Macromolecules 1991, *24*, 1435–1438

Comb-Burst Dendrimer Topology. New Macromolecular Architecture Derived from Dendritic Grafting

As early as 1984, we reported the synthesis and characterization of a new class of macromolecules referred to as Starburst dendrimers.[1a,b] They are distinguished from other classical macromolecules by their unique molecular structure, as described in Figure 1.

The essential features of this architecture include the systematic assembly of monomer units (〰) into *branch cells* (〰<), which are organized into treelike ensembles referred to as *dendrons*. These dendrons may be anchored to various initiator cores to produce a vast array of starburst dendrimers differing in size and morphology. Depending on the multiplicity of the core (N_c) and the branch cells (N_b), one can produce a wide variety of precise macromolecular architectures. The 2-dimensional projections shown illustrate a tridendron starburst dendrimer series with $N_c = 3$ and $N_b = 2$. Advancement from the initiator core to high generations $G = 1, 2, 3$, etc., leads to branch cell and terminal group proliferations that mimic biological cell division.

To date, successful synthetic strategies have involved either (a) in situ construction of branch cells around an initiator core[1a,b,2–5] or (b) coupling of preformed branch cells (derived from branch cell reagents) around such an attractor.[6–11] In either case, a reiterative branch cell assembly scheme is necessary for developing concentric generations and advancing the starburst architecture. As a result of these reiterative branch cell assembly operations, it is apparent that these constructions follow systematic branching rules (geometric progressions), if the assembly is near ideal. This allows one to predict the number of repeat units assembled (N_{RU}; degree of polymerization) and calculate dendrimer theoretical molecular weight as a function of initiator core multiplicity, N_c, branch cell multiplicity, N_b, and generations (G), according to the following relationships:

$$N_{RU} = N_c\left[\frac{N_b^{\,G+1} - 1}{N_b - 1}\right]$$

$$MW = M_c + N_c\left[M_{RU}\left(\frac{N_b^{\,G+1} - 1}{N_b - 1}\right) + M_t N_b^{\,G+1}\right]$$

Although starburst synthesis strategies produce very precise macromolecular structures with stoichiometric surfaces, it can be seen from the above expressions that the increase in molecular weight as a function of generation is not dramatic since the molecular weights of the repeat units, N_c, and N_b are usually small values. These issues and other details have been extensively reviewed elsewhere.[12]

We now report a new approach to dendrimer constructions, wherein N_c and N_b may be very large values as defined below, thus leading to dramatic molecular weight increases in relatively few generations. This scheme involves reiterative grafting of "reactive telechelic" polymer chains to form *dendritic graft polymers*. These "graft upon graft" comb-branched entities are referred to as *comb-burst dendrimers*. Conceptually, the scheme first involves grafting appropriate chains onto an "initiator core" chain to produce a "comb-branched" macromolecular precursor. (See Figure 2.)

Deprotection or introduction of suitable functionality onto the four "teeth" of the comb-branched polymer provides grafting sites for attachment of a second tier of branches to give the first generation in this comb-burst series. Further reiteration produces "grafts upon grafts", theoretically leading to dramatic increases in molecular weight in relatively few iterations. The number of monomer units assembled as a function of generation is determined by (a) the degree of polymerization of the graft chains and (b) the graft density upon the precursor chains. It can be seen in Figure 3 that substantial design and control of these macromolecular structures is possible. The use of appropriate nucleophilic or electrophilic moieties (B) pendant to the chains or in the backbone will permit grafting with either electrophilic or nucleophilic telechelic groups. Nongrafting comonomers may be introduced into the grafted chains, and the branch densities (graft sites) can be controlled as a function of generation. Furthermore, various R groups derived from graft chain initiator reagents may be inserted at specified generations. Most importantly, the degree of polymerization ($n_0 \rightarrow n_i$) can be controlled and introduced at desired generation levels.

In order to maintain good monodispersity, generation to generation, it is very desirable to use "living end-group" polymers (anionic and cationic) for the grafting stages, which exhibit efficient grafting characteristics. If that is not possible, effective methods for separating ungrafted chains from the comb-burst dendrimer are important to maintain monodispersity.

Architecturally, comb-burst dendrimers are similar to starburst dendrimers in that they possess three distinguishable components, namely, (a) an initiator core, (b) an interior (consisting of ensembles of graft sites to produce branch cells), and (c) terminal graft chains (i.e., analogous to terminal functionality/moieties in starburst systems). Topologically the two systems may differ dramatically. Whereas the starburst system builds by branch cell development at the termini, the comb-burst system involves branch cell construction by developing graft sites along the entire terminal graft chains.

Comb-burst branching strategies allow considerable versatility for controlling "critical molecular design parameters" (CMDP's) such as size, shape, surface chemistry, flexibility, and topology.[12] For example, size of the comb-burst dendrimer can be controlled by the size of the initiator core (N_c) as well as by the subsequent $n_0 \rightarrow n_i$ values introduced throughout the dendrimer construction. Comb-burst morphology (aspect ratios) can be designed or modulated by adjusting N_c values relative to the $n_0 \rightarrow n_i$ values (e.g., large N_c vs small $n_0 \rightarrow n_i$ values would lead to rod-type morphologies, whereas, spheroids would be expected from low N_c values). Surface chemistry will be determined by the selection of moieties for (A), (B), and R at the $n_i + 1$ generation. Interior design can be very specific by the introduction of $R_c \rightarrow R_i$ type moieties or more generally to give various interior properties (i.e., hydrophobic/hydrophilic or flexibility/rigidity, by introducing appropriate (A) and (B) comonomers). Other interior design may involve selection of appropriate graft (branching) moieties to assure thermal/hydrolytic stability. Topological control to develop hollow interiors can be envisioned by adjusting graft densities during the construction of the dendrimers (i.e., low graft densities for the early generations and higher graft densities for the latter iterations).

The first demonstration of this topology employed polyoxazoline methodology to produce comb-burst poly(ethylenimine)–poly(2-ethyl-2-oxazoline) copolymers and poly(ethylenimine) homopolymers. Model reactions involving the quenching of methyl tosylate initiated 2-ethyl-2-ox-

0024-9297/91/2224-1435$02.50/0

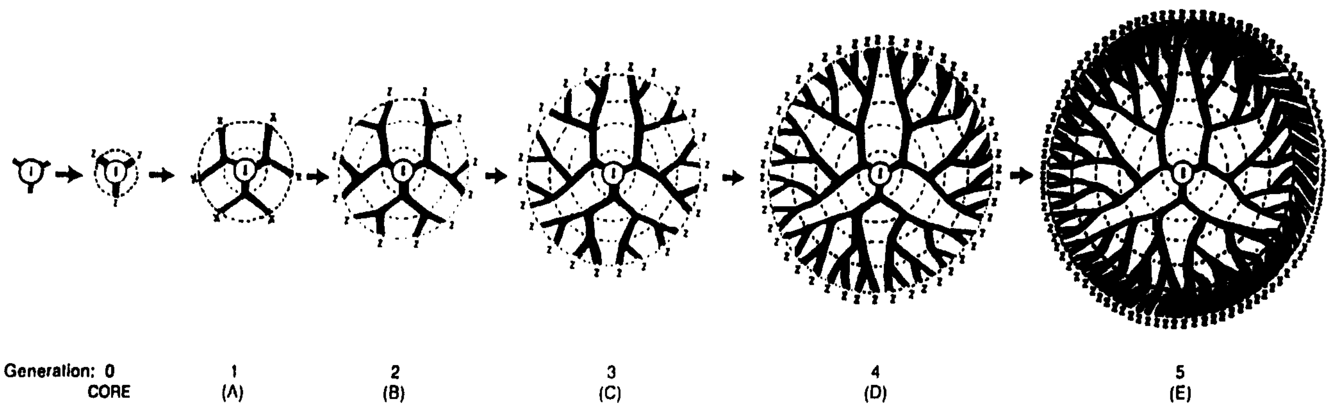


Figure 1. Two-dimensional projections of a starburst tridendron dendrimer series, where $N_c = 3$ and $N_b = 2$.

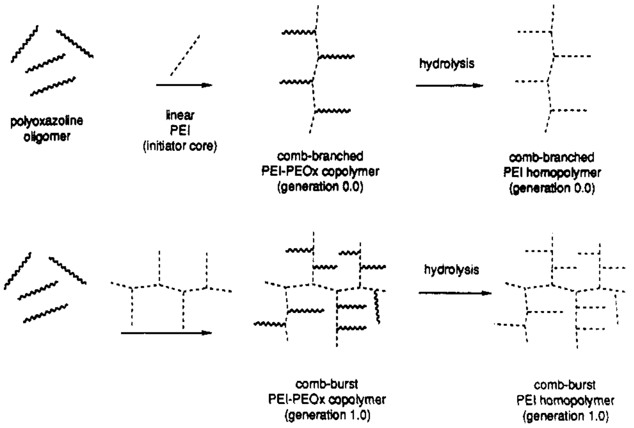


Figure 2. Two-dimensional projections of a comb-burst tetradendron dendrimer series, where $N_c = 4$ and $N_b = \sum_{0\rightarrow3}$ branch density.

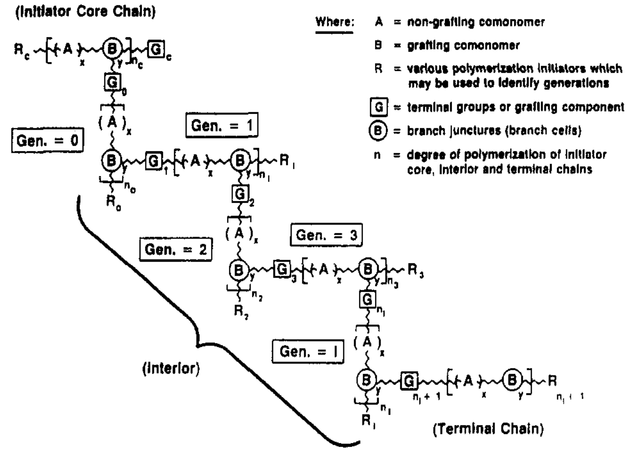
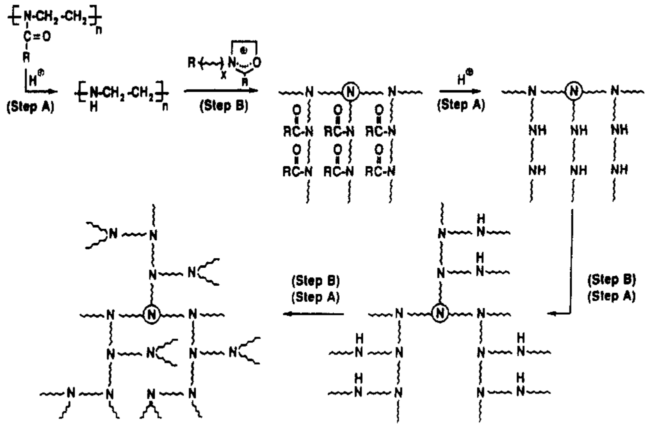


Figure 3. General representation of a comb-burst series consisting of an (a) initiator core, (b) interior A and B comonomers, and (c) terminal chains.

azoline oligomers (DP(n) = 5–20) onto secondary amines (e.g., morpholine, diethylamine) gave amine-terminated oligomers in essentially quantitative yields, proving the potential efficiency of grafting. The resulting end groups proved to be useful tags for appraising the degree of polymerization, by comparing NMR end-group integral values against oligomer chain values, and served as chemical shift references. Acidic hydrolyses of these oligomers as well as higher molecular weight poly(2-ethyl-2-oxazolines) (Dow Chemical Co.; MW = 11 000–14 000),[13] according to the methods of Saegusa,[14a,b] showed they could be deacylated nearly quantitatively or to any degree desired to generate secondary amines.

Scheme I
Synthetic Iteration Scheme Leading to Comb-Burst Poly(ethyleneimines)



The results of these model systems supported the use of these reactions as the reiterative scheme for demonstrating the proposed comb-burst concept. Therefore, step A involved acidic hydrolysis to produce LPEI's of various molecular weights (i.e., n = 5–300). Azeotropic removal (benzene or toluene) of water from these LPEI initiator cores was essential in order to avoid nongrafting, termination reactions of oxazoline oligomers. It was found that PEI becomes quite soluble in the hot toluene solution when all of the water has been removed, facilitating the handling of the anhydrous polymer. PEI dried in this manner was soluble in $CDCl_3$ for NMR analysis. (See Scheme I.)

In a separate reactor, desired poly(2-ethyl-2-oxazoline) oligomers (PEOX) (i.e., n = 5–300) were propagated by initiating anhydrous 2-ethyl-2-oxazoline with p-toluene sulfonic acid or methyl tosylate according to the methods of Saegusa[14] and others.[15] Step B involved complete addition of a hot solution of the initiator core LPEI (toluene) to a stirred solution of the oxazolinium-terminated PEOX oligomer. This reaction mixture was refluxed for 8 h, during which time the graft PEI–PEOX polymer fell out as a separate phase. The graft polymer phase was dissolved in methylene chloride and precipitated with diethyl ether. A product mixture was obtained in 95–100% yield, based on monomer and PEI, as a white-cream solid.

Figure 4 shows the SEC's[16] obtained for linear PEOX and comb-branched PEI–PEOX polymers prior to hydrolysis. The chromatogram in Figure 4A was obtained for linear PEOX with n = 20. LPEI (n = 100) was added to oxazolinium-terminated PEOX oligomers (n = 20) as described above. In this case, the oligomer chains to secondary amine (on the PEI core) ratio was 0.3. Analysis (SEC) indicated a mixture of ungrafted oligomers and

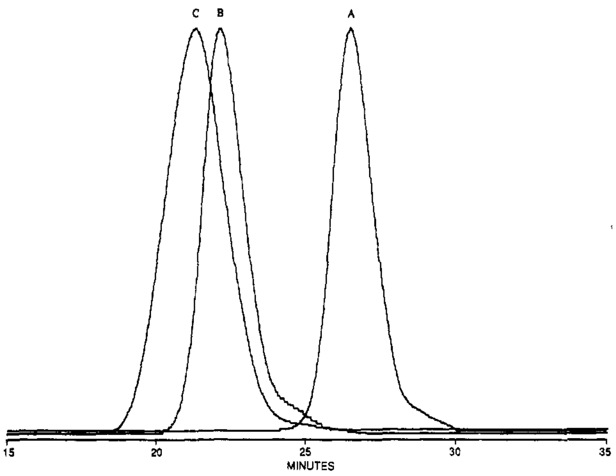


Figure 4. Size-exclusion chromatograms (SEC) of (a) PEOX prepared using a monomer to initiator ratio of 20 (M/I = 20), (b) comb-branched polymer containing PEOX grafts (M/I = 20) on a PEI core (M/I = 100), (C) comb-burst polymer obtained from the grafting of PEOX (M/I = 20) onto hydrolyzed comb-branched polymer. SEC's of comb-branched and comb-burst polymer were obtained after purification of dialysis.

higher molecular weight branched polymer. From the chromatogram of this product mixture it was estimated that 53% of the oligomers had grafted onto the LPEI in this experiment. Removal of ungrafted PEOX oligomers was achieved by dialysis[17] to give pure comb-branched PEI–PEOX polymer (Figure 4B).

Acid hydrolysis of this comb-branched PEI–PEOX copolymer gave the comb-branched PEI polymer (i.e., $G = 0$) in 90–100% yield, thus completing step A of the first iteration. Model reactions established the detectability of ungrafted PEI oligomers by ^{13}C NMR.[18] For example, poly(ethyloxazoline) oligomers were either deliberately terminated by addition of water to the reaction vessel or allowed to terminate during the purification and hydrolysis procedure used on the grafted materials. In either case, the methyl initiator end group (36.4 ppm) and the hydroxymethylene terminal end group (60.7 ppm) were clearly discernable in a 1:1 ratio, even in the presence of a strong linear PEI backbone resonance (49.4 ppm). Proton-initiated oligomers showed a distinctive aminomethylene initiator end resonance (41.8 ppm) and the same terminal group resonances. Thus, proton-initiated oligomers, which would be formed in the event of chain transfer, could also be detected. Percent grafting could also be estimated from the NMR spectra. These were consistent with SEC data and indicated that, in some cases, grafting yields in excess of 80% were possible.

Addition of preformed living end-group PEOX oligomers ($n = 20$) to this comb-branched PEI at an oligomer chain to secondary amine ratio of 0.3 produced the first comb-burst PEI–PEOX dendrimer, generation = 1, in this series. Yield of the product mixture (white solid) was 98–100% based on monomer and comb-branched PEI. Analysis indicated the presence of ungrafted PEOX oligomers and the comb-burst PEI–PEOX copolymer. In this example, 45% of the oligomers grafted onto the comb-branched PEI. After dialysis, the comb-burst PEI–PEOX copolymer exhibited a shorter retention time than the comb-branched PEI–PEOX copolymer used to prepare the comb-branched PEI core (see Figure 4C). Hydrolysis gave comb-burst PEI (generation = 1) in 96–98% yield as a white, hygroscopic solid.

The grafting was verified by ^{13}C NMR of the comb-burst poly(ethyleneimine) (PEI) formed via hydrolysis of the comb-burst PEI–PEOX copolymer. (See Figure 2.) The methyl- or proton-initiated end groups were readily detectable. Hydroxymethylene end-group resonances, which would be an indication of ungrafted oligomers, were present at approximately 20% of the intensity of the initiator end groups. Resonances corresponding to the graft branch points were also detectable, with the α-methylene signal occurring at 54.7 ppm and the β-methylene signal occurring at 47.8 ppm (when not obscured by the intense 49.4 ppm signal for LPEI). Thus, the presence of a higher molecular weight species in the SEC's and the detection of grafted sites by ^{13}C NMR support the viability of this "branch upon branch" methodology.

Work is in progress on the characterization of these hyperbranched polymers to determine hydrodynamic sizes and molecular weights. Also, we are continuing to investigate the affect of varying the length of the core polymer and the length of the PEOX oligomeric chain on the grafting efficiency. These results will be presented in future papers.

In conclusion, a general synthetic concept for the construction of a new macromolecular architecture referred to as comb-burst branching has been described, and the first examples of this new class of polymers have been synthesized. Model system, quenching experiments, SEC, and high-field ^{13}C NMR support the proposed branching motif. Molecular weight, rheology, and comb-burst dendrimer design studies are in progress.

Acknowledgment. We are grateful to the New Energy and Technology Development Organization (NEDO) of the Ministry of International Trade and Industry of Japan (MITI) for support of this work through a postdoctoral fellowship to M.S.F. Support from the U.S. Army CRDE Center Grant No. DAAL03-86-0001 is also gratefully acknowledged.

References and Notes

(1) (a) Tomalia, D. A. 1st Society of Polymer Science, Japan International Polymer Conference, Aug 1984, Kyoto, Japan. (b) Tomalia, D. A.; Baker, H.; Dewald, J. R.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* (*Tokyo*) **1985**, *17*, 117.

(2) Tomalia, D. A.; Baker, H.; Dewald, J. R.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466.

(3) Bashir-Hashemi, A.; Hart, H.; Wart, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 6675.

(4) Hart, H.; Bashir-Hashemi, A.; Luo, J.; Meador, M. *Tetrahedron* **1986**, *42*, 1641.

(5) Wilson, L.; Tomalia, D. A. *Polym. Prepr.* (*Am. Chem. Soc., Div. Polym. Chem.*) **1989**, *30*, 115.

(6) Hall, H.; Padias, A.; McConnell, R.; Tomalia, D. A. *J. Org. Chem.* **1987**, *52*, 5305.

(7) Padias, A.; Hall, H.; Tomalia, D. A. *Polym. Prepr.* (*Am. Chem. Soc., Div. Polym. Chem.*) **1989**, *30*, 119.

(8) Newkome, G. R.; Yao, Z.-q.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003.

(9) Newkome, G. R.; Yao, Z.-q.; Baker, G. R.; Gupta, V. K.; Russo, P. S.; Saunders, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 849.

(10) Frechet, J. M. J.; Jiang, Y.; Hawker, C. J.; Philippides, A. E. *Preprints of the IUPAC International Symposium on Functional Polymers*, Seoul, 1989; 6-1-07.

(11) Miller, T. M.; Neenam, T. X. *Chem. Mater.* **1990**, *2*, 346.

(12) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III *Angew. Chem., Int. Ed. Engl.* **1990**, 29, 138.

(13) Hydrolysis of DP = 2000 poly(ethyloxazoline) (PEOX; Dow Chemical) was found to give linear PEI of molecular weight 11 000–14 000 as determined by LALLS; end-group analysis by ^{13}C NMR supported this value by indicating a DP of LPEI = 200–300. Wilson, L. R.; Hedstrand, D. M.; Tomalia, D. A.; Dow Chemical, unpublished results.

(14) (a) Kobayashi, S.; Saegusa, T. In *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; Kroschwitz, J. L., Ed.; 1986, Vol. 4, p 525. (b) Kem, K. M. *J. Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 1977.

(15) Kobayashi, S.; Uyama, H.; Higuchi, N.; Saegusa, T. *Macromolecules* **1990**, *23*, 54.

(16) SEC samples were run on Beckman TSK 4000PW, 3000PW, and 2000PW, 7.5 mm by 30 cm columns using a Waters 510 HPLC pump and a Waters 410 differential refractometer. The eluting solvent run at a flow rate of 1.0 mL/min was 50 mM phosphate adjusted to pH 11 containing 0.025% NaN_3.

(17) The comb-branched and comb-burst polymers containing PEOX grafts were purified by dialyzing a water solution of the polymer in an Amicon 8400 ultrafiltration cell. Amicon flat stock membranes with molecular weight cutoffs of 10 000 (YM10) and 30 000 (YM30) were used to remove the ungrafted PEOX oligomers from the comb-branched and comb-burst polymers, respectively.

(18) For an analysis of ^{13}C NMR spectra of PEI, see: Lukovkin, et al. *Eur. Polym. J.* **1973**, *9*, 559–65.

Donald A. Tomalia,* David M. Hedstrand, and Michael S. Ferritto

Michigan Molecular Institute, 1910 West St. Andrews Road, Midland, Michigan 48640

Received August 30, 1990

Revised Manuscript Received January 22, 1991

* To whom correspondence should be sent.