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Multi-faced investigation for pH-sensitivity and solvent polarity in highly charged thermo-responsive hydro- and cryogels with strongly dissociated groups: A comparative evaluation of physico-chemical properties

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ABSTRACT

Different series of strong polyelectrolyte poly(*N*-isopropylacrylamide-*co*-sodium acrylate) P(NIPA-*co*-NaA) hydrogels and cryogels were prepared in aqueous solution. With changing the ionic comonomer NaA ratio in reaction mixture, the resulting physico-chemical and swelling properties varied significantly. The findings elucidated that ionic P(NIPA-*co*-NaA) gels exhibited multi-stimuli performances with pH-, temperature-, solvent-, surfactant- and salt-responsivity, showing more sensitivity than non-ionic PNIPA. Their swollen/collapsed behaviors were strongly dependent on various synthesis/external parameters, including the content of ionic comonomer, temperature and solvent polarity. The effects produced by non-solvents were qualitatively compared considering the aspects related to co-nonsolvency phenomenon and re-entrant swelling transition on the basis of weakening of PNIPA-water interactions. Measurements of the elastic properties and swelling degree of samples having different NaA content were treated by combining Flory-Rehner theory and rubber elasticity to interpret the experimental observations. The polymer-solvent interaction parameter χ of hydrogels was calculated from the swelling studies in water at different temperatures and was related to the composition and temperature. The ionic strength-reversibility and on-off switching kinetics of hydrogels and cryogels were studied in 10^{-5} M and 1.0 M of NaBr solutions. Diffusion kinetics showed that the swelling of ionic hydrogels is of non-Fickian-type transportation, however, non-ionic PNIPA hydrogels and P(NIPA-*co*-NaA) cryogels showed pseudo-Fickian diffusion. The resulting hydrogels and cryogels containing both temperature and pH-sensitive units are able to interact with oppositely charged groups via hydrophobic and electrostatic interactions.

1. Introduction

Because of their importance in artificial and biological systems, the applications of polyelectrolyte hydro- and cryogels range from the colloidal stabilization and nanoreactors to the carriers for controlled drug delivery [1–3]. From the viewpoint of these applications, it would be favorable if polyelectrolytes could respond to several types of stimuli simultaneously, either mutually or independently by the functional groups in their structure. It has been demonstrated that the coupling between the ionization degree and elasticity in these systems results in a variety of specific mechanical and scattering properties. Interestingly, while numerous experimental and theoretical works have examined the swelling performance of polyelectrolyte gels, the mechanical behaviors showing their rubberlike elasticity as well as the effect of interactions between the polyelectrolyte ions and the ions present in the solutions on the overall chain rigidity are not so abundant. Among the major open problems is the question of how the specific thermodynamic factors affect the swelling and deswelling behavior of ionic gels and redistribution of the mobile cations/water molecules between the external solution and the gel phase [4,5].

The formation of polyelectrolyte complexes between oppositely charged particles due to the electrostatic interactions has been extensively studied in the development of pharmaceutical formulations for gene therapy and oral vaccination, in printing, and other applications [6–8]. Horkay and coworkers studied the volume transition by addition of divalent or trivalent counterions in fully neutralized sodium polyacrylate gels swollen in NaCl solution. The ionization of the network chains plays an essential role in this transition which is governed by the interactions between the polyion and the counterions [9]. It is however not fully understood how the unequal concentration of ions inside and outside the swollen network affects the network structure and dynamic properties over a wide range of length and time scale. Su and coworkers investigated the influence of charged groups on the structure of poly(*N*-isopropylacrylamide-*co*-methacrylic acid) P(NIPA-

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co-MAAc) spherical microgels and volume phase transition [10]. The hydrophobic attraction of NIPA and the electrostatic repulsion of the carboxylate groups change the structure, swelling ability, and dehydration dynamics of the charged microgels. The molecular dynamics simulations to evaluate the effect of salt on the lower critical solution temperature (LCST) of PNIPA in aqueous solutions of NaCl, NaBr, NaI, KCl as well as on the protein stability showed that the direct interactions between the salt cations and the polymer lead to a shift of LCST and a subsequent change on the protein stability. Further, anions have a weaker affinity with the polymer, whereas cations bind strongly with the polymer and this cation-polymer binding affinity is inversely correlated with the cation-anion contact pair association in solution [11]. In another work, in solutions containing sufficient concentrations of strongly hydrated anions, the phase transition of PNIPA was directly correlated with the hydration entropy of the anions and the transition temperatures for PNIPA were found to be reduced in concentrated NaCl, NaBr, NaI, and KCl salt solutions, respectively [12]. In addition to temperature-induced conformational transitions, PNIPA gels exhibit peculiar conformational changes in water-solvent mixtures such as acetone, ethanol, 2-propanol and methanol [13–15]. In their recent work, Browarzik and coworkers developed a new thermodynamic model for the volume change in temperature-sensitive polymer gels that is based on the swelling equilibria of many finitely large crosslinked polymer molecules encaging different amounts of solvent [16].

Although the molecular thermodynamic models are convenient tools for quantitative description of the swelling and volume phase transition behavior of temperature-responsive hydrogels, the understanding of the mechanism of both polymer network-solvent interactions and the structure-formation among the solvent/or additive molecules would be quite important to elucidate these phenomena. In this work, the investigation for the effect of charge density on the overall elasticity, dynamic and swelling equilibrium as well as phase transition phenomena of highly charged copolymer hydrogels and cryogels of *N*-isopropylacrylamide (NIPA) and sodium acrylate (NaA) were reported. The equilibrium swelling behavior of crosslinked P(NIPA-*co*-NaA) hydrogels and cryogels in several water co-nonsolvent systems with comparable molecular structures were also detected in wide composition to determine the effect of individual chemical groups on the aspects of swelling degree-composition plots. The effects observed by the different solvents selected according to the similarity of the molecular structures and the miscibility with water in the whole range of compositions tested have been qualitatively compared and discussed considering non-polar groups for hydrophobic hydration as well as hydrogen bond formation. P(NIPA-*co*-NaA) hydrogels and cryogels were studied regarding their on-off switching ability and the swelling kinetics was determined in detail to explain the influence of the ionic composition on the transport properties.

2. Experimental section

2.1. Reagents

N-isopropylacrylamide (NIPA, Aldrich) as main monomer and sodium acrylate (NaA, Aldrich) as ionic comonomer were used for the preparation of strong polyelectrolyte hydrogels and cryogels. *N,N′*-methylenebis(acrylamide) (BAAm, Merck) as tetrafunctional crosslinker, ammonium persulfate (APS, Merck), and *N,N,N′,N′*-tetramethylethylenediamine (TEMED, Merck) were used as received without further purification. For pH-dependent swelling studies, potassium dihydrogen phosphate (Riedel-de Haen), hydrochloric acid (Merck), potassium phosphate (J.T. Baker) and disodium hydrogen phosphate (Merck) were used for the preparation of buffer solutions. Potassium iodide (KI, J.T. Baker), sodium bromide (NaBr, Merck) and sodium chloride (NaCl, Merck) were used for salt-sensitive swelling studies. Acetone, ethanol, 2-propanol and anionic surfactant sodium dodecylsulfonate (SDS, $CH_3(CH_2)_{11}SO_4Na$) as well as cationic surfactants cetyl trimethylammonium bromide (CTAB, $[(C_{16}H_{33})N(CH_3)_3]Br$) and cetyltrimethylammonium chloride (*CTAC)* $[(C_{16}H_{33})N(CH_3)_3]Cl$) were used for solvent and surfactant-dependent swelling studies.

2.2. Synthesis of multi-responsive P(NIPA-co-NaA) gels

A series of multi-responsive hydrogels (Hgs) and cryogels (Cgs) of non-ionic base monomer NIPA and ionic comonomer NaA with different components were prepared by free-radical crosslinking copolymerization in aqueous solution. The copolymerization reactions were performed in polypropylene syringes with an inner diameter of 4–4.5 mm and a length of 100 mm. An aqueous solution of 4.25 mM APS and 0.455 v/v% TEMED was used as initiator and accelerator, respectively. For the synthesis of ionic P(NIPA-*co*-NaA) gel containing 40 mol% of NaA in the feed, 485 mg NIPA and 271 mg NaA was dissolved in 5 mL of distilled water and 13 mg of BAAm were added to this monomer solution and then, the solution was stirred at room temperature for 5 min. The molar concentrations of the monomers and crosslinker; NIPA, NaA, and BAAm in the prepared gel sample were 4.28, 2.89 and 0.0856 mM, respectively. Then 1.0 mL of TEMED stock solution as accelerator was added and the pre-gel solution was bubbled with nitrogen for 15 min to remove the dissolved oxygen that could inhibit the reaction. Thereafter, 1.0 mL of APS stock solution was included and the solution was completed to 10 mL with distilled water. The solution was then placed in several syringes, after sealing the both ends of the syringes, the copolymerization reactions were conducted at 21 °C and −18 °C for 48 h for the preparation of ionic P(NIPA-*co*-NaA) Hgs as well as for Cgs, respectively. By completion of the reactions, the resulting gels were removed from the syringes, however, for cryogels, the syringes were first left at room temperature during 30 min before the sample preparation. Then, the gels were uniformly cut into the short cylindrical samples of 4–4.5 mm in diameter and 4–5 mm in length. The obtained hydrogels and cryogels were soft and elastic in nature when they were handled. The synthetic scheme for the preparation of ionic P(NIPA-*co*-NaA) gels by radicalic copolymerization reaction was given in Fig. 1. The feed compositions and characteristic parameters used in the preparation of ionic P(NIPA-*co*-NaA) gels were also collected in Table 1. The total molar concentration C_o of monomers in the pregel solution (NIPA, NaA and BAAm), and the crosslinker ratio X (mole ratio of the crosslinker BAAm to the monomers NIPA + NaA) were kept at 0.82 M and 1/83, respectively. The nominal mole fraction x_i of NaA monomer in the feed was varied from 0 to 0.90 and 1.0 for Hgs and Cgs, respectively. However, the hydrogels prepared at $x_i = 0.90$ were too weak to carry out the mechanical measurements.

2.3. Crosslinked polymer network concentration after preparation

The obtained Hgs and Cgs were first characterized by determining their crosslinked polymer network concentrations as-prepared state. Upon completion of the copolymerization reactions and cutting into small pieces, the gel samples were immersed in an excess of distilled water for one week in order to remove the unreacted monomers and cross-linker. During the first 24 h, water was changed twice and then once in at least three days. The samples were initially weighted and then, first dried at 40 °C to the constant mass and left at room temperature at least three weeks for complete drying. The volume fraction of the crosslinked polymer network after preparation ν_2^0 which gives the degree of dilution of the gel network as-prepared state was experimentally determined using the weight of gel after preparation m_o to the weight of dried gel m_d by:

$$\nu_{2,\exp}^0 = \left[1 + \frac{(m_o/m_d - 1)\rho}{d_1}\right]^{-1} \quad (1)$$

where d_1 and ρ are the densities of water and polymer, respectively, and used as 1.0 g/mL for water and 1.213 g/mL for P(NIPA-*co*-NaA) gels.