Synthesis of High Transition Temperature Hyperbranched poly(N-Isopropyl Acrylamide)

Kai Chang, Lakeshia J. Taite.
Georgia Institute of Technology, School of Chemical and Biomolecular Engineering

Statement of Purpose: Targeted drug delivery has long been a goal of the medical and drug development community. The ability to target certain organs or tissues in the body to the exclusion of others is an important step in the advancement of medical science. Highly branched molecules with large numbers of functionalizable end groups are currently being used for this purpose. We aim to synthesize hyperbranched poly(n-isopropyl acrylamide) (pNIPAAm) with high thermal transition properties in order to eventually make a hybrid drug delivery vehicle that provides targeted and controlled release of drugs based on external stimuli. Much has been published regarding the thermal transition properties of pNIPAAm; however the optimization of these properties for hyperbranched pNIPAAm has not been very well explored. The lower critical solution temperature (LCST) must be increased from its natural state at 32^0C to be at least 45^0C in order to be useful as a control mechanism in targeted drug delivery.

Hyperbranched pNIPAAm synthesis has been reported previously by Vogt et. al and Carter et. al.; however, to our knowledge, the manipulation of the LCST to higher temperatures has yet to be presented. In previous studies, Reversible Addition-Fragmentation Chain Transfer (RAFT) polymerization, a well established method for controlled "living" radical polymerization was used with hyperbranch inducing chain transfer agents (CTAs) in order to create these hyperbranched polymers.

The aim of this paper is to investigate the use of copolymerization with acrylic acid (AAc) and the targeting of uniform tacticity in tuning the LCST of hyperbranched pNIPAAm.

Methods: Three different CTAs were made and polymerization was conducted under three different conditions. S,S'bis(α,α'-dimethyl-α''-acetic acid)trithiocarbonate (CTA**1**) was synthesized according to the procedure set forth by Lai et al. Synthesis of 1-[3-(2-Methyl-2-dodecylsulfanylthiocarboxylsulfanyl-propionyloxy) propyl]-1H-[1,2,3]triazol-4-ylmethyl Acrylate (CTA**2**) was done according to the process set forth by Vogt et. al. Synthesis of 4-Vinylbenzyl-imidazole Dithioate (CTA**3**) was done according to the procedure set forth by Carter et al.

Polymerization was carried out with the three CTAs of interest. An example of the process was as follows: A 100:10:2:1 ratio of NIPAAm:AAc:CTA**1**: Azobisisobutyronitrile was placed in a sealed 100 mL roundbottom flask equipped with a magnetic stir bar. The mixture was purged with Nitrogen and Nitrogen purged Dioxane was added. The solution was reacted at 55^oC for 72 hours and was quenched by exposure to air. The p(NIPAAm-co-AAc) was precipitated into ether and dried under vacuum.

Results: Synthesis of CTA**1**, CTA**2**, and CTA**3**, were confirmed using proton NMR spectroscopy and mass spectroscopy. The results are shown in Fig.1

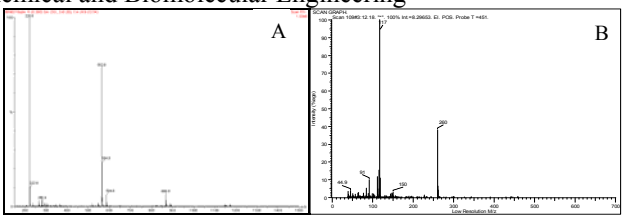

Fig.1: A) Electrospray Mass Spectrum of CTA1. B) Electron Impact Mass Spectrum of CTA2

NMR spectroscopy and gel permeation chromatography was conducted on the polymers to calculate the degree of polymerization and the polydispersity. Fig. 2 shows the proton NMR spectrum of pNIPAAm polymerized with CTA**1** as well as a GPC chromatograph of the same polymer. As seen in Fig.2, the NMR chromatograph shows a degree of polymerization (dp) of 34.7. GPC data of subsequent polymerization experiments show polydispersity as low as 1.04 (Fig.2B)

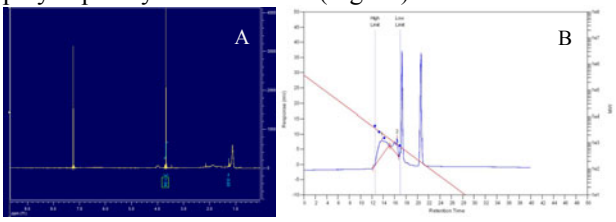

Fig.2: A) NMR of pNIPAAm polymerized with CTA**1**. B) GPC curve of pNIPAAm polymerized with CTA**1**

The LCST of pNIPAAm was measured via UV-Visual Spectrometry. Results of analysis of pNIPAAm polymerized with CTA**1** are shown in Fig.3.

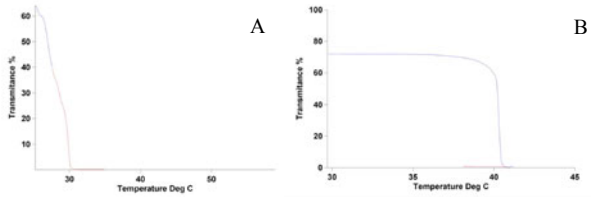

Fig.3: A) LCST of pNIPAAm at pH of 7.0. B) LCST of pNIPAAm at pH of 8.5

Visual LCST measurements were also taken for p(NIPAAm-co-AAc) and syndiotactic p(NIPAAm-co-AAc). At pH 11, syndiotactic p(NIPAAm-co-AAc) showed a LCST of 61^0C while at pH 11.5 atactic p(NIPAAm-co-AAc) showed a LCST of 75^0C.

Conclusions: We have shown the ability to synthesize pNIPAAm polymers, copolymers, and hyperbranched copolymers in a controlled manner with low polydispersity. We were also able to demonstrate the ability to control the LCST of pNIPAAm and raise to LCST to values above 40^0 C with sharp transitions. Further studies will be done to characterize the drug loading and delivery properties of these macromolecules.

References:

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