



## Short communication

## Ion-responsive fluorescence resonance energy transfer between grafted polyacrylic acid arms of star block copolymers

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## ABSTRACT

Interactions between polyacrylic acid (PAA) arms of star block copolymers through metal ions were investigated by fluorescence resonance energy transfer (FRET). Dendritic polyester (DPE) core was grafted with block copolymer arms of oligo (ethylene glycol) methyl ether acrylate (OEGA) and PAA. Fluorescein *o*-methacrylate (FMA) or methacryloxyethyl thiocarbonyl rhodamine B (MTR) was introduced via copolymerization to the terminated PAA blocks. The unique copolymer structure enabled FRET between PAA chains without causing precipitation, which inevitably occurs for linear PAA. Addition of metal ions such as Zn<sup>2+</sup>, Ca<sup>2+</sup>, or Na<sup>+</sup> induced FRET, the order of which was Zn<sup>2+</sup> > Ca<sup>2+</sup> >> Na<sup>+</sup>. FRET intensity was also correlated with concentration of each ion. Furthermore, *in situ* FRET measurement during the hydrogel formation of the star block copolymers was performed by mixing the star block copolymers and Zn<sup>2+</sup>.

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## 1. Introduction

Polyacrylic acid (PAA) is a representative polyelectrolyte in polymer science because of its unique physical characteristics and versatile industrial applications. Cross-linked PAA can absorb a much larger amount of water than its own weight [1]. In addition, PAA can chelate with various metal ions [2]. Thus, PAA has been used as an absorbent material for diapers [3], adhesive [4], flocculant [5], scale inhibitor [6], ion exchange resin [7] and hemodialysis membrane [8]. Also, the physicochemical properties of PAA including its chelation behavior have been investigated extensively as a model for biomolecules like polysaccharides, proteins and other synthetic polyelectrolytes because of its simple structure [9,10]. PAA tends to form strong intramolecular complexes with metal ions [2], which leads to aggregation, subsequent precipitation and formation of cross-linked hydrogels. Study of inter-versus intramolecular interactions in the cross-linked hydrogel is a difficult task. Thus, intermolecular interactions between PAAs complexed with metal ions have seldom been investigated [2,11].

Recently, we developed a star block copolymer composed of a dendritic polyester (DPE) core grafted with block copolymer arms

of oligo(ethylene glycol) methyl ether acrylate (OEGA) and acrylic acid (AA) [12,13]. Precipitation induced by chelation of its terminated AA blocks was prevented at any pH and ionic strength of calcium(II) ions (Ca<sup>2+</sup>) or iron(III) ions (Fe<sup>3+</sup>), probably because of the steric and hydration effects of its OEGA blocks. This enabled stable *in situ* gelation upon mixing a star block copolymer solution and ion solution such as Ca<sup>2+</sup> or Fe<sup>3+</sup> under physiological conditions. Thus, intermolecular interactions between PAA blocks via metal ions should be able to be analyzed using the star block copolymer.

Fluorescence resonance energy transfer (FRET) is now recognized as a promising technique to analyze polymer chain interactions [14,15]. FRET is a phenomenon where an excited donor fluorophore transfers energy to a neighboring acceptor. Because FRET efficiency is highly sensitive to fluorophore distance (inversely proportional to the sixth power of separation distance), FRET-based techniques have been used to observe interactions and conformational changes of proteins [16], peptides [17], cell membranes [18] and polymer chains [14,15] in a non-invasive, real-time manner. Although several studies have used fluorescently labelled PAA as a chemosensor [19,20], the intermolecular interactions between chelated PAA chains have not been investigated by the FRET technique.

Here, we report the FRET analysis of intermolecular interactions between chelated PAA chains. We first label the arms of the star

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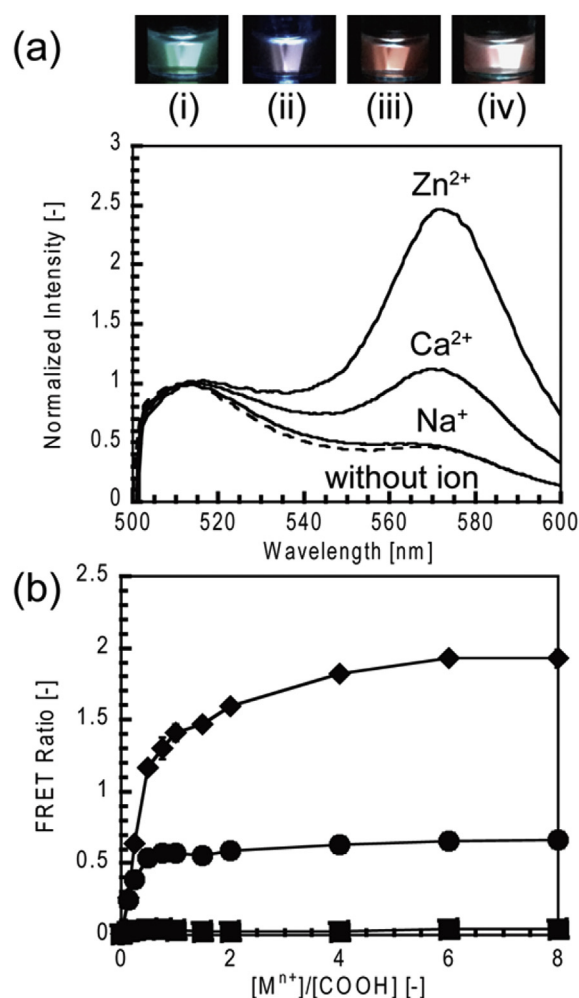
block copolymer with either fluorescein *o*-methacrylate (FMA) or methacryloxyethyl thiocarbamoyl rhodamine B (MTR) (Fig. 1a). FMA works as a donor and MTR behaves as an acceptor in this system (Fig. 1b). When the star block copolymers are isolated, FMA and MTR are distant and thus FRET does not occur between them. However, when the arms of different star block copolymers interact, FMA and MTR become close enough for FRET to occur from FMA to MTR. These changes in FRET signal are used to detect intermolecular interactions between the grafted PAA arms of the star block copolymers. We use  $\text{Ca}^{2+}$ , zinc(II) ions ( $\text{Zn}^{2+}$ ) and sodium(I) ions ( $\text{Na}^{+}$ ) as stimuli to induce FRET. The ion dependence of PAA arm interactions under dilute conditions, as well as the time course of hydrogel formation under condensed conditions, are explored through FRET measurements.

## 2. Results and discussion

We first synthesized two fluorescently labelled star block copolymers (FMA- and MTR-conjugated polymers) via atomic transfer radical polymerization based on previously reported procedures [12], as summarized in Scheme S1 (see supplementary data).

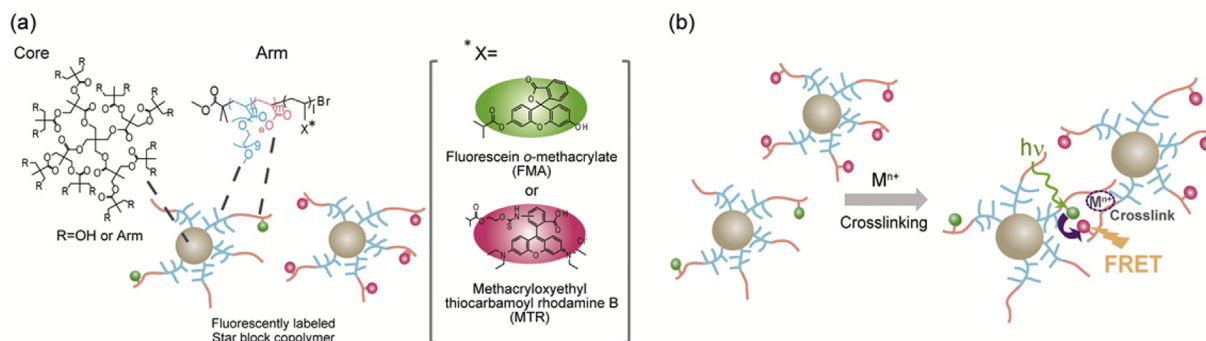
Briefly, OEGA arms were first grafted on the DPE core, followed by the random copolymerization of *tert*-butyl acrylate (*t*BA) and fluorescent monomers. The synthesis of the star block copolymers was confirmed by  $^1\text{H}$  NMR spectroscopy (Fig. S1, see supplementary data). The degrees of polymerization of OEGA blocks and AA blocks were 20 and 30, respectively. In addition, we measured the degree of fluorophore copolymerization by fluorescence intensity measurements, as shown in Fig. S2 (see supplementary data). The copolymerization ratios of FMA and MTR were 0.55 and 5.0 mol%, respectively.

FRET measurements were conducted under dilute condition (0.01 wt%) that is lower enough than critical concentration ( $C^*$ ) of the star block copolymers (1.7 wt%) to investigate the polymer interaction with ions while avoiding the decrease of the mobility of the PAA chains caused by gelation. The composition of the polymer solution was FMA-conjugated polymer: MTR-conjugated polymer: unmodified polymer = 20: 20: 60. The number of acceptor fluorophores was ten times larger than that of donor fluorophores in this solution because of the different copolymerization ratios (FMA: MTR = 1: 10). Under these conditions, FRET is expected to occur efficiently. Fig. 2a shows fluorescence spectra of the star block copolymer solutions with  $\text{Zn}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Na}^{+}$  and without ions obtained following excitation at 488 nm. Fluorescence intensities were normalized to FMA emission intensity at 513 nm. The original spectra are shown in Fig. S4 (see supplementary data). The ion concentration was 2.0 mM (8 eq. based on the concentration of carboxylic groups in the star arms). For the solution with  $\text{Na}^{+}$ , fluorescence from MTR at 570 nm was hardly observed. In contrast,



**Fig. 2.** (a) Fluorescence spectra of the star block copolymer solutions with a polymer concentration of 0.01 wt% and different concentrations of metal ions. The excitation wavelength was 488 nm. The inset shows the fluorescence images of (i) FMA-conjugated star polymer solution and the mixture of FMA- and MTR-conjugated star polymer solution mixed with (ii)  $\text{Na}^{+}$ , (iii)  $\text{Ca}^{2+}$  and (iv)  $\text{Zn}^{2+}$ . Blue light (470–495 nm) was used for excitation. Note that a higher polymer concentration of 5 wt% than that for spectrum measurement was used for the visualization. (b) Effect of ion concentration on FRET ratio for the star block copolymer solutions with  $\text{Zn}^{2+}$  (diamonds),  $\text{Ca}^{2+}$  (circles) and  $\text{Na}^{+}$  (squares). The polymer concentration was set at 0.01 wt%.

$\text{Ca}^{2+}$  and  $\text{Zn}^{2+}$  addition caused prominent increases in MTR fluorescence at 570 nm, meaning that fluorescence energy was



**Fig. 1.** Schematic illustration of (a) the structure of fluorescently labelled star block copolymers and (b) FRET induced by their crosslinking with metallic ions.

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