Macromolecules

ARTICLE

pubs.acs.org/Macromolecules

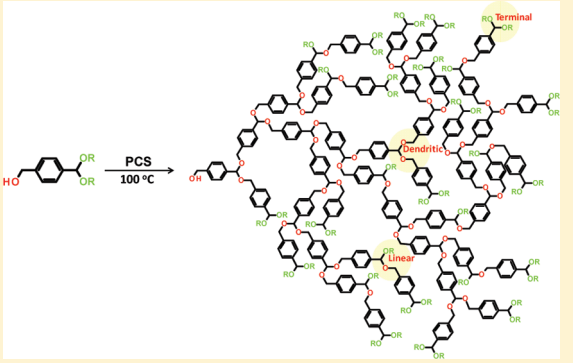
Hyperbranched Polyacetals with Tunable Degradation Rates

Saptarshi Chatterjee and S. Ramakrishnan*

Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore 560012, India

Supporting Information

ABSTRACT: We report the first synthesis of hyperbranched polyacetals via a melt transacetalization polymerization process. The process proceeds via the self-condensation of an AB_2 type monomer carrying a hydroxyl group and a dimethylacetal unit; the continuous removal of low boiling methanol drives the equilibrium toward polymer formation. Because of the susceptibility of the acetal linkage to hydrolysis, the polymer degrades readily under mildly acidic conditions to yield the corresponding hydroxyl−aldehyde as the primary product. Furthermore, because of the unique topology of hyperbranched structures, the rate of polymer degradation was readily tuned by changing just the nature of the end-groups alone; instead of the dimethylacetal bearing monomer, longer chain dialkylacetals (dibutyl and dihexyl) monomers yielded hyperbranched polymers carrying longer alkyl groups at their molecular periphery. The highly branched topology and the relatively high volume fraction of the terminal alkyl groups resulted in a significant lowering of the ingress rates of the aqueous reagents to the loci of degradation, and consequently the degradation rates of the polymers were dramatically influenced by the hydrophobic nature of the terminal alkyl substituents. The simple synthesis and easy tunability of the degradation rates make these materials fairly attractive candidates for use as degradable scaffolds.



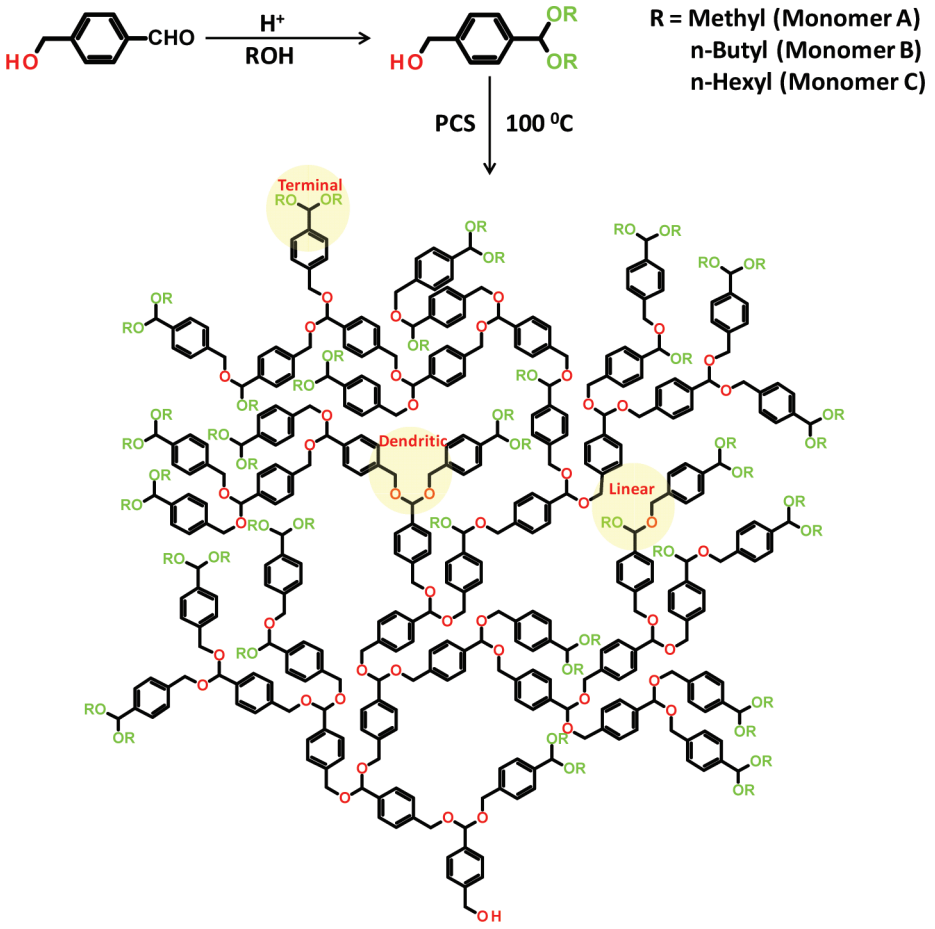
INTRODUCTION

Polymeric materials containing readily degradable (hydrolyzable) linkages in their backbone have been explored extensively in view of their potential biomedical applications.[1] Of these polymers, those containing anhydride, acetal, or ketal linkages are among the most well-studied. While polyanhydrides upon degradation yield carboxylic acids that could have some unwanted side effects, polyacetals and polyketals generate relatively benign degradation products and hence have been the focus of several recent investigations.[3] Anhydride and ketal linkages have also been incorporated into cross-linkers to generate polymeric systems that de-cross-link upon degradation.[4] Polymers that carry degradable acetal linkages in the pendant units have also been reported.[5] Murthy and co-workers reported an interesting transketalization strategy wherein they used acetone dimethylketal as one of the monomers and condensed it under acid-catalyzed transketalization conditions with a variety of diols to generate polymers that contain degradable ketal linkages in their backbone.[6] They further demonstrated the use of these polymers for drug-delivery applications.[7] Some years ago, Lemcoff et al. reported the synthesis of a second generation polyacetal dendrimer via a solution transacetalization process, although evidently extending this approach for the synthesis of higher generation may have been cumbersome.[8]

Hyperbranched polymers have attracted a great deal of attention during the past decade because of their unique properties, amenability to numerous structural modifications, and potential for applications. Many reviews and books describe the range of structures that have been reported in the literature and highlight some of their interesting applications.[9] One of the unique features of hyperbranched structures is the dominant role of the large number of peripheral end-groups in governing their solution and bulk properties.[10] Several interesting methods to modify the nature of the terminal groups of hyperbranched polymers have been recently reported.[9,11] Of the various approaches to modify the terminal groups, the AB_2 + A−R type copolymerization strategy that we had developed some years ago permits the chains ends to be modified in a single step by suitable selection of the R-group in the A−R comonomer;[12] core−shell type polymers where the peripheral shell is either hydrophobic or hydrophilic were thus prepared, and their unimolecular micellar properties were investigated.[13] A drawback of this approach is the incomplete transformation of the numerous end-groups that leads to residual B-groups in the hyperbranched structures. In a more recent improvement, we reported the direct synthesis of "clickable" hyperbranched polymers that carry either terminal propargyl[14] or allyl groups;[15] this provided an alternate route to quantitatively transform the peripheral groups to the desired units. In this report, we present a novel approach for the preparation of hyperbranched polyacetals using a simple AB_2 type monomer (**A**), namely 4-hydroxymethylbenzaldehyde, dimethylacetal. Melt-condensation of this monomer at 100 °C in

Received: February 27, 2011
Revised: May 17, 2011
Published: May 31, 2011

Scheme 1. Synthesis of Hyperbranched Polyacetals



the presence of a mildly acidic catalyst yields a hyperbranched polyacetal by exclusion of low-boiling methanol (Scheme 1). Variation in the structure of the hyperbranched polymer was achieved by starting with monomers bearing alternate dialkylacetals (monomer **B**), such as dibutylacetal or dihexylacetal; this yielded polymers that carried longer dialkylacetal end-groups, which in turn helped modulate the degradation rates of the polymer.

RESULTS AND DISCUSSION

Synthesis and Structural Elucidation. Some years ago, Murthy and co-workers reported the use of transketalization process to prepare linear polyketals;[6] they carried out the reaction in the presence of a solvent and drove the reaction to completion by continuous removal of low-boiling methanol. Over a decade ago, we reported a novel melt transetherification process for the preparation of specific types of polyethers, wherein a monomer carrying two benzylmethyl ether groups was allowed to condense with a diol in the presence of an acid catalyst by exclusion of low-boiling methanol as a condensate.[16] We further extended this approach for the preparation of a variety of hyperbranched polyethers using a suitably designed AB_2 type monomer.[17] In the polyether case, it was essential to ensure that side-reactions, such as electrophilic aromatic substitution which could lead to cross-linking, are precluded by the use of permethylated aromatic monomers. On the basis of the studies of Heffernan et al.,[6] it was evident that electrophilic aromatic substitution may not pose a serious problem during the transketalization process because of the intrinsic lower reactivity of the incipient carbocation; this is possibly due to both electronic (a more stable cation due to adjacent oxygen) and steric reasons (a secondary cation). On the basis of this premise, we designed a fairly simple AB_2 monomer based on 4-hydroxymethylbenzaldehyde. Reduction of one of the aldehyde groups in terephthaladehyde yielded 4-hydroxymethylbenzaldehyde, which upon treatment with trimethyl orthoformate gave the required dimethylacetal monomer **A** (Scheme 1). Polymerization of this monomer was carried out in the melt at 100 °C using a mildly acidic catalyst, namely pyridinium camphorsulfonate (PCS).[18] Rapid bubbling of the melt due to the evolution of methanol suggested that the polymerization was proceeding as expected. After a 1.5 h under dry nitrogen purge, the polymerization was continued for 30 min at 100 °C under reduced pressure using a Kugelrohr setup to ensure uniform mixing. The polymer HPBA-Me was dissolved in THF and reprecipitated into methanol (containing triethylamine to prevent inadvertent degradation); this dissolution and reprecipitation was done twice to ensure removal of residual catalyst and low molecular weight oligomers. The polymer was obtained as a soft white solid. The molecular weight (M_w) of the polymer was determined by GPC and was found to be about 21 000 with a PDI of 3.0; the high polydispersity being typical for hyperbranched polymers prepared via the self-condensation of an AB_2 monomer.[19]

dx.doi.org/10.1021/ma2004663 |*Macromolecules* 2011, 44, 4658–4664

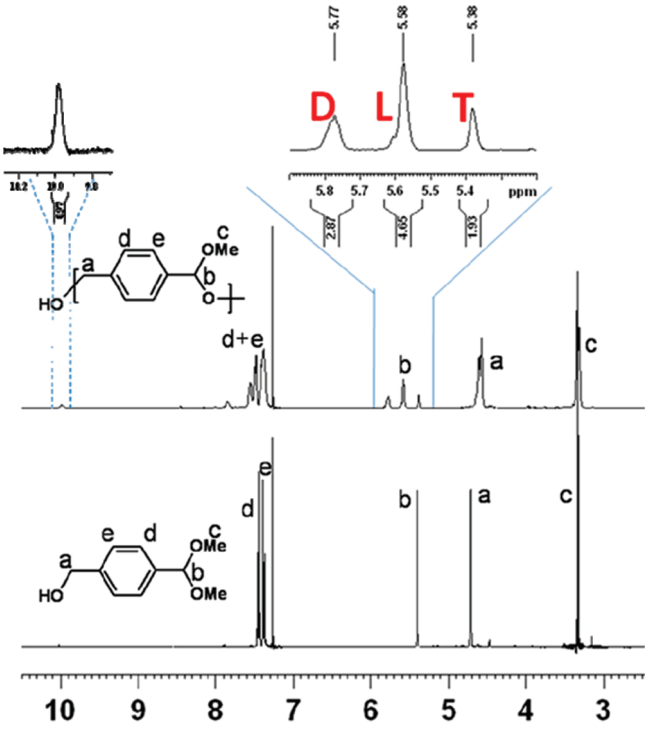


Figure 1. Proton NMR spectra of monomer **A** and the polymer HBPA-Me recorded in $CDCl_3$.

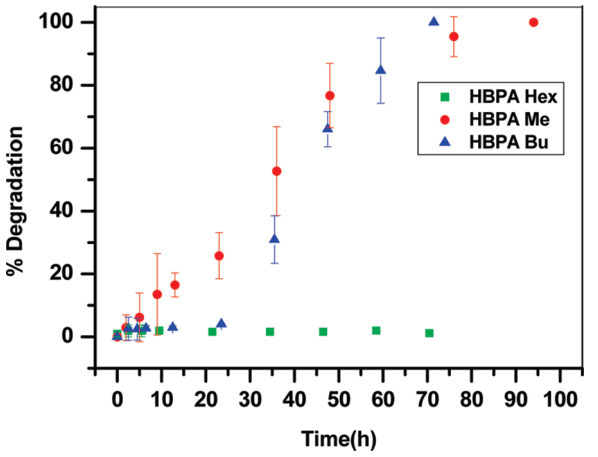


Figure 2. Plot of percent degradation versus time for the three different hyperbranched polyacetals: HBPA-Me, HBPA-Bu, and HPBA-Hex. Inset shows the expanded region of the early stages of degradation.

The proton NMR spectra of the monomer and the polymer HPBA-Me, along with their peak assignments, are shown in Figure 1. Apart from the broadening of the peaks in the polymer spectrum, a substantial reduction in the relative intensity of the methoxy protons (peak c), because of the expected loss of 1 mol of methanol, is evident. Additionally, the benzylic methylene protons in the monomer (peak a) undergoes the expected upfield shift upon polymerization, and interestingly, the methine proton of the acetal unit (peak b), which is a singlet in the monomer, splits into three well-resolved peaks in the polymer. On the basis of the relative positions of these three peaks, the peaks can be assigned to dendritic (D), linear (L), and terminal (T) units, as shown in the figure (see Scheme 1, for the structures of these subunits); the most upfield peak is assigned to terminal units (by comparison with the monomer) and the center one to the linear units while the most downfield peak is assigned to dendritic units. This assignment was further confirmed by carrying out T_1 measurements, which clearly helps distinguish the relatively less mobile dendritic methine units from the linear and terminal ones;[20] the D methine protons had the shortest T_1 (937 ms), followed by the L units (1118 ms) and then the T ones (1875 ms) (see Figure S1). From the relative intensities of these three peaks the degree of branching (DB) of the polymer was estimated to be around 0.55, which is roughly the expected value for a statistically random growth process.[21] In the present polymer, since the methine proton is directly linked to the branching carbon atom, the peaks due to the three types of units (D, L, and T) are well-resolved; this permits the direct estimation of the DB by comparison of their relative intensities without having to resort to comparison with model compounds. Earlier, we had shown that the use of an aromatic solvent,[20a] like C_6D_6, for recording the NMR spectrum leads to a remarkable improvement in peak separation, which permitted a similar estimation of the DB in the case of polyethers. Interestingly, in the present system also, the use of C_6D_6 led to further splitting of two of the methine peaks (see Figure S2), the origin of which we think may be due to tacticity. It is important to recognize here that the linear (L) and dendritic (D) units are chiral and therefore different sequences of these chiral centers may be expected to exhibit distinct peaks, as in simple linear polymers, such as polypropylene. Further experiments would be required to confirm this hypothesis. Another interesting aspect of the spectrum is the presence of an aldehyde proton peak at around 10 ppm, which is clearly evident in the *y*-expanded spectrum; this presumably is due to inadvertent hydrolysis of some of the acetal groups. The relative intensities of the three acetal methine peaks (peaks b) appear to suggest that preferential hydrolysis of the terminal dimethylacetal (T) units may have occurred; this is reflected by the commensurate decrease in the intensity of the terminal methine peak with increase in the intensity of the aldehyde peak.[22] This is particularly true in the case of the butoxy- and hexyloxy-teminated polymers (HBPA-Bu and HBPA-Hex), wherein the increase in the intensity of the aldehyde protons results in a perfectly matched reduction in the intensity of the terminal (T) methine proton peak at 5.38 ppm (see Figure 3); this confirms that inadvertent hydrolysis may have occurred primarily at the terminal acetal units. A new peak, having twice the intensity of the aldehyde peak, due to the two aromatic (ortho) protons is also seen at ca. 7.85 ppm.

Degradation Studies. The degradation studies of the polymer HBPA-Me were carried out by taking a fixed amount of the polymer in a glass vial along with a buffer solution of pH 4; the solution was gently agitated and aliquots of the supernatant were taken after varying times and analyzed by HPLC to quantify the amount of 4-hydroxybenzaldehyde (Figure S4). A plot of the percent degradation as a function of time is shown in Figure 2; it is evident that the hyperbranched polymer HBPA-Me degrades rapidly, although at very early stages the rate is evidently slower, as seen in the inset (Figure 2), which is suggestive of a short induction period.

Thus, it appears that the overall degradation rate of HBPA-Me is fairly rapid, possibly because of the completely amorphous nature of the polymer. As the intrinsic hydrolysis rates of the acetal linkages may be rather difficult to control, an alternate approach would be to control the rate of ingress of water into the

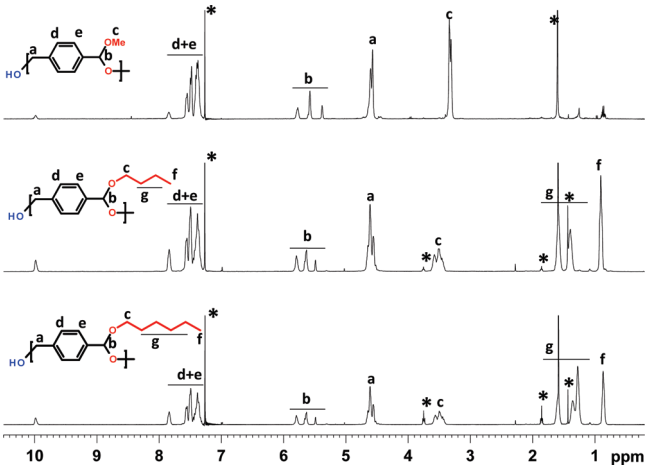


Figure 3. Comparison of proton NMR spectra of polymers HBPA-Me, HBPA-Bu, and HPBA-Hex. Peaks marked with an asterisk is due to water or residual solvent (THF).

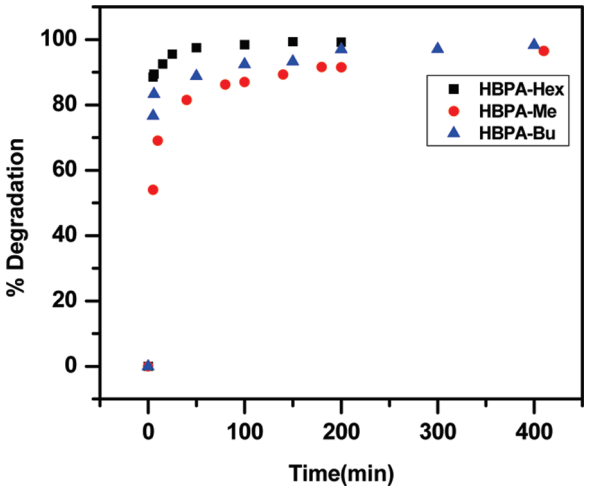


Figure 4. Plot of percent degradation versus time for the three different hyperbranched polyacetals: HBPA-Me, HBPA-Bu, and HPBA-Hex in $CDCl_3$ solution having catalytic amount of TFA.

matrix, which in turn would control the degradation rates; this is a strategy that has been utilized in a variety of linear degradable matrices.[23] In hyperbranched polymers, the control of water ingress should be achievable by varying the nature of the peripheral end-groups. Our first attempt at doing so utilized the AB_2 + A−R type copolymerization route that we had recently developed;[12] to achieve this the dimethylacetal monomer (**A**) was taken along with 0.95 equiv of a long-chain aliphatic alcohol, such as cetylalcohol, and polymerized under the previously described melt transacetalization conditions. The NMR spectrum of the resulting polymer showed that complete transformation of the methyl ketal units to cetyl units had occurred (Figure S7); however, the molecular weight of the polymer was significantly lower (M_w = 1800). Therefore, we chose to develop an alternate route to prepare hyperbranched polyacetals carrying long chain alkyl groups at the termini. To achieve this, two other AB_2 type monomers (**B** and **C** in Scheme 1) were prepared by treating 4-hydroxymethylbenzaldehyde with other alcohols, such as butanol and hexanol; these monomers also could be polymerized at 100 °C, and during the second step of the polymerization under reduced pressure (20 mbar) the condensate (butanol or hexanol) was readily removed to drive the reaction to completion. While the butoxy-terminated polymer (HBPA-Bu) was isolated as a semisolid, the hexyloxy-terminated polymer (HBPA-Hex) was a highly viscous liquid. The proton NMR spectra of these two polymers are compared with that of HPBA-Me in Figure 3. The NMR spectra of both HBPA-Bu and HBPA-Hex exhibit the same type of splitting of the acetal methine region, into three distinct peaks, as was earlier seen in HBPA-Me. However, in both these cases the inadvertent hydrolysis of some of the acetal linkages appears to have occurred to a greater extent than in HBPA-Me, as evident from the relatively more intense peaks at around 7.85 and 10 ppm, which are associated with the hydrolyzed unit. As mentioned earlier, the intensity of the aldehyde peak has clearly grown at the expense of the terminal (T) unit; comparison of the intensities of peaks due to the D and T units, which are expected to have the same intensity, clearly reveals that the extent of decrease of the intensity of the T methine protons almost exactly matches the increase in the aldehyde peak intensity (see Supporting Information for details). On the basis of the assumption that the depletion of T peak intensity is due to inadvertent hydrolysis, the DB was estimated as before and the values were in the vicinity of 0.6, slightly higher than expected. This also implies that the inadvertent hydrolysis need not have resulted in a substantial decrease in the overall molecular weight of the polymers; this was confirmed from the M_w values of HPBA-Bu and HPBA-hex, which were determined to be 22 300 and 50 100, respectively, using GPC.

The influence of the terminal long chain alkyl groups on the degradation rates of the hyperbranched polymers was examined by subjecting the polymers to degradation studies as was done earlier. Comparison of the degradation profiles (Figure 2) clearly reveals that the HPBA-Bu exhibits a significantly longer induction period when compared to HBPA-Me. However, once the degradation begins the rate of degradation is not significantly different, as evident from the similar slopes immediately following the induction period. The induction period in these systems may reflect the occurrence of selective degradation of the terminal units during the initial stages; since HPLC monitors only the release of 4-hydroxymethylbenzaldehyde, degradation of the terminal acetals linkages alone would not noticeable. Subsequently, however, when the degradation of the backbone acetal linkages occur, 4-hydroxymethylbenzaldehyde would be released and monitored. The similar slopes after the induction period is also consistent with the fact that, once the removal of the terminal dibutyl acetals groups is complete, the remaining structure in all cases would be essentially the same, except for the linear defect units (L); these units, it appears, exert a smaller influence on the degradation rates. One must recall here that the primary difference in the structures of the three different hyperbranched polyacetals is the nature of their terminal groups, and in the perfect dendrimeric limit,[24] the rest of the units in the polymer are identical. The hyperbranched polymer HBPA-hex, on the other hand, exhibited effectively no degradation even after 3 days, suggesting that the peripheral hexyl groups, as anticipated, do present a hydrophobic barrier to the aqueous acid and prevents diffusion to the sites of degradation. As in the case of the butyl polymer HPBA-Bu, in this case too once this barrier is broken one may anticipate the onset of a rapid degradation process; this observation provides an intriguing opportunity to design systems that may exhibit a burst release profile.

dx.doi.org/10.1021/ma2004663 |*Macromolecules* 2011, 44, 4658–4664

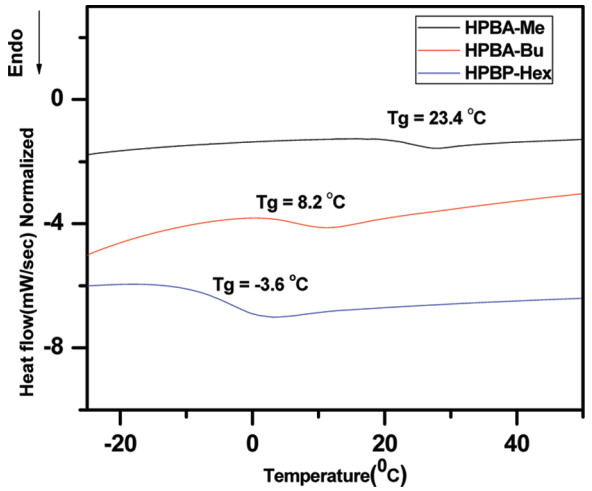


Figure 5. DSC thermograms of hyperbranched polyacetals.

In an effort to further confirm this hypothesis of the role of the peripheral groups, the degradation rates of all the three hyperbranched polyacetals were also examined in solution, using NMR spectroscopy. $CDCl_3$ solutions of the polymer samples were taken in an NMR tube, and a catalytic amount of CF_3COOH (3 mol %) was added to it; the proton NMR spectra of the sample was then recorded after different time intervals. The catalyst concentration was chosen to ensure that the rate of degradation was reasonably slow so that their degradation kinetics can be followed reasonably well using NMR spectroscopy; even so as seen from Figure 4, the degradation rates in all cases appear to reach a plateau within the first 6−10 min. Importantly, the solution degradation rates clearly suggests that the intrinsic degradation rates of the acetal linkages in all the polymers, as expected, is not very different, and hence the difference in the degradation rates seen in the bulk samples indeed reflects the diffusion rates of the aqueous acid into the polymer matrix.

It is well-known that the thermal properties of hyperbranched polymers are also strongly influenced by the nature of the peripheral groups.[25] To understand the influence in the present series of hyperbranched polyacetals, DSC studies of the samples were carried out; it is evident from Figure 5 that all the polymers are amorphous, and their glass transition temperature decreases significantly as the length of the peripheral alkyl groups increases—while the T_g of HBPA-Me is around 23 °C that of HBPA-Hex is −3.6 °C. From the applications point of view, it may be beneficial to deal with polymers having higher T_g which are solids at room temperature; this we believe can be readily achieved by inclusion of a certain mole fraction of strongly interacting groups at their periphery, such as aromatic units.

In conclusion, we have shown that hyperbranched polyacetals can be readily prepared via a melt transacetalization process of an AB_2 monomer bearing a single hydroxyl group and a dialkyl acetal; the polymerization is driven to high conversion by the continuous removal of the alcohol from the polymerization mixture, under reduced pressure. Hyperbranched polyacetals carrying three different peripheral alkyl groups (methyl, butyl, and hexyl) were thus prepared by suitable modification of the monomer structure; the dihexyl acetal based monomer was also shown to undergo transacetalization at 100 °C under reduced pressure that enabled the removal of *n*-hexanol as the condensate. The bulk degradation rates of these hyperbranched polyacetals under mildly acidic pH (pH = 4) clearly revealed the strong dependence of the degradation rates on the nature peripheral alkyl substituents; HBPA-Me exhibited a short induction period while HBPA-Hex did not degrade even after 72 h. On the basis of NMR studies that showed similar of solution degradation rates for all the three polymers, it was concluded that the ingress rates of the aqueous acid into the bulk polymer sample was the main factor that affects the bulk degradation kinetics. Interestingly, the primary difference between the bulk degradation profiles of HBPA-Me and HBPA-Bu was in the induction period; once the degradation began, the rates in both cases appear to be very similar. Since, we were following the degradation rates by monitoring the formation of 4-hydroxybenzaldehyde, we reasoned that during the induction period only the terminal dibutyl acetal (or the dimethyl acetal in the case of HBPA-Me) linkages could be cleaving; once these peripheral acetal groups are cleaved, the access of the reagent to the remaining acetal linkages is enhanced and causes a rapid increase in the degradation rates. Importantly, the similar rates after the induction period in both HPBA-Me and HPBA-Bu appear to support this hypothesis, as it is clear that once the peripheral dialkyl acetals linkages are removed the remaining structure is rather similar for all the hyperbranched polyacetals.[26] In essence, therefore, these hyperbranched polyacetals may be viewed as peripherally encased molecular systems wherein the initial induction period is governed by the access of the aqueous regents to the peripheral acetal units—once the casing is removed, a rapid degradation ensues. Such degradation profiles may find some interesting applications in drug delivery where a sudden release of a drug may be required. Further studies to tune the degradation rates by using a variety of peripheral groups using alternate strategies, such as AB_2 + A−R copolymerization or generation of clickable hyperbranched polyacetals, are currently underway.

EXPERIMENTAL SECTION

Materials. Terephthalaldehyde, sodium borohydride, triethyl orthoformate, and *p*-toluenesulfonic acid were purchased from Sigma-Aldrich Chemical Co. and used directly. Butanol and hexanol were purchased from Spectrochem Chemicals Ltd., while common organic solvents and reagents were procured from Ranbaxy, Spectrochem, or Nice Chemicals. Solvents were distilled prior to use and, if necessary, were dried following the standard procedures.

Methods. ^{1}H NMR spectra were recorded using a Bruker 400 MHz spectrometer using $CDCl_3$ as the solvent and TMS as internal reference, unless otherwise mentioned. The absorption spectra were recorded using Cary UV−vis spectrophotometer. GPC measurements were carried out using Viscotek triple detector analyzer (TDA) model 300 system, which has a refractive index (RI), a differential viscometer (DV), and light scattering (LS) connected in series. The separation was achieved using a series of two PL gel 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 RI and DV detectors using narrow polystyrene standards. The glass transition temperature of the sample was determined using a Mettler Toledo DSC instrument at a heating rate of 10 °C/min, under dry N_2 atmosphere. The samples were first heated to 100 °C (to ensure that the sample flows and makes the contact with the pan) and quenched prior to recording the T_g.

Synthesis of the Monomers. *4-(Hydroxymethyl)benzaldehyde.* $NaBH_4$ (0.35 g, 9.25 mmol) was added at −5 °C with continuous stirring

for 30 min to a solution of terepthalaldehyde (5 g, 37.3 mmol) in a mixture of 95% EtOH (70 mL) and THF (100 mL). Then the mixture was stirred for 6 h, while the temperature was maintained 0 °C. Then the reaction mixture was neutralized with 2 M HCl to pH 5, the solvents were evaporated, water (200 mL) was added to the residue, and products were extracted with ethyl acetate. Combined organic extracts were dried with $MgSO_4$, and the solvent was evaporated. The product was purified by column chromatography using an AcOEt−Petether (1:4) mixture of solvents. The yield was 4.1 g (82%); mp 40 °C. NMR (400 MHz, $CDCl_3$, δ ppm): 10 (s, 1H, C**H**O) 7.88 (d, 2 H, Ar−H's), 7.54 (d, 2 H, Ar−H's), 4.80 (d, 2 H, ArC$\mathbf{H}_2$).

[4-(Dimethoxymethyl)phenyl]methanol. 1.5 g (12.1 mmol) of 4-hydroxymethylbenzaldehyde was taken in 20 mL of dry methanol in a round-bottomed flask, and 9.7 g (90.9 mmol) of trimethyl orthoformate was added to it. A catalytic amount of methanolic HCl was added, and it was refluxed for 24 h. Then a small amount of $NaHCO_3$ was added and stirred for half an hour to neutralize the acid. The reaction mixture was filtered, and solvent was removed using a rotary evaporator. The pale yellow liquid product was purified by column chromatography using AcOEt−Petether (2:8) mixture of solvents. The yield was 1.5 g (75%). NMR (400 MHz, $CDCl_3$, δ ppm): 7.46 (d, 2H, Ar−H's) 7.38 (d, 2 H, Ar−H's), 5.4 (s, 1 H, ArC**H**$(OCH_3)_2$), 4.71 (d, 2 H, ArC$\mathbf{H}_2$), 3.34 (s, 6H, ArCH(OC$\mathbf{H}_3)_2$).

[4-(Dibutoxymethyl)phenyl]methanol. 2.5 g (18.38 mmol) of 4-(hydroxymethyl)benzaldehyde was taken in a RB along with 10 mL of dry *n*-butanol. 50 mL of dry benzene was added into it. A catalytic amount of PTSA was added in it. The reaction mixture were then heated to 85 °C for 24 h, and the water formed during this step was azeotropically removed using a Dean−Stark's apparatus. The acid was neutralized using $NaHCO_3$. Benzene and excess butanol were removed under reduced pressure. Product was purified as pale yellow oil by column chromatography using AcOEt−Petether (2: 8) mixture of solvents. The yield was 2 g (40%). NMR (400 MHz, $CDCl_3$, δ ppm): 7.48 (d, 2H, Ar−H's) 7.37 (d, 2 H, Ar−H's), 5.5 (s, 1 H, ArC**H**$(OBu)_2$), 4.71 (d, 2H, ArC$\mathbf{H}_2$), 3.56−3.44 (t, 4H, OC$\mathbf{H}_2$C$\mathbf{H}_2$C$\mathbf{H}_2$C$\mathbf{H}_3$), 1.67−1.3 (m, 8H, C$\mathbf{H}_2$C$\mathbf{H}_2$C$\mathbf{H}_3$), 0.9 (t, 6H, C$\mathbf{H}_3$).

[4-(Dihexoxymethyl)phenyl]methanol. 2.0 g (14.7 mmol) of 4-(hydroxymethyl)benzaldehyde was taken in a RB along with 20 mL of dry *n*-hexanol. 50 mL of dry benzene was added into it. A catalytic amount of PTSA was added in it. The reaction mixture were then heated to 85 °C for 24 h, and the water formed during this step was azeotropically removed using a Dean−Stark's apparatus. The acid was neutralized using $NaHCO_3$. Benzene and excess hexanol was removed under reduced pressure. Product was purified as pale yellow oil by column chromatography using AcOEt−Petether (1: 9) mixture of solvents. The yield was 4 g (85%). NMR (400 MHz, $CDCl_3$, δ ppm): 7.47 (d, 2H, Ar−H's) 7.35 (d, 2 H, Ar−H's), 5.5 (s, 1 H, ArC**H**$(OBu)_2$), 4.71 (d, 2H, ArC$\mathbf{H}_2$), 3.56−3.41 (t, 4H, OC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.69−1.25 (m, 16H, C$\mathbf{H}_2$C$\mathbf{H}_2$C$\mathbf{H}_2$C$\mathbf{H}_2$), 0.9 (t, 6H, C$\mathbf{H}_3$).

General Polymerization Procedure. 4-(Dimethoxymethyl)phenyl] methanol 0.5 g (2.74 mmol) was taken in a polymerization flask along with 2 mol % of pyridinium camphorsulfonate. The reaction mixture was degassed by purging N_2 for 15 min and then heated to 80 °C under a N_2 atmosphere to ensure homogeneous mixing of the catalyst and monomers. Then the polymerization was carried out at 100 °C for 1 h under N_2 purging. Then the polymerization tube was connected to a Kugelrohr apparatus, and the polymerization was continued at 100 °C under reduced pressure of 20 Torr for 30 min. The polymer was dissolved in THF, and the solution of the polymer was neutralized by solid $NaHCO_3$ and filtered. The filtrate was concentrated and poured into dry methanol containing a little triethylamine to obtain the polymer. This polymer was further purified through dissolution followed by reprecipitation using THF−methanol. Yield = 72%. In the case of HPBA-Bu polymerization was carried out in Kugehlrohr for 1 h and yield was 59%, while in the case of HPBA-Hex, polymerization was carried out in an oil bath for 1.5 h, followed by 1 h in Kugehlrohr; the yield was 75%.

Degradation Studies. For degradation study of the polymer in water, typically 2−3 mg of polymer was taken in a vial containing 10 mL of pH 4 buffer solution. The solution was agitated mildly, 5 μL of supernatant solution was injected in HPLC in a certain time interval, and the peak at 254 nm, which corresponds to degradation product 4-(hydroxymethyl)benzaldehyde, was monitored. Percentage hydrolysis was calculated from area under curve and comparing to a standard calibration curve for 4-(hydroxymethyl)benzaldehyde.

For degradation studies in chloroform, 5−6 mg of polymer was dissolved in 400 μL of $CDCl_3$. Proton NMR spectra were taken. Then 40 μL of 0.04 M $CDCl_3$ solution of TFA was added into it. Proton NMR spectra of the solution were taken in certain intervals. Percentage hydrolysis was calculated from the relative increment of the aldehyde peak at 10 ppm.

■ ASSOCIATED CONTENT

Supporting Information. Spin-inversion recovery plots for T_1 determination, solution degradation studies by NMR, and heterogeneous degradation studies in D_2O by NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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

■ ACKNOWLEDGMENT

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

■ REFERENCES

(1) (a) *Handbook of Biodegradable Polymers*; Bastioli, C., Ed.; Rapra Technology: Shrewsbury, UK, 2005. (b) *Synthetic Biodegradable Polymer Scaffolds*; Mooney, D. J., Atala, A., Eds.; Birkhauser: Boston, MA, 1997. (c) *Principles of Tissue Engineering*; Lanza, R. P., Langer, R., Vacanti, J., Eds.; Academic Press: Austin, TX, 1997. (d) *Controlled Release of Biologically Active Agents*; Baker, R., Ed.; John Wiley & Sons: New York, 1987. (e) *Biodegradable Polymers as Drug Delivery Systems*; Chasin, M., Langer, R., Eds.; Marcel Dekker: New York, 1990.

(2) (a) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181. (b) Langer, R. *Acc. Chem. Res.* **1993**, *26*, 537. (c) Green, J. J.; Langer, R.; Anderson, D. *Acc. Chem. Res.* **2008**, *41*, 749. (d) Gombotz, W.; Pettit, D. *Bioconjugate Chem.* **1995**, *6*, 332. (e) Burkoth, A. K.; Anseth, K. S. *Biomaterials* **2000**, *21*, 2395. (f) Heller, J.; Barr, J. *Biomacromolecules* **2004**, *5*, 1625.

(3) (a) Wang, Y.; Morinaga, H.; Sudo, A.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 596. (b) Tomlinson, R.; Klee, M.; Garrett, S.; Heller, J.; Duncan, R.; Brocchini, S. *Macromolecules* **2002**, *35*, 473. (c) Falco, E. E.; Patel, M.; Fisher, J. P. *Pharm. Res.* **2008**, *25*, 2348.

(4) (a) Murthy, N.; Thng, Y. X.; Schuck, S.; Xu, M. C.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2002**, *124*, 12398. (b) Murthy, N.; Xu, M.; Schuck, S.; Kunisawa, J.; Shastri, N.; Fréchet, J. M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 4995. (c) Kwon, Y. J.; Standley, S. M.; Goodwin, A. P.; Gillies, E. R.; Fréchet, J. M. J. *Mol. Pharmaceutics* **2005**, *2*, 83. (d) Broaders, K. E.; Pastine, S. J.; Grandhe, S.; Fréchet, J. M. J. *Chem. Commun.* **2011**, *47*, 665. (e) Li, Y.; Du, W.; Sun, G.; Wooley, K. L. *Macromolecules* **2008**, *41*, 6605.

(5) (a) Morinaga, H.; Morikawa, H.; Wang, Y.; Sudo, A.; Endo, T. *Macromolecules* **2009**, *42*, 2229. (b) Murthy, N.; Campbell, J.; Fausto, N.; Hoffman, A. S.; Stayton, P. S. *J. Controlled Release* **2003**, *89*, 365.

(c) Gillies, E. R.; Jonsson, T. B.; Frechet., J. M. *J. Am. Chem. Soc.* **2004**, *126*, 11936.
(6) Heffernan, M. J.; Murthy, N. *Bioconjugate Chem.* **2005**, *16*, 1340.
(7) (a) Lee, S.; Yang, S. C.; Heffernan, M. J.; Taylor, W. R.; Murthy, N. *Bioconjugate Chem.* **2007**, *18*, 4. (b) Yang, S. C.; Bhide, M.; Crispe, I. N.; Pierce, R. H.; Murthy, N. *Bioconjugate Chem.* **2008**, *19*, 1164.
(8) Lemcoff, N. G.; Fuchs, B. *Org. Lett.* **2002**, *4*, 731.
(9) (a) Voit, B. I.; Lederer, A. *Chem. Rev.* **2009**, *109*, 5924. (b) Gao, C.; Yan, D. *Prog. Polym. Sci.* **2004**, *29*, 183. (c) Jikei, M.; Kakimoto, M. *Prog. Polym. Sci.* **2001**, *26*, 1233. (d) Voit, B. I. *J. Polym. Sci., Polym. Chem.* **2000**, *38*, 2505. (e) Hawker, C. J. *Adv. Polym. Sci.* **1999**, *147*, 113.
(10) (a) Zhou, Y.; Yan, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4896. (b) Mai, Y.; Zhou, Y.; Yan, D. *Macromolecules* **2005**, *38*, 8679. (c) Satoh, T.; Tamaki, M.; Kitajyo, Y.; Maeda, T.; Ishihara, H.; Imai, T.; Kaga, H.; Kakuchi, T. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 406.
(11) (a) Kricheldorf, H. R.; Bolender, O.; Wollheim, T. *Macromolecules* **1999**, *32*, 3878. (b) Xu, Y.; Gao, C.; Kong, H.; Yan, D.; Luo, P.; Li, W.; Mai, Y. *Macromolecules* **2004**, *37*, 6264. (c) Sunder, A.; Krämer, M.; Hanselmann, R.; Mülhaupt, R.; Frey, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3552. (d) Haag, R.; Stumbé, J.; Sunder, A.; Frey, H.; Hebel, A. *Macromolecules* **2000**, *33*, 8158.
(12) (a) Kumar, A.; Ramakrishnan, S. *Macromolecules* **1996**, *29*, 2524. (b) Kumar, A.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem.* **1996**, *34*, 839. (c) Saha, A.; Ramakrishnan, S. *Macromolecules* **2008**, *41*, 5658. (d) Saha, A.; Ramakrishnan, S. *Macromolecules* **2009**, *42*, 4028.
(13) Saha, A.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem.* **2009**, *47*, 80.
(14) (a) Saha, A.; Ramakrishnan, S. *Macromolecules* **2009**, *42*, 4956. (b) Ramkumar, S. G.; Rose, K. A. A.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem.* **2010**, *48*, 3200.
(15) Roy, R. K.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem.* **2011**, *49*, 1735.
(16) Jayakannan, M.; Ramakrishnan, S. *Macromol. Chem. Phys.* **2000**, *201*, 759.
(17) (a) Jayakannan, M.; Ramakrishnan, S. *Chem. Commun.* **2000**, 1967. (b) Behera, G.; Ramakrishnan, S. *Macromolecules* **2004**, *37*, 9814.
(18) Behera, G.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem.* **2004**, *42*, 102.
(19) Flory, P. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1953; p 361.
(20) (a) Behera, G.; Ramakrishnan, S. *J. Polym. Sci., Polym. Chem.* **2007**, *45*, 1474. (b) Meltzer, A. D.; Tirrel, D. A.; Jones, A. A.; Inglefield, P. T.; Hedstrand, D. M.; Tomalia, D. A. *Macromolecules* **1992**, *25*, 4541. (c) Jansen, J. F. G. A.; de Brander-van den Berg., E. M. M.; Meijer, E. W. *Science* **1994**, *266*, 1226.
(21) (a) Holter, D.; Burgath, A.; Frey, H. *Acta Polym.* **1997**, *48*, 30. (b) Hölter, D.; Burgath, A.; Frey, H. *Acta Polym.* **1997**, *48*, 298.
(22) In hyperbranched polymers, the numbers of dendritic (D) and terminal (T) units are expected to be the same for high molecular weight samples; on the basis of this, the extent of depletion of the T units can be readily estimated.
(23) (a) Tamada, J. A.; Langer, R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 552. (b) Ron, E.; Turek, T.; Mathiowitz, E.; Chasin, M.; Hageman, M.; Langer, R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 4176. (c) Rosen, H. B.; Chang, J.; Wnek, G. E.; Linhardt, R. J.; Langer, R. *Biomaterials* **1983**, *4*, 131. (d) Leong, K.; Brott, B.; Langer, R. *J. Biomed. Mater. Res.* **1985**, *19*, 941. (e) Domb, A. J.; Nudelman, R. *Biomaterials* **1995**, *16*, 319. (f) Domb, A. J.; Nudelman, R. *J. Polym. Sci., Polym. Chem.* **1995**, *33*, 717.
(24) In a perfect dendrimer-like structure that does not possess linear (L) defects, only terminal and dendritic units are present; in this limit the three different hyperbranched polymers will possess identical D units but will differ only in the nature of the terminal (T) units.
(25) (a) Kim, Y. H.; Webster, O. W. *Macromolecules* **1992**, *25*, 5561. (b) Wooley, K. L.; Fréchet, J. M. J.; Hawker, C. J. *Polymer* **1994**, *35*, 4489. (c) Uhrich, K. E.; Hawker, C. J.; Fréchet, J. M. J.; Turner, S. R. *Macromolecules* **1992**, *25*, 4583. (d) Miravet, J. F.; Fréchet, J. M. J. *Macromolecules* **1998**, *31*, 3461. (e) Ishizu, K.; Tsubaki, K.; Mori, A.; Uchida, S. *Prog. Polym. Sci.* **2003**, *28*, 27.
(26) Preliminary studies to further understand the origin of the induction period in the degradation profiles was carried out by monitoring the formation of both the aldehyde and the alkanol, using NMR spectroscopy. A measured amount of the HBPA-Bu polymer was taken in the bottom of the NMR tube, and the required buffer (pH 4 buffer prepared in D_2O) was added to it. The NMR spectrum of the supernatant solution was directly monitored as a function of time, and the intensities of peaks due to the aldehyde and butanol were independently monitored; the rates of hydrolysis under these conditions were very slow and did not correspond to the bulk degradation studies done earlier under agitation. These preliminary studies do not confirm the selective hydrolysis of the peripheral dialkylacetal groups, as peaks due to the aldehyde and the alkanol appear to be growing very slowly but at similar rates. Thus, while the presence of an induction period, which varies with the hydrophobicity of the peripheral groups, not in question, further studies are required to unravel the exact mechanism for this behavior. For details refer to Figure S8.