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Thermal Control over the Topology of Cleavable Polymers: From Linear to Hyperbranched Structures

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Since polymer topology has significant influence on polymer properties, discovering novel and facile methods to prepare polymers with different topologies has been the focus for polymer chemists.[1,2] Hyperbranched polymers have distinct properties from their linear analogues which leads to numerous applications in controlled drug release, delivery of gene and drug, etc.[1] Easily cleavable hyperbranched polymers are very intriguing, however, they are seldom reported.[1d] On the other hand, most of the hyperbranched polymers reported were prepared from specially designed monomers. Therefore, to prepare polymers with cleavable backbone and tunable topologies from linear to hyperbranched even to dendritic structures simply by tuning polymerization conditions would be highly desirable.

It is well-known that the polymerization behaviors are strongly affected by polymerization conditions.[3] Recently, Guan et al. discovered that polymer architecture can be successfully tuned from linear to hyperbranched to "dendritic" by controlling the relative rates of chain propagation and chain walking or chain transfer.[2a,4] Instead of designing specially structured monomers for preparing polymers with different topologies, we were hoping to find an easy method to tune polymer topology simply via varying polymerization conditions. Michael-addition polymerization is one of the most used methods to prepare linear and hyperbranched polymers,[1b,5a,b] and Szoka et al. reported the synthesis of polyamidoamine dendrimers via Michael-addition reaction.[5c] Here, we reported the synthesis of cleavable polymers which contain many stimuli-sensitive linkages (disulfide bonds) in the backbone via Michael-addition polymerization, moreover, the structures of the produced polymers can be tuned from linear to hyperbranched simply by varying the polymerization temperature.

The Michael-addition polymerization of disulfide-based diacrylate and equimolar *N*-methyl ethylenediamine (MEDA) was performed at 40 °C. Poly(amino ester) was obtained with M_n of 29000 and PDI of 1.9. Similar to the polymerization of 1,4-butanediol diacrylate and equimolar MEDA at 40 °C,[5a] the peaks of carbon a, b, c, d, e, f, g, and h of linear poly(amino ester) at ca. 56.9, 52.9, 47.0, 45.2, 42.2, 37.4, 34.9, and 32.5 ppm were clearly observed in its ^{13}C NMR spectrum (Figure 1A).[5a,6] There was almost no peak resulted from the 2° amines (formed) taking part in the polymerization, indicating that the 2° amines (formed) were almost inactive and did not take part in the polymerization at 40 °C, owing to the high steric hindrance of polymer backbone on the 2° amines (formed).[5a] The polymerization behaviors below 40 °C (such as at 25 °C) are similar to that at 40 °C: 2° amines (formed) did not get involved in the polymerization and linear polymers were obtained. Therefore, Michael-addition polymerization of disulfide-based diacrylate and equimolar MEDA at a temperature ≤ 40 °C afforded linear poly(amino ester)s containing disulfide bonds (as shown Scheme 1A) in the backbone via AB-type intermediates (B′ did not take part in the reaction).

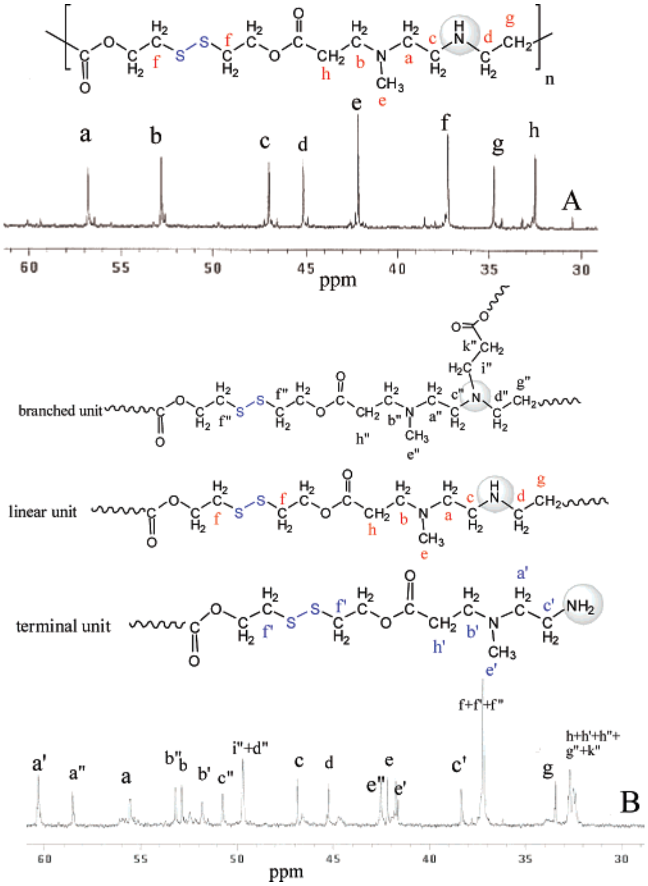

Figure 1. ^{13}C NMR spectra of poly(amido ester) obtained at 40 °C (A) and 65 °C (B)

We found that the relative reactivity of 2° amines (formed) can be easily changed by elevating the temperature. The 2° amines (formed) became reactive and involved in the polymerization (with an equimolar ratio of monomers) when the polymerization was performed at relatively high-temperature (e.g., above 48 °C). The 2° amines (formed) participating in polymerization resulted in poly(amino ester) with branched structure based on the change of chemical shifts for the carbons adjacent to 2° amines (formed) as shown in Figure 1B. Besides the peaks of carbon a, b, c, d, e, f, g, h from linear units in poly(amino ester), the peaks of carbon such as a′, b′, c′, e′, f′ corresponding to terminal units and the peaks of carbon a″, b″, c″, d″, e″, g″, h″, i″ and k″ corresponding to the

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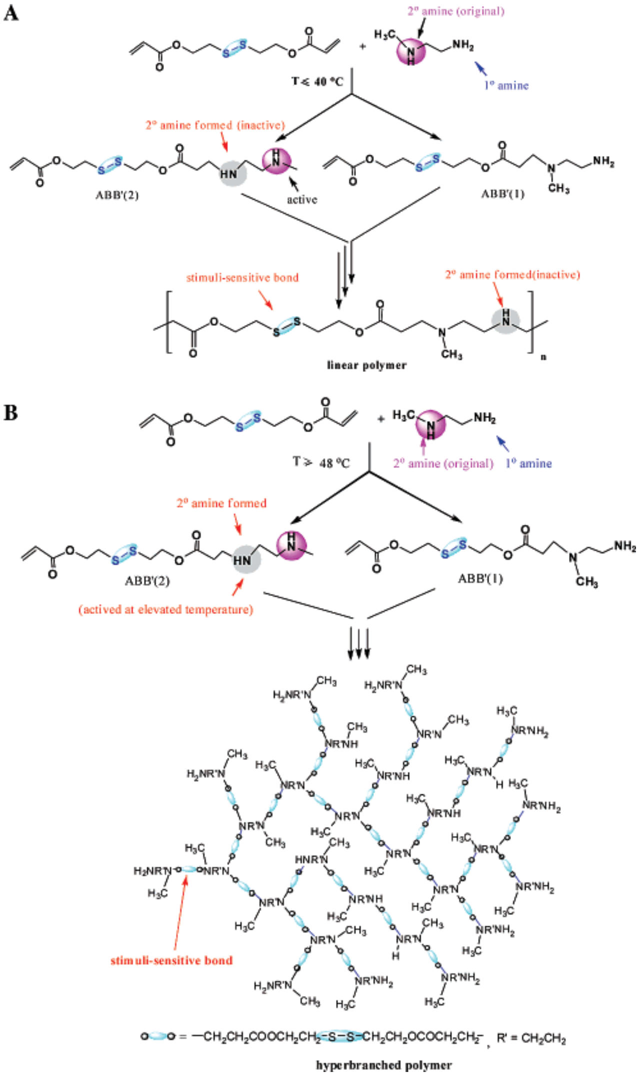
Scheme 1



branched units also appeared in Figure 1B. All these facts indicated that elevated temperature activated the 2° amines (formed) and they participated in polymerization, producing polymer with branched structure.[6] Branched poly(amino ester)s were obtained at 48, 55, 60, and 65 °C with M_n of 21000, 40400, 32000, and 65500 and PDI of 2.1, 1.4, 2.2, 2.0, respectively. The degree of branching (DB) calculated on the basis of ^{13}C NMR using the definition by Hawker and Fréchet are 0.21, 0.38, 0.52, and 0.69 for the poly(amino ester)s obtained at 48, 55, 60, and 65 °C, respectively, which clearly shows that DB of the polymers obtained increased with the increase of the temperature. All these findings demonstrate that polymerization temperature can tune the topology of prepared poly(amino ester)s from linear to hyperbranched structures.

Synthesis of polymer with stimuli-cleavable backbone is one of the most active research areas for polymer chemists.[8] Disulfide/thiol chemistry is well-known to protein chemists and is becoming increasingly popular in conventional polymer syntheses because the disulfide bond is very sensitive to biological stimuli (such as glutathione) and chemical stimuli (such as dithiothreitol (DTT) and tributylphosphine) at room temperature.[9] The as-synthesized linear and hyperbranched poly(amido ester)s contain so many disulfide bridges in the backbone that they can be easily cleaved into small molecules in the presence of stimuli. The linear and hyperbranched poly(amido ester)s were stirred in DMF solution in the presence of DTT for 2 days at room temperature, and it is obvious that the whole SEC curves for linear and hyperbranched poly(amido ester)s after treated with DTT shifted to the position corresponding to small organic molecules (see Supporting Information), indicating that the linear and hyperbranched poly(amido ester)s have been completely cleaved into small organic molecules. The conditions of the cleaving reaction are very mild without requirements of catalyst and elevated temperature.

In conclusion, Michael-addition polymerization of disulfide-based diacrylate and equimolar MEDA forms ABB′ type intermediates first; 2° amines (formed) were inactive below 40 °C, resulting in the formation of linear poly(amino ester) via AB-type intermediates (B′ did not participate in the reaction). However, elevated temperature activated 2° amines (formed), and they took part in the reaction, resulting in the formation of hyperbranched poly(amino ester)s via ABB′-type intermediates (both B and B′ participated in the reaction). DB of the hyperbranched polymers obtained increased with the increase of temperature. Therefore, polymer topology from linear to hyperbranched can be tuned simply by varying the polymerization temperature. These poly(amino ester)s have stimuli-sensitive disulfide bonds in the backbone which can be cleaved under DTT, affording these poly(amino ester)s with potential applications in the delivery of drug and gene, nanomedicine, and preparation of environment-friendly materials.

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Supporting Information Available: The detailed experimental procedures, ^{1}H NMR spectra and ^{13}C NMR spectra of samples, SEC curves of polymers before and after degradation. This material is available free of charge via the Internet at http://pubs.acs.org.

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