AB_2 + A Type Copolymerization Approach for the Preparation of Thermosensitive PEGylated Hyperbranched Polymers

Animesh Saha and S. Ramakrishnan*

Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore 560 012, India

Received April 18, 2008; Revised Manuscript Received June 16, 2008

ABSTRACT: Hyperbranched polyethers having poly(ethylene glycol) (PEG) segments at their molecular periphery were prepared by a simple procedure wherein an AB_2 type monomer was melt-polycondensed with an A-type monomer, namely, heptaethylene glycol monomethyl ether. The presence of a large number of PEG units at the termini rendered a lower critical solution temperature (LCST) to these copolymers, above which they precipitated out of an aqueous solution. In an effort to understand the effect of various molecular structural parameters on their LCST, the length of the hydrophobic spacer segment within the hyperbranched core and the extent of PEGylation were varied. Additionally, linear analogues that incorporates pendant PEG segments were also prepared and comparison of their LCST with that of the hyperbranched analogue clearly revealed that hyperbranched topology leads to a substantial increase in the LCST, highlighting the importance of the peripheral placement of the PEG units.

Introduction

Thermoresponsive polymers, such as those that exhibit a lower critical solution temperature (LCST), have attracted a great deal of attention, specifically from the viewpoint of utilizing them as smart gels, drug-delivery vehicles etc.[1] Poly(*N*-isopropylacrylamide), PNIPAM, which exhibits a dramatic decrease of solubility in water at 32 °C, is one of the most extensively investigated of such systems.[2] The molecular origin of such a transition is the thermally induced destabilization of the H-bonds between water and the pendant amide units in favor of formation of intrachain H-bonds between amide units. This causes the polymer chain to undergo a coil-to-globule transition and consequently to the observed macroscopic precipitation (or volume transition in gels). Several molecular parameters, such as molecular weight,[3,4] nature of the end groups,[4] comonomer incorporation[5] etc., have been shown to affect the LCST, the most influential being the incorporation of a hydrophobic/hydrophilic comonomer. Other interesting linear polymers that exhibit LCST are those that incorporate PEG segments as simple as well as dendritic pendant units.[6] Such PEG-containing polymers are particularly attractive as they are far less sensitive to concentration, ionic strength, and chain length.[7]

Unlike linear polymeric systems, alternate topologies, such as star polymers, dendrimers, and hyperbranched polymers, provide a larger number of structural variables to control the LCST. In dendrimers, it has been shown that incorporation of isobutyramide (IBAM) units at the numerous chain ends leads to systems that exhibit a sharp LCST.[8] Unlike in linear PNIPAM, in these dendritic systems increasing the generation (molecular weight) of the dendrimer leads to a significant decrease in the LCST. This has been ascribed to the increased density of IBAM end groups in the shell region of higher generation dendrimers, and consequently to the enhanced tendency of the IBAM units to dehydrate at a lower temperature in favor of intrachain association between isobutyramide units. Similarly, variation of the level of IBAM incorporation and also co-inclusion of other hydrophobic (or conformationally rigid) alkylamide units have been shown to dramatically influence the LCST.[9] In PAMAM dendrimers, the presence of a large number of protonatable amine functionalities leads to a significant increase in the LCST upon lowering the pH; this indirectly reflects the importance of the hydrophilicity of the core region.[8,9b] Apart from modifying the end groups, core−shell systems containing PNIPAM chains grafted to the dendritic core reveal a collapse of the shell region that causes a significant decrease in their hydrodynamic radius and consequently a macroscopic precipitation above LCST.[10] Similar investigations on star-branched polymers also reveal several unique features in such branched topologies.[11] Other interesting dendrons that carry switchable hydrophobic−hydrophilic segments were also shown to exhibit generation-dependent LCST.[12]

In contrast to dendrimers, studies of LCST in hyperbranched systems have mostly focused on polymers that contain thermosensitive oligomeric chains grafted onto their molecular periphery. Hyperbranched polyesters (Boltron-40) containing grafted PNIPAM segments were shown to exhibit an interesting two-step chain collapse, which has been ascribed to the stronger tendency of the anchored segments to undergo a collapse when compared to the segments that lie in the peripheral region.[13] In another interesting report, Yan and co-workers directly observed the morphological changes in PEG-modified hyperbranched polyethers as a function of temperature and suggested that vesicle coalescence induced by dehydration of the peripheral PEG segments could be the underlying mechanism for the macroscopic phase separation that occurs at LCST.[14] They also demonstrated that variation of the hydrophobicity in backbone-responsive hyperbranched polyethers, prepared via the proton-transfer polymerization, could be yet another approach to control the LCST.[15] More recently, Liu et al. have compared the LCST properties of hyperbranched polyethylenimines bearing terminal isobutyramide (IBAM) units with those of analogous dendrimers and linear systems.[16]

From the above discussion it is evident that several molecular parameters play a crucial role in controlling the LCST of thermoresponsive polymers, and that branched systems are clearly more structurally rich and interesting than their linear counterparts. We have, over the years, been interested in developing a comprehensive understanding of structure−property correlations in hyperbranched structures; for instance, we have studied the effect of molecular weight and branching density on chain compactness,[17] the effect of branching levels on crystallinity and crystallization propensities,[18] the role of comonomer incorporation on T_g of hyperbranched copolymers,[19] etc. In the present study, we describe a straightforward synthetic

---

* Corresponding author. E-mail: raman@ipc.iisc.ernet.in.

10.1021/ma800870q CCC: $40.75

strategy to access thermoresponsive hyperbranched polyethers via a single-step $AB_2 + A$ type copolymerization. Apart from demonstrating the utility of this simple approach, the study also addresses the importance of several crucial structural features in governing the LCST of hyperbranched systems, such as (a) the role of the size and hydrophobicity of the core, (b) the effect of the level of peripheral PEGylation, and (c) the importance of the "hyperbranching effect".

Experimental Section

2,4,6-Trimethylphenol (Mesitol), 1,4-butanediol, 1,6-hexanediol, 1,8-octanediol, 1,10-decanediol, triethylene glycol, tetraethylene glycol, *p*-toluenesulfonyl chloride, 10% Pd/C, and camphorsulfonic acid were purchased from Aldrich Chemical Co. Heptaethylene glycol monomethyl ether monotosylate was synthesized adopting the general procedure for the preparation of well-defined PEG units.[20] Dimethyl sulfate was distilled prior to use. THF and acetonitrile were purified by refluxing over sodium/benzophenone or CaH_2, respectively, followed by distillation. Structures of all intermediates, monomers, and polymers were confirmed by ^1H NMR spectroscopy. NMR spectra were recorded on a Bruker AV400 MHz spectrometer, using $CDCl_3$ or C_6D_6 as the solvent and TMS as reference. GPC measurements were carried out using Viscotek TDA model 300 system, coupled to a refractive index (RI) and a differential viscometer (DV) in series. The separation was achieved using a series of two PLgel mixed bed columns (300 × 7.5 mm) operated at 30 °C using THF as the eluent. Molecular weights were determined using a universal calibration curve based on the data from the refractive index (RI) and differential viscometric (DV) detectors using narrow polystyrene standards. Cloud point measurements were done using a temperature-controlled Varian 300 UV−visible spectrophotometer.

Cloud Point Measurements. A 0.4 wt % (4 mg in 1 mL) aqueous solution of the polymer was taken in a standard UV cuvette and the transmittance at 600 nm (where there is no absorption by the solution) was monitored as a function of temperature. At each temperature, the transmittance was monitored as a function of time and the value was noted down after it becomes invariant (ca. 10 min). The temperature at which the transmittance of the solution drops to 50% of its original value is taken as the LCST.

1-(6-Hydroxyhexyloxy)-3,5-bis(methoxymethyl)-2,4,6-trimethylbenzene (2b). A mixture of K_2CO_3 (4.6 g, 33.4 mmol), a catalytic amount of KI, and 1-bromohexanol (1.8 g, 10.0 mmol) was taken in 40 mL of dry CH_3CN. The mixture was degassed for 20 min, after which 1.5 g (6.7 mmol) of **1** was added to it. The reaction mixture was degassed for an additional 20 min and then refluxed for 72 h under N_2 atmosphere. The solvent was then removed using a rotary evaporator, and 50−60 mL of cold water was added to it. The product was extracted with 100 mL (2 × 50 mL) of ether and the ether layer was washed with 10% (w/v) aq NaOH solution (4 × 30 mL) followed by a wash with distilled water. The ether layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The excess bromoalcohol was removed by distillation in Kugelrohr at 110 °C/0.5 mm of Hg, followed by distillation of the product at 220 °C/0.5 mm of Hg. Finally, it was recrystallized from hot petroleum ether to get a white solid product (yield = 75%, mp = 73 °C; Lit.[17] 73 °C).

^1H NMR (*δ*, ppm, $CDCl_3$): 1.40−1.85 (m, 8H, $ArOCH_2(\mathit{CH_2})_4$-CH_2OH); 2.30(s, 6H, Ar($\mathit{CH_3}$)$_2$); 2.36 (s, 3H, Ar($\mathit{CH_3}$); 3.38 (s, 6H, $ArCH_2O\mathit{CH_3}$); 3.61−3.63 (m, 4H $ArO\mathit{CH_2}(CH_2)_4\mathit{CH_2}OH$); 4.45 (s, 4H, $Ar\mathit{CH_2}OCH_3$).

All other monomers (**2a**−**2d**) were prepared using a similar procedure. The yields ranged from 60−85%.

Compound 3. A mixture of K_2CO_3 (7.7 g, 55.5 mmol), a catalytic amount of KI, and heptaethylene glycol monomethyl ether monotosylate (5.24 g, 10.5 mmol) were taken in 60 mL of dry CH_3CN. The mixture was degassed for 20 min, after which 2.5 g (11.1 mmol) of **1** was added to it. The reaction mixture was degassed for an additional 20 min and then refluxed for 72 h under N_2 atmosphere. The solvent was then removed with a rotary evaporator, and 50−60 mL of cold water was added to it. The product was extracted with 100 mL (2 × 50 mL) of dichloromethane and the dichloromethane layer was washed with 10% (w/v) aq NaOH solution (4 × 30 mL) followed by a wash with distilled water. The dichloromethane layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Finally, the product was purified by silica column using 70% EtOAc as the eluent to get the colorless viscous liquid (yield = 77%).

^1H NMR (*δ*, ppm, $CDCl_3$): 2.32 (s, 6H, Ar($\mathit{CH_3}$)$_2$); 2.36 (s, 3H, Ar($\mathit{CH_3}$)); 3.38 (s,3H, glycol-O$\mathit{CH_3}$); 3.40 (s, 6H, $ArCH_2O\mathit{CH_3}$); 3.53−3.82 (m, 28H, glycol-$\mathit{CH_2}$); 4.47 (s, 4H, $Ar\mathit{CH_2}OCH_3$).

3,5-Bismethoxymethyl-1-methoxy-2,4,6-trimethylphenol (4). 1.0 g (4.46 mmol) of Mesitol was dissolved in 10 mL of dry EtOH. Then, NaOEt solution (made by adding 0.2 g, 9.92 mmol of Na into 5 mL of dry EtOH) was added to it dropwise at 0 °C. After stirring for 10 min, dimethyl sulfate (1.12 g, 9.92 mmol) was added to it dropwise at 0 °C. After completion of addition, it was stirred for 5 h at room temperature under N_2 atmosphere. Ethanol was then removed and the residue was stirred with NaOH solution to destroy the excess dimethyl sulfate. It was extracted with dichloromethane (2 × 15 mL), washed with brine and passed through Na_2SO_4. The crude product was distilled using a Kugelrohr at 190 °C/0.5 mm of Hg to yield a white solid product upon cooling (yield = 90%, mp = 45 °C).

^1H NMR (*δ*, ppm, $CDCl_3$): 2.33 (s, 6H, Ar($\mathit{CH_3}$)$_2$); 2.37 (s, 3H, Ar($\mathit{CH_3}$))**;** 3.40 (s, 6H, $ArCH_2O\mathit{CH_3}$); 3.64 (s, 3H, $ArO\mathit{CH_3}$), 4.47 (s, 4H, $Ar\mathit{CH_2}OCH_3$).

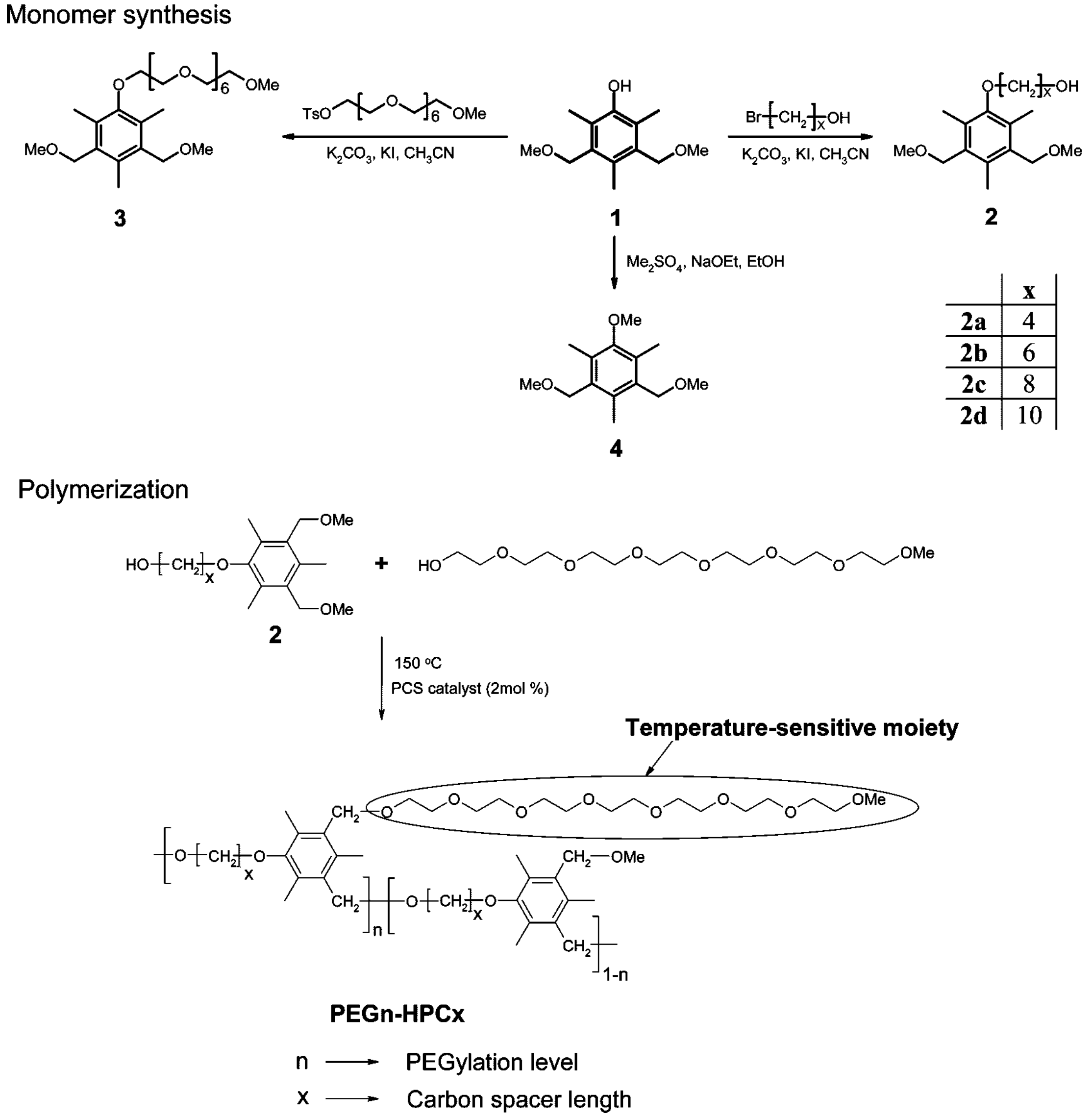
Typical Polymerization Procedure. Monomer **2b** (500 mg, 1.54 mmol), along with heptaethylene glycol monomethyl ether (472.8 mg, 1.38 mmol) and 2 mol % of pyridinium camphorsulfonate (PCS)[21] was taken in the polymerization vessel. It was degassed for 10 min and maintained at a temperature of 110 °C under continuous N_2 purge to ensure homogeneous mixing of catalyst and monomers. The polymerization was then carried out at 150 °C under N_2 for 4−6 h with constant stirring. Subsequently, using a Kugelrohr apparatus, the polymerization was continued for an additional period (0.5−2 h) at 150 °C under reduced pressure (50 mm), with continuous mixing of the melt by rotation. The resultant polymer was dissolved in THF, and the acid catalyst was neutralized with solid $NaHCO_3$ and then filtered. The filtrate was concentrated and poured into petroleum ether to obtain the polymer **PEG-HPC6**. Typical yields of the purified polymer ranged from 50 to 60%. All the polymers, both hyperbranched and linear, were prepared using a similar procedure by taking the required mole fraction of the appropriate monomers. In the case of the linear polymers, a slightly longer polymerization time (7 h under N_2 flow and 3 h under reduced pressure) was used to ensure formation of high molecular weight polymers. All the polymers were purified by two dissolution−reprecipitation steps using THF−petroleum ether.

Results and Discussion

Synthesis and Structural Elucidation. The AB_2 monomer (**1**) was readily prepared from Mesitol in two steps, as described previously.[17] Intermediate **1** serves as an ideal starting point for the incorporation of hydrophobic alkylene segments of various lengths and thereby to modulate the size and hydrophobicity of the resulting hyperbranched polymers. A series of monomers **2a**−**d** were prepared, wherein the length of the alkylene segment was varied from C4 to C10 (Scheme 1).

The general approach we adopted for the preparation of peripherally modified hyperbranched structures utilizes the copolymerization of an AB_2 monomer with a molecule containing a single A-type group (Scheme 1). In a slightly different context, we had utilized a similar strategy to prevent cross-linking in hyperbranched polyurethanes[22] and subsequently also to incorporate mesogenic units at the molecular periphery of hyperbranched structures. Since an AB_2 monomer carries a stoichiometric excess of 1 equiv of B groups, it can tolerate up to 1 equiv of any species that carries a single A group, without any detrimental effect on the molecular weight. Thus, copo-

Scheme 1. Synthesis of Monomers and Hyperbranched Polymers (PEGn-HPCx)



	x
2a	4
2b	6
2c	8
2d	10

lymerization of a simple aliphatic alcohol, such as heptaethylene glycol monomethyl ether, with the various AB_2 monomers (**2a**−**d**) yielded a series of peripherally PEGylated hyperbranched polymers, wherein the size and hydrophobicity of the hypercore is systematically varied. In order to ensure that there is no reduction of molecular weight, a constant ratio of AB_2:A of 1:0.9 was used. ^{1}H NMR spectra of the polymers were expected to reveal the extent of peripheral PEGylation achieved via this single-step copolymerization approach. However, the peaks corresponding to the residual $\mathbf{CH_3}OCH_2Ar$ and that due to the terminal methoxy protons of the heptaethylene glycol monomethyl ether segment merged to give a single peak (~3.4 ppm) when the spectra were recorded in $CDCl_3$, as seen in Figure 1.

As was shown in our earlier paper[23] under such circumstances the use of an aromatic solvent, like benzene, to record the spectrum results in a considerable enhancement of resolution due to aromatic solvent induced shift (ASIS). In order to study the effect of solvent composition on the spectral resolution, the ^{1}H NMR spectra of a representative polymer−**PEG66-HPC6** were recorded in $CDCl_3$−C_6D_6 mixtures of varying composition. It is evident from Figure 1 that the $\mathbf{CH_3}O$ peak at around 3.4 ppm splits into two peaks and becomes almost baseline-resolved when the $CDCl_3$−C_6D_6 ratio is around 2:1. Some of the other peaks, like the aromatic methyl protons (between 2.0 and 3.0 ppm), however, become better resolved only in pure benzene. The Ar$\mathbf{CH_2}$−O− peaks (~4.5 ppm), on the other hand, become best resolved in an intermediate composition before partly remerging in pure benzene. Of the two methoxy proton peaks (in 2:1 $CDCl_3/C_6D_6$), the downfield one (labeled 5) is assigned to the residual $\mathbf{CH_3}OCH_2Ar$ protons while the more intense upfield peak (labeled 6) is assigned to the methoxy protons of the PEG unit. On the basis of this assignment, the extent of peripheral PEGylation was determined to be ca. 66 mol % in **PEG66-HPC6** sample. The most upfield benzylic proton peak at 4.35 ppm (labeled 3) was assigned to Ar$\mathbf{CH_2}$−O−CH_3, based on its relative intensity. Efforts to assign the remaining two benzylic proton peaks to the dendritic, linear, or terminal units (as was done earlier)[23] was difficult because of the additional complication resulting from incomplete PEGylation. The sum total of all the three peaks (4.4−4.6 ppm), however, matched well with the expected value; for instance, its intensity was in the ratio 4:9 with respect to the aromatic methyl protons (sum of two peaks ~ 2.4 ppm).

The ^{1}H NMR spectra of the series of polymers, **PEG-HPCx**, bearing varying spacer segments are shown in Figure 2. All the peaks in the spectra are readily assigned as was done earlier. The extent of PEGylation was determined and was found to

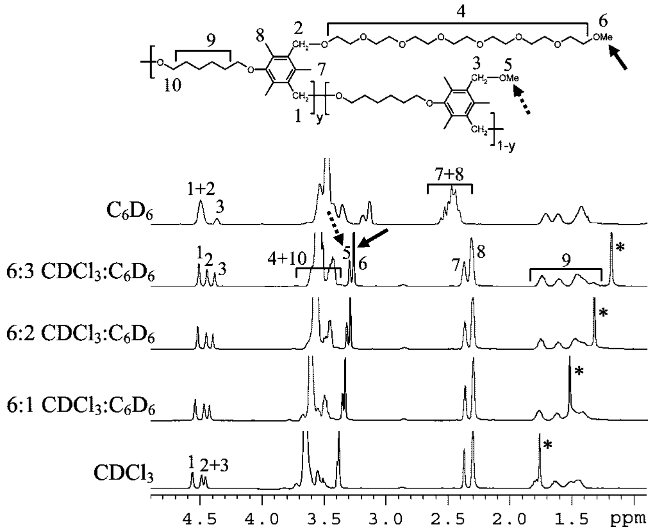


Figure 1. ^{1}H NMR spectra of a representative hyperbranched polymer, **PEG66-HPC6** as a function of solvent composition ($CDCl_3$/C_6D_6). The peaks indicated by the arrows were used for determination of the PEGylation level. The peaks marked with asterisk are due to solvent.

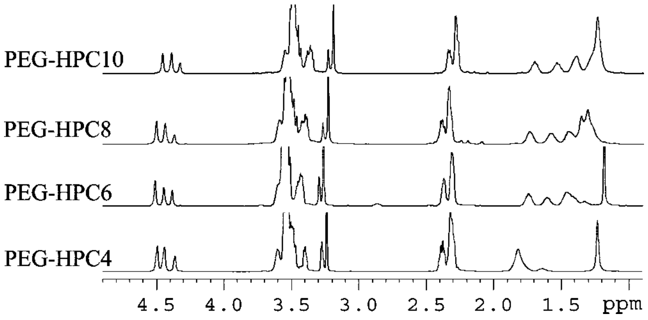


Figure 2. ^{1}H NMR spectra of the hyperbranched polymers, **PEG-HPCx** recorded in a mixture of $CDCl_3$ and C_6D_6. The exact solvent composition was varied between 2:1 to 1:1 for optimal resolution.

fall in the range 66−70 mol %, even though the maximum expected value would be around 90 mol % for a 1:0.9 mole ratio of AB_2:A.[24] Although the exact reason for the significantly lower limiting value is not clear, one possible explanation is that this is a reflection of the relative inaccessibility of some of these terminal groups, which might be buried within the interior of the hyperbranched structures. Thus, causing preferential functionalization of the peripheral end groups and possibly leaving behind some of methoxymethyl groups belonging to the linear defect units. Unfortunately, the NMR spectra do not provide unequivocal evidence for this hypothesis. The M_w values of the various copolymers were found to be moderately high ranging from 12 100 to 28 100, with PDI's ranging from 2.5 to 5.7. The sample **PEG-HPC10** exhibited the highest molecular weight of 28 100 (PDI = 5.7) while all the other samples were around 12 000−16 000 (see Table 1).

In an effort to control the level of PEGylation, the ratio of AB_2:A was varied and this yielded a second series of structures **PEGn-HPC6** (where *n* is the percent PEGylation), wherein the extent of peripheral PEGylation was varied from 42 to 67 mol %. Samples with even lower levels of PEGylation were not of interest for this study because of their poor solubility in water.[25] In this entire series, **2b** was used as the AB_2 type monomer thereby fixing the length of the hydrophobic spacer segment. The level of PEGylation was established from the relative intensities of the two methoxy protons in the region 3.2−3.4 ppm (Figure 3), as was done earlier using a $CDCl_3$−C_6D_6 mixture as the solvent. The M_w values of the various copolymers were found to be moderately high ranging from 14 700 to 17 400, with PDI's ranging from 2.5 to 3.2. (Table 1).

Further, in order to establish the real effect of "hyperbranching" on the LCST, a linear analogue of the PEGylated hyperbranched polymer was prepared as shown in Scheme 2. A PEGylated monomer **3** containing a pendant heptaethylene glycol monomethyl ether unit was condensed with 1,6-hexanediol[26] under the standard melt transetherification conditions. The resulting polymer **L1** was designed to reflect the composition of the hyperbranched sample **PEG66-HPC6**, although the level of PEGylation was significantly higher (every repeat unit of **L1** bears a pendant PEG segment). To reflect the correct PEGylation level of the hyperbranched polymer (PEGylation level ∼ 66 mol %), an additional copolymer was prepared by cocondensing the comonomer **4** (not containing the pendant PEG segment) and monomer **3** (in a ratio 35:65) along with 1,6-hexanediol to give the linear copolymer **L2**.

The ^{1}H NMR spectra of the two linear analogues along with that of the hyperbranched polymer **PEG66-HPC6** are shown in Figure 4.

The presence of two peaks in the region ∼3.2 ppm even in the homopolymer **L1** is due to the methoxymethyl end groups (reflecting its relatively moderate molecular weight). Consequently, in the copolymer **L2** the peak due to the chain ends and the pendant methoxy units of comonomer **4** could not be well resolved even using mixed solvents. Therefore, the exact incorporation level of the PEGylated comonomer was established by comparing the intensities of the peaks due to the methoxy protons of the PEG units with that of all the aromatic methyl protons (∼2.2−2.4 ppm). The extent of incorporation of the monomer **3** was found to be 67 mol %, which matched well with that of the feed confirming the anticipated similar reactivity of the two comonomers, **3** and **4**. The M_w's of the two linear copolymers were estimated by GPC and found to be 16 500 and 12 700, respectively (Table 1).

Solution Properties. In order to measure the LCST of the polymers, the transmission at 600 nm (where there is no absorption by the polymer) was monitored as a function of temperature. The solutions were allowed to stabilize at each temperature for ca. 10 min before the percent transmission was measured. A plot of the variation of percent transmission as a function of temperature for the series **PEG-HPCx** is shown in Figure 5. It is clear from the figure that as the length of the hydrophobic spacer within the hypercore increases the LCST is lowered. This could either be due to the apparent increase in the size of the hyperbranched core and/or due to the increased hydrophobicity. In the case of isobutyramide-functionalized PAMAM dendrimers, the LCST was observed to decrease with increasing generation, apparently because of the increased density within the shell region.[8] A similar explanation based on the density of the shell region was also invoked to explain the increase in LCST seen in these PAMAM systems as the pH is lowered.[8] In our system, the more probable reason for the decrease may be the increase of hydrophobicity of the core because as the length of the spacer increases the number of chain ends are expected to remain constant (noting that the variation in molecular weights are small, except in the case of **PEG-HPC10**) and therefore no densification of the periphery is anticipated, unlike in the dendrimer case, where increasing the generation increases the number of terminal units as well. In a slightly different type of hyperbranched systems, wherein the backbone is designed to be thermoresponsive, an increase in the backbone hydrophobicity was indeed shown to lower the LCST.[15]

Similarly, the variation of the LCST as a function of PEGylation (Figure 6) clearly depicts a decrease in LCST as

Table 1. Structural Characteristics and Properties of the Hyperbranched and Linear Polymers

polymer	AB_2:A	PEGylation level (%)[a]	yield (%)	M_w[b]	M_n[b]	PDI[b]	DP_w[b]	LCST[c] (°C)
			Hyperbranched Polymers					
PEG-HPC4	1:0.9	67	52	13 200	5200	2.5	28	38.5
PEG-HPC6	1:0.9	66	55	15 800	4800	3.2	31	35.4
PEG-HPC8	1:0.9	70	51	12 100	3400	3.5	22	31.4
PEG-HPC10	1:0.9	67	59	28 100	4900	5.7	50	24.2
PEG42-HPC6	1:0.6	42	50	14 700	5900	2.5	34	17.3
PEG50-HPC6	1:0.7	50	56	14 900	5300	2.8	33	25.5
PEG59-HPC6	1:0.8	59	54	17 400	6300	2.7	36	30.4
PEG66-HPC6	1:0.9	66	55	15 800	4800	3.2	31	35.4
			Linear Analogues					
L1	–	100	61	16 500	6100	2.7	27	31.4
L2	–	67	57	12 700	4200	3.0	25	19.2

[a] Calculated from ^{1}H NMR. [b] Determined by GPC. [c] Determined by using a standard UV–visible spectrometer.

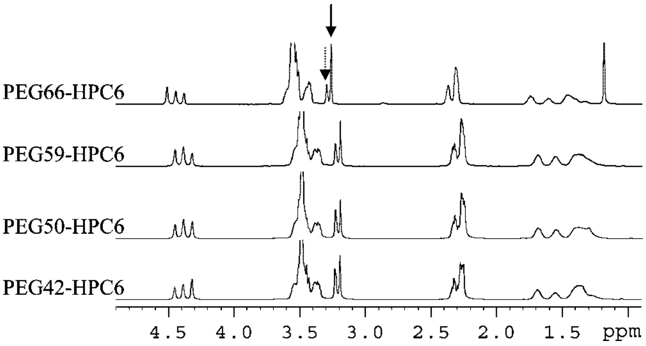


Figure 3. ^{1}H NMR spectra of the hyperbranched polymers, **PEGn-HPC6** recorded in a mixture of $CDCl_3$ and C_6D_6. Note that the exact position of the peaks varies a little because of differences in solvent composition.

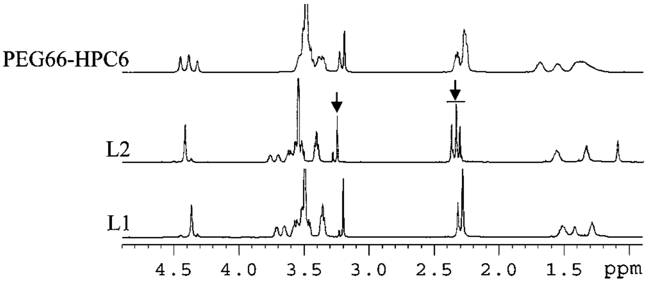
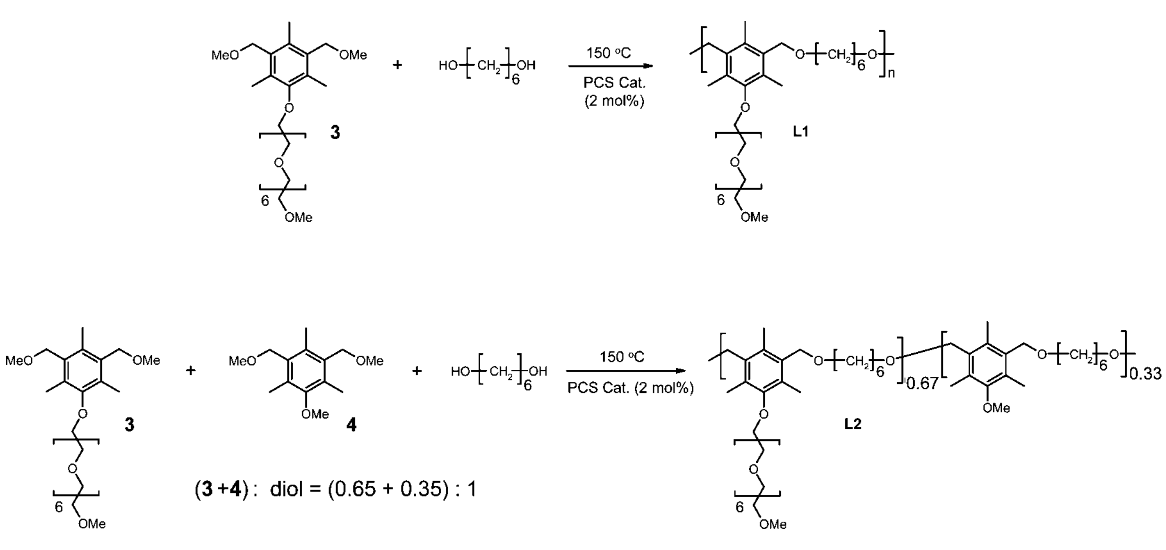


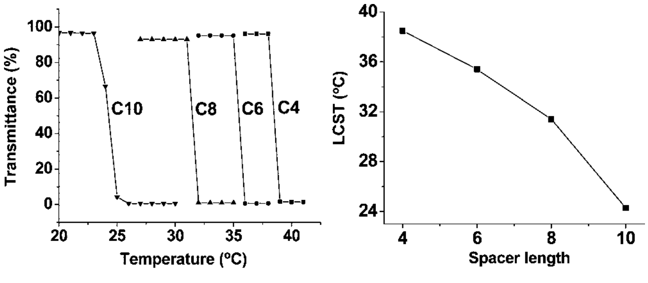
Figure 4. ^{1}H NMR spectra of the PEGylated linear analogues (**L1**, **L2**) along with that of the hyperbranched polymer **PEG66-HPC6** recorded in a mixture of $CDCl_3$ and C_6D_6. The peaks marked by arrows were used for estimating the composition. Note that the exact position of the peaks varies a little because of differences in solvent composition.

the PEGylation level is lowered. The peripheral PEG segments that renders water solubility to these hyperbranched polymers controls the LCST: lower the level of PEGylation lower is the temperature at which the polymer desolvates. A similar observation was also made by Yan and co-workers in the case of PEGylated hyperbranched polyethers, wherein the length of the PEG chains were varied.[14a] They observed that as the length of the PEG chain increases the LCST also increases, reflecting a similar balance between the volume ratio of the hydrophobic core to that of the hydrophilic PEG shell. Liu et al. have also made a similar observations in IBAM functionalized hyperbranched polyethylenimines; the difference in this case being that the core was chosen to be water soluble and therefore the LCST increased with decrease in the extent of peripheral functionalization.[16]

In order to examine the effect of polymer topology on the LCST, a comparison of the solution properties of PEGylated hyperbranched polymer, namely **PEG66-HPC6**, was made with that of a linear analogue (**L1**) bearing pendant PEG units of the same length (see Scheme 2). From Figure 7, it is evident that the "hyperbranching effect" leads to a significant increase in the LCST of the hyperbranched polymer when compared to **L1**. This observation is similar to those made by Kono and co-workers in a recent paper, wherein they compared linear poly(*N*-isopropylacrylamide) with that of a dendrimer decorated with *N*-isopropylamide groups on their periphery.[28] They too observed a 10° higher LCST for the dendrimer when compared

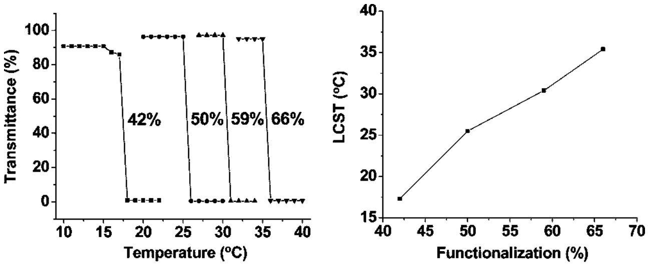
Scheme 2. Synthesis of PEGylated Linear Analogues (L1, L2) of the Hyperbranched Polymer PEG66-HPC6





A B

Figure 5. Percent transmittance of 0.4 wt % aqueous solution of the hyperbranched polymers, **PEG-HPCx** as a function of temperature measured at 600 nm (A), and variation of LCST as a function of spacer length of the hyperbranched polymers **PEG-HPCx** (B).



A B

Figure 6. Percent transmittance of 0.4 wt % aqueous solution of the hyperbranched polymers **PEGn-HPC6** as a function of temperature measured at 600 nm (A), and LCST as a function of level of PEGylation of the hyperbranched polymers **PEGn-HPC6** (B).

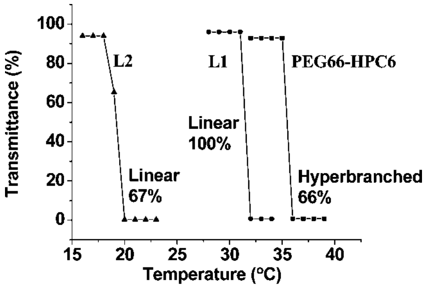


Figure 7. Transmittance of 0.4 wt % aqueous solution of the linear (**L2**, **L1**) and hyperbranched (**PEG66-HPC6**) polymers as a function of temperature measured at 600 nm.

to the linear analogue. They also suggested that, unlike linear polymers, dendrimers undergo small changes in the overall dimension as the polymer goes through its LCST and importantly it also retains the hydrophobic nature of the core making such systems potentially useful as intelligent nanocapsules for drug delivery.

Since our hyperbranched systems are incompletely PEGylated, a more meaningful comparison would be with that of linear analogue that carries an appropriately lower level of pendant PEG units. Thus, a comparison of the LCST of **PEG66-HPC6** with that of the copolymer **L2** (which has 67 mol % of PEGylated repeat unit) suggests a more significant effect of hyperbranching; the LCST of the hyperbranched polymer was 16° higher than that of the linear analogue. This significantly higher LCST of the PEGylated hyperbranched polymer is clear evidence for the topological separation of the peripheral PEG chains from the hydrophobic core region. We must note that, unlike in dendrimers, wherein terminal functionalization occurs at the structural periphery, in hyperbranched polymers, which contain a large number of structural (linear) defects, the peripheral functionalization refers more to the *functional* periphery as reflected by their solution conformational characteristics.[27] In other words, the solution conformation of such terminally functionalized hyperbranched polymers in aqueous medium present the PEG units at their periphery. Similar conclusions were inferred by Frey and co-workers, while comparing the dye-uptake studies of core−shell hyperbranched structures with that of their linear analogues.[29] Another important structural control parameter is the molecular weight of these peripherally functionalized hyperbranched polymers. Our attempts to examine this in the present system, however, proved to be difficult as efforts to fractionate these polymers based on molecular weights were unsuccessful; fractionation invariably appeared to occur based on the extent of functionalization in addition to the molecular weight. This is a reflection of the inherent heterogeneity in the functionalization level of these core−shell type hyperbranched polymers generated via the $AB_2 + A$ type approach. An improvement of this aspect, in addition to attaining higher levels of peripheral functionalization, would be of interest and would add greater value to this copolymerization strategy.

Conclusions

In conclusion, we have shown that peripherally PEGylated hyperbranched polymers can be readily accessed by a straightforward $AB_2 + A$ type condensation approach. We have utilized a melt transetherification strategy, wherein a AB_2 monomer (**2**), containing two benzylmethyl ether groups and one hydroxyl group, was condensed with heptaethylene glycol monomethyl ether. This approach provided an easy access to an interesting class of PEGylated hyperbranched polymers that exhibited a sharp LCST. The LCST was seen to depend strongly on the size and hydrophobicity of the core, and on the level of peripheral PEGylation. Increase in the size and hydrophobicity of the hypercore resulted in a continuous lowering of its LCST. Further, for a given hypercore, increase in the level of PEGylation resulted in an increase of the LCST as anticipated. A particularly interesting finding relates to the effect of topology; placement of the PEG units on the peripheral shell region around the hypercore resulted in a substantial increase in the LCST, when compared to placing them as pendant units on a linear polymer backbone. This observation also provides indirect evidence for the development of core−shell type topology in these peripherally functionalized hyperbranched structures as was earlier inferred by Frey and co-workers.[29] The incomplete level of peripheral functionalization and the high level of linear defects[30] remain two challenges that need to be addressed to further enhance the general utility of this $AB_2 + A$ type copolymerization strategy to generate other interesting peripherally functionalized systems. Nevertheless, our study clearly demonstrates the richness and complexity in correlating structure−property relationship in hyperbranched structures.

Acknowledgment. We thank the Department of Atomic Energy for the ORI Award for the period 2006−2011.

Supporting Information Available: GPC chromatograms and LCST reversibility curves of the polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Galaev, I. Y.; Mattiasson, B. *Trends Biotechnol.* **1999**, *17*, 335. (b) Lopez, V. C.; Raghavan, S. L.; Snowden, M. J. *React. Funct. Polym.* **2004**, *58*, 175. (c) Jeong, B.; Gutowska, A. *Trends Biotechnol.* **2002**, *20*, 305. (d) Yoshida, R.; Takahashi, T.; Yamaguchi, T.; Ichijo, H. *Adv. Mater.* **1997**, *9*, 175. (e) Yuk, S. H.; Cho, S. H.; Lee, S. H. *Macromolecules* **1997**, *30*, 6856.

(2) (a) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163–249. (b) Gil, E. S.; Hudson, S. M. *Prog. Polym. Sci.* **2004**, *29*, 1173–1222.

(3) Aoshima, S.; Oda, H.; Kobayashi, E. *J. Polym. Sci., Polym. Chem. Ed.* **1992**, *30*, 2407.

(4) Jiang, X.; Zhao, B. *J. Polym. Sci. Polym. Chem. Ed.* **2007**, *45*, 3707.

(5) (a) Chen, G.; Hoffman, A. S. *Nature (London)* **1995**, *373*, 49. (b) Hoffman, A. S.; Stayton, P. S.; Bulmus, V.; Chen, G.; Chen, J.; Cheung, C.; Chilkoti, A.; Ding, Z.; Dong, L.; Fong, R.; Lackey, C. A.; Long, C. J.; Miura, M.; Morris, J. E.; Murthy, N.; Nabeshima, Y.; Park, T. G.; Press, O. W.; Shimoboji, T.; Shoemaker, S.; Yang, H. J.; Monji, N.; Nowinski, R. C.; Cole, C. A.; Priest, J. H.; Harris, J. M.; Nakamae, K.; Nishino, T.; Miyata, T. *J. Biomed. Mater. Res.* **2000**, *52*, 577.

(6) (a) Lutz, J.-F.; Hoth, A. *Macromolecules* **2006**, *39*, 893. (b) Lutz, J.-F.; Weichenhan, K.; Akdemir, Ö.; Hoth, A. *Macromolecules* **2007**, *40*, 2503. (c) Li, W.; Zhang, A.; Feldman, K.; Walde, P.; Schlüter, A. D. *Macromolecules* **2008**, *41*, 3659.

(7) (a) Lutz, J.-F.; Akdemir, Ö.; Hoth, A. *J. Am. Chem. Soc.* **2006**, *128*, 13046. (b) Lutz, J.-F. *J. Polym. Sci., Polym. Chem. Ed.* **2008**, *46*, 3459.

(8) Haba, Y.; Harada, A.; Takagishi, T.; Kono, K. *J. Am. Chem. Soc.* **2004**, *126*, 12760.

(9) (a) Haba, Y.; Kojima, C.; Harada, A.; Kono, K. *Macromolecules* **2006**, *39*, 7451. (b) Tono, Y.; Kojima, C.; Haba, Y.; Takahashi, T.; Harada, A.; Yagi, S.; Kono, K. *Langmuir* **2006**, *22*, 4920. (c) Kono, K.; Miyoshi, T.; Haba, Y.; Murakami, E.; Kojima, C.; Harada, A. *J. Am. Chem. Soc.* **2007**, *129*, 7222.

(10) You, Y.-Z.; Hong, C.-Y.; Pan, C.-Y.; Wang, P.-H. *Adv. Mater.* **2004**, *16*, 1953.

(11) (a) Plamper, F. A.; Ruppel, M.; Schmalz, A.; Borisov, O.; Ballauff, M.; Müller, A. H. E. *Macromolecules* **2007**, *40*, 8361. (b) Plummer, R.; Hill, D. J. T.; Whittaker, A. K. *Macromolecules* **2006**, *39*, 8379.

(12) Aathimanikandan, S. V.; Savariar, E. N.; Thayumanavan, S. *J. Am. Chem. Soc.* **2005**, *127*, 14922.

(13) (a) Xu, J.; Luo, S.; Shi, W.; Liu, S. *Langmuir* **2006**, *22*, 989. (b) Luo, S.; Xu, J.; Zhu, Z.; Wu, C.; Liu, S. *J. Phys. Chem. B* **2006**, *110*, 9132.

(14) (a) Zhou, Y.; Yan, D.; Dong, W.; Tian, Y. *J. Phys. Chem. B* **2007**, *111*, 1262. (b) Yan, D.; Zhou, Y.; Hou, J. *Science* **2004**, *65*, 303. (c) Zhou, Y.; Yan, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4896. (d) Mai, Y.; Zhou, Y.; Yan, D. *Small* **2007**, *3*, 1170. (e) Mai, Y.; Zhou, Y.; Yan, D. *Macromolecules* **2005**, *38*, 8679. (f) Zhou, Y.; Yan, D. *J. Am. Chem. Soc.* **2005**, *127*, 10468.

(15) Jia, Z.; Chen, H.; Zhu, X.; Yan, D. *J. Am. Chem. Soc.* **2006**, *128*, 8144.

(16) Liu, H.; Chen, Y.; Shen, Z. *J. Polym. Sci., Polym. Chem. Ed.* **2007**, *45*, 1177.

(17) Behera, G. C.; Ramakrishnan, S. *Macromolecules* **2004**, *37*, 9814.

(18) (a) Jayakannan, M.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem. Ed.* **1998**, *36*, 309. (b) Jayakannan, M.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem. Ed.* **2000**, *38*, 261.

(19) Behera, G. C.; Saha, A.; Ramakrishnan, S. *Macromolecules.* **2005**, *38*, 7695.

(20) Loiseau, F. A.; Hii, K. K. M.; Hill, A. M. *J. Org. Chem.* **2004**, *69*, 639.

(21) Behera, G. C.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem. Ed.* **2004**, *42*, 102.

(22) Kumar, A.; Ramakrishnan, S. *Macromolecules* **1996**, *29*, 2524.

(23) Behera, G. C.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem. Ed.* **2007**, *45*, 1474.

(24) The use of a 1:1 ratio did not give any substantial increase in the extent of PEGylation, although a slight apparent reduction of molecular weight was noticeable, and hence a 1:0.9 ratio was used.

(25) Hyperbranched polymer, PEG38-HPC6, containing 38 mol % of PEGylation was prepared and found to be insoluble in water.

(26) This diol was selected to match alkylene segment length in the PEG-HPC6 polymer.

(27) A study by Frey and co-workers[29] addresses a similar issue and confirms the importance of the hyperbranched topology for the generation of unimolecular core−shell type structures.

(28) Haba, Y.; Kojima, C.; Harada, A.; Kono, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 234.

(29) Stiriba, S.-E.; Kautz, H.; Frey, H. *J. Am. Chem. Soc.* **2002**, *124*, 9698.

(30) The degree of branching (DB) in the parent hyperbranched homopolymers is in the vicinity of the statistically expected value of 0.5, as was shown in our earlier investigations.[23]

MA800870Q