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COMMUNICATIONS

Published on Web 09/16/2006

Point by Point Comparison of Two Thermosensitive Polymers Exhibiting a Similar LCST: Is the Age of Poly(NIPAM) Over?

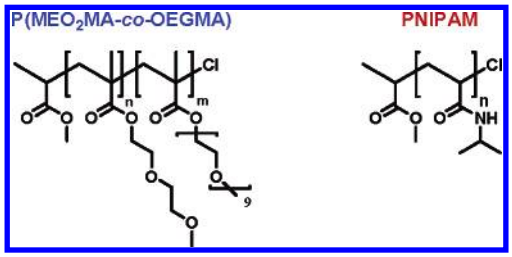
Jean-François Lutz,* Özgür Akdemir, and Ann Hoth

Research Group Nanotechnology for Life Science, Fraunhofer Institute for Applied Polymer Research, Geiselbergstrasse 69, Golm 14476, Germany

Received July 25, 2006; E-mail: lutz@iap.fhg.de

Thermoresponsive polymers have been recently increasingly investigated in nanotechnology and biotechnology applications.[1] For instance, water-soluble polymers exhibiting a lower critical solution temperature (LCST) in water are potentially useful for several biomedical applications such as smart bioactive surfaces, selective bioseparation, phase separation immuno-assays or hyperthermia-induced drug delivery.[1−4] So far, poly(*N*-isopropylacrylamide) (PNIPAM), which display a LCST in water around 32 °C, has been the most studied thermosensitive polymer in bioapplications, although it is not the only known macromolecule exhibiting an aqueous LCST.[1,5] The often forgotten main reason for such biomedical popularity is not really the fact that the LCST of PNIPAM is close to body temperature (other polymers exhibit LCST values even closer to 37 °C) but rather the fact that its LCST is relatively insensitive to environmental conditions. Indeed, slight variations of pH, concentration, or chemical environment are generally affecting the LCST of PNIPAM by a few degrees only.[5]

Scheme 1. Molecular Structures of the Thermosensitive Polymers Compared in the Present Work



We recently reported that the copolymerization of two oligo(ethylene glycol) macromonomers of different chain-lengths (i.e., of different hydrophilicity but similar chemical nature) leads to the formation of thermosensitive copolymers with a tunable LCST.[6] For instance, random copolymers of 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) and oligo(ethylene glycol) methacrylate (OEGMA, M_n = 475 g·mol^{-1}) exhibit LCST values between 26 and 90 °C, which can be precisely adjusted by varying the comonomer composition.[6,7] For example, the LCST of 32, 37, or 39 °C was observed in pure water for copolymers possessing on average, respectively, 5, 8, or 10% of OEGMA units per chain. These novel thermosensitive macromolecules are very promising for biomedical applications since they are principally composed of biocompatible oligo(ethylene glycol) segments. Indeed, poly(ethylene glycol) (PEG) is an uncharged, water-soluble, nontoxic, nonimmunogenic polymer and therefore the most applied synthetic polymer in the biomedical field.[8] So far, linear PEG macromolecules were mostly utilized in bioapplications, but several recent reports indicated that nonlinear PEG analogues (i.e., macromolecules constructed from oligo(ethylene glycol) macromonomers) are as biocompatible as their linear counterparts.[9−13] In this context, thermosensitive PEG analogues could become in a near future

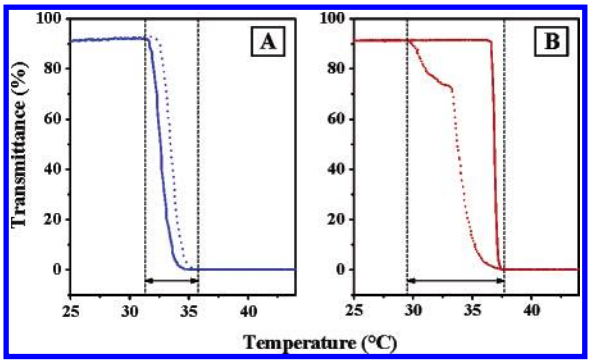


Figure 1. Plots of transmittance as a function of temperature measured for aqueous solutions (3 mg·mL^{-1}) of either (A) a copolymer P(MEO_2-MA-*co*-OEGMA) containing 5 mol % of OEGMA per chain ($DP_n \approx 100$; $M_w/M_n = 1.34$) or (B) a homopolymer of NIPAM ($DP_n \approx 100$; $M_w/M_n = 1.12$): solid lines, heating cycles; doted lines, cooling cycles.

extremely popular materials for biotechnology applications. However, their stimuli-responsive properties still have to be carefully evaluated. Hence, the goal of the present study is to compare the thermoresponsive properties of the copolymers P(MEO_2MA-*co*-OEGMA) to those of PNIPAM, which can be considered as the "gold standard" of thermoresponsive polymers.

Copolymers P(MEO_2MA-*co*-OEGMA) and PNIPAM were both prepared via atom transfer radical polymerization (ATRP).[6,14−16] Initiators and catalysts were carefully selected in order to obtain polymers with a comparable degree of polymerization (DP_n) and chain-ends. Nevertheless, the copolymers P(MEO_2MA-*co*-OEGMA) were prepared from an initial comonomer feed containing 95% of MEO_2MA and 5% of OEGMA, to be comparable with PNIPAM (as aforementioned, such optimized comonomer composition lead to the formation of copolymers exhibiting a LCST of 32 °C).[6] Figure 1 shows phase transitions observed by turbidimetry for P(MEO_2-MA-*co*-OEGMA) and PNIPAM samples of comparable DP_n. PNIPAM exhibits a very sharp transition when heated. However, a broad hysteresis can be observed in the cooling process. This behavior was previously observed by Wu et al. with PNIPAM of narrow molecular weight distribution and corresponds to an irreversible coil-to-globule transition involving four distinct thermodynamically stable states.[17] In comparison, the copolymer P(MEO_2MA-*co*-OEGMA) exhibits a much more uniform thermal profile (i.e., heating and cooling cycles are roughly comparable).

Figure 2 compares the cloud points of P(MEO_2MA-*co*-OEGMA) and PNIPAM as measured by turbidimetry in various experimental conditions. A first important parameter for biomedical applications is indeed the influence of salts on the thermal behavior of the polymers.[18,19] Figure 2A shows cloud points recorded for both polymers in the presence of increasing amounts of sodium chloride. A typical salting-out effect was observed in both cases. The presence of sodium chloride leads to a partial dehydration of the macromol-

10.1021/ja065324n CCC: $33.50

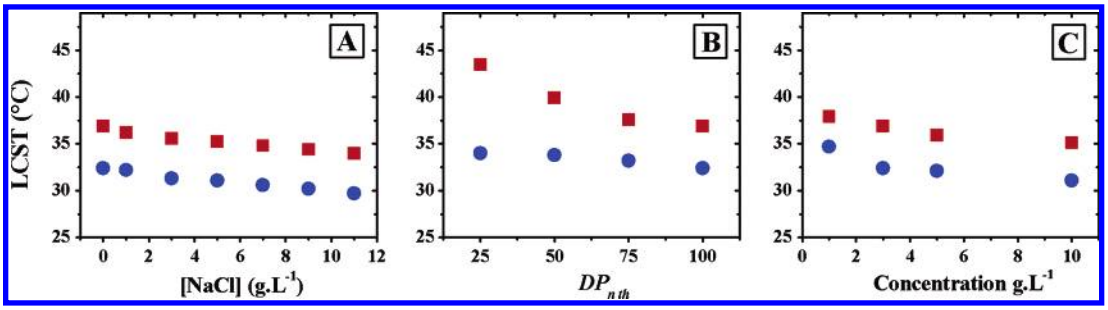


Figure 2. Plots of the measured cloud points as function of (A) NaCl concentration (polymer concentration in water is 3 mg·mL^{-1} in each case), (B) the theoretical degree of polymerization DP_{nth} (polymer concentration in water is 3 mg·mL^{-1} in each case) and (C) polymer concentration in deionized water. In all figures, cloud points of P(MEO_2MA-*co*-OEGMA) and PNIPAM are represented by blue dots and red squares, respectively. Data in Figures A and C were measured with a copolymer P(MEO_2MA-*co*-OEGMA) containing 5 mol % of OEGMA per chain ($DP_n \approx 100$; $M_w/M_n = 1.34$) and a homopolymer of NIPAM ($DP_n \approx 100$; $M_w/M_n = 1.12$). The presented values are the inflection points of the heating cycles.

ecules and consequently to a decrease of the LCST. Nevertheless, this effect was observed to be somewhat comparable for P(MEO_2MA-*co*-OEGMA) and PNIPAM. For instance, both polymers behave similarly in physiological medium (e.g., TRIS buffered saline solution). For a polymer concentration of 3 mg·mL^{-1}, the cloud point in physiological buffer is roughly 3 °C lower than in pure deionized water for both polymers.

Another fundamental parameter is the influence of chain-length on the phase transition.[20,21] A series of copolymers P(MEO_2MA-*co*-OEGMA) of similar composition (i.e., 5% of OEGMA units) but different DP_n was compared to corresponding PNIPAM samples (Figure 2B). At a copolymer concentration of 3 mg.mL^{-1} in pure water, the DP_n was found to have very little influence on the thermal behavior of P(MEO_2MA-*co*-OEGMA), whereas for PNIPAM, differences in LCST as high as 7 °C could be observed between long and short samples.[20]

Nevertheless, the cloud point of P(MEO_2MA-*co*-OEGMA) copolymers was found, similarly to PNIPAM, to be relatively independent of their concentration in water. Figure 2C compares the influence of concentration on the cloud points measured for P(MEO_2MA-*co*-OEGMA) and PNIPAM. In the studied range of concentration (1−10 mg·mL^{-1}), the LCST was found to increase a few degrees only with dilution.

In conclusion, copolymers P(MEO_2MA-*co*-OEGMA) possessing in average 5% of OEGMA per chain exhibit a thermoresponsive behavior generally comparable, and in some cases, superior to PNIPAM. Thus, P(MEO_2MA-*co*-OEGMA) copolymers can be considered as ideal structures, which combine both the properties of PEG (i.e., nontoxicity, anti-immunogenicity) and PNIPAM (i.e., thermosensitivity almost independent of external conditions) in a single macromolecule. Hence, these novel stimuli-responsive copolymers are very relevant for many applications in material science and biotechnology.

Acknowledgment. Fraunhofer society and Deutsche Forschungsgemeinschaft (LU 1195/1-1) are greatly acknowledged for financial support. Moreover, J.F.L. thanks professor André Laschewsky (Universität Potsdam) for fruitful discussions and Marlies Gräwert (MPI-KGF) for the SEC measurements.

Supporting Information Available: Full experimental part and additional discussion (influence of composition, polydispersity, and molecular weight on LCST). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA065324N