the most important factors for the functions and properties of a substance. Even in the molecular scale, pursuing functionalities derived from topology and the construction of nanometer-scale materials have been actively conducted to pioneer academic fields called nanotechnology. In this regard, the topology of the functional polymers had been limited to linear and branched. However, recently, synthetic methods utilizing living polymerization and self-organization have been developed, and the selective synthesis of precisely controlled branched [1–3] and cyclic polymers [4–11] became possible. In particular, it is noteworthy that the synthesis of monocyclic or multicyclic polymers with various chemical structures and functional groups became feasible with high purity, and the scale to allow for the physical property measurements and useful to applications is now practicable. The development of such cyclic polymer synthesis, purification and measurement techniques are expected to contribute to advanced polymer chemistry, polymer physics and polymer material developments based on the polymer topology.

It has been known that cyclic polymers show unique properties (*topology effects*) based on their "shapes" [4–9], and studies are actively conducted from both theoretical and experimental points of view. For example, a cyclic polymer exhibits a high glass transition temperature (T_g), a low viscosity, a small hydrodynamic volume, etc. as compared with a linear polymer possessing the same chemical composition and molecular weight [4]. Recently, *topology effects* were also observed in a photoisomerization reaction [12], biodegradability [13,14], and lower critical solution temperature (LCST) [15,16]. There are also reports that the use of cyclic polymers as a carrier of a drug delivery system (DDS) suppresses excretion from the kidney and shows the effect of maintaining drug concentration in the blood [17,18]. In these ways, the exploration of polymer *topology effects* has remarkably advanced in recent years.

We have developed a novel synthesis method for cyclic polymers and explored *topology effects*. Therein, intramolecular metathesis [19,20], disulfide bond formation [21,22], and electrostatic self-assembly and covalent fixation (ESA–CF) process [23–29] were used as synthetic methods of cyclic polymers. In addition, as a result of self-assembly of cyclic amphiphilic block copolymers as the manifestation of *topology effects*, micelle was constructed, and the heat tolerance of the formed micelles was improved as high as 50 °C as compared with micelle formed from the linear precursor [30,31].

2. *Topology effects* of cyclic polymers

The *topology effects* of cyclic homopolymers have been extensively studied [4–9]. In recent years, the synthesis of a wide variety of cyclic polymers has been reported, so it is becoming possible to verify the unique characteristics expected from theory and simulation and attracting attention as a research subject of computational chemistry

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[32–34]. In addition, researches on liquid chromatography of multicyclic polymers through the cooperation of simulation and synthetic experiments greatly contribute to the identification of complex topologies and the establishment of purification methods, which had been considered difficult [35].

Here, two factors of *topology effects*, which cyclic polymers express, are explained. One of the best known *topology effects* is the change in T_g, which is also mentioned above. This phenomenon shows a high T_g value as compared with a linear polymer of the same molecular weight because cyclic polymers do not have chain ends with high mobility. However, as the molecular weight increases, the proportion of the end groups occupies decreases, and the difference in T_g becomes smaller [4]. On the other hand, hydrodynamic volume and viscosity ratios do not depend on the molecular weight, and it is known that cyclic polymers always show smaller values [4]. In other words, these phenomena are caused by two completely different factors derived from the topology of cyclic polymers. The former factor, which is dependent on the molecular weight, is the disappearance effect of the end groups of the polymer chain, and the latter factor, which is independent on the molecular weight, is the property inherently possessed by the cyclic topology. These two factors are intricately combined intramolecularly and intermolecularly to exhibit *topology effects*.

In nature, cyclic DNA, cyclic peptides and cyclic polysaccharides as well as cyclic polypeptides called cyclotides [36] are present, and these are known to exhibit high resistance to biodegradation. In relation to this, *topology effects* on the hydrolysis of aliphatic polyesters were reported. Grayson et al. hydrolyzed cyclic poly(ε-caprolactone) (PCL) and compared the time course of the molecular weight change with linear PCL [13,14]. The average molecular weight determined by matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI–TOF MS) of linear PCL (M_n(MALDI) = 6220) decreased to approximately 3000 in 3 h whereas the cyclic PCL (M_n(MALDI) = 6180) took 12 h to achieve the similar molecular weight. In addition, observation of the change in the average molecular weight by size exclusion chromatography (SEC) measurements exhibited that linear PCL has a simple decrease, whereas the average molecular weight of cyclic PCL increased once and then decreased. The latter phenomenon seems to be due to the fact that the hydrodynamic volume increased when the initial hydrolysis reaction opened the ring structure to give the linear form, and then decomposition progressed as a linear polymer.

As another example of *topology effects* involves poly(*N*-isopropylacrylamide) (PNIPAM). PNIPAM is one of the most important functional polymers due to its biocompatibility and temperature responsiveness. In particular, the LCST of PNIPAM is 32 °C [37], and it has been applied to various fields including the latest technology such as cell sheet utilizing the phase transition occurring in the range of this biological temperature [38–40]. The *topology effects* on this LCST was reported by Winnik et al. [15] and Liu et al. [16] at about the same time. Winnik et al. reported that cyclic PNIPAM shows LCST several degrees higher than linear PNIPAM of the corresponding molecular weight. In addition, the rate change of the solution transmittance was remarkably slow in the cyclic form. On the other hand, Liu et al. reported concentration dependence of the phase transition. The LCST of the linear and cyclic PNIPAM aqueous solutions was 44 °C and 46 °C, respectively, at the concentration of 0.2 g/L, showing the same trend as Winnik reported, but in the case of 2.0 g/L, 37 °C and 35 °C, respectively, indicating that LCST is reversed depending on the concentration.

Furthermore, cyclic polymers are also expected to be applied to DDS using the kidney dialysis mechanism, in which waste in the body is sorted and discharged by nano-sized pores in the kidney. Thus, Fréchet, Szoka and colleagues considered that cyclic polymers are difficult to be excreted by the renal function as compared with the linear counterparts, because cyclic polymers are constrained by the conformation when passing through the kidney pores [17,18]. First, a functionalized cyclic PCL copolymer (M_n = 9300, PDI = 1.38) was synthesized by the method of Jérome et al. [41], and poly(ethylene oxide) with different molecular weights were grafted using click chemistry to be a molecular weight near the threshold of kidney dialysis (M_n ~ 32,000, 50,000, 90,000). Further, a phenol group was introduced to one site on average per polymer, and radioactive labeling with ^{125}I was carried out. These cyclic and corresponding linear polymers were injected into mice to investigate the accumulation amount in each organ. As a result, when the cyclic polymers with a molecular weight of 50,000 were used, they were discharged into the urine by 12% less than the linear polymers, and conversely, a high accumulation amount was observed in each organ. On the other hand, with the polymer with a molecular weight of 90,000, the difference between the cyclic and linear topologies decreased. However, in the case of a molecular weight of 32,000, the linear polymer was more likely to be retained in the body. For this reason, it was considered that the dialysis threshold of the kidney pores is a molecular weight of 30,000 to 40,000, and in the case where the molecular weight is comparable or less than this value, the cyclic polymers having a smaller hydrodynamic volume is more likely to be dialyzed. The discovery of this topology effect is expected to lead to the development of DDS carriers and contrast agents by controlling the retention time in the body based on the topology of the polymer.

We have proposed to use cyclization reactions using metathesis [42] and the electrostatic self-assembly and covalent fixation (ESA–CF) process [23], and various *topology effects* were investigated. Herein, representative *topology effects* on self-assembly by using cyclic amphiphilic block copolymers are described. It was revealed that removal of the chain ends forms the core of dense hydrophobic segments and prevents dynamic crosslinking between micelles and remarkably stabilizes the micelles [30,31,43,44]. In addition, we succeeded in the preparation of vesicles using cyclic polymers [45,46] and the development of gelling agents with photocleavable cyclic polymeric micelles [47]. Moreover, repetition of the reversible cyclic–linear topological conversion was achieved [48], and self-assembled monolayers (SAMs) [49] and Langmuir–Blodgett (LB) films [50] were also constructed from cyclic molecules.

3. Self-assembly of cyclic amphiphilic block copolymers

One of the very effective processes for constructing functionalized nanostructures with molecular level accuracy is self-assembly, and micelles and vesicles formed from amphiphilic molecules, including block copolymers, attract broad interests because of their possibility for various applications [51]. In nature, unicellular organisms such as thermophilic archaebacteria surviving in high-temperature environments such as hot springs and submarine volcanic environments have lipid molecules with a ring structure as cell membrane components [52]. Motivated by this phenomenon of the self-assembly of the ring lipid molecules utilized by the biological system, we have developed a series of amphiphilic linear copolymers of PBA–PEO–PBA and cyclized PBA–PEO block copolymers, where PBA is poly(*n*-butyl acrylate) and PEO is poly(ethylene oxide) (PEO) (Fig. 1a and b) [30]. Due the amplification of *topology effects* by self-assembly, a significant enhancement on the stability of the micelles by the cyclized block copolymers compared to those by the linear block copolymers was revealed. That is, in cloud point (T_c) measurements, it was observed that the linear polymeric micelles were suspended at 24–27 °C, whereas the cyclic polymer micelle was stable up to high temperatures of 71–74 °C. Therefore, despite the unchanged chemical structure and molecular weight due to linear–cyclic conversion of the polymer topology, the thermal stability of the micelles was greatly improved. In addition, we succeeded in systematically adjusting T_c by the use of a series of micellar assemblies formed by merely mixing linear and cyclic block copolymers with various ratios.

Moreover, amphiphilic linear and cyclic pairs of copolymers with poly(methyl acrylate) (PMA) as the hydrophobic moieties were made using PEO, and the salinity tolerance of the micelles was contrasted