The dendritic state

by Donald A. Tomalia

Historically, each of the three macromolecular architectural classes, i.e. (I) linear, (II) crosslinked, and (III) branched, has spawned rich polymer science. These architectural discoveries have been characterized by the emergence of new syntheses, structures, phenomena, properties, and products that have dramatically improved the human condition[1]. In the past five years, nanotechnology initiatives[2] have focused on new synthesis strategies, structures, phenomena, and properties associated with length scales of 1-100 nm. These dimensions encompass biological building blocks (protein, DNA, RNA, etc.) and abiotic application areas (nanophotonics and nanoelectronics) (Fig. 1)[2-4]. This review will focus on an emerging, fourth class of architecture, 'the dendritic state', and its convergence with nanotechnology[5,6].

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Dendritic architecture is one of the most pervasive topologies observed in nature at the macro- and micro-dimensional length scales (i.e. meters to micrometers). At the nanoscale (molecular level), there are relatively few natural examples of this architecture. The most notable are glycogen and amylopectin, macromolecular hyperbranched structures that nature uses for energy storage. In the polymer field, dendritic topology has now been recognized as a fourth major class of macromolecular architecture[7-10]. The signature for such a distinction is the unique repertoire of new properties manifested by this class of polymers[6,8,9,11-15]. Numerous synthetic strategies have been reported for the preparation of these materials, which have led to a broad range of dendritic structures. Presently, this architectural class consists of four dendritic subclasses: (IVa) random hyperbranched polymers, (IVb) dendrigraft polymers, (IVc) dendrons, and (IVd) dendrimers (Fig. 2). The order of this subset, from IVa to IVd, reflects the relative degree of structural control present in each of these dendritic architectures[7,8].

The relationship of dendritic polymers to traditional polymer classes can be better understood by reviewing the significant role this new topology plays in the continuum of architectures that reside between the two classical areas of 'thermoplastic' and 'thermoset' polymers[16-18]. It is now recognized that a continuum of architectures and properties,

Fig. 1 Dimensional comparison of poly(amidoamine) (PAMAM) dendrimers with an NH_3 core (G = 0-7) with biological building blocks (cell, proteins, DNA, lipid bilayer), small molecules, atoms, and the electromagnetic energy spectrum.

Fig. 2 Comparison of polymer architectures, (I) linear, (II) crosslinked, and (III) branched with (IV) dendritic, and their relationship in the transition from the thermoplastic to the thermoset state. The derivation of all architectural classes from classical monomers is noted, whereas dendrons and dendrimers may function as nanoscale monomers in megamers.

beginning with classical branched polymers, resides between these two areas. In contrast to linear random coil polymers, typical branched structures such as starch or high-pressure poly(ethylenes) are characterized by more than two terminal groups per molecule. Hence, they possess other architecturally driven properties, such as substantially smaller hydrodynamic volumes and different intrinsic viscosities compared to their linear polymer counterparts, yet exhibit unexpected segmental expansion near the 'theta state'[19]. Completing this continuum, we may now focus on the intermediary role that class IV dendritic polymers play, both in architecture and properties, as penultimate thermoplastic precursors to class II crosslinked thermoset systems. Thermoset polymer pioneers such as Dusek *et al.*[20] have thoroughly examined the critical architectures residing between these traditional thermoplastic and thermoset systems. They conclude that random hyperbranched polymers (IVa) best represent the critical, penultimate thermoplastic architectural precursors that lead to the thermoset state (Fig. 2)[21]. It is now widely recognized that within the four dendritic subsets, dendrons, dendrimers, and, to a lesser extent, dendrigraft polymers represent higher complexity with extraordinary structure control. This is in contrast to random hyperbranched polymers, which are statistical distributions of molecular weights and structures much like the first three traditional polymer classes. Therefore, the 'dendritic state' may be visualized as a progression from lower order, statistical complexities

(i.e. Class I-III) to substantially higher levels of monodisperse, structure-controlled complexity[22]. As such, covalent bridging or crosslinking of these preformed dendron/dendrimer modules would be expected to give rise to a completely new class (V) of regio-specific bridged (crosslinked in a new way) and more ordered (structure-controlled) complexity. Examples of these new architectures have been synthesized and been termed 'megamers'[6,23,75]. These new topologies and their unique properties are described later.

All dendritic polymers are open, covalent assemblies of branch cells or BCs (Fig. 3). They may be organized as very symmetrical, monodisperse arrays as is the case for dendrimers, or as irregular, polydisperse assemblies that typically define random hyperbranched polymers. The respective subclasses and the level of structure control are defined by the propagation methodology used to produce
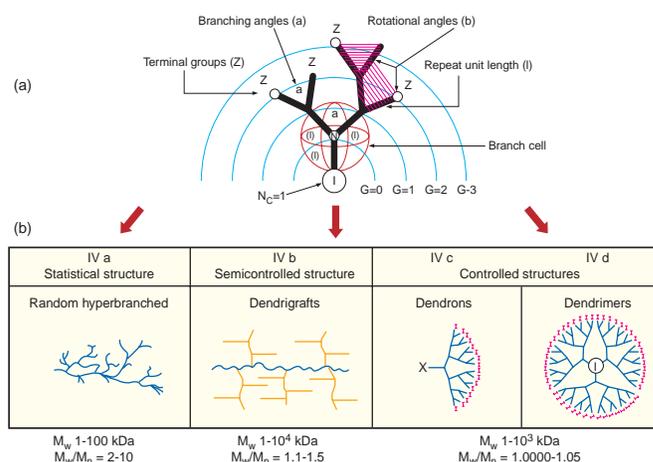
Fig. 3 (a) Dendritic polymers are open, covalent assemblies of BCs. (b) Dendritic polymer subclasses (IVa-d). (Reproduced with permission from[6]. © 2004 Sigma-Aldrich Co.)

these assemblies, as well as the BC construction parameters determined by the composition of the BC monomers and the nature of the BC excluded volume. The excluded volume of the BC is determined by the length of the arms; the symmetry, rigidity, or flexibility; and the branching and rotation angles within each of the BC domains. As shown in Fig. 3, these dendritic arrays of BCs usually manifest covalent connectivity relative to some molecular reference marker or core (I). As such, these BC arrays may be nonideal and polydisperse (e.g. $M_w/M_n \cong 2\text{-}10$) as observed for random hyperbranched polymers (IVa), or ideally organized into highly controlled core-shell-type structures as noted for dendrons (IVc) and dendrimers (IVd) ($M_w/M_n \cong 1.0000\text{-}1.05$). Dendrigraft polymers reside between these two extremes of structure control, frequently manifesting narrow polydispersities of $M_w/M_n \cong 1.1\text{-}1.5$, depending on their mode of preparation (Fig. 3).

Random hyperbranched polymers

Flory first hypothesized dendritic polymer concepts[18,24], which are now recognized to apply to statistical or random hyperbranched polymers. However, the first experimental confirmation of dendritic topologies did not produce random hyperbranched polymers but rather the more precise, structure-controlled dendrimer architecture[7,8,25,26]. This work was initiated nearly a decade before the first examples of random hyperbranched polymers were confirmed independently by Gunatillake et al.[27] as well as Kim and Webster[28,29] in 1988. At that time, Kim and Webster coined the popular term 'hyperbranched polymers' that has been widely used to describe this subclass of dendritic macromolecules. Hyperbranched polymers are typically prepared by polymerization of AB_x monomers. When x is 2 or more, polymerization of such monomers gives highly branched polymers (see Fig. 3), as long as A reacts only with B from another molecule. Reactions between A and B from the same molecule result in termination of polymerization by cyclization. This approach produces hyperbranched polymers with a degree of polymerization n, possessing one unreacted A functional group and $[(x\text{-}1)n + 1]$ unreacted B terminal groups. In a similar fashion, copolymerization of A_2 and B_3, or other such polyvalent monomers, can give hyperbranched polymers[30,31] if the polymerization is maintained below the gel point by manipulating monomer stoichiometry or limiting polymer conversion. Random hyperbranched polymers are generally produced by one-pot polymerization of AB_x-type monomers or macromonomers involving polycondensation, ring-opening, or polyaddition reactions. Hence, the products usually have broad, statistical molecular weight distributions, as observed for traditional polymers. Over the past decade, literally dozens of new AB_2-type monomers have been reported, leading to an enormously diverse array of hyperbranched structures. Some general types include poly(phenylenes) obtained by Suzuki coupling[28,29]; poly(phenylacetylenes) prepared by the Heck reaction[32]; polycarbosilanes, polycarbosiloxanes[33], and poly(siloxysilanes) by hydrosilylation[34]; poly(ether ketones) by nucleophilic aromatic substitution[35]; and polyesters[36] or polyethers[37] by polycondensations or ring-opening polymerization[38].

New advances beyond the traditional AB_2 Flory-type monomers have been reported by Fréchet and coworkers[39,40]. They have introduced the concept of latent AB_2 monomers, referred to as self-condensing vinyl polymerizations (SCVP). These monomers, which possess both initiation and propagation properties, may follow two modes of polymerization; namely, polymerization of the double bond (i.e. chain growth) and condensation of the initiating group with the double bond (i.e. step growth). Recent progress involving the derivative process of self-condensing ring-opening polymerizations (SCROP) has been reviewed by Sunder et al.[41]. In addition, the use of enhanced processing techniques, such as pseudo-chain growth by slow monomer addition[42], allows somewhat better control of hyperbranched structures[41].

Dendrigraft polymers

Dendrigraft polymers are the most recently discovered and currently the least understood subset of dendritic polymers. The first examples were reported in 1991 independently by Tomalia et al.[43] and Gauthier and Möller[44]. Whereas traditional monomers are generally employed in constructing dendrimers, reactive oligomers or polymers are used in protect-deprotect or activation schemes to produce dendrigrafts. Consequently, dendrigraft polymers are generally larger structures than dendrimers, grow much faster, and amplify surface groups more dramatically as a function of generational development. Both hydrophilic (e.g. polyoxazolines and poly(ethyleneimines)) and hydrophobic dendrigrafts (e.g. polystyrenes) were reported in

these early works. The first methodologies involved the iterative grafting of oligomeric reagents derived from living polymerization processes in various iterative, 'graft-on-graft' strategies. By analogy to dendrimers, each iterative grafting step is referred to as a generation. An important feature of this approach is that branch densities, as well as the size of the grafted branches, can be varied independently for each generation. Furthermore, by initiating these iterative grafting steps from a point-like core or a linear core, it is possible to produce spheroidal and cylindrical dendrigrafts, respectively. Depending on the graft densities and molecular weights of the grafted branches, ultrahigh molecular weight dendrigrafts (e.g. M_W > 104 kDa) can be obtained at very low generation levels (e.g. G = 3). Dramatic molecular weight enhancements *vis-à-vis* other dendrimer propagation methodologies are possible using dendrigraft techniques[45]. Further elaboration of these dendrigraft principles has allowed the synthesis of a variety of core-shell-type dendrigrafts, in which elemental composition as well as the hydrophobic or hydrophilic character of the core is controlled independently[46].

In general, the methodologies above have involved convergent-type grafting principles, where preformed, reactive oligomers are grafted onto successive branched precursors to produce semicontrolled structures. Compared to dendrimers, dendrigraft structures are less controlled since grafting may occur along the entire length of each generational branch, and the exact branching densities are somewhat arbitrary and difficult to control. More recently, both Gnanou *et al.*[47,48] and Trollsäs and Hedrick[49,50] have developed approaches to dendrigrafts that mimic dendrimer topologies by confining the graft sites to the branch termini for each generation. These methods involve so-called 'graft from' techniques and allow better control of branching topologies and densities as a function of generation. Topologies produced by these methods are reminiscent of the dendrimer architecture. Since the BC arms are derived from oligomeric segments, they are referred to as 'polymeric dendrimers'[51]. These more flexible and extended structures exhibit different properties compared with the more compact traditional dendrimers. Fréchet, Hawker, and coworkers[52] have utilized living polymerization and a staged polymerization process – in which latent polymerization sites are incorporated within growing chains – to produce dendrigrafts of mixed composition and narrow polydispersity.

Another exciting development is the emerging role that dendritic architecture is playing in the production of commodity polymers. A recent report by Guan *et al.*[53] has shown that ethylene polymerizes to *dendrigraft*-polyethylene at low pressures, while high-pressure conditions produce only branched topologies. This occurs when using late-transition-metal or Brookhart catalysts. Furthermore, these authors state that small amounts of *dendrigraft*-polyethylene architecture may be expected from analogous early-transition-metal metallocene catalysts.

Dendrons and dendrimers

Dendrons and dendrimers are the most intensely investigated subsets of dendritic polymers. In the past decade, over 6000 papers have appeared dealing with this unique class of structure-controlled polymer. The word dendrimer is derived from the Greek words *dendri-* (tree-branch-like) and *meros* (part of), and was coined by Tomalia *et al.* about 20 years ago in the first full paper on poly(amidoamine) (PAMAM) dendrimers[54]. Since this early disclosure, over 100 dendrimer compositions (families) and 1000 dendrimer surface modifications have been reported. The two most widely studied dendrimer families are the Fréchet-type polyether compositions and the Tomalia-type PAMAM dendrimers. PAMAM dendrimers constitute the first dendrimer family to be commercialized, and represent the most extensively characterized and best-understood series at this time[6,7].

In view of the vast amount of literature in this field, the remaining overview will focus on PAMAM dendrimers. The scope will be limited to a discussion of the critical properties and unique quantized nanomodule features that make these materials suitable for nanoscale syntheses and manipulations[6].

Dendrimer synthesis: divergent and convergent methods

In contrast to traditional polymers, dendrimers are unique core-shell structures possessing three basic architectural components (Fig. 4): a core (I), an interior of shells (generations) consisting of repeating BC units (II), and terminal functional groups (the outer shell or periphery) (III). In general, dendrimer synthesis involves divergent or convergent hierarchical assembly strategies that require the construction components shown in Scheme 1. Within each of these major approaches, there may be variations in
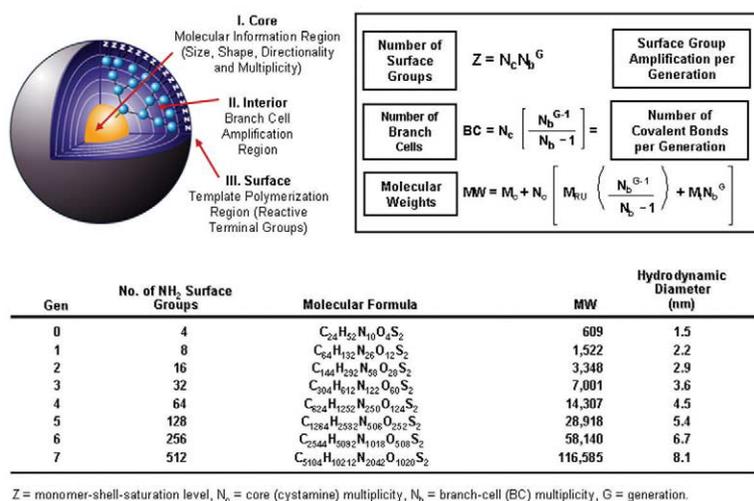
Fig. 4 Mathematical expressions for calculating the theoretical number of surface groups (Z), branch cells (BCs), and molecular weights (MWs) for cystamine core PAMAM dendrimers as a function of generation (G). Approximate hydrodynamic diameters (G = 0-7) based on gel electrophoretic comparison with the corresponding ethylenediamine core PAMAM dendrimers are given.

methodology for BC or dendron construction. Many of these issues, together with experimental procedures, have been reviewed elsewhere[55-57].

PAMAM dendrimers are synthesized by the divergent approach. This involves *in situ* BC construction around a core in stepwise, iterative stages to produce mathematically defined core-shell structures. Typically, ethylenediamine (core multiplicity, $N_c = 4$), ammonia ($N_c = 3$), or cystamine ($N_c = 4$) may be used as cores and allowed to undergo iterative, two-step reaction sequences. These sequences consist of: (a) an exhaustive alkylation of primary amines

(Michael addition) with methyl acrylate; and (b) amidation of amplified ester groups with a large excess of ethylenediamine to produce primary amine terminal groups (Scheme 2). This first reaction sequence on the exposed core creates generation $G = 0$ (i.e. the core BC), where the number of arms (i.e. dendrons) anchored to the core is determined by N_c. Iteration of the alkylation-amidation sequence produces an amplification of terminal groups from one to two with the *in situ* creation of a BC at the anchoring site of the dendron constituting $G = 1$. Repeating these iterative sequences (Scheme 2) produces additional shells or generations of BCs
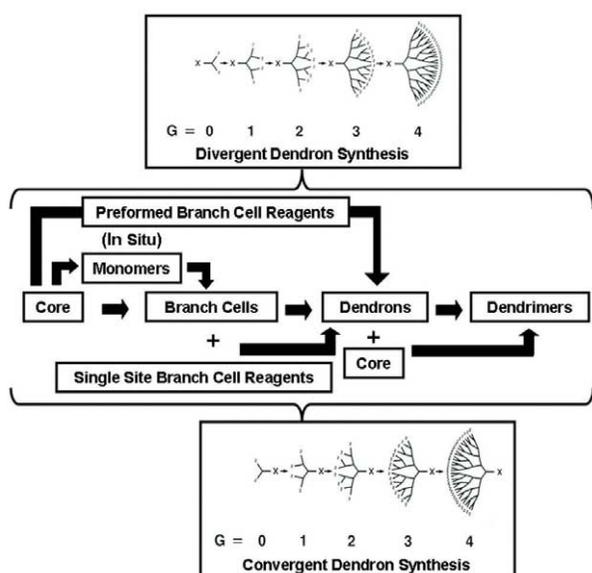
Scheme 1 Hierarchical assembly scheme illustrating the options for constructing dendrimers by either divergent or convergent synthetic strategies.
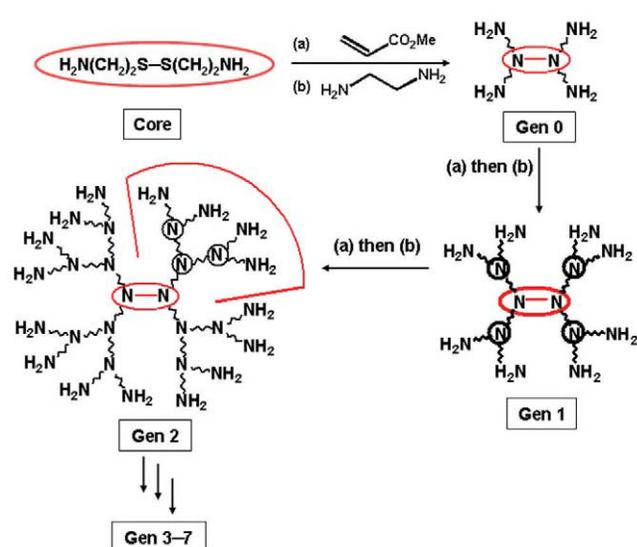
Scheme 2 Divergent synthesis of cystamine-dendri-PAMAM dendrimers utilizing the iterative sequence, (a) alkylation with methyl acrylate, followed by (b) amidation with excess ethylenediamine, to produce G = 3-7.

that amplify mass and terminal groups according to the mathematical expressions described in Fig. 4, box section. It is apparent that both the core multiplicity (N_c) and BC multiplicity (N_b) determine the precise number of terminal groups (Z) and mass amplification as a function of generation (G). One may view these generation sequences as 'quantized polymerization' events. The assembly of reactive monomers[25,26,58], BCs[7,12,59,62], or dendrons[7,60,61] around atomic or molecular cores to produce dendrimers according to divergent or convergent dendritic branching principles has been well demonstrated. Such systematic filling of molecular space around cores with BCs as a function of generational growth stages (BC shells) to give discrete, quantized bundles of nanoscale mass has been shown to be mathematically predictable[62-64]. Predicted molecular weights have been confirmed by mass spectrometry[65-68] and other analytical methods[12,60,69,70]. Predicted numbers of BCs, Zs, and molecular weights as a function of G for a cystamine-core ($N_c = 4$) PAMAM dendrimer are shown in Fig. 4. It should be noted that molecular weights approximately double as one progresses from one generation to the next. The Zs and BCs amplify mathematically according to a power function, thus producing discrete, monodisperse structures with precise molecular weights and a nanoscale diameter enhancement (Fig. 4). These predicted values are routinely verified by mass spectrometry for early generations ($G = 4-5$); however, with divergent dendrimers, minor mass defects are often observed for higher generations as congestion-induced de Gennes dense packing begins to take effect[12,71].

Unique dendrimer properties

Nanoscale monodispersity
The monodisperse nature of dendrimers has been verified extensively by mass spectrometry[62,75], size-exclusion chromatography (SEC), gel electrophoresis[70], and transmission electron microscopy (TEM)[72]. Comparison of a traditional, linear polymer size distribution $M_w/M_n = 2-10$ with PAMAM dendrimers ($G = 1-7$) is illustrated by SEC (Fig. 5). The respective dendrimer generations, as illustrated by TEM images for a $G = 5-10$ series of PAMAM dendrimers, are also displayed (Fig. 5)[72]. As is often the case, the level of monodispersity is determined by the skill of the synthetic chemist as well as the isolation and purification methods used. In general, convergent methods produce the most nearly monodisperse dendrimers, as determined by mass
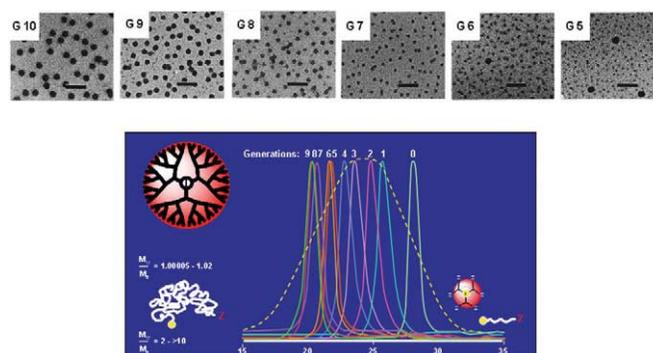
Fig. 5 TEM images of ethylenediamine core PAMAM dendrimers (G = 5-10) with their respective SEC traces (G = 0-9) illustrating their monodispersity.

spectrometry. This is because the convergent growth process allows purification at each step of the synthesis and eliminates cumulative effects because of failed couplings[7]. Appropriately purified, convergently produced dendrimers are probably the most precise synthetic macromolecules that exist today. Mass spectrometry has shown that PAMAM dendrimers produced by the divergent method are remarkably monodisperse and have masses consistent with predicted values for earlier generations ($G = 0-5$) (Fig. 4)[63,64,68]. Even for higher generations, as one enters the de Gennes densely packed region, the molecular weight distributions remain very narrow ($M_w/M_n = 1.05$) and consistent, in spite of the fact that experimental masses deviate substantially from predicted theoretical values. Presumably, de Gennes dense packing produces a very regular and dependable effect that is manifested in the narrow molecular weight distributions[4,71].

Nanoscale container and scaffolding properties
Unimolecular container and scaffolding behavior appear to be periodic properties that are specific to each dendrimer family or series. These properties are determined by the size, shape, and multiplicity of the construction components that are used for the core, interior, and surface of the dendrimer (Fig. 4)[4]. Higher multiplicity components and those that contribute to 'tethered congestion' will hasten the development of container properties and rigid-surface scaffolding as a function of generation. Within the PAMAM dendrimer family, these periodic properties are generally manifested in three phases as shown in Fig. 6. The earlier generations ($G = 0-3$) do not exhibit any well-defined interior characteristics, whereas interior development related to geometric closure is observed for the intermediate generations ($G = 4-7$). Accessibility and departure from the
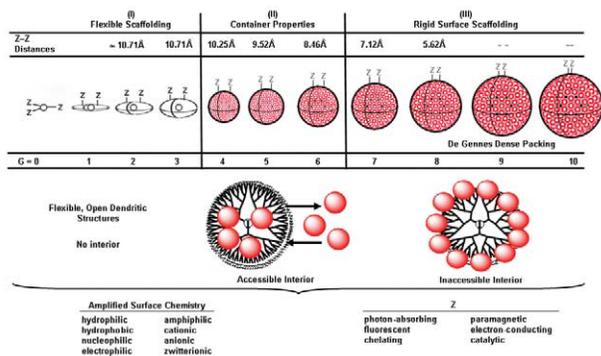
Fig. 6 Periodic properties of PAMAM dendrimers as a function of generation. Various chemophysical dendrimer surfaces amplified according to Z = $N_cN_b{}^G$. (Reproduced with permission from[6]. © 2004 Sigma-Aldrich Co.)

Fig. 7 Options for modifying amine-terminated dendrimers using classical subnanoscale and nanoscale reagents. (Reproduced with permission from[6]. © 2004 Sigma-Aldrich Co.)

interior is determined by the size and gating properties of the surface groups. At higher generations ($G > 7$), where de Gennes dense packing is severe, rigid-scaffolding properties are observed, allowing relatively little access to the interior except for very small guest molecules. The site-isolation and encapsulation properties of dendrimers have been reviewed recently by Esfand and Tomalia[73], Hecht and Fréchet[11], and Weener et al.[74].

Amplification and functionalization of surface groups

Dendrimers within a generational series can be expected to present their terminal groups in at least three different modes, namely as flexible, semiflexible, or rigid functionalized scaffolding (Fig. 6). Based on mathematically defined dendritic branching rules ($Z = N_cN_b{}^G$), the various surface presentations become more congested and rigid as a function of increasing generation level. It is implicit that this surface amplification can be designed to control gating properties associated with unimolecular-container development. Furthermore, dendrimers may be viewed as versatile, nanosized objects that can be surface-functionalized with a vast array of chemical and application features (Fig. 7). The ability to control and engineer these parameters provides endless possibilities for use as modules in nanodevice design[6,64,75-78]. Recent reviews have begun to focus on this area[11,58,77-81].

Nanoscale dimensions and shapes that mimic proteins

In view of the extraordinary structure control and nanoscale dimensions observed for dendrimers, it is not surprising to find extensive interest in their use as globular protein mimics (Fig. 8)[4,82]. Based on their systematic size-scaling properties and electrophoretic and hydrodynamic behavior[69,70], they are referred to as artificial proteins[4,73,75]. Substantial effort has
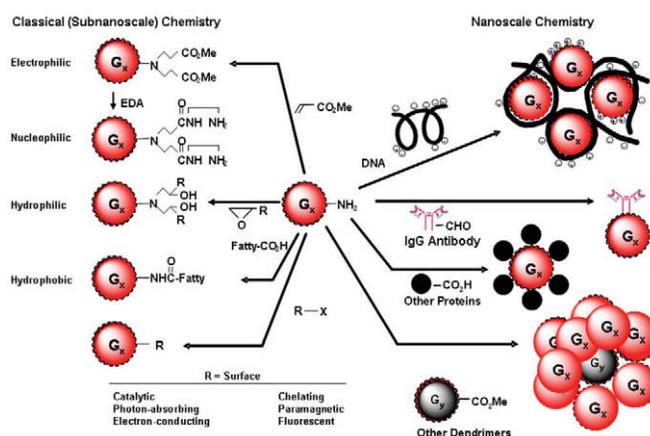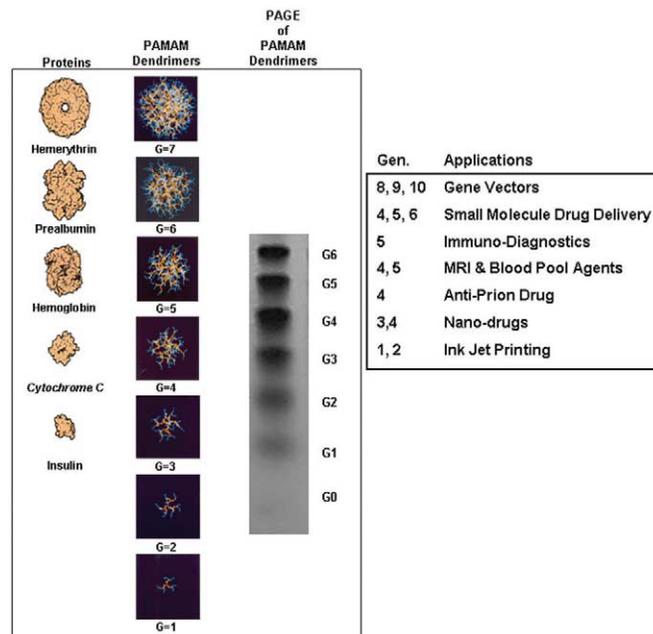
Fig. 8 Comparison of nanoscale protein dimensions with NH$_3$-core PAMAM dendrimers (G = 1-7) and generational specific applications.

focused recently on the use of dendrimers for site-isolation mimicry of proteins[11,12], enzyme-like catalysis[83], other biomimetic applications[75,84], drug delivery[73,84], surface engineering[85], and light harvesting[86,87]. These fundamental properties have, in fact, led to their commercial use as globular protein replacements for gene therapy[88,89], immunodiagnostics[90,91], and a variety of other biological applications. Interestingly, properties optimized for dendrimer applications have been found to be size (generation)-specific as indicated in Fig. 8, and have been reviewed elsewhere[4].

Dendrimer features of interest to nanoscientists

Nanosynthesis, self-assembly, and manipulation with dendrimers

Dendrimers may be viewed as unique, information-processing nanoscale devices. Each architectural component manifests a specific function, while at the same time defining properties for nanostructures as they are grown generation by generation. For example, the *core* may be thought of as the molecular information center from which size, shape, directionality, and multiplicity are expressed via covalent connectivity to the outer shells. Within the *interior*, one finds the BC amplification region, which defines the type and volume of interior void space that may be enclosed by the terminal groups as the dendrimer is grown. BC multiplicity (N_b) determines the density and degree of amplification as an exponential function of generation (G). The interior composition and volume of solvent-filled void space determines the extent and nature of the guest-host (endo-receptor) properties that are possible within a particular dendrimer family and generation. Finally, the *surface* consists of reactive or passive terminal groups that may perform several functions. With appropriate functionalization, they serve as a 'template polymerization region' as each generation is amplified and covalently attached to the precursor generation. The surface groups may also function as passive or reactive gates controlling entry or departure of guest molecules from the dendrimer interior. These three architectural components (core, interior, and surface) essentially determine the physical and chemical properties, as well as the overall size, shape, and flexibility of a dendrimer. It is important to note that dendrimer diameters increase linearly as a function of shells or generations added, while the terminal functional groups increase exponentially as a function of generation. This dilemma enhances the 'tethered congestion' of the anchored dendrons as a function of generation because of the steric crowding of the end groups. As a consequence, lower generations are generally open, floppy structures, while higher generations become robust, less deformable spheroids, ellipsoids, or cylinders, depending on the shape and directionality of the core (Fig. 6).

In view of their precise, quantized nanoscale features, both dendrons and dendrimers have been used extensively in a variety of nanosynthesis and nanomanipulation operations. A small sampling of these activities includes the decorating of

linear polymer backbones with dendrons to produce so-called linear-dendritic architectural copolymers or 'dendronized polymers', a term coined by Schluter et al.[92]. Such dendronized polymers, if advanced to a sufficiently congested generational level, have exhibited rigid rod (dendrimeric nanotube) topologies reminiscent of carbon nanotubes when analyzed by TEM[93,94]. This area has been researched extensively by Schluter and others[95], and these prototypes have been used in a variety of nanomanipulations including the atomic force microscopy (AFM) study shown in Fig. 9a.

Dendrons possessing thiol-functionalized focal points have been used to dendronize both Au nanoparticles and CdSe/CdS core-shell quantum dots by ligand-exchange of the protective surfactants used for their synthesis[96-98] (Fig. 9b). The 'self assembly' of functionalized dendrons on these nanoparticle surfaces leads to new 'nanometal core-dendron shell megamers'. Such dendronizations yield passified nanometal clusters possessing innumerable chemical functionality options suitable for a wide variety of applications.

A related nanosynthesis involves the encapsulation of various metal salts within the interiors of PAMAM dendrimers (Fig. 9c). The dendrimers function as nanoreactors or containers, wherein the encapsulated salts are reduced to their respective zero valence metal states to produce a new class of 'subnanoscale quantum dots'[99-101]. In some instances, these metal/dendrimer nanocomposites were electrostatically assembled 'layer by layer' to produce uniform multilayered thin films with the potential for tunable optical, electronic, or catalytic properties[102]. Recent work by
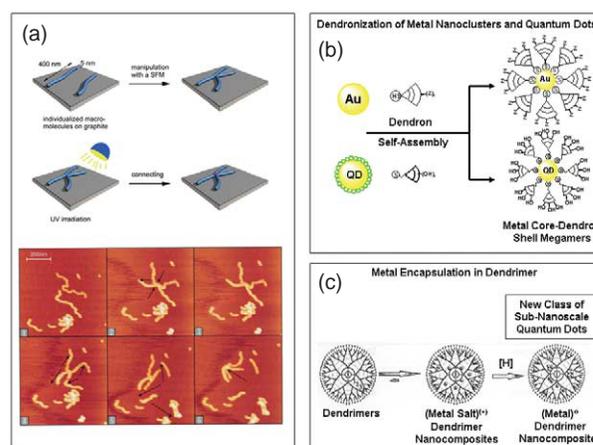
Fig. 9 Examples of (a) nanomanipulating dendronized linear polymers; (b) nanosynthesis of metal core-dendron shell megamers; and (c) nanosynthesis of subnanoscale quantum dots by metal encapsulation within a PAMAM dendrimer. (Part (a) reproduced with permission from[95]. © 2003 Wiley-VCH.)

Zheng et al.[103] has shown that variations of these prototypes (i.e. few-atom Au quantum dots) are highly fluorescent and water soluble[104]. They behave as multielectron artificial atoms with discrete, size-tunable electronic transitions throughout the visible and near-infrared region. It has been proposed that these constructs provide the 'missing link' between atomic and nanoparticle behavior in noble metals, and may open new opportunities for biological labels, energy-transfer pairs, and light-emitting sources in nanoscale optoelectronics.

Nanostructure control beyond the dendrimer

Dendrimer synthesis strategies now provide virtual control of macromolecular nanostructures as a function of size[72,105], shape[82,93], and surface or interior functional groups[12]. These strategies involve the covalent assembly of hierarchical components such as reactive monomers (A)[26], BCs (B)[7,59,62], and dendrons (C)[61] around atomic or molecular cores according to divergent or convergent dendritic branching principles (Fig. 10)[7,62,106]. Systematic filling of the space around a core with shells of BCs (i.e. generations) produces discrete core-shell dendrimer structures (D). Dendrimers are quantized bundles of mass that possess amplified surface functionality and are mathematically predictable[64]. Predicted molecular weights and surface stoichiometry have been confirmed experimentally by mass spectrometry[65,66], gel electrophoresis[69,70], and other analytical methods[72,105]. It is now recognized that empirical structures such as A, B, and C

Fig. 10 Approximate nanoscale dimensions as a function of atoms, monomers, branch cells, dendrons, dendrimers, and megamers. (Reproduced with permission from[6]. © 2004 Sigma-Aldrich Co.)

may be used to define these hierarchical constructions. Such synthetic strategies have produced dendrimers with dimensions that extend well into the lower nanoscale region (1-20 nm)[107]. The precise structure control and unique new properties exhibited by these dendrimeric architectures have yielded many interesting advanced material properties[11,108,109]. Nanoscale dendrimeric containers[100,108,110] and scaffolding[12,81] have been used to template zero-valent-metal nanodomains[79,100], nanoscale magnets[111-113], electron-conducting matrices[114,115], and provide a variety of novel optoelectronic properties[116,117]. However, the use of such strategies for the synthesis of precise nanostructures (dendrons (C) and dendrimers (D)) larger than 15-20 nm has several serious disadvantages. Firstly, it is hampered by the large number of iterative synthetic steps required to attain higher dimensions (e.g. a G = 9 PAMAM dendrimer with a diameter of ~10 nm requires 18 reaction steps). Secondly, these constructions are limited by the de Gennes dense-packing phenomenon, which precludes ideal dendritic construction beyond certain limiting generations[62,118]. For these reasons, our attention has turned to the use of dendrimers as reactive modules for the rapid construction of controlled nanoarchitectures possessing a higher complexity and dimensions beyond the dendrimer. We refer to these generic poly(dendrimers) as 'megamers' (E) (Fig. 10)[23]. Both randomly assembled megamers[23], as well as structure-controlled megamers[23,119,120], have been demonstrated. Recently, new mathematically defined megamers (dendrimer clusters) or core-shell tecto(dendrimers) have been reported[109,119-121]. The principles of these structure-controlled megamer syntheses mimic those used for the core-shell construction of dendrimers. First, a megamer core reagent (usually a spheroid) is selected. Next, a limited amount of this reactive core reagent is combined with an excess of a megamer shell reagent. The objective is to completely saturate the target spheroid core surface with covalently bonded spheroidal shell reagent. Since the diameters of the megamer core and shell reagents are very well defined, it is possible to predict mathematically the number of megamer shell molecules required to saturate a targeted core dendrimer[122].

These core-shell relationships have been analyzed mathematically as a function of the ratio of core (r_1) and shell (r_2) radii[122]. At low r_1/r_2 values (0.1-1.2), very important symmetry properties emerge as shown in Fig. 11. It can be
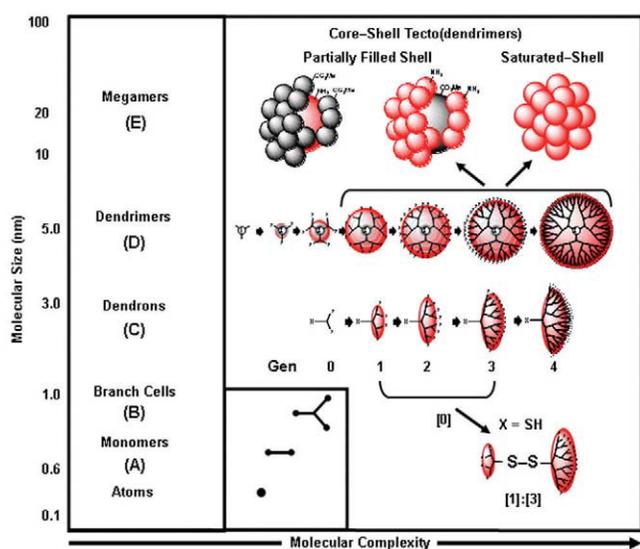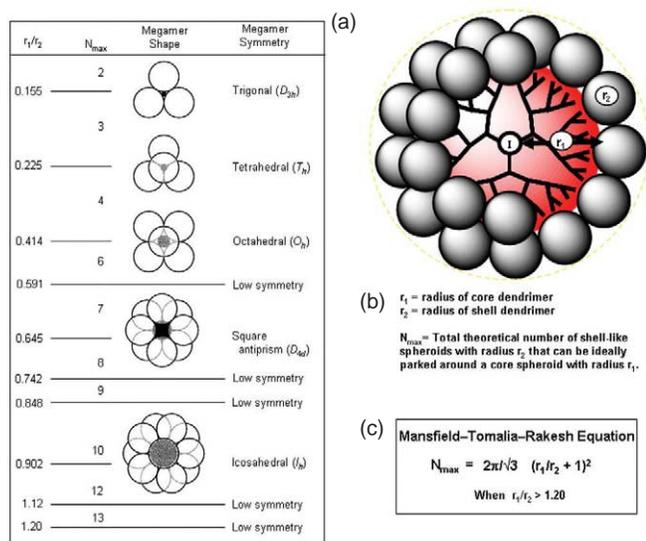
Fig. 11 (a) Symmetry properties of core-shell structures, where $r_1/r_2 < 1.2$. (b) Sterically induced stoichiometry based on the respective radii of core and shell dendrimers. (c) Mansfield-Tomalia-Rakesh equation for calculating maximum shell filling when $r_1/r_2 > 1.2$. (Reproduced with permission from[6]. © 2004 Sigma-Aldrich Co.)

seen that, when the core reagent is small and the shell reagent is larger, only a very limited number of shell dendrimers can be attached to the core dendrimer based on available space. However, when $r_1/r_2 \geq 1.2$, the space becomes available to attach many more spheroidal shell reagents up to a discrete saturation level. The saturation number (N_{max}) is well defined and can be predicted from the Mansfield-Tomalia-Rakesh equation (Fig. 11).

Synthesis of megamers

Saturated-shell-architecture approach

The general chemistry used in this approach involves the combination of a limited amount of an amine-terminated dendrimeric core reagent (e.g. a $G = 5$-7, NH_2-terminated PAMAM dendrimer) with an excess of a carboxylic acid terminated dendrimeric shell reagent (e.g. PAMAM)[120]. These two charge-differentiated species are allowed to self assemble into an electrostatically driven, supramolecular, core-shell tecto(dendrimer) architecture. After equilibration, covalent-bond formation at these charge-neutralized dendrimer contact sites is induced with carbodiimide reagents (Fig. 12a)[120,121].

The carboxylic acid terminated shell-reagent dendrimers (e.g. $G = 3$ or 5) are synthesized by ring opening of succinic anhydride with the appropriate amine-terminated PAMAM dendrimers. All reactions leading to core-shell tecto(dendrimers) are performed in the presence of LiCl at room temperature as dilute solutions (~0.5 wt.%) in water.

Equilibration times of 16-20 hours are required to complete the charge-neutralized self assembly of excess shell reagent around the limited core dendrimer reagent. Following this self assembly and equilibration, a linking reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, is added to bond the assembly of dendrimeric shell reagents covalently to a single dendrimeric core reagent at the amine-carboxylic acid interaction sites. These sites are presumed to reside primarily at the exterior of the core dendrimer reagent[23,120].

Remarkably, monodisperse products are obtained by performing the core-shell self-assembly reactions in the presence of LiCl. In the absence of LiCl, these reactions yield bimodal or trimodal product mass distributions as observed by SEC, and are presumed to be the result of clustering of the amine-terminated core reagent into various domain sizes. Such clustering of amine-terminated PAMAM dendrimers has been noted in earlier work[72]. Attempts to charge neutralize these polydisperse domains subsequently with anionic dendrimeric shell reagent produces a broad product distribution. Reversing the terminal functional groups on the core and shell reagents (i.e. using carboxylic-acid-terminated PAMAM dendrimer as the core and excess amine-terminated PAMAM dendrimer as the shell reagent) under identical reaction conditions does not yield the
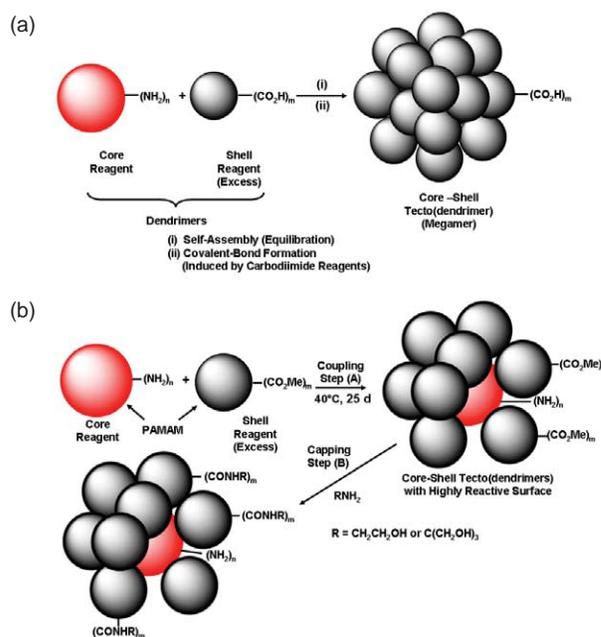
Fig. 12 (a) Saturated-shell-architecture approach to megamer synthesis. All surface dendrimers are carboxylic acid terminated. (b) Step A: unsaturated-shell-architecture approach to megamer synthesis. Step B: surface-capping reactions.

desired product. The reason for this is not evident from our studies so far.

Unsaturated-shell-architecture approach

The second approach, the direct covalent-bond-formation method, produces semicontrolled, partially filled shell structures[23,75]. It involves the reaction of a limited amount of a nucleophilic dendrimeric core reagent with an excess of an electrophilic dendrimeric shell reagent, Fig. 12b[121]. This route involves the random parking of the reactive shell reagent on a core-substrate surface. As a consequence, partially filled shell products are obtained, which possess relatively narrow but not precise molecular weight distributions, as noted for saturated core-shell architectures[120]. These distributions are determined by the core-shell parking efficiency prior to covalent bond formation.

Various PAMAM dendrimeric core reagents (either amine- or ester-functionalized) are each allowed to react with an excess of an appropriate PAMAM dendrimeric shell reagent. The reactions are performed at 40°C in methanol and monitored by Fourier transform infrared spectroscopy, ^{13}C nuclear magnetic resonance, SEC, and gel electrophoresis. Conversions in step A (Fig. 12b) are monitored by SEC and confirmed by observing the formation of shorter retention time products, consistent with higher molecular weight structures. Additional evidence can be gained by observing the loss of the migratory band associated with the dendrimeric core reagent present in the initial reaction mixture, accompanied by the formation of a higher molecular weight product, which displays a much shorter migratory band position on the electrophoretic gel. In fact, the molecular weights of the resulting core-shell tecto(dendrimers) can be estimated by comparing the migratory time of the core-shell products with the migration distances of the PAMAM dendrimer reagents (e.g. G = 2-10) used for their construction[69,70].

It is important to perform capping reactions on the surface of the resulting unsaturated, ester-terminated core-shell products in order to pacify the highly reactive amine cleft surfaces against further reaction. Preferred capping reagents for pacifying the ester domains of the surface are either 2-aminoethanol or tris(hydroxymethyl)aminomethane[75].

Reactivity of dendrimers

Dendritic species possessing an unsaturated outer monomer shell of ester and amine domains exhibit autoreactive behavior. They are often encountered if a completely saturated state of either ester or amine groups is not attained. These species, which include missing-branch structures, lead to the formation of monodendrimers containing macrocyclic terminal groups as well as moderate amounts of megamers (i.e. dimeric, trimeric species, etc.). Ideal dendrimer structures (i.e. saturated outer-monomer-shell products) can, however, be separated from these side products by silica gel column chromatography and preparative thin-layer chromatography isolation techniques. Ideal dendrimer structures that exhibit mathematically predictable masses, as well as unsaturated monomer-shell products exhibiting mass defects, are readily characterized by electrospray and matrix-assisted laser desorption/ionization-time of flight mass spectrometry[65-68].

Recently, we reported additional evidence that unfilled outer-monomer-shell species are indeed autoreactive intermediates that do lead to megamer formation. In general, saturated-shell PAMAM dendrimers (i.e. all-amine- or all-

	Atoms	Dendrimers	Core–Shell Tecto(dendrimers)
Dimensions	0.05–0.6 nm	1–15 nm	5.0 ≥ 100 nm
Valency (Reactivity)	Unfilled Outer Electron Shell	Unfilled Outer Branch Cell Shell	Unfilled Outside Dendrimer Shell
(Core–Shell) Architecture Induced Reactivity (Unfilled Shells)	(e.g., fluorine) Unfilled Shell (x)	Unfilled Shell (x)	Unfilled Shell (x)
Functional Components Directing Valency	Missing One Electron (y) in Outer Shell (x) Penultimate to Saturated Noble Gas Configuration	Missing One Terminal Branch Cell in Outer Shell (x) Exposing Functionality (y)	Missing One Dendrimer Shell Reagent Exposing Functionality (y)

Fig. 13 Quantized module (building block) reactivity patterns at the subnanoscale (atoms), lower nanoscale (dendrimers), and higher nanoscale (core-shell tecto(dendrimers)) levels, involving unsaturated electron, monomer, or dendrimer shells, respectively. (Reproduced with permission from[6]. © 2004 Sigma-Aldrich Co.)

ester-group-saturated surfaces) are very robust species (analogous to inert gas configurations observed at the atomic level). In this regard, *they do not exhibit autoreactive characteristics*. Such samples may be stored for months or years without change. On the other hand, PAMAM dendrimer samples possessing unfilled monomer shells (amine and ester group domains on the dendrimer surface) are notorious for exhibiting autoreactive properties leading to terminal looping (macrocycle formation) and megamer formation[63,64].

Remarkably, these autoreactivity patterns are also observed for the dimensionally larger core-shell tecto(dendrimer) architectures. For example, saturated-shell core-shell tecto(dendrimer) architectures *exhibit no autoreactivity*[120]; whereas partially filled shell, core-shell tecto(dendrimers) *exhibit profound autoreactivity*[75], unless pacified by reagents possessing orthogonally reactive functionalities. This behavior is comparable to the modular reactivity patterns of atoms and basic dendrimers as illustrated in (Fig. 13)[6,75,121].

Conclusions

Dendritic polymers are expected to play a key role as enabling building blocks for nanotechnology[6] during the 21st century, just as the three traditional architectural classes of synthetic polymers have successfully fulfilled critical material and functional needs over the past half-century. The controlled shape, size, and differentiated functionality of dendrimers; their ability to provide both isotropic and anisotropic assemblies; their compatibility with many other nanoscale building blocks such as DNA, metal nanocrystals, and nanotubes; their potential for ordered self-assembly; their ability to combine both organic and inorganic components; and their propensity to either encapsulate or be engineered into unimolecular functional devices make dendrimers uniquely versatile among existing nanoscale building blocks and materials. Dendritic polymers, especially dendrons and dendrimers, are expected to fulfill an important role as fundamental modules for nanoscale synthesis. It is from this perspective that it is appropriate to be optimistic about the future of this new major polymer class, *the dendritic state*. MT

Acknowledgments

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