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Feature Article

Specific ion effects on thermoresponsive polymer brushes: Comparison to other architectures

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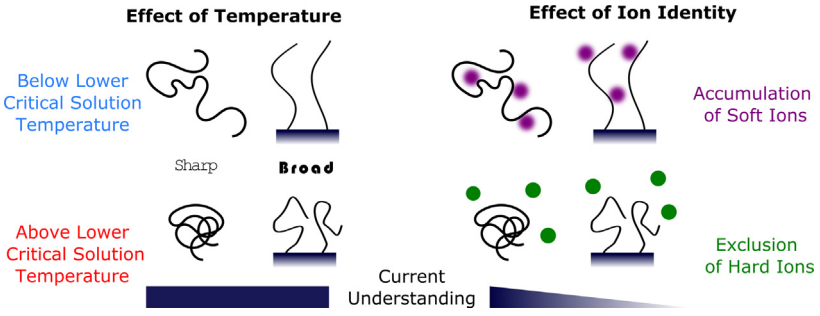
GRAPHICAL ABSTRACT



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ABSTRACT

Thermoresponsive polymers have received significant research attention as smart materials with particular interest in biomedical applications. The composition and architecture are known to strongly influence the thermoresponsive properties of the materials. For example, the strong overlap of end-grafted polymer chains in polymer brushes leads to a broader collapse transition relative to linear ungrafted chains as well as temperature dependent adhesion. The temperature response of free polymer has been widely reported to depend on the concentration and identity of ions in solution and is further modified by the composition of the solvent and presence of cosolutes. However, the influence of polymer architecture on these specific ion effects is relatively unknown. Herein, we compare the current understanding of specific ion effects on free polymer chains and gels with recent studies of polymer brushes. Further studies on mixed salt systems are found to be the next step to predicting the behaviour of these materials in biological systems.

1. Introduction

Responsive polymers that change their physicochemical properties when exposed to stimuli such as changes in pH [1,2], electric field strength [3], temperature [4,5] and salt concentration and identity [6–8] have received significant research attention. These so-called smart materials are particularly promising for high-value applications such as sensors, nanoactuation and microfluidics [9,10]. Field based stimuli such as temperature are attractive for these applications as they can repeatedly be triggered externally without affecting the composition of the system. Temperature responsive polymers have been investigated extensively for biomedical applications such as tissue engineering [5] and controlled drug delivery [5,11–15]. These polymers may be split into

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two classes: those whose solubility decreases with increasing temperature display lower critical solution temperature (LCST) type behaviour, while those with upper critical solution temperature (UCST) type behaviour display the opposite trend [4,5]. LCST type polymers are far more common than UCST type in aqueous solutions [4,16,17].

Six primary categories of LCST-type thermoresponsive polymers were identified by Chen et al. [18] poly[*oligo*(*ethylene glycol*)(*meth*)*acrylate*]s [19–24], poly(2-alkyl-2-oxazo-line)s [23], poly(vinyl methyl ether)s [25,26], polypeptides [27,28], *N*-alkyl-substituted poly(aminoethyl methacrylate)s [29–32], and *N*-substituted poly(meth)acrylamides [33]. From this last category, poly(*N*-isopropylacrylamide) (PNIPAM) is by far the most studied neutral thermoresponsive polymer owing in part to its low sensitivity to environmental conditions (e.g. salt, pH, polymer concentration), its biologically relevant transition temperature (~32 °C) and its structural similarity to proteins [34,35]. However, PNIPAM is cytotoxic under certain conditions [36], which has led to a number of alternative, biocompatible polymers receiving increasing interest [15,22,37].

Recent advances in monomer synthesis have facilitated a rapid expansion in the range of available monomers [4]. The LCST transition temperature may be tuned by varying the hydrophilicity of the monomer [18], or through copolymerisation of monomers with differing hydrophilicity [4,19]. For example, increasing the length of the hydrophilic ethylene glycol side chain length raises the LCST of oligo ethylene glycol methacrylates ($OEGMA_x$), where x is the molar mass of the monomer [19]. Incorporation of additional components such as bioconjugates [38–41], ligands [42], fluorescent markers [43,44], or charged moieties [41,45–47] into copolymers can further modify the phase transition, add greater specificity for interactions between polymers and other solutes [39,45,46], or even facilitate new ways to study their behaviour [44].

Improved synthetic methods, such as reversible addition-fragmentation chain transfer (RAFT) or atom transfer radical polymerisation (ATRP) [20–22,24], have allowed access to a wide range of polymer geometries and architectures such as statistical, block and gradient copolymers, stars, dendrimers and gels (Fig. 1) [5,37]. Differing regions of hydrophilicity allows many of these molecules to self-assemble, which is particularly promising for controlled release applications [12]. Decorating surfaces with initiator sites and subsequent polymerisation directly from the surface allows the formation of polymer brushes [48]. This is known as the *grafting from* approach which allows higher grafting densities than the sterically hindered adsorption of end-functionalised chains to the surface, i.e. the *grafting to* approach. Polymer brushes are assemblies of polymer chains end-grafted at a sufficiently high areal density to force self-interaction. The forced confinement of the chains, in addition to the chemistry of the polymer, allows tailoring of interfacial properties such as wettability, adhesion and lubricity [10]. These properties can be switched in responsive polymer brushes as the polymer conformation swells and contracts with changing solvent quality. In addition to the potential applications noted previously, surface-confined thermoresponsive polymer brushes have been utilised in applications ranging from chromatography supports [49–51] to the enzyme free removal of cells from tissue culture substrates [52–54].

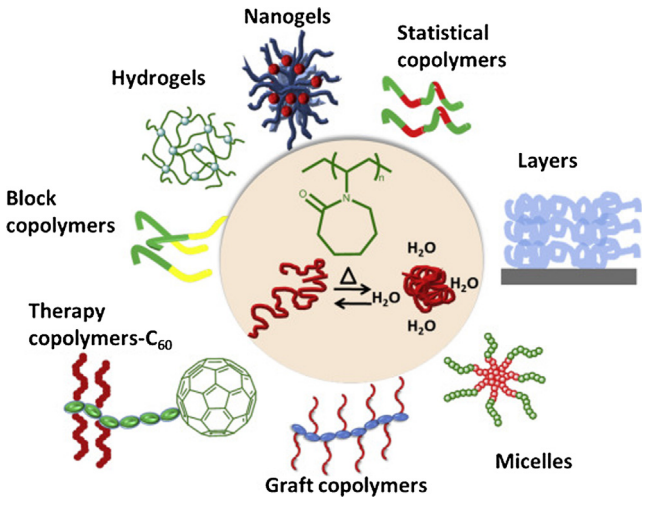

Fig. 1. Different architectures of a typical thermoresponsive polymer, poly(*N*-vinylcaprolactam) (PNVCL). Reprinted from Ref. [37] with permission from Elsevier, copyright (2016).

Many factors affect the properties of thermoresponsive polymers in solution, including the polymer concentration [55,56], molecular weight (MW) [56–58], end-group chemistry [57–60], the presence of cosolutes such as salts and osmolytes [6,8,61], and the composition of the solvent [6,8]. Understanding the effect of added salt is important for many applications of these polymers as the background electrolyte concentration in the human body is around 100 mM [7]. It has been demonstrated extensively that the temperature response of ungrafted chains is affected by both the concentration and identity of ions in solution [6,8,61]. The tendency to either raise or lower the LCST of the polymer is often correlated with the degree to which a particular ion is excluded or accumulated at the polymer-solvent interface. However, this simplistic picture is inadequate in many cases [62,63].

Recent studies on thermoresponsive polymer brushes have shown that the influence of added ions cannot be solely explained by a shift in the LCST [64–68]. Herein, we seek to demonstrate the importance of architecture on the specific ion response of thermoresponsive polymers. Firstly, a brief overview of how composition and architecture affects the thermoresponse in salt-free water, with a focus on polymer brush coated surfaces provides context to observed salt-dependent behaviour. This is followed by a discussion of the current experimental and theoretical understanding of specific ion effects on thermoresponsive polymers with ungrafted and gel architectures. Comparison of these results with studies on brushes then allows the emerging picture of how the confined architecture of polymer brushes influences specific ion effects to be emphasised. Discussion of multi-responsive polymers containing pH and salt sensitive ionisable groups has been avoided as there is a strong, often non-monotonic [69], interplay between the degree of charge, the ionic strength and the temperature response [29,30,32,47,70–74]. Furthermore, reports of polymer brushes synthesised using the *grafting from* approach have already been discussed comprehensively by Klok and co-workers [75,76]. Below we demonstrate the need for systematic studies to elucidate the complex interplay of solution and polymer composition convolved with polymer architecture in determining the overall response to temperature.

2. Thermoresponsive polymers

2.1. The lower critical solution temperature of ungrafted chains

This article focusses on neutral polymers that have an LCST in aqueous solutions. In these systems, the LCST arises from the competition between enthalpic gain from hydration of hydrophilic moieties against the entropic penalty for the hydration of hydrophobic moieties via an ice-like, clathrate cage [33]. At temperatures above the LCST intra- and inter-molecular bonds dominate and the polymer collapses leading to an increase of the system entropy via the release of bound water molecules. It must