Communication

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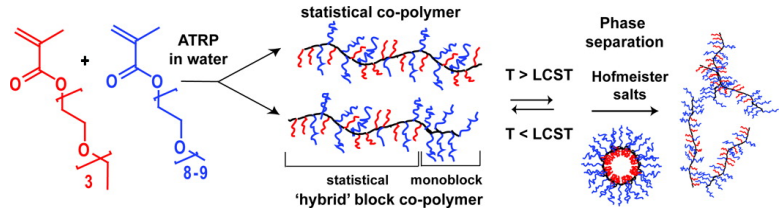
J. Am. Chem. Soc., **2008**, 130 (33), 10852-10853 • DOI: 10.1021/ja802609r • Publication Date (Web): 24 July 2008



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Published on Web 07/24/2008

Ion-Sensitive "Isothermal" Responsive Polymers Prepared in Water

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Responsive or "smart" materials have been an increasing focus for chemists in the pharmaceutical and biomedical sectors.[1–3] Potential applications for these materials include drug, gene, and cell delivery;[4,5] surface engineering;[6,7] sensing and actuation.[8–10] Until recently, however, most responsive polymers have relied on an *in situ* temperature stimulus to effect a change in properties. Here we describe polymers wherein the side-chain functionality normally exploited for aqueous solubility is used as an ion-responsive component. Of key importance is that the ionic response allows a phase transition to be triggered in thermosensitive polymers *without* a temperature change. By designing polymer architectures such that the coil-to-globule transition affects micellization,[11] the effect of a polymer response to the presence of ions[12–15] should lead to formation or destruction of supramolecular architectures. This in turn enables the generation of "isothermal" ionic-responsive release systems.

The route to these responsive polymers was designed to be carried out in one pot, without organic solvents, and to lead to a family of materials with potential biomedical applications. We based our strategy on commercially available ether-tipped poly(ethyleneglycol) (PEG) methacrylates, polyethylene glycol ethyl ether methacrylate (M_n 246, PEGMA-EE 246), and polyethylene glycol methyl ether methacrylate (M_n 475, PEGMA-ME 475). These monomers are similar to those used recently[16] for biocompatible thermoresponsive polymers but differ, crucially, in their specific solubility and ionic-binding properties. The cosolubility profiles of these monomers enabled aqueous solutions to be prepared at 4 °C, and polymerization via the AGET ATRP method[17] allowed polymers of a statistical, block, and "hybrid" statistical-co-block sequence to be prepared (Figure 1).

The AGET methodology afforded a high degree of control, with molar masses of ~20 kDa being achievable within 3 h even at 2 °C. Solution properties of the polymers could be controlled by comonomer content and addition sequence, with all the polymers containing PEGMA-EE 246 exhibiting a Lower Critical Solution Temperature (LCST).

Statistical copolymers **P1**−**P5** showed a linear correlation between the mole fraction of PEGMA-EE 246 in the polymer and the LCST properties as expected (Figure 1, Table 1). The versatility of the AGET ATRP synthesis also allowed the preparation of "hybrid" block copolymers, **P6** and **P7**, composed of statistical sequences of PEGMA-EE 246 with PEGMA-ME 475, from which were grown an outer block of PEGMA-ME 475. Solutions of these polymers exhibited smaller changes in turbidity with temperature compared to the statistical copolymers, while dynamic light scattering (DLS) and TEM (Figure 1c) suggested formation of micelle-like assemblies (R_H = 40−100 nm) in water above their critical transition temperatures. NMR spectra of polymers **P6** and **P7** in water (ESI) showed diminution in peak integrals for protons in the more hydrophobic domains compared to those in PEGMA-ME 475 side-chain termini as temperature increased above LCST,

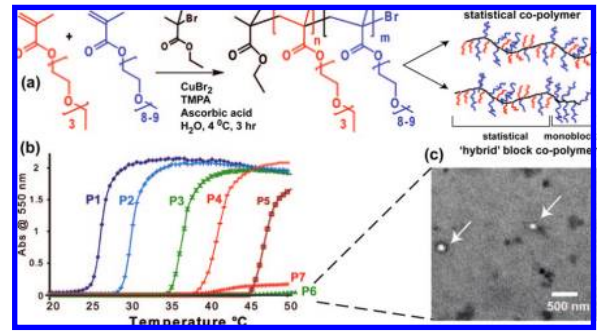

Figure 1. (a) Polymer synthesis and schematic of copolymer structures; (b) Temperature−turbidity curves for copolymers **P1**−**P7**; (c) Transmission Electron Micrograph (TEM) of hybrid block copolymer with micelle-like assemblies of 40−100 nm radius.

Table 1

polymer − n/m[a]	$M_{n\,th}$[b]	M_n[c]	M_W/M_n[c]	% m[d]	LCST, °C[e]
P1 − 100:0	21.6	24.5	1.18	0	24
P2 − 95:05	23.6	25.0	1.17	5.6	28
P3 − 90:10	23.0	22.8	1.13	10.6	33
P4 − 85:15	25.1	16.7	1.09	14.9	37.5
P5 − 80:20	25.8	16.9	1.10	20.3	42.5
P6 − Hybrid block g-PEGMA ME 475 ([n/m]/m = 85:15:6)	26.4	22.2	1.46	44	45
P7 − Hybrid block g-PEGMA ME 475 ([n/m]/m = 89:11:17)	15.5	14.7	1.33	30	37

[a] n/m = molar ratio of PEGMA-EE 246/PEGMA-ME 475. [b] Theoretical, from monomer/initiator ratio. [c] From GPC (THF, poly(styrene) standards). [d] NMR integrals. [e] From sharp increase in UV absorption of solutions in water at 550 nm.

again indicative of the formation of higher-order micellar/vesicular structures. Nonlinear increase of pyrene fluorescence with block copolymer concentration was observed (ESI), further supporting a micellar model, whereas this behavior was not apparent for statistical copolymers **P1**−**P5**.

Having established the primary thermal response for these materials, we evaluated the effect of ions known for their "salting out" and "salting in" behavior. Elegant prior work had established that ions in the Hofmeister series caused changes in the LCST of poly(*N*-isopropylacrylamide) (PNIPAm).[18] We reasoned that the long side chains in the PEGMA-ME 475 segments would be more strongly affected by Hofmeister ions owing to the high interfacial water structuring normally associated with PEG. We screened polymers **P1**−**P5** with NaSCN, a strong chaotrope (water "structure breaker"), NaCl, and Na_2SO_4, a strong kosmotrope (water "structure maker"). We further selected polymer **P3** (PEGMA-EE 246_{90}/PEGMA-ME 475_{10}) with an LCST just below 37 °C, to establish whether more subtle changes in phase transition could be caused through addition of ions around body temperature. In view of the

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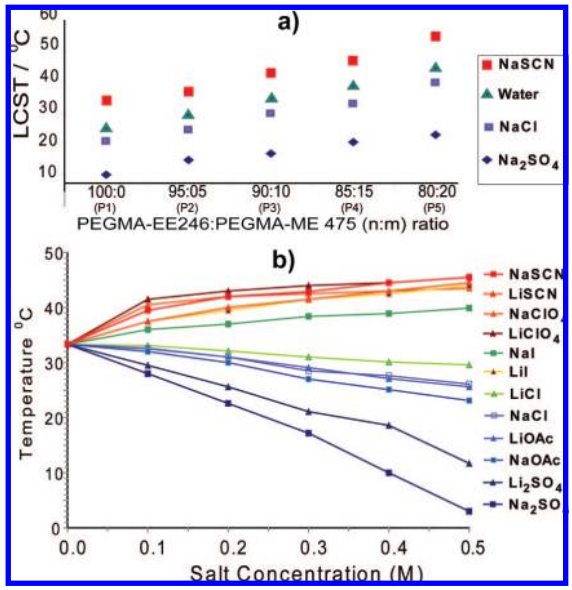

Figure 2. (a) Effect of selected salts from the Hofmeister series on LCST of statistical PEGMA-EE 246/PEGMA-ME 475 copolymers **P1**−**P5**; (b) Li^+ and Na^+ salts of Hofmeister series ions on LCST of polymer **P3**.

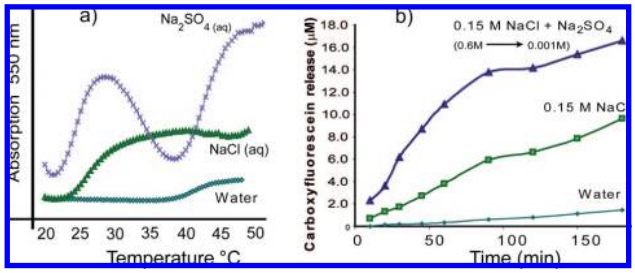

Figure 3. Temperature−turbidity profile of **P7** (a) and release of encapsulated carboxyfluorescein dye (b) from co-polymer micelle-like assemblies at 37 °C in water, saline, and kosmotrope solutions.

strong interactions of PEG chains with Lewis acids, we used both Li^+ and Na^+ counterions with **P3**. As can be seen in Figure 2, very marked changes in LCST occurred following the admixture of strong chaotropes (SCN^-) or kosmotropes (SO_4^{2-}). The differences in LCST were greater than those for PNIPAm when challenged with the same ionic species and concentration, supporting the working hypothesis of increasing lengths of side chains impacting solvation and local water structure.

The effects of salts on the hybrid block copolymers **P6** and **P7** were more complex, with two-step temperature−turbidity curves at high concentrations of salt and the effect being most marked with Na_2SO_4 at 0.3 M (Figure 3a). The relative shapes of the curves at 37 °C for **P7** in water and solutions of NaCl and Na_2SO_4 suggested that there were likely to be differences in the solution conformations of the **P7** micellar assemblies at this temperature in the different environments. To probe this further we encapsulated a dye, carboxyfluorescein, into **P7** micelles and monitored for release of dye with salt addition at 37 °C (Figure 3b).

As apparent in Figure 3b, a sharp burst release of carboxyfluorescein was obtained following addition of Na_2SO_4 in 0.15 M NaCl solution, and this was faster than the release from micelles in 0.15 M NaCl solution alone. Both DLS and NMR indicated concomitant changes in micelle state (ESI) around transition temperatures with the salts, indicating that sulfate ions altered the association state of the **P7** block copolymers, thereby liberating the dye. While a detailed mechanism for this sulfate-induced transformation in micelles remains to be established, it is likely that the salting-out effect of the kosmotrope involves a subtle balance between increasing the hydrophobic association of interior groups in the micelles and precipitating the polymers from solution. Such a process accords with prior reports of multistage[18] polymer interactions with Hofmeister ions. However, the overall effect of kosmotrope addition in this case was release from thermosensitive polymer micelles without requiring an external temperature change.

In conclusion we have shown that it is possible to change the phase transition of fully aqueous synthesized biocompatible nonionic polymers through addition of salts. Furthermore, the control in polymer structure through living synthesis enables the response from a phase transition to be tuned to an organized self-assembly process, and its reverse, and this in turn allows for a new modality in release systems. Potential advantages of using synthetic polymers for delivery type applications are numerous but, in reality, are strongly dependent on using biocompatible precursors and aqueous processing. Applications of these materials in controlled release and ionic recognition are in progress.

Acknowledgment. We thank the EPSRC (Grants EP/D022347/1 and EP/E021042/1), AstraZeneca, and the University of Nottingham, U.K. for funding and Dr. Martin Grosvenor and anonymous reviewers for helpful comments.

Supporting Information Available: Synthetic procedures, characterization of polymers, assay conditions for LCST responses. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA802609R