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Single Step Synthesis of Peripherally "Clickable" Hyperbranched Polyethers

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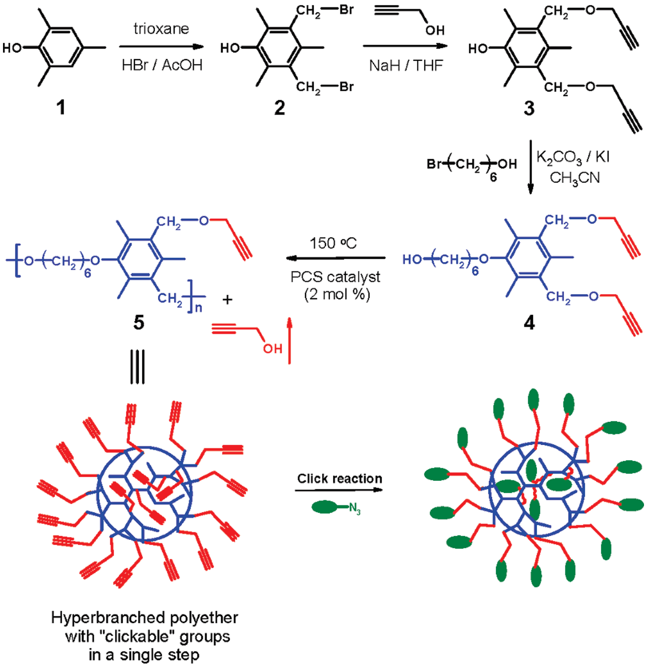
Dendrimers and hyperbranched polymers have attracted a great deal of attention because of their unique molecular topology and the consequent interesting physical properties.[1] While the battle for application potential between these two classes of polymers is still very much alive, it is evident that each of them have begun to carve out their own distinct specialties and unique domains for possible applications. One of the very attractive features of both these classes of polymers is the very large number of readily accessible peripheral functionalities. Modifying these has enabled researchers to modulate several of their properties[2] and also access interesting core−shell-type structures that can exhibit unimolecular micellar behavior.[3] Most of the application-driven derivatization of the terminal groups is generally carried out in a postpolymerization step, which unfortunately is seldom complete.[4] Furthermore, the derivatization step often requires harsh conditions that could lead to degradation of the polymer skeleton. In recent times, the "*click reaction*",[5] which is a Cu(I)-catalyzed Huisgen-type 1,3-dipolar cycloaddition, has become a very popular approach to perform quantitative ligation of various functional units onto different types of polymeric architectures.[6]

Dendrimers carrying propargyl groups at the periphery were recently prepared by Malkoch et al.,[7] and the authors demonstrated the richness of the click approach by transforming them into a wide range of peripherally derivatized dendritic structures. Although dendrimers are monodisperse and structurally perfect macromolecules, they require tedious stepwise synthesis, each step requiring purification. On the other hand, even though hyperbranched polymers bear a large number of structural defects, many of the more salient properties of dendrimers, such as adoption of compact conformations and the presence of a large number of readily accessible peripheral functional groups, are exhibited by these highly branched polymers as well. Hence, there is ample motivation to develop strategies to directly prepare hyperbranched polymers bearing clickable peripheral groups. In one of the first attempts to directly prepare hyperbranched polymers bearing propargyl groups, Scheel et al.[8] used the click reaction itself as the polymer-forming reaction. An alternate approach using an $A_2 + B_3$ strategy, based on diazide and tris-ethynyl monomers, respectively, also yielded hyperbranched polytriazoles with potentially functionalizable end-groups.[9] Both these strategies use click reaction directly as the polymer-forming process and hence suffers from some drawbacks, most important of which is scalability and commercial viability. More recently, propargyl groups have also been placed on hyperbranched polyglycerols in a postpolymerization step to generate peripherally clickable hyperbranched structures.[10] We too have recently developed an $AB_2 + A{-}R$ type copolymerization approach to generate hyperbranched polymers that carry peripheral propargyl groups; however, the maximum level of functionalization was only about 60 mol %.[11] Despite the availability of several such approaches, it would be very useful to develop a *simple polymerization process starting from a single monomer* that would directly generate hyperbranched polymers bearing "clickable" functionalities at their molecular periphery.

Scheme 1. Synthesis of the Monomer and the Hyperbranched Polymer



Bearing this in mind, we have developed an interesting strategy to prepare peripherally "clickable" hyperbranched polyethers in *a single step* using a suitable AB_2 type monomer (**4**) that carries two propargylbenzyl ether groups and one hydroxyl group. A melt-transetherification process, catalyzed by an acid, transformed this AB_2 monomer into a hyperbranched polymer (**5**) bearing a large number of peripheral propargyl groups, as depicted in Scheme 1. The melt-transetherification approach for the preparation of polyethers was developed in our laboratory several years ago, and it generally proceeds by driving the equilibrium toward polymer formation by the continuous removal of a low boiling alcohol, typically methanol.[12] Since the melt-transetherification process is carried out at temperatures above 150 °C, we reasoned that other benzylalkyl ether linkages, such as benzylpropargyl ether, could also condense to generate hyperbranched polymers, the condensate propargyl alcohol being adequately volatile under the polymerization conditions. Because of relatively easy access to the peripheral functional groups in such hyperbranched structures, these propargyl group bearing structures could serve as nanodimensional scaffolds (*hyperscaffolds*) for quantitative ligation of a wide range of useful functionalities onto its molecular periphery.

The AB_2 monomer **4** was readily synthesized from mesitol following the procedure depicted in Scheme 1. Bromomethylation of mesitol followed by coupling with propargyl alcohol in the presence of NaH yielded **3** in reasonable overall yields. **3** serves as an excellent intermediate that permits the inclusion of a variety of spacer segments by straightforward coupling with

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suitable ω-bromoalcohols. For this study, we have coupled **3** with 6-bromohexanol to yield the monomer **4**, which carries a C6 spacer. This monomer was polymerized under the optimized melt-transetherification conditions using pyridinium camphorsulfonate (PCS) as the catalyst; first for 3 h under nitrogen purge and then for another 3 h under reduced pressure.[12c] The condensate, propargyl alcohol, was seen to evolve during the polymerization as evident from the continuous formation of bubbles from the melt, especially under reduced pressure. The melt gradually became viscous and finally developed a thick honeylike consistency, which solidified upon cooling to room temperature. The polymer was found to be readily soluble in a variety of organic solvents, and its M_n was estimated by GPC to be around 6800 with a PDI of 2.8, which is typical for hyperbranched polymers. Comparison of the polymerization kinetics of this new propargylated monomer **4** with the previously studied bismethoxymethyl monomer[12d] suggested that polymerization of the former is slightly slower. However, neither the yield nor the molecular weight of the final polymer was affected significantly.[13]

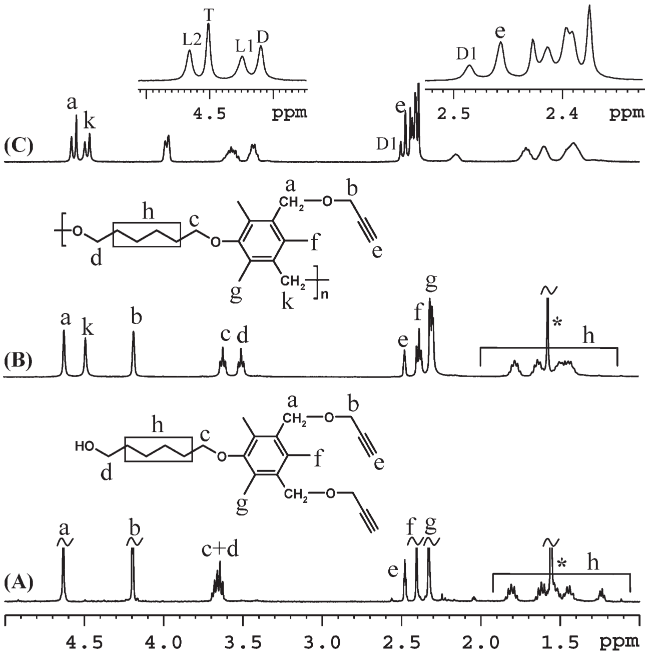
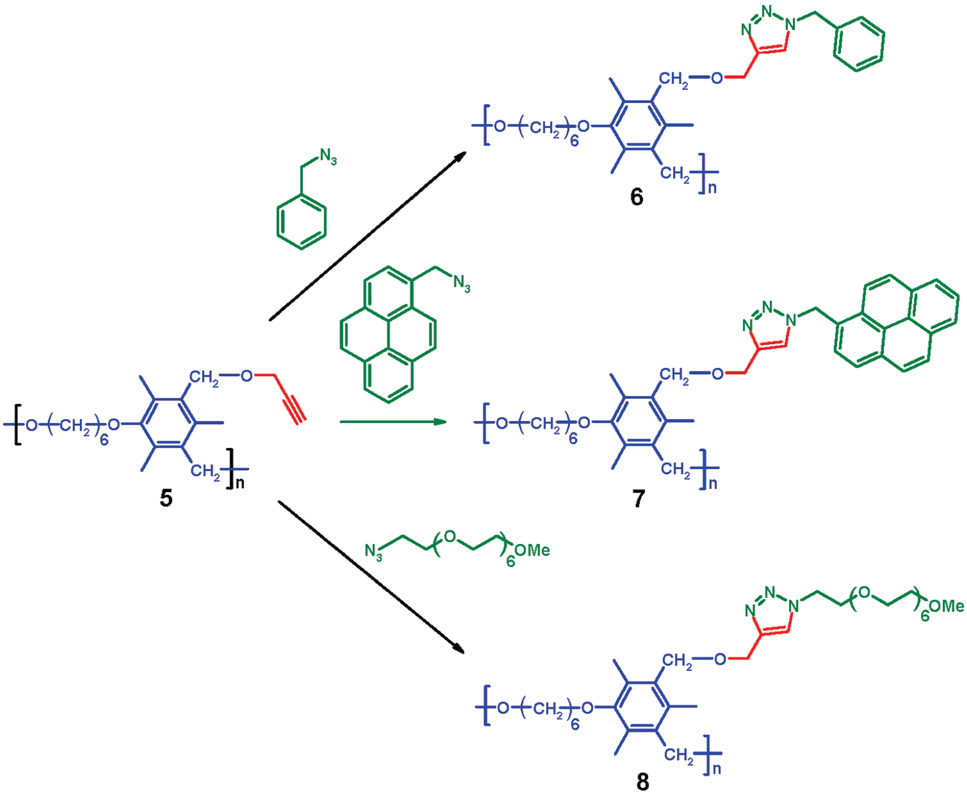


Figure 1. ^{1}H NMR spectra of monomer **4** in $CDCl_3$ (A), polymer **5** in $CDCl_3$ (B), and polymer **5** in a mixture of $CDCl_3$ and C_6D_6 (1:3.75) (C). The peaks marked by asterisks are due to water in the solvent.

The proton NMR spectra of the monomer **4** and the hyperbranched polymer **5** are shown in Figure 1 along with their peak assignments. The spectra of the monomer and the polymer differ in several features: (i) the relative intensities of the peaks belonging to the propargyl group (**b**, **e**) go down reflecting the loss of the propargyl alcohol as a condensate; (ii) the peak due to the benzylic protons, which is a singlet in the monomer, splits into two peaks of nearly equal intensity (**a**, **k**) in the polymer reflecting two different environments—one belonging to the backbone while other to the end-group; (iii) the peaks **c** and **d** due to the methylene protons in the C6 spacer become well-separated in the polymer; and (iv) the peaks due to the methyl protons linked to the aromatic core (**f**, **g**) exhibit multiplicity reflective of the various types of units, namely dendritic (D), linear (L), and terminal (T) units, which are present in such hyperbranched structures. It was shown earlier by us that recording the spectrum in an aromatic solvent, like benzene, results in a dramatic enhancement in the spectral peak separation, and this in turn permitted the direct determination of the degree of branching (DB) without the need for a model compound.[14] We also showed that solvent mixtures containing varying amounts of C_6D_6 also results in a similar enhancement.[15] Thus, recording the spectrum of the polymer in a $CDCl_3/C_6D_6$ mixture yielded a spectrum (Figure 1C), wherein peaks due to each of the two types of benzylic protons (**a**, **k**) are further split into two peaks. On the

Scheme 2. Clicking Functional Units onto the Periphery of Hyperbranched Polyethers



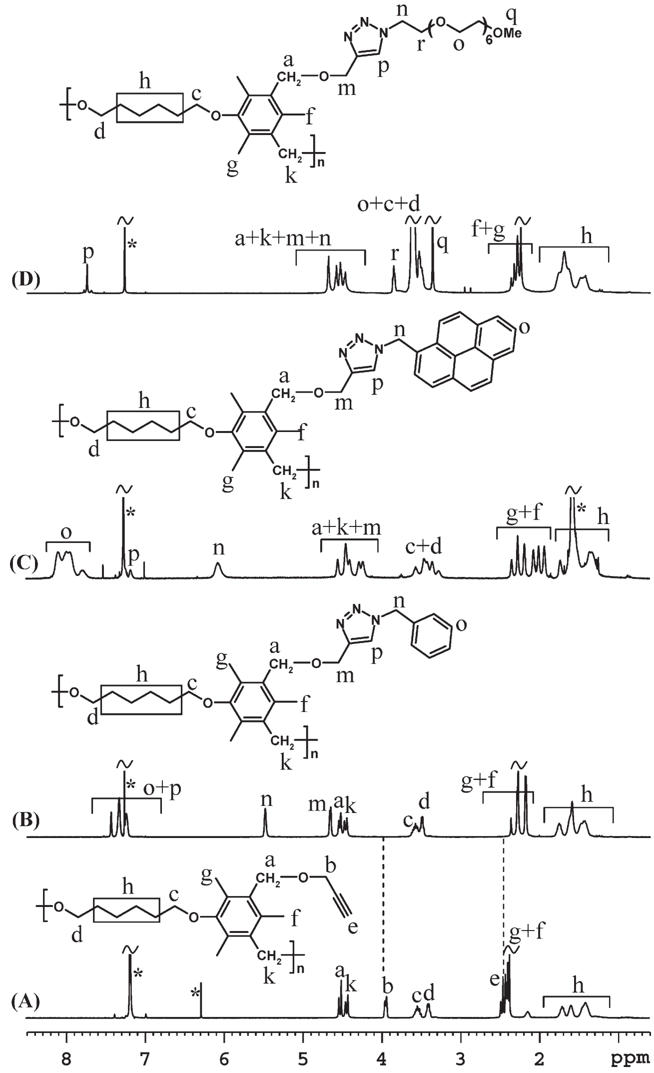


Figure 2. ^{1}H NMR spectra of polymer **5** in a mixture of $CDCl_3$ and C_6D_6 (1:3.75) (A), polymer **6** in $CDCl_3$ (B), polymer **7** in $CDCl_3$ (C), and polymer **8** in $CDCl_3$ (D). The peaks marked by asterisks are due to residual protic solvent or water.

basis of our earlier studies, these peaks can be assigned (as depicted in the figure) to the benzylic protons belonging to the different types of units, namely D, T, and L units.[16] From the relative intensities of these peaks the DB was estimated to be around 0.55, which is roughly in accordance with the statistically expected value of 0.5.[17] This structural assignment confirms two important points: one is that the propargyl group is unaffected under the rather drastic melt-transetherification conditions, and second is that the transetherification process works just as well for benzylpropargyl ethers as for benzylmethyl ethers to yield hyperbranched polymers of moderately high molecular weights. Two other attempts yielded polymers with M_n values of 8200 and 9800, respectively.[18] Obtaining even higher molecular weights appears to be difficult probably due to impeded diffusion under melt-polymerization conditions.

The hyperbranched polyether bearing numerous propargyl groups on its molecular periphery serves as an excellent scaffold for linking various functional units. In Scheme 2, the reaction of the hyperbranched polymer with three different azides is depicted. First, in order to test for the efficacy of the clicking process onto the hyperbranched polymer, a control experiment was done using benzyl azide. Comparison of the NMR spectra of the polymer before and after the click reaction (Figure 2) clearly demonstrated that the reaction is nearly quantitative. In the spectrum of the clicked polymer (Figure 2B), peaks due to the propargyl group (**b**, **e**) are absent, and new peaks corresponding to the product are evident. From the relative intensities of the peaks belonging to the "clicked" units (**m**, **n**, **o**, **p**), it was established that the reaction has proceeded almost quantitatively.

Similarly, the click reaction was performed with two other organic azides, namely 1-azidomethylpyrene and a PEG-azide (heptaethylene glycol monomethyl ether, monoazide). The former yielded a polymer **7** with a large number of fluorophores at the periphery, while the latter yielded a fully PEGylated hyperbranched polymer **8** that exhibited a core–shell behavior when dissolved in water. Here again, the NMR spectra provided clear evidence for the almost quantitative ligation of the azides on to the hyperbranched scaffold; in both cases a complete disappearance of the propargyl group peaks and the appearance of peaks due to the clicked unit, having the expected relative intensity, are seen. The molecular weights of the polymers after clicking increased a little, while the glass transition temperatures varied substantially depending on the nature of the end-group.[19] The polymer **7** carrying a large number of pyrene units did not readily redissolve in most organic solvents although it swells considerably, permitting the observation of an almost solution-like NMR spectrum (Figure 2C). The insolubility of the pyrene-containing hyperbranched polymer may be due to the strong intermolecular $\pi-\pi$ interactions between the peripheral pyrene units leading to physical cross-linking.[20]

In conclusion, we have shown that the melt-transetherification process, using a suitably designed AB_2 monomer, permits the generation of a hyperbranched polyether carrying a large number of peripheral propargyl groups *in a single step*. This is the first example wherein the direct synthesis of a hyperbranched polymer carrying clickable propargyl groups at its molecular periphery has been achieved, without the use of click reaction itself as the polymer forming reaction. Furthermore, the monomer **4** provides ample scope for structural variation by inclusion of spacers of varying lengths, stiffness, and polarity.[21] Importantly, we have shown that the terminal propargyl groups can be reacted with a wide range of organic azides under standard click reaction conditions, in a *nearly quantitative manner,* to create interesting hyperbranched structures that are decorated with various functional units, such as fluorophores, PEG chains, etc. Despite the presence of a large number of linear defect sites, the postpolymerization click reaction appears to functionalize the propargyl groups in a nearly quantitative fashion, at both the terminal units and those at the linear defect sites, suggesting that all the sites are accessible when the polymer is dissolved in a good solvent. The ease of synthesis of such propargylated hyperbranched structures, in conjunction with the mild and quantitative click reaction, makes these systems particularly attractive as *nanodimensional hyperscaffolds* for the placement of a variety of interesting functional units that could have relevance from both the materials and biological viewpoint. Importantly, multiple functions can be readily imparted to such structures by the simultaneous reaction with several different suitably designed organic azides, each of which serves a specific purpose, such as selective binding, detection, and possibly delivery of a drug. Furthermore, this approach of using an AB_2-type monomer that carries two propargyl groups can be readily adapted for the synthesis of polyesters by using the standard transesterification approach, wherein propargyl alcohol is removed as a condensate. Work along these lines is being currently pursued and will be reported shortly.

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Supporting Information Available: Experimental details of synthesis, polymerization kinetics, GPC data, DB calculations, and thermal analysis of polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) For recent reviews on dendrimers and hyperbranched polymers, respectively, see: (a) Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 3713. (b) Gao, C.; Yan, D. *Prog. Polym. Sci.* **2004**, *29*, 183.

(2) For review describing structure−property relationships, see: (a) Kim, Y. H. *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 1685. (b) Gitsov, I.; Lin, C. *Curr. Org. Chem.* **2005**, *9*, 1025.

(3) (a) Moorefield, C. N.; Newkome, G. R. *C. R. Chim.* **2003**, *6*, 715. (b) Stevelmans, S.; van Hest, J. C. M.; Jansen, J. F. G. A.; van Boxtel, D. A. F. J.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *J. Am. Chem. Soc.* **1996**, *118*, 7398. (c) Sunder, A.; Krämer, M.; Hanselmann, R.; Mülhaupt, R.; Frey, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3552. (d) Saha, A.; Ramakrishnan, S. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 80. (e) Gitsov, I. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 5295.

(4) Hummelen, J. C.; van Dongen, J. L. J.; Meijer, E. W. *Chem.—Eur. J.* **1997**, *3*, 1489.

(5) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(6) (a) O'Reilly, R. K.; Joralemon, M. J.; Hawker, C. J.; Wooley, K. L. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5203. (b) Joralemon, M. J.; O'Reilly, R. K.; Matson, J. B.; Nugent, A. K.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **2005**, *38*, 5436. (c) Antoni, P.; Nyström, D.; Hawker, C. J.; Hult, A.; Malkoch, M. *Chem. Commun.* **2007**, 2249. (d) Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.; Kaltgrad, E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.; Hawker, C. J. *Chem. Commun.* **2005**, 5775. (e) Antoni, P.; Nyström, D.; Hawker, C. J.; Hult, A.; Malkoch, M. *Polym. Prepr.* **2007**, *48*, 171. (f) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192. (g) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928. (h) O'Reilly, R. K.; Joralemon, M. J.; Hawker, C. J.; Wooley, K. L. *Chem.—Eur. J.* **2006**, *12*, 6776. (i) O'Reilly, R. K.; Joralemon, M. J.; Wooley, K. L.; Hawker, C. J. *Chem. Mater.* **2005**, *17*, 5976. For recent review on the use of click chemistry in polymer science, see: (j) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2008**, *29*, 952. (k) Lundberg, P.; Hawker, C. J.; Hult, A.; Malkoch, M. *Macromol. Rapid Commun.* **2008**, *29*, 998.

(7) Malkoch, M.; Schleicher, K.; Drockenmuller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V. *Macromolecules* **2005**, *38*, 3663.

(8) Scheel, A. J.; Komber, H.; Voit, B. I. *Macromol. Rapid Commun.* **2004**, *25*, 1175.

(9) (a) Qin, A.; Lam, J. W. Y.; Jim, C. K. W.; Zhang, L.; Yan, J.; Häussler, M.; Liu, J.; Dong, Y.; Liang, D.; Chen, E.; Jia, G.; Tang, B. Z. *Macromolecules* **2008**, *41*, 3808. (b) Xie, J.; Hu, L.; Shi, W.; Deng, X.; Cao, Z.; Shen, Q. *J. Polym. Sci., Part B: Polym. Phys.* **2008**, *46*, 1140. (c) Li, C.; Finn, M. G. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5513.

(10) (a) Papp, I.; Dernedde, J.; Enders, S.; Haag, R. *Chem. Commun.* **2008**, 5851. (b) Sisson, A. L.; Papp, I.; Landfester, K.; Haag, R. *Macromolecules* **2009**, *42*, 556.

(11) Saha, A.; Ramakrishnan, S. *Macromolecules* **2009**, *42*, 4028.

(12) (a) Jayakannan, M.; Ramakrishnan, S. *Macromol. Chem. Phys.* **2000**, *201*, 759. (b) Jayakannan, M.; Ramakrishnan, S. *Chem. Commun.* **2000**, 1967. (c) Behera, G. C.; Ramakrishnan, S. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 102. (d) Behera, G. C.; Ramakrishnan, S. *Macromolecules* **2004**, *37*, 9814.

(13) For a detailed description of the comparative polymerization kinetics, refer to the Supporting Information.

(14) Behera, G. C.; Ramakrishnan, S. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1474.

(15) Saha, A.; Ramakrishnan, S. *Macromolecules* **2008**, *41*, 5658.

(16) For a detailed discussion of the DB calculation, refer to the Supporting Information and ref 14.

(17) Hölter, D.; Burgath, A.; Frey, H. *Acta Polym.* **1997**, *48*, 30.

(18) Two other attempts to prepare the polymer were made, and samples having M_n's of 9800 and 8200 (M_w = 72 300 and 62 000) were obtained, although with the expected broader distribution that typically accompanies higher conversions in such AB_2-type polymerizations. The GPC chromatograms of all the three samples are shown in Figure S7.

(19) The T_g of the parent polymer **5** was 1 °C, while those of the peripherally modified polymers, **6**, **7**, and **8** were 35, 97, and −36 °C, respectively.

(20) In a very recent paper, Gorodetskaya et al. report the preparation of soluble hyperbranched polymers that carry a large number of pyrene units at their termini using a ADMET polymerization followed by metathesis-based ligation. However, the maximum level of derivatization was only 75%, similar to what we had reported using an $AB_2 + A-R$ approach.[15] The difference in solubility characteristics of their system and ours may be due to the level of pyrene incorporation in their case. Gorodetskaya, I. A.; Gorodetsky, A. A.; Vinogradova, E. V.; Grubbs, R. H. *Macromolecules* **2009**, *42*, 2895.

(21) An AB_2 monomer carrying a tri(oxyethylene) spacer was synthesized and polymerized to give clickable hyperbranched polymer bearing a hydrophilic spacer within the core region. For details refer to the Supporting Information (Figure S9).