Quasi-Living Polymerization of *N*-Isopropylacrylamide onto Poly(ethylene glycol)

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Introduction. The unique properties of poly(ethylene glycol)-poly(*N*-isopropylacrylamide) (PEG−PNIPAAm) block and graft copolymers in water have recently attracted a lot of attention.[1−3] Part of the interest concerns the lower critical solution temperature (LCST) of PNIPAAm in water that can be tuned close to body temperature by copolymerization and may therefore be applied in the biomedical field as a stimulus-sensitive material. Since the hydrophilic PEG provides steric stabilization of the block copolymer in aqueous solution, the combination of the temperature-sensitive PNIPAAm and PEG should exhibit interesting thermosensitive aggregational behavior that may be used for example as stimuli-sensitive drug delivery systems.

The PNIPAAm−PEG block copolymers can be conveniently synthesized from monohydroxy or bishydroxy end-functionalized PEG by radical polymerization of NIPAAm using cerium(IV) redox initiation.[2] Using this redox reaction, the CH_2−OH end groups of the PEG are oxidized to give macroradicals. Performing this polymerization in water above the LCST, the resulting block copolymers form micelles in the early stage of the polymerization reaction, and subsequent monomer conversion occurs exclusively within the micellar core. We report here a detailed analysis of the course of the NIPAAm polymerization onto PEG macroradicals and on the quasi-living nature of these radicals as established from reaction calorimetry, gas chromatography, ultracentrifugation, and Ce(IV) titration.

Results and Discussion. PEG−PNIPAAm diblock copolymers were prepared from monohydroxy end-functionalized PEG ($M_n = 12 \times 10^3$ g/mol) and NIPAAm in water at 60 °C.[2] PEG macroradicals were formed upon redox reaction of the CH_2−OH end groups with Ce(IV) (Ce(IV)/CH_2−OH end groups: 1.75/1). Rapid phase separation within the first few minutes of the polymerization results from the acquirement of an LCST by the growing PNIPAAm blocks and subsequent aggregation into a micellar core with the PEG chains forming the micellar shell.

Detection of the heat flow (HF) during the polymerization with reaction calorimetry[4] (Figure 1) showed no more heat development after approximately 70 min, indicating complete monomer conversion. Independent determination of the monomer conversion by gas chromatography[5] was in good agreement and confirmed the completion of the polymerization after 70 min.

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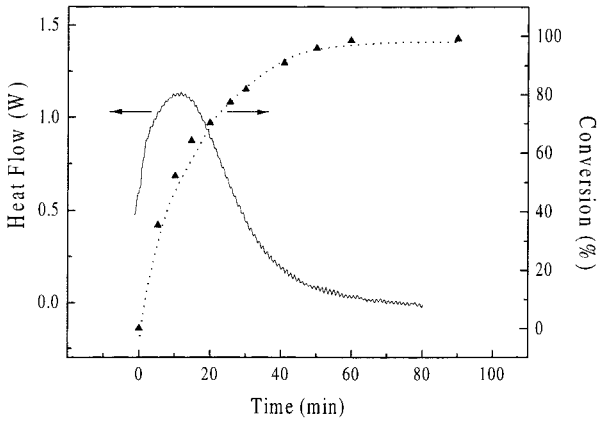

Figure 1. Heat flow (reaction calorimetry) and conversion (gas chromatography) of NIPAAm during its polymerization onto PEG in water at 60 °C. [PEG] = 4.17 mmol/L, $[NIPAAm]_0$ = 0.35 mol/L, and $[(NH_4)_2Ce(NO_3)_6]$ = 7.30 mmol/L.

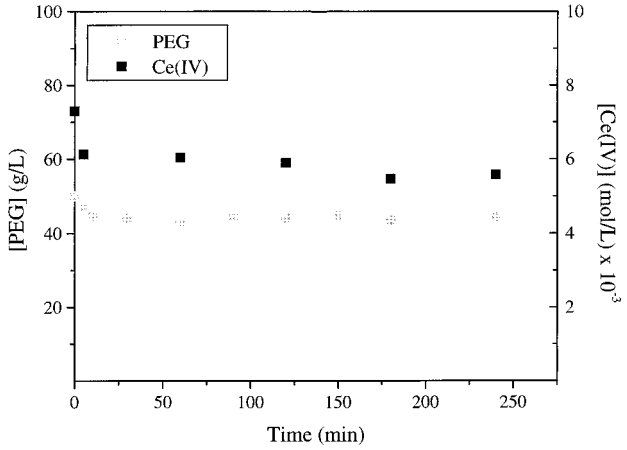

Figure 2. Concentration of nonparticipating PEG (g/L) and concentration of ceric ions (mol/L) as a function of time. $[PEG]_{total}$ = 4.17 mmol/L, $[NIPAAm]_0$ = 0.35 mol/L, and $[(NH_4)_2Ce(NO_3)_6]_0$ = 7.30 mmol/L.

Titration of the Ce(IV) ions in samples taken from the polymerization mixture[6] (Figure 2) showed a sharp decrease in the ceric ion concentration immediately after the start of the reaction. During the rest of the reaction the ceric ion concentration remains almost unchanged. This indicates that most of the PEG chains are oxidized within the first 5 min of the reaction. The decrease corresponds to the conversion of approximately 18 mol % of the initial amount of Ce(IV), namely 1.3 mmol of ceric ions. Ultracentrifugation[7] of samples taken during the polymerization allowed the isolation of the PEG chains present in the aqueous phase that had not participated in the radical polymerization. After the short initiation period an almost constant amount of PEG remains in the water (Figure 2). These data suggest that only approximately 10 mol % of the initially present PEG takes part in the initiation reaction. This suggests that the PEG macroradicals may undergo oxidative termination in the polymerization stage prior to the micelle formation. Termination by ceric ions is the main cause for termination in similar ceric ion initiated systems.[8−10] At 60 °C part of the PEG chains in the shell of the micelles[11,12] do not participate in the radical polymerization but do stabilize the emulsion.

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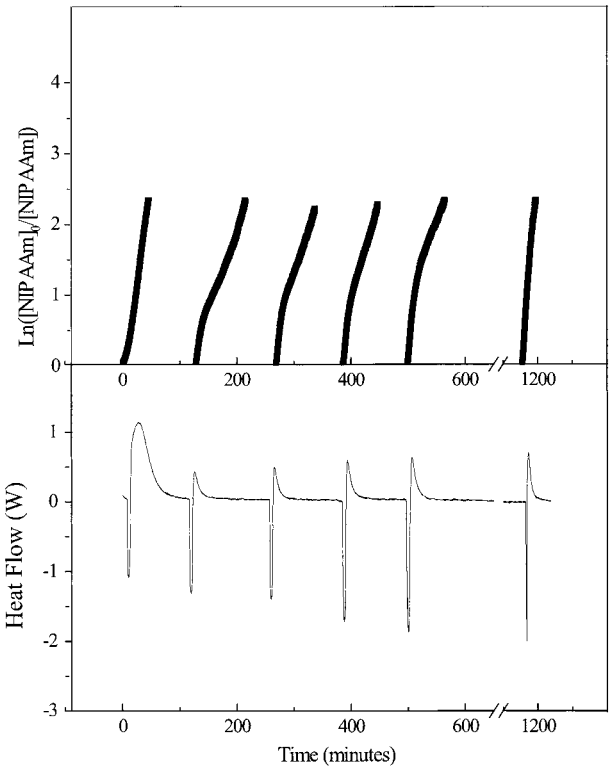

Figure 3. Heat of polymerization as developed during the sequential polymerization of NIPAAm as recorded by reaction calorimetry. [PEG] = 5 g/100 mL (0.42 mmol). First polymerization [NIPAAm] = 0.035 mol/100 mL. Initiation by injection of $(NH_4)_2Ce(NO_3)_6$ (0.73 mmol/4 mL 1 M nitric acid). At t = 2, 4, 6, and 21 h injection of extra NIPAAm (7.96 mmol/4 mL water).

Once the micelles are formed, the propagation of NIPAAm appears to proceed unhindered. Reaction calorimetric measurements show that additional amounts of monomer polymerize even 1 day after the first polymerization is complete. Each consecutive polymerization proceeds at approximately the same rate with an almost identical slope when ln([NIPAAm]$_0$/[NIPAAm]) is plotted as a function of the polymerization time (Figure 3). The S-shaped curves at the beginning of each of the lines represent the time that the NIPAAm needs to equilibrate between the aqueous phase and the micelles. The slopes of the lines are proportional to $k_p[R^\bullet]$, which indicates that the same concentration of radicals is present throughout the six subsequent polymerizations of NIPAAm.

According to the above-mentioned relations regarding the time behavior of the ceric ions and PEG concentrations, it is very unlikely that additional initiation reactions could take place upon addition of further monomer. This is proven by the following experiments. Ultracentrifugation of samples taken during the polymerization allowed the quantification of the dry weight of the residue[13] containing the micelles and the dry weight of the PEG chains that did not participate in the polymerization and that were isolated from the supernatant. Figure 4 shows that the amount of PEG chains in the supernatant remains constant during all four polymerizations, whereas the total mass of the micelles steadily increases. During each of the sequential polymerizations, the polymer mass further increases. Even 22 h after the first polymerization, the polymer mass increases upon the addition of new monomer whereas

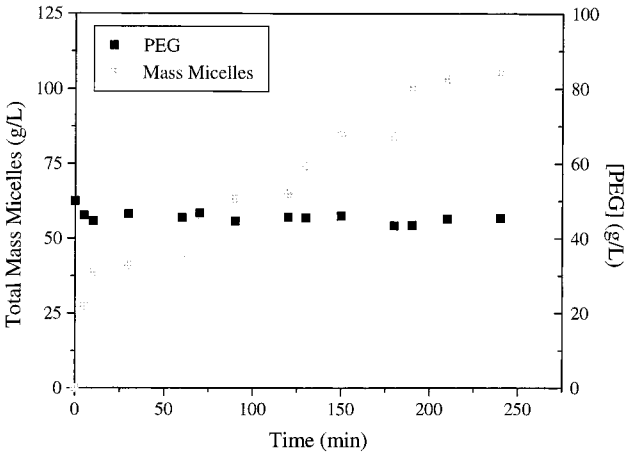

Figure 4. Total mass of micelles (g/L) and concentration of nonparticipating PEG (g/L) and as a function of time for sequential polymerization. $[PEG]_{total}$ = 5 g/100 mL (0.42 mmol). First polymerization [NIPAAm] = 0.035 mol/100 mL. Initiation by injection of $(NH_4)_2Ce(NO_3)_6$ (0.73 mmol/4 mL 1 M nitric acid). At t = 1, 2, and 3 h addition of extra NIPAAm (17.7 mmol).

the PEG concentration not changes. This demonstrates that no further increase occurs even on a long time scale.

Therefore, the radicals formed at the beginning of the polymerization remain active without termination, and hence, sequentially added monomer is polymerized multiple times. The apparent lack of termination by combination is especially interesting since each micelle contains more than one radical. This may be due to a very effective compartmentalization of the precipitated PNIPAAm chains inside the micelles in a way that the radical end is protected against deactivation inside the quasi-solid PNIPAAm blocks. This is a completely different mechanism than the reinitiation in the case of controlled or living radical polymerizations. Note that also in the case of methyl methacrylate emulsion polymerization the electron spin resonance signal decays very slowly in the glassy particles after the monomer is consumed.[14]

Up to now an adequate GPC analysis of the block copolymers has not been possible due to micelle formation. This is the subject of further research.

In conclusion, the block copolymerization of NIPAAm onto PEG using a ceric ion redox initiation in water results in a quasi-living polymerization of NIPAAm as the radicals survive inside the micellar core. Only approximately 10% of the PEG chains lead to initiated radicals during the redox reaction with the ceric ions. Part of the remaining PEG chains is incorporated in the shell of the micelles, where they contribute to the stabilization of the PEG-*b*-PNIPAAm micelles. The stabilized radicals inside the micelles survive for several hours and allow sequential polymerizations, which proceed with an almost identical rate compared as the first monomer addition.

References and Notes

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(4) Polymerizations were carried out in a reaction calorimeter RM2-S from Chemisens AB (Lund, Sweden). For details see: Nilsson, H.; Silvergren, C.; Törnell, B. *Angew. Makromol. Chem.* **1983**, *112*, 125.
(5) Samples were taken from the polymerization mixture, and NIPAAm was extracted with chloroform and quantified by gas chromatography (Varian 3600 + HP 3396A, Carbowax columns (Alltech-Econo-cap) 30 × 0.32 mm i.d. × 0.25 μm, FID detector, N_2 carrier gas, injection temperature 270 °C, column temperature at start 50 °C with heating rate 10 °C/min).
(6) The Ce(IV) in the samples were quenched with excess Fe(II) and the remaining Fe(II) was titrated with Ce(IV).
(7) The micelles were separated from the aqueous phase by ultracentrifugation (Centrikon T-2180). Samples were centrifuged at 40 °C at 330 g for 20 min and subsequently for 5 min at 1000*g*. After lyophilization of the supernatant and the residue, the dry weight of the nonparticipating PEG chains in the supernatant and the dry weight of the micelles in the residue was quantified. To ensure that all PEG radicals and growing block copolymers were separated from the nonparticipating PEG chains, samples were cross-linked at 60 °C immediately upon sample taking with 16 μL of ethylene glycol dimethacrylate per 4 mL sample. During cross-linking remaining Ce(IV) ions were reduced to Ce(III) by $(NH_4)_2Fe(SO_4)_2$ to prevent additional initiation.
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(12) Dialysis at room temperature of cross-linked particles that form a stable emulsion at 60 °C (Spectra/Por membrane, MWCO 25 × 10^3) results in an increased PNIPAAm/PEG ratio as determined with NMR (Bruker AC 250) and in the loss of the stability of the emulsion at 60 °C.
(13) The amount of residual PEG in the supernatant was estimated from ^{1}H NMR spectra (D_2O) after lyophilization (Bruker AC 250 operating at 250 MHz).
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