Synthesis and Self-Assembly of Hyperbranched Polyethers Peripherally Modified with Adenosine 5'-Monophosphate

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ABSTRACT: The chloride functionalized hyperbranched poly(3-ethyl-3-oxetanemethanol) (HBPO) was prepared via reaction of thionyl chloride with hydroxyl groups. Adenosine 5'-monophosphate (AMP) groups were attached to HBPO in CH_2Cl_2 in the presence of triethylamine (TEA) as an acceptor of HCl. The self-assembly of resultant hyperbranched molecules bearing self-complementary hydrogen-bonding patterns would allow the generation of a highly organized supramolecular architecture in a selected solvent. The morphologies of self-assembly structures were depended on the level of AMP in polymer and the concentration in solvent. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 99: 1147–1152, 2006

Key words: supramolecular; self-assembly; hyperbranched polymer

INTRODUCTION

In the past decades, much attention has been focused on the design and synthesis of molecules in a supramolecular network based on noncovalent interactions (such as hydrogen bonding, π–π stacking, and/or weak interactions between molecules),[1,2] due to their interesting molecular topologies and crystal packing motifs, along with potential applications as functional materials.[3] Particular attention has been paid to supramolecular polymers and materials derived from the polyassociation of monomeric components through noncovalent interactions, which may have many amusing features.[4,5] As for the structural features of supramolecular self-assembly structures, the component of the monomeric molecules determines the morphology and ordering of supramolecular polymeric associations.[6] Up to now, the reported self-assembled molecules usually possess well-defined molecular structures, such as small amphiphiles,[7,8] dendrimers,[9–11] linear block copolymers,[12–14] or rodcoil polymers.[15–17] Simple self-assembly methods can produce a broad range of intricate self-assembled structures such as nano- or micro-tubes,[18,19] ropes,[20] rods,[21] rings,[12] vesicles,[22–25] and micelles.[26–29] However, little attention has been paid to the molecular self-assembly of ill-defined polymers such as hyperbranched molecules. Compared to block copolymers, hyperbranched polymers possess unique properties such as good solubility, special viscosity behavior, and high density of their functional groups.[30] Some of the earlier works demonstrated that hyperbranched polymers with amphiphilic core-shell structure conveniently prepared in two synthetic steps exhibit unimolecular reverse micelle properties, i.e., encapsulation and phase transfer of ionic guest molecules in analogy to amphiphilic dendrimers.[31,32] It has been believed that the intriguing self-assembly properties of hyperbranched polymers are induced by their hydrophobic shell/hydrophilic core structure, and have potential applications as processing modifiers, toughening additives, drug-delivery vehicles, synthesis-supporting materials, advanced coatings, polymeric electrolytes, and optical wave guide materials.[33–35] Although some significant progresses have been made in the synthesis and applications of hyperbranched polymers, there is still very little detailed information on factors that affect the formation of such self-assembly system.

In this study, we report the synthesis of a series of novel hyperbranched poly(3-ethyl-3-oxetanemethanol) (HBPO) tailoring peripherally modified with adenosine 5'-monophosphate (AMP) groups. The self-assembly behaviors of these hyperbranched polymers in a mixed solvent are also investigated.

EXPERIMENTAL

Materials

Chloroform (reagent grade), acetone (analysis grade), tetrahydrofuran (THF) (analysis grade), dichlo-

romethane (CH$_2$Cl$_2$, analysis grade), trichloromethane (CHCl$_3$, analysis grade), ethyl alcohol (EtOH, analysis grade), pyridine (analysis grade), triethylamine (TEA, analysis grade), diethyl carbonate (99%), and potassium hydroxide (KOH, 99%) were purchased from East of China Chem. Ltd. Co. (China) and used as received. Trimethylopropane (TMP, 99%) and adenosine 5′-monophosphate (AMP, 99%) were used as received from Acros.
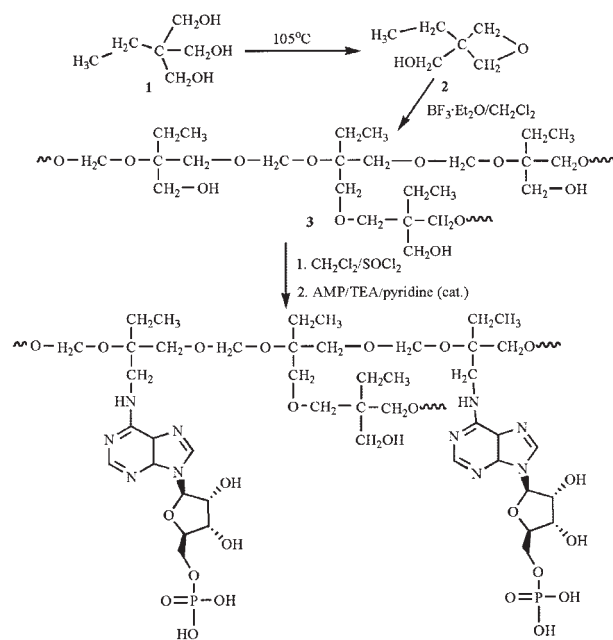
Synthesis of 3-ethyl-3-oxetanemethanol

3-Ethyl-3-oxetanemethanol was prepared by a modified procedure described in the literature.[36] A mixture of trimethylopropane (1, 26.8 g, 0.2 mol), diethyl carbonate (23.6 g, 0.2 mol), potassium hydroxide (0.1 g, 1.8 mmol) in 2 mL of absolute ethyl alcohol was refluxed in oil bath at 110°C for 1 h. Then, the mixture was distilled at 110°C for 1 h. Distillation was continued until the temperature of the oil bath reached 140°C. After the distillation, the vacuum was supplied for 1 h to remove the excess solvent. On heating above 185°C, the distilled materials were collected in the cold trap under vacuum and obtained >85% of the theoretical yield. ^{1}H NMR (δ, ppm): 0.80–0.83 (t, 3H, —CH$_2$CH$_3$), 1.61–1.66 (q, 2H, —CH$_2$CH$_3$), 3.62 (s, 2H, —CH$_2$OH), 3.66 (s, 1H, —CH$_2$OH), 4.31–4.32 and 4.38–4.39 (d, 4H, —CH$_2$O).

Cationic ring-opening polymerization of 3-ethyl-3-oxetanemethanol (2) using BF$_3$·OEt$_2$[37]

The cationic polymerization of 3-ethyl-3-oxetanemethanol directly initiated by BF$_3$·OEt$_2$ was carried out at under a dry nitrogen atmosphere in a three-necked round-bottomed flask with a stirrer and a funnel. The reaction temperature was controlled at 0°C, and after 24 h, the polymerization was quenched with water. The poly(3-ethyl-3-oxetanemethanol) (HBPO, 3) was precipitated in distilled water and dried at 100 °C under vacuum. ^{1}H NMR (δ, ppm): 0.82–0.85 (—CH$_3$), 1.16–1.29 (—CH$_2$CH$_3$), 2.85–3.10 (—OCH$_2$—), 3.35–3.68 (—CH$_2$OH).

Synthesis of hyperbranched polymers peripherally modified with adenosine 5′-monophosphate (4)

First, the chloride functionalized HBPO was prepared via reaction of thionyl chloride with hydrogen groups. Then, AMP groups were attached by the reaction of terminal chloride groups with AMP in CH$_2$Cl$_2$ in the presence of TEA as an acceptor of HCl. As the reaction proceeds, TEA hydrochloride precipitates from the reaction medium, and its quantity corresponds to the consumed benzoyl chloride. A precipitate of TEA hydrochloride was filtered off, and the solvent was removed under vacuum. The residue was washed several times with cold hexane. The number of hydroxyl groups consumed by AMP corresponded to 15, 45, and 75%, and the corresponding specimens were designated as HBPO-AMP1, HBPO-AMP2, and HBPO-AMP3, respectively. All the compounds were low-melting materials and soluble in most organic solvents. ^{1}H NMR (δ, ppm): 0.82–0.85 (—CH$_3$), 1.16–1.29 (—CH$_2$CH$_3$), 1.38–1.41 (—OH), 1.75–1.84 (—NH(C)N), 3.12–3.17 (—CH$_2$NH), 3.21–3.27 (—OCH$_2$—), 3.61–4.64 (—CH$_2$OH for HBPO, >CHOH and —CH$_2$OP in AMP), 4.73–4.83 (—CH$_2$NH, —CH in fructose rings), 5.30–5.32 (protons from dichloromethane), 7.67–7.70 (protons from pyridine), 8.60–8.63 (—CH(N)N in imidazole and pyrimidine rings).

Scheme 1 Reaction scheme for synthesis of hyperbranched polymer tailoring peripheral groups with adenosine 5′-monophosphate (AMP).

Characterization

^{1}H NMR spectra were recorded with an AVANCE DMX-500 NMR spectrometer by using tetramethylsilane (TMS) as internal standard at room temperature. The gel permeation chromatography (GPC) measurements were carried out on a Waters 201 with a micronstyragel column and dimethylformamide (DMF) as an eluent, and the molecular weight was calibrated with standard polystyrene (PS). Infrared spectra were recorded on Jasco IR-700 infrared spectrophotometer. The UV–visible spectra of the samples were recorded for the wavelength range 200–700 nm at 25°C on a Hawlett–Packard 8452A diode array spectrophotometer. Transmission electron micrographs were obtained

TABLE I
Characteristics of HBPO and HBPO-AMP

Sample	GPC[a]			[AMP]%[b]
	M_n	M_w	M_w/M_n	
HBPO	4650	7485	1.6	–
HBPO-AMP1	5262	8050	1.53	11.6
HBPO-AMP2	7855	11,468	1.46	40.8
HBPO-AMP3	10,250	16,605	1.62	54.6

[a] As calibrated against linear polystyrene standards with low polydispersity index. The eluent used was DMF.
[b] $[AMP]\% = (M_{HBPO-AMPn(n\ =\ 1-3)} - M_{HBPO})/M_{HBPO-AMPn(n\ =\ 1-3)}] \times 100\%$, where $M_{HBPO-AMPn\ (n\ =\ 1-3)}$, M_{HBPO} and M_{AMP} are the molar weights of HBPO-AMP, HBPO, and AMP. N_{OH} is the number of hydroxyl groups in HBPO.

on a JEOL model 1200EX instrument operated at an accelerating voltage at 160 kV.

RESULTS AND DISCUSSION

Characterization of hyperbranched polymers

The synthetic procedure for various polymers is outlined in Scheme 1. Aliphatic hyperbranched polymer with multifunctional hydroxy groups was first synthesized by the cationic polymerization of 3-ethyl-3-oxetanemethanol directly initiated by $BF_3 \cdot OEt_2$. The polymerization was carried out at under a dry nitrogen atmosphere in a three-necked round-bottomed flask with a stirrer and a funnel. The reaction temperature was controlled at 0°C, and after 24 h, the polymerization was quenched with water.[37] A series of hyperbranched polymers (HBPO) with a variable composition of AMP groups at the peripheral of HBPO cores was synthesized through the reaction of the hyperbranched polymer cores by substituting a controlled

fraction of the terminal chloride groups with AMP, using TEA as an acceptor of HCl. The molecular characteristics of synthesized compounds are shown in Table I.

The molecular weight of AMP-terminated hyperbranched polymers shows a gradual increase with substitution content. The experimentally measured molecular weights obtained from the GPC measurements were possibly lower than the factual values. The reason for this phenomenon is that PS standard-based GPC measurements underestimate the molecular weight of hyperbranched macromolecules because of their different hydrodynamic volumes compared with linear polystyrene having the same molecular weight.[38] Therefore, molecular weight obtained by GPC should be used only for comparison.[39] Meanwhile, the theoretical content of AMP groups in hyperbranched polymers gradually increases with the substitution content. However, attempts to obtain 100% substituted molecules were not successful.

^{1}H NMR data confirmed the chemical composition of the compounds (as shown in Fig. 1). Comparing the ^{1}H NMR spectrum of EOM and the isolated polymer HBPO, it is clearly seen that no rings are present in the final polymer, neither as free monomer nor incorporated in the structure.[39] By the reaction between chloride end-groups of HBPO-Cl and amido groups of AMP, HBPO is transferred into HBPO-AMP1, HBPO-AMP2, and HBPO-AMP3, respectively, with adjusting the amount of AMP. The characteristic resonances at 4.50–4.64 ppm are originated from >C*H*OH and —C*H*₂OP of AMP, and the resonances at 4.73–4.83 are originated from methylene that is connected to AMP. The resonances at 5.30–5.32 ppm and 8.60–8.63 ppm are attributed to the —C*H* in imidazole rings, while resonances at 7.67–7.70 ppm are attributed to —C*H* in pyrimidine rings.
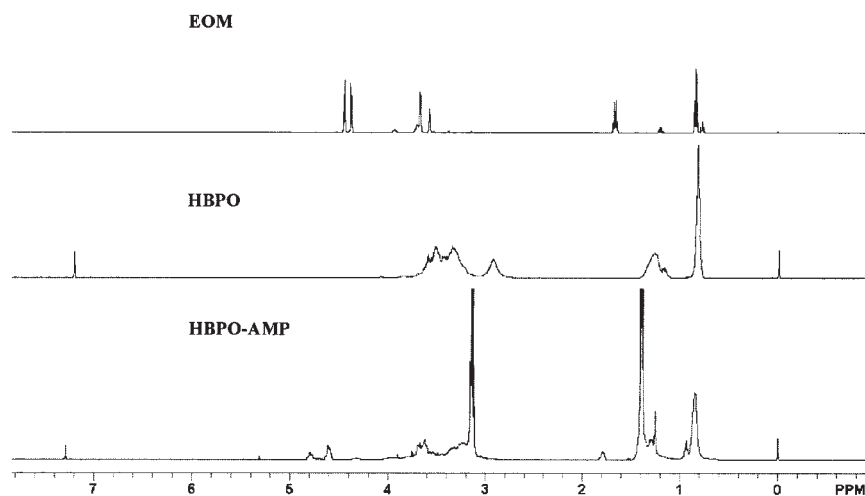

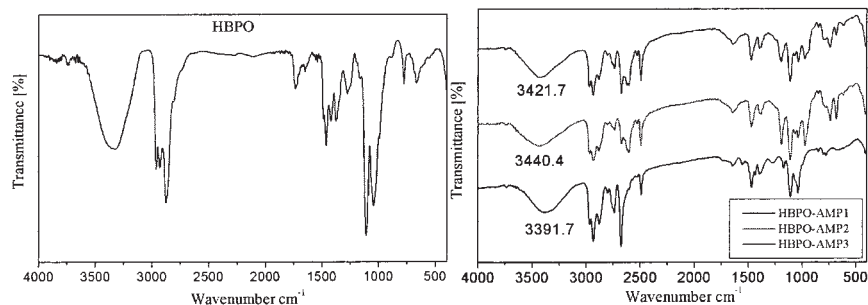**Figure 1** ^{1}H NMR spectra of EOM, HBPO, and HBPO-AMP1.

Figure 2 FTIR spectra of HBPO and HBPO-AMPn (n = 1–3).

Figure 2 exhibits FTIR transmission spectra of HBPO, HBPO-AMP1, HBPO-AMP2, and HBPO-AMP3 on substrates from $CHCl_2$ solution. All four polyester samples (HBPO-AMPn (n = 1–3) and HBPO) show the characteristic peak of the hydroxyl groups around at 3400 cm^{-1}. However, the maximum absorbance peaks of hydroxyl have slightly red-shift as increasing the level of AMP. Two strong bands deposited near 2970 and 2935 cm^{-1} in HBPO-AMPn and HBPO are attributed to the antisymmetric and symmetric CH stretching vibrations of long hydrocarbon chains, respectively. The bands located at 2738, 2675, and 2495 cm^{-1} are observed in the HBPO-AMPn samples, which are attributed to the antisymmetric and symmetric CH_2 stretching vibrations of imidazole and pyrimidine rings.

Hyperbranched polymers tailoring peripheral groups with AMP in DMF solution exhibit a broad absorption band with a maximum absorption around 270 nm for HBPO-AMP1, HBPO-AMP2, and HBPO-AMP3, respectively, (Fig. 3), which are close to those of aqueous adenosine (260 nm)[40] solution. However, by increasing content of AMP, the distinct increase in intensity can be observed.
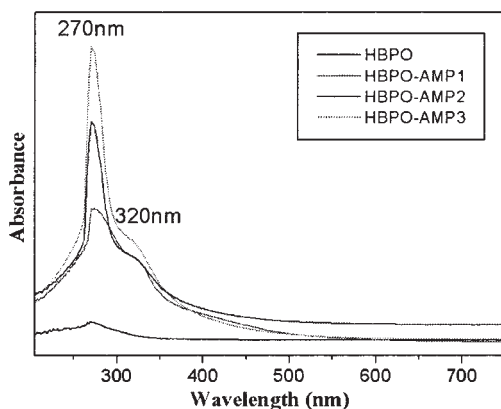

Figure 3 UV–visible spectra of HBPO and HBPO-AMPn (n = 1–3).

Self-assembly properties in trichloromethane/acetone

To observe the self-assembly behaviors, the samples were treated as follows: HBPO-AMP1, HBPO-AMP2, and HBPO-AMP3 were separately dissolved in $CHCl_3$ at room temperature. To 1 mL of each solution, 0.5 mL of acetone was dropped under whisk. The concentration of HBPO-AMPn (n = 1–3) was controlled at 5 mg/mL. After stirring 10 min, the solutions were placed overnight. A few drops of the above mixture were poured onto a carbon-coated copper grid. The samples were left at room temperature for one night before observation.

The morphologies of HBPO-AMP1, HBPO-AMP2, and HBPO-AMP3 formed from trichloromethane/acetone mixed solution were directly observed by TEM. From TEM images, we found that the star-shaped aggregates had formed in the sample of HBPO-AMP1(as shown in Fig. 4 (top)). The average diameters of star-shaped aggregates are around 150 nm. In amplificatory TEM image of HBPO-AMP1, the star-shaped aggregates are consisted of darkish arms with length around 30–50 nm and atrous cores with diameter about 130 nm. Acetone is a good solvent for AMP arms and a poor-solvent for HBPO cores.[41] In the trichloromethane/acetone mixed solvent, HBPO core tends to aggregate, and AMP groups, thus, extends the range of amphiphiles that are capable of micelles formation. The amusing aggregates are observed in HBPO-AMP1, which we believe is due to the AMP groups that extend beyond the surface of the HBPO cores. The AMP headgroups occupies a large volume because of its hydrophilic nature. Meanwhile, acetone is a strong polar solvent, and it can form polarization between the acetone and AMP. All these ensure that it enjoys maximum repulsion with its nearest neighbors. The extended AMP is a feature of micelles produced from HBPO-AMP with a low level of AMP.

On increasing the level of AMP, spherical nanoparticles are observed in the TEM images. In the cases of HBPO-AMP2 and HBPO-AMP3, the average diameter of the nanoparticles is around 100 and 110 nm, respec-
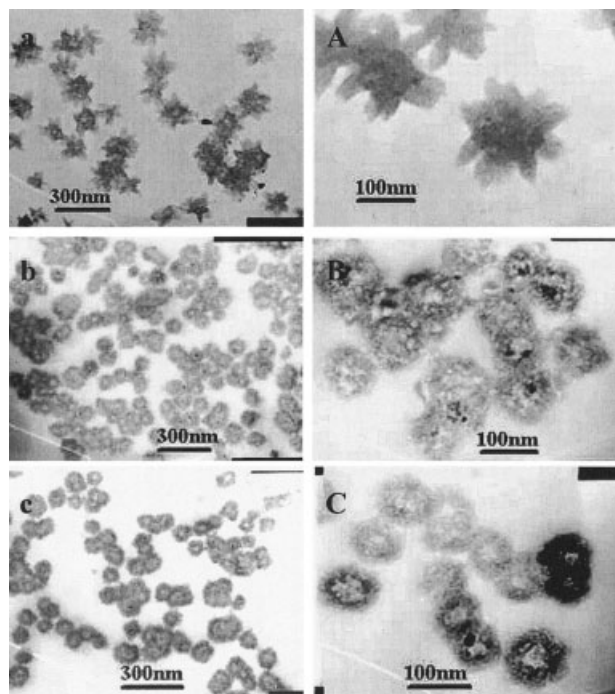
Figure 4 TEM images of HBPO-AMP1 [(a) and (A)], HBPO-AMP2 [(b) and (B)], and HBPO-AMP3 [(c) and (C)] in trichloromethane/acetone with concentration at 5 mg/mL under the room temperature.

Figure 5 TEM images of HBPO-AMP3 in trichloromethane/acetone with different concentration: (A) 1mg/mL; (B) 2.5 mg/mL; (C) 7 mg/mL; and (D) 10 mg/mL.

tively. Meanwhile, the size and shape of aggregates formed by HBPO-AMP2 and HBPO-AMP3 are homogenous. Interestingly, the spherical aggregates have core-shell structures and somewhat similar to red-blood cells in shape. The mean diameter of cores in HBPO-AMP2 and HBPO-AMP3 is around 30 nm, and the average thick of shell is about 50 nm. Comparing the amplificatory TEM images of HBPO-AMP2 and HBPO-AMP3, the core-shell structure in the HBPO-AMP3 is clearer than that in HBPO-AMP2. From these phenomena, we concluded that the shape of the aggregates and the dense of the structures depend on the level of AMP.

The morphologies of the self-assembly structure can also be affected by the concentration of polymers. Figure 5 shows the TEM images of HBPO-AMP3 in trichloromethane/acetone with different concentration. No aggregated micelles were obtained from very dilute solution below 1 mg/mL [Fig. 5(A)]. As increasing the concentration from 2.5 to 7 mg/mL in the mixed solvent, granule particles were formed [Fig. 5(B,C)]. However, even at 10 mg/mL, the particles number density is sufficiently high for the onset of self-packing of the nanoparticles [Fig. 5(D)].

From the above phenomena, we use Scheme 2 to explain the formation of self-assembly structures. Once the hydrophilic AMP content of a molecule exceeds a critical value, with the aggregation of HBPO cores, the distance between hydroxyl and imine
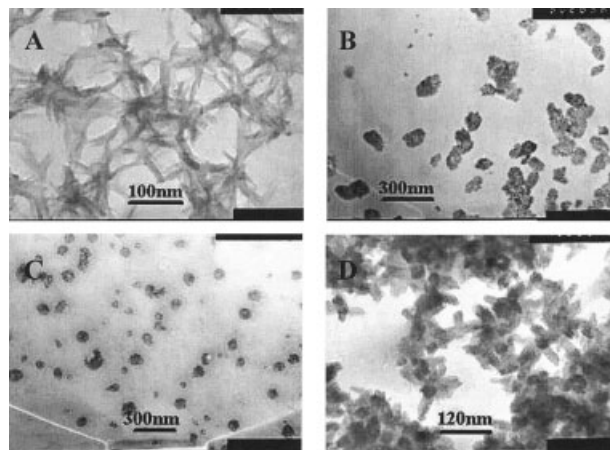
groups, hydroxyl groups in HBPO, and hydroxyl and phosphatic groups decreases, and facilitates the formation of hydrogen bonds. The hydrogen bonds from O—H—N and O—H—O drive the molecular self-assembly process. The hydrogen bond interactions from the hydroxyl groups in HBPO cores can further drive the molecular self-assembly process and strengthen the core-shell self-assembly structures. When the concentration is high enough, the particles number density is sufficiently high for the onset of self-packing of the self-assembly nanoparticles. Because the size, mesostructure, and properties of micellar building blocks can be tailored through copolymer architecture and composition, as well as the solution chemistry,[42] we suggest that the type of self-assembly structures de-
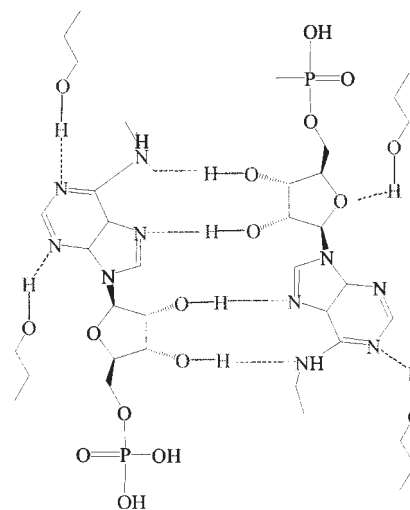
Scheme 2 The mechanism of formation the core-shell self-assembly structures driven by hydrogen bonds between H, O, and N atoms.

scribed here offers a new synthetic route to well-defined organic microstructures.

CONCLUSIONS

In summary, AMP groups were attached by reaction of terminal chloride groups with AMP in CH_2Cl_2 in the presence of TEA as an acceptor of HCl. The chloride functionalized HBPO was prepared via reaction of thionyl chloride with hydrogen groups. The resultant hyperbranched polymers were characterized by ^1H NMR, FTIR, and UV. The self-assembly of hyperbranched molecules bearing self-complementary hydrogen-bonding patterns would allow the generation of a highly organized, directional supramolecular architecture in a selected solvent. The morphologies of self-assembly structures were dependent on the level of AMP in polymer and the concentration in solvent.

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