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# Aqueous RAFT (co)polymerization of *N*-isopropylacrylamide above lower critical solution temperature of poly(*N*-isopropylacrylamide) and stimuli-responsive properties of the polymers formed

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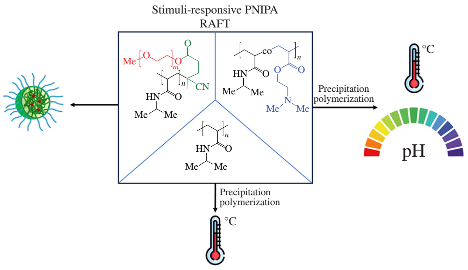
**Well-defined stimuli-responsive linear polymers of *N*-isopropylacrylamide, its block and random copolymers have been synthesized *via* aqueous reversible addition–fragmentation chain transfer polymerization performed above the lower critical solution temperature of poly(*N*-isopropylacrylamide).**



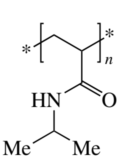
*Keywords*: stimuli-responsive polymers, poly(*N*-isopropylacrylamide), reversible addition–fragmentation chain transfer polymerization, polymerization-induced self-assembly.

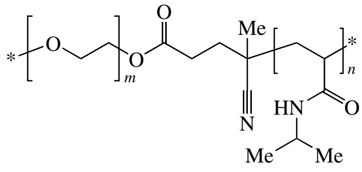
Poly(*N*-isopropylacrylamide) (PNIPA) is a typical example of a temperature-responsive polymer with a lower critical solution temperature (LCST) in aqueous solutions about 32 °C.[1] This value is relatively close to physiological temperature and can be adjusted by copolymerization with either hydrophilic or hydrophobic monomers.[2] Temperature-responsive properties of NIPA-based polymers provide their wide application in biomedicine and drug delivery systems.[3]

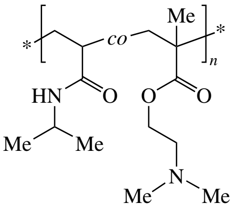
NIPA-based copolymers are synthesized *via* radical polymerization, which can be performed in organic, aqueous or aqueous-organic media.[4] However, biomedical applications impose limitations on the purity of the polymers used. Therefore, polymerization processes in aqueous media are of particular interest, following the trend towards green chemistry.[5,6] Due to the low value of the LCST of aqueous PNIPA solutions, homogeneous or heterogeneous (co)polymerization of NIPA can be realized in aqueous media. Homogeneous NIPA radical polymerization proceeds below the LCST; however, when it is conducted below 30 °C, the temperature control is difficult, resulting in the formation of PNIPA with a broad molecular weight distribution (MWD).[7] Above the LCST, heterogeneous polymerization of NIPA occurs, resulting in the formation of macro- or microgels due to intense chain transfer reaction to polymer.[8]

The reversible activation–deactivation radical polymerization (RDRP) can solve this problem due to the ability to convert reversibly propagating radicals into dormant species, thus decreasing the concentration of the former. Activation of dormant species and their further propagation can provide the formation of the polymer with a controlled molecular weight (MW) and a narrow MWD even in heterogeneous polymerization. Moreover, if the RDRP of NIPA starts from a macroinitiator soluble in aqueous solution at reaction temperature, then the formation of block copolymers self-assembled in core–shell particles during the synthesis is expected.[9] Among other RDRP techniques, RAFT polymerization is a versatile technique to produce polymers with precise architecture under rather mild conditions.[10] It has been already used to synthesize PNIPA-based polymers. However, the polymerization was performed mostly in organic solvents or in aqueous solutions below the LCST.[11–18] In a few cases it was performed above the LCST to synthesize microgels.[8,19–21]

In the present paper, we report on the synthesis of linear thermo-responsive NIPA-based polymers *via* the RAFT technique in aqueous solutions above the LCST of PNIPA, and study their stimuli-responsive properties. The following polymers were synthesized: (*1*) NIPA homopolymer, (*2*) block

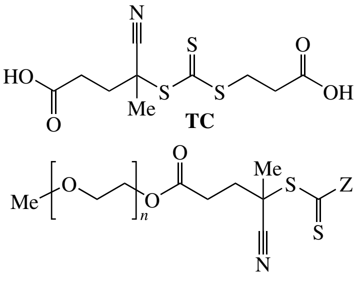

PNIPA


PEG-*b*-PNIPA


copoly(NIPA/DMAEMA)

copolymers of NIPA and hydrophilic polyethylene glycol, and (*3*) random copolymers of NIPA and cationic 2-dimethylaminoethyl methacrylate (DMAEMA) with variable molar percentage of DMAEMA units.

(Co)polymerization of NIPA was performed in water at $m_{\mathrm{NIPA}}/m_{\mathrm{water}} = 1:5$ wt/wt at 60 °C using 4-{[(2-carboxyethylthio)-carbonothioyl]thio}-4-cyanopentanoic acid (TC), poly(ethylene glycol) *O*-methyl ether *O′*-(4-cyano-4-{[(methylthio)carbonothioyl]thio}pentanoate) (PEG1, $M_n = 5400$), and poly(ethylene glycol) *O*-methyl ether *O′*-{4-cyano-4-[(phenylcarbonothioyl)-thio]pentanoate} (PEG2, $M_n = 2000$) as RAFT agents.



**TC**

**PEG1** Z = *n*-$H_{25}C_{12}S$
**PEG2** Z = Ph

RAFT homopolymerization of NIPA was performed at a [TC]/[PSA] ratio of 6.3. After one hour of the polymerization, the reaction mixture changed from transparent to an opalescent state, then acquired a milky consistency, and the polymer partially separated into a distinct phase. However, a narrow MWD of PNIPA [Figure 1(*a*), curve *1*, and Table 1) suggests that the RAFT mechanism was kept and the chain transfer to the polymer was suppressed. Cooling the reaction mixture from 60 °C to room temperature caused the solution to become clear and transparent. Similar trends were observed for RAFT copolymerization of NIPA and DMAEMA in the presence of TC [Figure 1(*b*)]. However, with an increase in the molar fraction of DMAEMA (from 3.7 to 68.6 mol%), the conversion of monomers decreased (see Table 1) and it did not exceed 10% for RAFT homopolymerization of pure DMAEMA.

With the use of PEG1 or PEG2 as RAFT agents, the formation of the diblock copolymer PEG-*b*-PNIPA is expected (Scheme 1). The propagating radicals of PNIPA$^\bullet$ formed due to PSA initiation reaction with the macroRAFT agent PEG–SC(=S)S–Z, resulting in the release of propagating radicals PEG$^\bullet$ and formation of a macroRAFT agent PNIPA–SC(=S)S–Z. Radicals PEG$^\bullet$ then reinitiate the polymerization of the NIPA monomer. In subsequent stages, new propagating radicals PEG–PNIPA$^\bullet$ interact with the initial or newly formed macroRAFT agents, leading to the formation of block copolymers with terminal dithiocarbonyl groups PEG–PNIPA–SC(=S)–Z. The key step in this process, ensuring the growth of MWs of block copolymers, is the reaction between radicals PEG–PNIPA$^\bullet$ and the macroRAFT agent PEG–PNIPA–SC(=S)–Z. Side reactions are shown as stages (5) and (6), and lead to the formation of the homopolymer PNIPA–SC(=S)–Z (see Scheme 1).

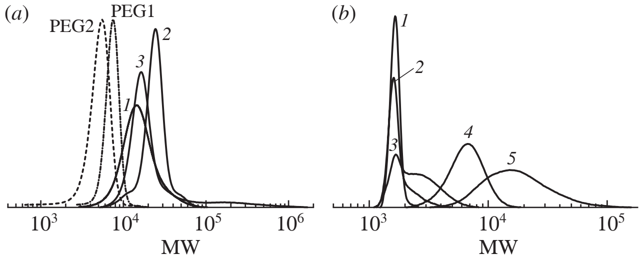
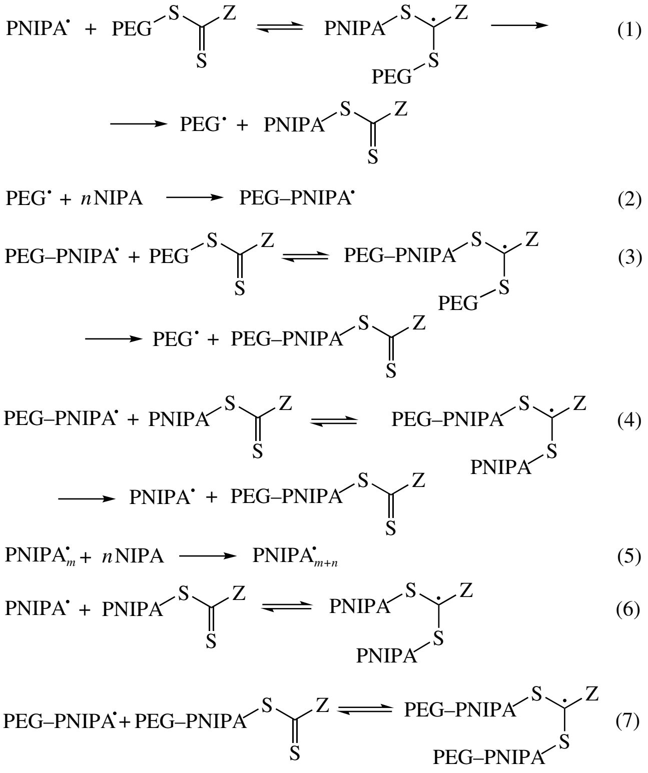


**Figure 1** MWD of polymers synthesized at 60 °C in aqueous solution at [RAFT]/[PSA] = 10: (*a*) PNIPA; (*1*) TC, (*2*) PEG1, and (*3*) PEG2; (*b*) copolymers of NIPA and DMAEMA, $f_{\mathrm{DMAEMA}}$ = (*1*) 68.6, (*2*) 42.0, (*3*) 19.5, (*4*) 9.4, and (*5*) 3.7 mol%.

**Table 1** Molecular weight characteristics of NIPA-based polymers.

| Polymer | RAFT agent | $f_{\mathrm{DMAEMA}}$$^a$/ mol% | $M_n$$^b$ | Đ | Conversion (%) |
|---|---|---|---|---|---|
| PNIPA | TC | 0 | 13200 | 1.25 | >99 |
| PEG1-*b*-PNIPA | PEG1 | 0 | 21500 | 1.13 | >99 |
| PEG2-*b*-PNIPA | PEG2 | 0 | 17000 | 2.0 | >99 |
| Copoly(NIPA/DMAEMA) | TC | 68.6 | 1600 | 1.06 | 20.4 |
| Copoly(NIPA/DMAEMA) | TC | 42.0 | 1640 | 1.03 | 27.7 |
| Copoly(NIPA/DMAEMA) | TC | 19.5 | 2000 | 1.18 | 35.3 |
| Copoly(NIPA/DMAEMA) | TC | 9.4 | 6000 | 1.12 | 50.8 |
| Copoly(NIPA/DMAEMA) | TC | 3.7 | 13600 | 1.42 | 83.6 |

$^a$ $f_{\mathrm{DMAEMA}}$ is the molar content of DMAEMA in the monomer feed. $^b$ $M_n$ is number-average molecular weight.



**Scheme 1** Mechanism of the formation of the PEG-*b*-PNIPA diblock copolymer in the course of RAFT polymerization of NIPA in the presence of the macroRAFT agent PEG–SC(=S)S–Z.

According to SEC data, the products of block copolymerization are characterized by higher MWs than initial macroRAFT agents while the traces of initial PEG1 and PEG2 are absent, confirming the formation of PEG-*b*-PNIPA block copolymers [see Figure 1(*a*), curves *2* and *3*; Table 1]. However, under the chosen conditions, RAFT polymerization is complicated by the separation of the polymer into a different phase. In this case, the hydrophilic PEG block is still soluble in water at 60 °C, while the growing PNIPA block loses its solubility. After reaching the critical length of the PNIPA block copolymer, the block copolymer self-assembles into micelles or aggregates with a core–shell structure (PEG is a shell-forming block, PNIPA is a core-forming block) in accordance with RAFT polymerization-induced self-assembly (PISA) mechanism (Figure 2).[17] Further polymerization of the NIPA monomer occurs inside these particles, providing the formation of a well-defined block copolymer. The control of the MWD of the block copolymer diminishes with decreasing MW of the PEG block due to difficulties in the stabilization of block copolymer particles.

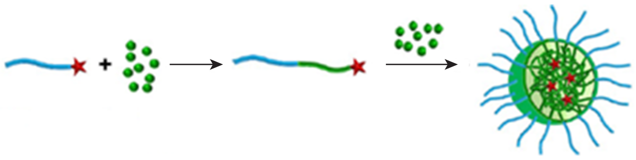


**Figure 2** Schematic presentation of the RAFT PISA mechanism.

The copolymer composition was confirmed by $^1$H NMR spectroscopy. The signals corresponding to ethylene glycol and NIPA monomer units are observed in the $^1$H NMR spectrum [see Online Supplementary Materials, Figure S1(*a*)]. The signals at $\delta_H$ 7.16 (br. s, 1H, NH), 3.83 (s, 1H, C*H*Me$_2$), 1.94 (s, 1H, CH), 1.43(s, 2H, CH$_2$), and 1.03 (s, 6H, 2×CH$_3$) correspond to the protons for the PNIPA block, while the signals at $\delta_H$ 3.49 (s, 4H, OCH$_2$CH$_2$O) correspond to the protons for the PEG block. In the $^1$H NMR spectrum of copolymers of NIPA and DMAEMA the signals referred to both monomer units are observed [Figure S1(*b*)]: $\delta_H$ 6–7 (br.m, 1H, NH), 4.02 (2H, CH$_2$O and 1H, C*H*Me$_2$), 2.34 (2H, CH$_2$N), 2.16 [6H, N(CH$_3$)$_2$], 1.84 (2H, CH$_2$), 1.36 (1H, CH), and 1.15 (3H, CH$_3$ and 6H, 2×CH$_3$). However, some of DMAEMA units contain protonated nitrogen, which is manifested in the appearance of signals in the region of 3.55–3.8 ppm corresponding to the protons located next to a charged nitrogen atom (6H, N$^+$Me$_2$ and 2H, CH$_2$N$^+$).

PNIPA and both block copolymers have comparable values of the MWs, so they should have similar values of the average hydrodynamic radii ($R_h$) before cloud point. Indeed, using the dynamic light scattering method (DLS), $R_h$ values were found to be equal to 2.7±0.2, 3.5±0.3, and 2.4±0.2 nm for PNIPA, PEG1-*b*-PNIPA, and PEG2-*b*-PNIPA, respectively. Rough estimates of the mean-square distance between the chain ends $<h^2>^{1/2} = n^{1/2}l$ ($n$ is the number of monomer units and $l = 0.25$ nm is the length of the monomer unit) give the values of 3.1–4.5 nm and the radius of gyration $<R_g^2>^{1/2} = (<h^2>/6)^{1/2} \sim 1.3–1.9$ nm. So, for all the polymers the observed values of $R_h$ are close to the estimated value of $<R_g^2>^{1/2}$, and the conformational behavior of polymers in aqueous solutions is similar before cloud point. The similar trend is observed for copolymers of NIPA with DMAEMA. As an example, at room temperature, $R_h$ of copolymers with $f_{DMAEMA} = 3.7–9.4$ mol% in the dilute aqueous solutions is 2–4 nm depending on the pH of the solution.

Upon heating, PNIPA demonstrates temperature-responsive properties. Cloud point temperatures ($T_{cp}$) of PNIPA and its block copolymers with PEG were determined from the temperature dependences of scattering intensity as the half-width of a sharp increase in the scattered light intensity determined by dynamic light scattering (DLS). The $T_{cp}$ for PNIPA with terminal hydrophilic groups derived from the initial RAFT agent, TC, is 35.0±0.5 °C, and the transition from transparent to turbid solution occurs at a narrow temperature range $\Delta T_{cp} = 4$ °C (Figure 3, curve *1*). Previously, we have found that $T_{cp}$ for PNIPA containing hydrophobic terminal groups with $M_n \sim 6–7$ kDa was about 31–32 °C, while $\Delta T_{cp}$ was ~8–11 °C.[10] The value of $T_{cp}$ for PNIPA is known to be sensitive to the presence of hydrophilic groups as well.[18] Thus, it may be supposed that hydrophilic terminal groups of PNIPA of a relatively low MW may affect $T_{cp}$ of the polymer.

The incorporation of the PEG block changes temperature-responsive behavior of PNIPA drastically. These blocks have similar lengths of the PNIPA block, while the length of the PEG block is different. In case of a longer PEG block, PEG1-*b*-PNIPA, which contains 44 mol% of NIPA units according to $^1$H NMR spectroscopy, $T_{cp}$ was not detected even upon heating at 65 °C (Figure 3, curve *2*). In case of PEG2-*b*-PNIPA, containing 86 mol% of NIPA units with a shorter PEG block, the $T_{cp}$ is slightly higher than for pure PNIPA, *i.e.* 36.2 °C, while the temperature range of the transition is much broader, $\Delta T_{cp} = 12$ °C (Figure 3, curve *3*). This difference may come from the ability of the block copolymer to self-assemble into micelles or aggregates, which is in agreement with the temperature changes of $R_h$ of PNIPA and both block copolymers (Figure 4). We observed similar patterns in our previous studies of aqueous solutions of block copolymers PNIPA-*b*-poly(1-vinylimidazole) during their self-assembling at various pH values.[18] Comparing number-averaged distributions of hydrodynamic radius $R_h$ observed at different temperatures for PNIPA [Figure 4(*a*)] and block copolymers [Figure 4(*b*),(*c*)], it may be concluded that upon heating, both block copolymers formed micelles with $R_h$ about 13 nm for PEG1-*b*-PNIPA and 7 nm for PEG2-*b*-PNIPA. However, a shorter block of PEG compared to PNIPA in PEG2-*b*-PNIPA cannot provide the aggregative stability of the particle's dispersion. This leads to phase separation, which is observed above ~50 °C.

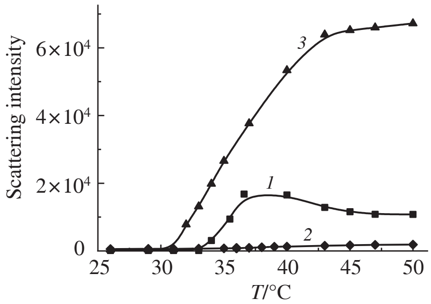


**Figure 3** Dependence of scattered light intensity on temperature of (*1*) PNIPA, (*2*) PEG1-*b*-PNIPA, and (*3*) PEG2-*b*-PNIPA aqueous solutions measured at an angle of 90°.

The presence of cationic DMAEMA units in the polymer chain endows the NIPA copolymer with pH sensitive properties.[22] As was shown above, the increase in molar content of DMAEMA in the monomer feed leads to a decrease in the monomer conversion. Thus, we have studied double stimuli-sensitive properties of the samples obtained at high conversions from the monomer feed with $f_{DMAEMA} = 3.7$ (Copolymer 1) and 9.4 mol% (Copolymer 2). Figure 5 illustrates the typical double-sensitive behavior of the copolymer of PNIPA and DMAEMA. At pH 10, DMAEMA units become hydrophobic and $T_{cp}$ measure by turbidimetry shifts to lower temperatures (see Figure 5, curve *1*), while at pH 4, DMAEMA units are charged and hydrophilic, and

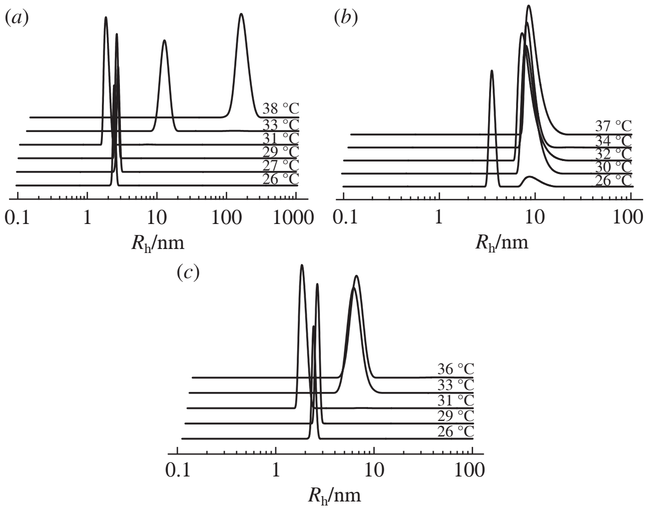


**Figure 4** Hydrodynamic radius $R_h$ distribution curves at the selected temperatures for (*a*) PNIPA, (*b*) PEG1-*b*-PNIPA, and (*c*) PEG2-*b*-PNIPA. The measurements were taken under the scattering angle of 90°; $R_h$ is number-averaged.

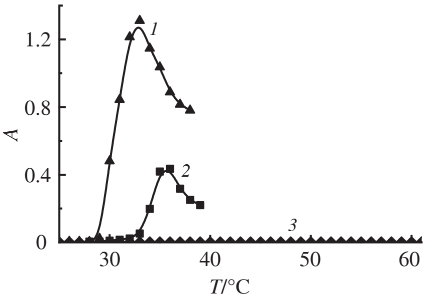


**Figure 5** Turbidimetric curves for sample Copolymer 1 at (*1*) pH 10, at (*2*) its own pH, and at (*3*) pH 4.

**Table 2** The values of $T_{cp}$ for copolymers of NIPA and DMAEMA at various pH.

| Copolymer | $f_{DMAEMA}$ (mol%) | Conditions | $T_{cp}$/°C |
|---|---|---|---|
| Copolymer 2 | 9.4 | Buffer, pH 4 | >85 |
| Copolymer 2 | 9.4 | Water | 45 |
| Copolymer 2 | 9.4 | Buffer, pH 10 | 41 |
| Copolymer 1 | 3.7 | Buffer, pH 4 | >65 |
| Copolymer 1 | 3.7 | Water | 34 |
| Copolymer 1 | 3.7 | Buffer, pH 10 | 30 |

the copolymer loses its temperature-sensitivity (curve *3*). The intermediate case is the aqueous solution of the copolymer, which contains both charged and uncharged units of DMAEMA (curve *2*). The $T_{cp}$ values depend on both the DMAEMA content and pH, which is typical for the copolymers of NIPA and DMAEMA (Table 2).

The interesting feature of the studied systems is the formation of the copolymer with partly charged DMAEMA units (according to $^1$H NMR data) resulting in the growth of the hydrophilicity of the copolymer. Thus, for copolymer Copolymer 2 it leads to the higher values of $T_{cp}$ when comparing to pure PNIPA even at pH 10.

Summarizing, we have synthesized well-defined NIPA-based polymers in aqueous solutions above the LCST of pristine PNIPA through the RAFT polymerization. The main advantage of this approach is the suppression of the chain transfer to polymer, which leads to uncontrolled polymer cross-linking. The synthesized polymers exhibit typical stimuli-responsive properties in aqueous solutions.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7545.

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