Macromolecules **2007,** *40,* 7069−7071

Temperature-Induced Phase Transition of Well-Defined Cyclic Poly(*N*-isopropylacrylamide)s in Aqueous Solution

Xing-Ping Qiu,[†] Fumihiko Tanaka,[‡] and
Françoise M. Winnik*[,†]

Department of Chemistry and Faculty of Pharmacy,
University of Montreal, CP6128 Succursale Centre Ville,
Montreal, QC, Canada H3C 3J7, and Department of
Polymer Chemistry, Graduate School of Engineering, Kyoto
University, Katsura, Kyoto 615-8510, Japan

Received June 19, 2007
Revised Manuscript Received August 15, 2007

The thermosensitivity of aqueous polymer solutions is the driving force at work in various soft "intelligent" devices used in biotechnology and nanotechnology.[1] Poly(*N*-isopropylacrylamide) (PNIPAM) is considered by many as the prototype of such "smart" polymers. It is highly soluble in cold water, but it becomes insoluble as its solution temperature exceeds 32 °C, the lower critical solution temperature (LCST) or cloud point (T_{CP}).[2] It is generally accepted that this phase transition is governed by the cooperative dehydration of PNIPAM chains and concomitant collapse of individual chains from hydrated coils into hydrophobic globules, which associate to form larger mesoglobules.[3] The conformational change of PNIPAM in water has motivated many fundamental investigations aimed at understanding the physics of the coil-to-globule transition. In parallel, a long line of studies has been devoted to cyclic polymers and the impact of topology on polymer properties in solution and in the bulk.[4] Recent advances in the synthesis of cyclic polymers with narrow molecular weight distribution have stimulated theoretical studies to predict the difference in the behavior of cyclic chains and their linear counterparts, for polymers such as poly(styrene), poly(butadiene), poly(ethylene), poly(tetrahydrofuran), and poly(ethylene oxide).[5] The importance of PNIPAM in terms of practical applications and as a model in polymer physics prompted us to prepare cyclic PNIPAM and assess the impact of the topology on the phase transition of PNIPAM aqueous solutions.

We synthesized cyclic PNIPAMs by ring closure of α,ω-heterodifunctional telechelic PNIPAM precursors, following the strategy reported recently for the synthesis of cyclic poly(styrene)s[6] based on the copper(I)-catalyzed 1,3-dipolar azide to alkyne cycloaddition or "click chemistry."[7] In order to obtain telechelic PNIPAMs suitable for "click" ligation, an azide and a propargyl group were introduced on the α- and ω-ends of each PNIPAM chain. This was accomplished in three steps (Scheme 1). First, telechelic PNIPAMs were synthesized by reversible addition−fragmentation chain transfer (RAFT) polymerization of *N*-isopropylacrylamide (NIPAM) using an azide containing trithiocarbonate, 2-(2-azidoethoxy)ethyl 2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methyl propionate) (AIP) as chain transfer agent. A low initiator/AIP (1:10) ratio was selected in order to ensure high terminal functionality and narrow molecular weight distribution. The precursor polymers (p-PNIPAM) carry an azidoethoxyethyl group on one end and an isobutylsulfanylthiocarbonylsulfanyl group on the other. The latter was converted to a propargyl group in a one-pot aminolysis/Michael addition sequence,[8] carried out in THF, using *n*-butylamine as aminolysis agent and propargyl acrylate as Michael addition agent, yielding the desired α-azido ω-propargyl telechelic linear precursors (l-PNIPAMs). The structure of the l-PNIPAM samples was confirmed by analysis of their ^{1}H NMR spectra (Figure 1, bottom), which present signals at 3.41 ppm due to the resonance of the methylene protons 3, α to the azido group and at 4.72 and 2.81 ppm due to the protons 2 and 7 of the propargyl end group, in addition to the signals characteristic of the NIPAM units ($\delta \sim$ 1.0−2.5 ppm). The high end group functionality of the polymers

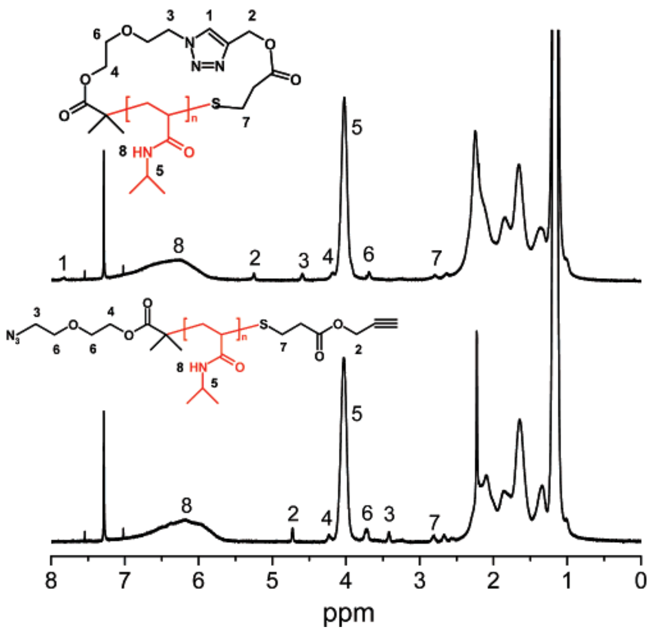

Figure 1. ^{1}H NMR spectra of l-PNIPAM-12K (bottom) and c-PNIPAM-12K (top) in CDCl$_3$.

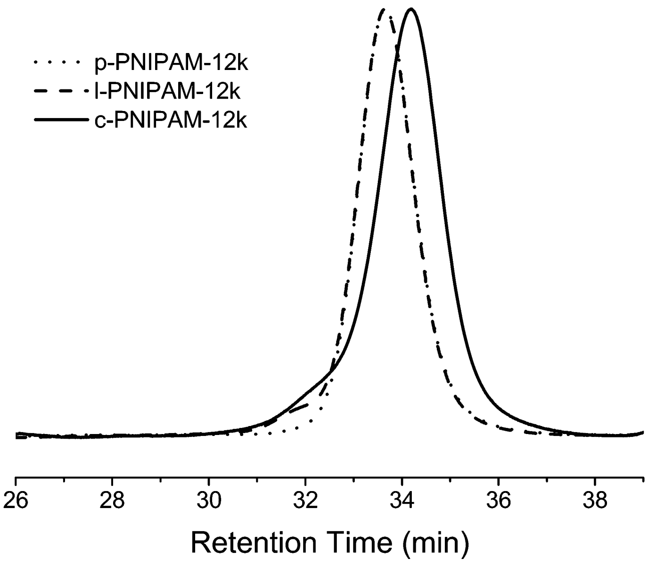

Figure 2. Gel permeation chromatograms of the samples p-PNIPAM-12K, l-PNIPAM-12K, and c-PNIPAM-12K (eluent = DMF, 40 °C, refractive index detection).

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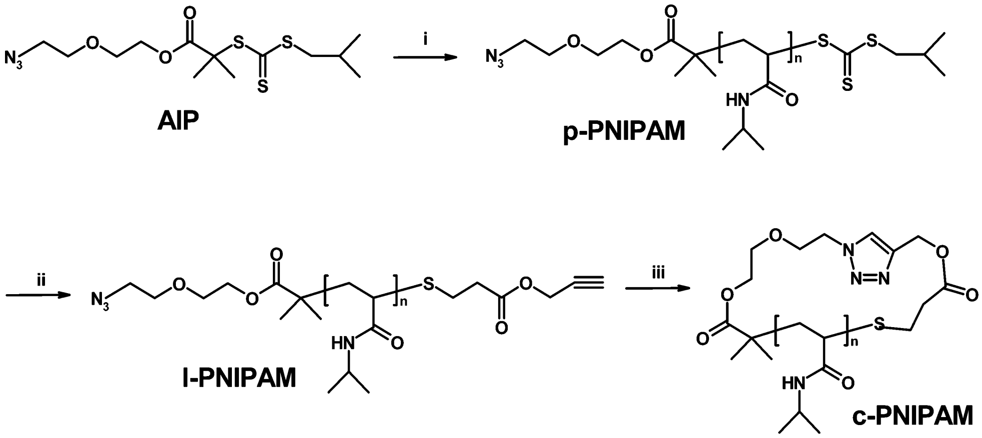
* Corresponding author. E-mail: francoise.winnik@umontreal.ca

[†] Department of Chemistry and Faculty of Pharmacy, University of Montreal.

[‡] Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University.

10.1021/ma071359b CCC: $37.00

Scheme 1. Synthesis of Cyclic PNIPAM[a]



[a] Key: (i) NIPAM, AIBN, dioxane; (ii) propargyl acrylate, *n*-butylamine, THF; (iii) $CuSO_4$, sodium ascorbate, H_2O.

Table 1. Gel Permeation Chromatography Data, Phase Transition Temperatures and Enthalpies for Linear and Cyclic PNIPAM Samples

sample	M_n[a] (kDa)	M_w/M_n[a]	T_M[c] (°C)	ΔH[c] (kJ/mol)	T_{CP}[d] (°C)
l-PNIPAM-6K	6.8	1.10 (55)[b]	40.3	6.06	37.0
c-PNIPAM-6*K*	6.9	1.11	45.8	3.86	40.4
l-PNIPAM-12K	12.7	1.08 (110)[b]	36.6	6.40	34.8
c-PNIPAM-12K	12.7	1.11	41.6	4.47	38.1
l-PNPAM-19K	19.2	1.09 (165)[b]	35.6	6.40	34.1
c-PNIPAM-19K	19.4	1.16	39.6	5.38	36.3

[a] From GPC analysis (eluent: DMF). [b] Degree of polymerization. [c] Temperature of maximum of the endotherm from microcalorimetric analysis (heating rate 1.0 °C/min; concentration 1.0 g/L). [d] Cloud point temperature from turbidity measurements (heating rate 0.2 °C/min; concentration 1.0 g/L; transition midpoint)

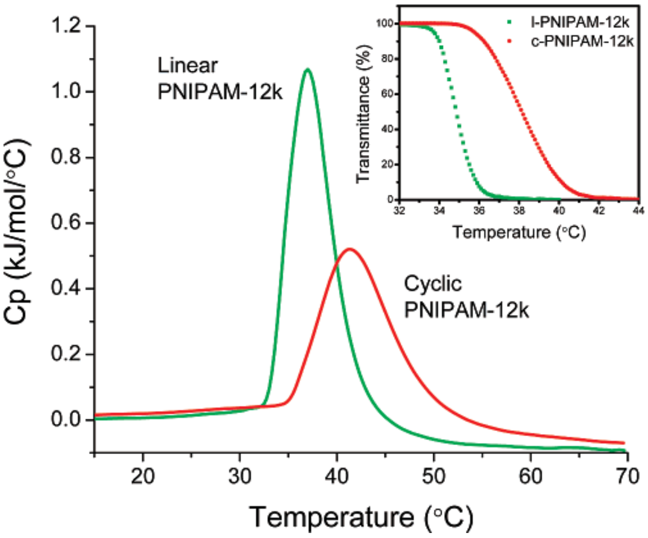


Figure 3. Temperature dependence of the specific heat capacity (Cp) and transmittance (inset) of l-PNIPAM-12K and c-PNIPAM-12K in water (1.0 g/L) upon heating rates of 1.0 and 0.2 °C/min, respectively.

was ascertained from the area integrations of the relevant signals in the spectra.

The l-PNIPAM samples underwent cyclization upon treatment with Cu(I) in water at 30 °C under highly dilute conditions. In the ^{1}H NMR spectrum of the cyclization product (c-PNIPAM) (Figure 1, top), the resonances of the methylene protons 2 and 3 appear at 5.25 and 4.60 ppm, respectively. A signal at 7.85 ppm, attributed to the resonance of the proton 1 of the triazole ring, is direct evidence that the ligation reaction has occurred.[9] The FTIR spectrum of l-PNIPAM (Supporting Information) displays a band at 2113 cm^{-1} attributed to the azide stretching. This band was not detected in the spectrum of the cyclized polymer, bringing further support to the success of the transformation.

The entire synthetic sequence was carried out with p-PNIPAM samples of M_n as high as 19 000 g/mol (Table 1), as determined by gel permeation chromatography with multiangle laser light scattering detector (GPC-MALLS). GPC traces of the linear polymers p-PNIPAM-12K and l-PNIPAM-12K (Figure 2) almost overlap,[10] while the trace corresponding to the cyclic polymer (c-PNIPAM-12K) is shifted to longer retention time, compared to the trace of the linear precursors. The *g* factor, the ratio of the apparent peak molar mass (M_p) of the cyclic PNIPAMs with respect to their linear precursors derived from the GPC curves is 0.82−0.84, a value comparable to those reported for cyclic poly(styrene)s and cyclic poly(tetrahydrofuran)s.[4,11] The *g* factor reflects the difference in the solution dimension of cyclic and linear polymer chains of identical polymerization degree.

Aqueous solutions of c-PNIPAM and their linear precursors were analyzed by high sensitivity differential scanning microcalorimetry (HS−DSC) and turbidimetry. Results obtained in the case of the samples of M_n ~12 kDa are presented in Figure 3, and key parameters for all samples are listed in Table 1. For cyclic/linear pairs of identical molecular weight, we observed the following: (i) the endotherm is broader for solutions of c-PNIPAM; (ii) the maximum of the endotherm (T_M) of c-PNIPAM solutions is shifted to higher temperature by ~ 5 °C; (iii) the enthalpy of the transition per NIPAM unit (ΔH) is smaller for c-PNIPAM, and the value decreases with decreasing ring size, whereas in the case of l-PNIPAMs, ΔH is independent of chain length;[12] (iv) the transmittance of c-PNIPAM solutions decreases gradually upon heating, whereas solutions of l-PNIPAM undergo a sharp decrease in transmittance.

The ring topology is expected to affect the phase separation of PNIPAM solutions as a consequence of (i) the existence of repulsive forces between rings due to the topological prohibition of intermolecular linking,[13] an effect that will trigger an upward shift of the cloud point temperature; (ii) the absence of end groups believed to affect the heat-induced dehydration and coil-to-globule collapse of low molecular weight PNIPAM; and (iii) steric constraints, which will favor the formation of intrachain hydrogen bonds between NIPAM units at the expense of water/NIPAM hydrogen bonds. The latter effect becomes more important as the ring size decreases. It may be reflected by the observed decrease in the transition enthalpy with decreasing ring size. For the three samples tested so far, the phase transition of aqueous c-PNIPAM solutions takes place over a much wider temperature range, compared to their linear counterpart, implying partial inhibition of the cooperativity of the transition effective in the linear chain. Connecting the end groups of a linear chain hinders the packing of chain segments upon coil-to-globule collapse. In addition, the phase transition of c-PNIPAMs may also be affected by the chemical composition and stereochemistry of the moiety linking the two end groups, especially as the ring size decreases. Efforts are in progress to evaluate the role of the connector. Other current work is aimed at assessing the implications of the ring topology on other characteristics of linear PNIPAM, such as the stability of PNIPAM mesoglobules formed in water at elevated temperature.

Acknowledgment. The work was supported by a grant of the Natural Sciences and Engineering Council of Canada. The authors thank Dr. V. Darras for recording GPC chromatograms. They also acknowledge useful insights provided by the reviewers.

Supporting Information Available: Text giving experimental procedures for the synthesis and characterization of the polymers, a table of charaterization data, and figures showing NMR, FT-IR, and UV/vis spectra, GPC data plots, and additional thermograms and turbidity curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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MA071359B