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Thermosensitive amphiphilic polyphosphazenes and their interaction with ionic surfactants

Sungsook Ahn, Sung Won Ahn, Soo-Chang Song*

Life Sciences Research Division, Korea Institute of Science & Technology (KIST), 39-1 Hawolgok-dong, Wolsong-gil 5, Seongbuk-gu, Seoul 136-791, Republic of Korea

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ABSTRACT

Temperature-responding physical hydrogels are promising materials as injectable drug delivery carriers which could hold useful bioactive materials inside the polymer networks for further controlled releases. Aimed at desired qualities at body temperature, those gel characteristics need to be adjusted carefully. In this point of view, surfactant is one of the useful molecules to be used by simple formulations without harmful chemical reactions. In this study, thermothickening of amphiphilic nonionic polyphosphazene solution is modified by anionic and cationic surfactants with different alkyl chains and counter-ions. Specified in the thermothickening system, a maximum viscosity (η_{max}) and a temperature at that point (T_{max}) are changed independently reflecting unique intermolecular interactions. At low concentration (1–9 mM) of the added surfactant, the η_{max} is maximized at 3 mM surfactant regardless of the surfactant type while the T_{max} is increased continuously along with the surfactant concentration. From a kinetic point of view, this 3 mM surfactant at the maximized η_{max} reflects a polymer-dominating interaction and highly favorable polymer–surfactant interaction with a low selectivity in the surfactant type. However, the magnitude of the maximum viscosity (η_{max}) is dependent on the surfactant tail, which reflects the lifetime and the strength of the hydrophobic domains of the polymer network affected by the surfactants. Meanwhile, the magnitude of the T_{max} depended on the surfactant head group, which means the interfacial tension of the polymer solutions changed by the surfactants. At high concentration (10 and 30 mM) of the cationic surfactants added to the polymer solutions with two different viscosities, the cationic surfactants are supposed to interact either with the hydrophobic parts of the aggregated polymer with high viscosity or on the backbone of the less- or non-aggregated polymer with low viscosity.

Ionic surfactants change the thermothickening of the amphiphilic nonionic polyphosphazene solution in a unique tail- or head-dependent way. Moreover, the concentration of the added surfactants and the association pattern of the pure polymer solutions are also crucial for the thermothickening phase behaviors. Temperature-responsive polyphosphazenes in this work exhibit unique and controllable interactions with ionic surfactants.

1. Introduction

Surfactant interactions with polymers have been studied widely because of their useful applications in paints, foods, lubricants, cosmetics and pharmaceutics, etc. [1]. de Gennes [2] discussed the surfactant bilayer films that become rigid or curved by the adsorption of neutral and flexible polymer chains. Ruckenstein [3] reported the changes in the surfactant aggregate concentrations by macromolecule additions. Both has focused on the changes in the surfactant aggregations modified by polymers or macromolecules. Focused on the modification of the polymer aggregations by surfactants, Cabane et al. [4] explained the connectivity and microstructure changes in the polymer network affected by surfactant additions. Rička et al. [5] discussed the condensed polymer aggregates coated with surfactant layers, where the polymer conformations were changed from globules to coils. In terms of the surfactant interactions with temperature-responsive polymers, poly(*N*-isopropylacrylamide) [6–8] and cellulose derivatives [9–13] have been studied using various characteristic methods such as NMR, fluorescence [6,9–11], swelling, conductivity [7], calorimetry [8,12] and rheology [13], etc. In application aspects, viscosity of the hydrogel reflects the strength of the delivery carrier which can effectively hold useful bioactive materials inside the polymer network for further controlled releases [14,15]. In this point of view, surfactants could be one of the useful molecules to modify those gel characteristics by simple formulation even in *in vivo* without hazardous reaction. To our best knowledge, only a few studies have been done on the physical mixture of

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* Corresponding author. Tel.: +82 2 958 5123; fax: +82 2 958 5189.
E-mail address: scsong@kist.re.kr (S.-C. Song).

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the thermosensitive polyphosphazenes with surfactants. In our previous work, we observed thermothickening behaviors of the polyphosphazenes [16] and modifications of those behaviors by surfactant additions [17]. The changes in the cloud-points of the aqueous polyphosphazene solutions have been observed from which hydrophobic co-associations between the polymers and the surfactants were suggested. In this study, systematic studies have been performed on the polyphosphazenes thermothickening and their interactions with ionic surfactants, which have different alkyl chain lengths and counter-ions. Specified in thermothickening system, as temperature increases the viscosity of the polymer solution also increases and there is a characteristic maximum viscosity point ($\eta_{\max}$) at a specific temperature ($T_{\max}$), which is unique in each polymer system. Right after that maximum viscosity point, the polymer solutions become phase-separated (become turbid in appearance) thus, the temperature at the maximum viscosity point ($T_{\max}$) is also expressed as phase inversion temperature in this work. Under a fixed shear rate, a maximum viscosity ($\eta_{\max}$) and a phase inversion temperature ($T_{\max}$) were measured, which moved independently reflecting unique intermolecular interactions. Different from steady-state cloud-point measurements that depend on complicated settling down conditions [18], this dynamic viscosity measurement could generate unique information especially in lower critical solution temperature (LCST) system. The selected shear rate is low enough to range all the polymer solutions in this study in the Newtonian fluid region. Therefore, measured viscosities can be considered zero shear viscosity for reasonable comparisons. Depending on the type and the concentration of the surfactants, the thermothickening of the polyphosphazene has been modified in a unique way.

2. Experimental

2.1. Materials

Hexachlorocyclotriphosphazene (Aldrich) was sublimated under reduced pressure at around 55 °C. Ethyl ester forms of the amino acids were synthesized starting from the corresponding amino acids (Aldrich), so that L-isoleucine ethyl ester (IleOEt) and L-valine ethyl ester (ValOEt) were prepared [19]. By changing the end-capped hydroxyl group of the polyethylene glycol (Fluka) with molecular weight 550 Da, into amine group α-amino-ω-methoxy poly(ethylene glycol) 550 Da (AMPEG 550) was prepared [20]. Tetrahydrofuran (Aldrich) was dried by refluxing over sodium metal/benzophenone (Fluka) under dry nitrogen atmosphere. Hexachlorocyclotriphosphazene was polymerized by ring-opening polymerization with $AlCl_3$ catalyst at 250 °C for 8 h to make poly(dichlorophosphazene). This poly(dichlorophosphazene) was substituted step-by-step by the amino acid ester (IleOEt or ValOEt) and the AMPEG 550 prepared above. Complete substitution onto the poly(dichlorophosphazene) was confirmed by the single ^{31}P NMR peak and the ratio of the two substituents was determined by integrating the ^{1}H NMR peaks. All the detailed procedures were reported in our previous work [16]. The final polymers were expressed as $[NP(IleOEt)_x(AMPEG550)_{2-x}]_n$ for L-isoleucine ethyl ester (IleOEt) and AMPEG 550 substituted polymers and $[NP(ValOEt)_x(AMPEG550)_{2-x}]_n$ for L-valine ethyl ester (ValOEt) and AMPEG 550 substituted polymers where x indicates corresponding substitution ratio. In Table 1, the chemical formula and the molecular weight of each polymer **1**, **2** and **3** are given together with the maximum viscosity ($\eta_{\max}$) and the phase inversion temperature ($T_{\max}$) obtained with 10 wt% aqueous solution under the 0.1 s^{-1} shear rate and 0.5 °C/min heating rate. Sodium dodecyl sulfate (SDS), sodium tetradecyl sulfate (STS), dodecyltrimethylammonium bromide (DTAB), dodecyltrimethylammonium chloride (DTAC) and tetradecyltrimethylammonium bromide (TTAB) (ACROS) were used without further purification. The information of the surfactants including chemical formula and critical micelle concentration (cmc) were reported in detail [21–24].

2.2. Instruments and measurements

^{1}H NMR measurements were taken with a Varian Gemini-300 spectrometer operating at 300 MHz in the Fourier transform mode. Proton-decoupled ^{31}P NMR spectra were measured with the same spectrometer operating at 121.4 MHz using triphenyl phosphate as an external standard. Gel permeation chromatography was carried out (Waters 1515 system) with a refractive index detector (Waters 2410) and two styragel columns (Waters styragel HR 5E) connected in a line. The eluting solvent was tetrahydrofuran containing 0.1 wt% of tetrabutylammonium bromide and eluted under 0.8 ml/min flow rate at 35 °C. The molecular weights of the polymers were determined by the elution time compared with those of the polystyrene standards. Viscosity measurements were carried out with a Brookfield RVDV-III+ rheometer between 5 and 95 °C where the shear viscosity (η) has been determined by the shear stress (τ) divided by the shear rate ($d\gamma/dt$). Polymer solutions were prepared at 4 °C with de-ionized Millipore water and the viscosities of the aqueous polymer solutions with and without surfactants were measured as a function of temperature with a 0.5 °C/min heating rate at a fixed shear rate. From this temperature vs. viscosity scanning, maximum viscosity ($\eta_{\max}$) and the temperature at that point ($T_{\max}$) have been determined.

3. Results and discussions

3.1. Thermothickening of the amphiphilic nonionic polyphosphazene solutions

Depending on the ratio of the hydrophobic and hydrophilic side groups, polymer solutions exhibit unique phase behaviors and physical characteristics [25]. As temperature increases in aqueous condition, water becomes poorer solvent due to high cohesive energy, which leads to the breakage of the hydrogen bonding and the separation of the hydrophores from water [26]. More generally even in non-aqueous media, as temperature increases the conformations of the polymers are changed into hydrophobic state compensating unfavorable enthalpy and entropy [27]. In Fig. 1, the phase changes of the amphiphilic nonionic polymer solutions which show LCST phase behavior, are schematically suggested from phase stage I to IV. At lower temperature, water is good solvent therefore the hydrophilic parts are extended into water while hydrophobic parts are avoided from water contact (Phase stage I). These hydrophilically enclosed particles are suspended in water, which could generate apparently transparent solution depending on the water-solubility of the whole molecule. As temperature increases, the hydrophobic associative forces become comparable to the hydrophilic forces forming cross-links (Phase stage II). With increased viscosity by this hydrophobic association, the total network generates maximum viscosity ($\eta_{\max}$) at a specific temperature ($T_{\max}$). Therefore, $T_{\max}$ is the temperature at which such physical cross-links become maximized by optimized total associative forces. Balancing the hydrophobic shrinking and the hydrophilic swelling, this optimized point is also affected by the geometrical arrangement of the elastically active chains. Before that optimum temperature ($T_{\max}$), the increase in the hydrophobic force leads to the increase in the viscosity due to more of physical cross-links