Birth of a New Macromolecular Architecture: Dendrimers as Quantized Building Blocks for Nanoscale Synthetic Organic Chemistry

Donald A. Tomalia
Dendritic NanoTechnologies, Inc.
Central Michigan University
2625 Denison Drive
Mt. Pleasant, MI 48858, USA
Email: tomalia@dnanotech.com

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1. Introduction

During the 20th century, at least six major technological movements emerged and evolved into mature disciplines that have revolutionized scientific thinking, enhanced the prosperity of many countries, and dramatically improved the human condition. They have been referred to as major technological ages and, in approximate chronological order, are recognized as the *chemical, nuclear, plastics, materials, biotechnology, and computer* ages. An apparent driving force behind each technological age has been the quest for "new properties". As proposed by Philip W. Anderson, (Nobel Laureate in Physics, 1977) an attractive list of rewards, consequences, and possibilities accrue for society whenever scientists are successful at "breaking through new boundaries in the hierarchical complexity of matter" and such new properties emerge.[1] Presently, just such an event may be occurring at the interface of two very active scientific frontiers: the nanotechnology revolution[2,3] and the birth of a new class of macromolecular architecture, namely dendritic polymers.[4,5] This review will describe the emergence of the dendritic state relative to the traditional small-organic-molecule and traditional polymer chemistries. An overview of the critical properties and function of dendritic nanostructures, and the synthetic opportunities that are enabling the design and use of these nanostructures as fundamental building blocks in the emerging field of synthetic nanochemistry, will follow.[6]

Historically, the introduction of well-defined, quantized building blocks (e.g., atoms or monomers) into new synthetic strategies has led to major technological revolutions. Such has been the significance of Dalton's atom modules and Staudinger's monomers in the evolution of traditional small-molecule (organic) chemistry, macromolecular chemistry and, now, nanoscale chemistry **(Figure 1)**.[3] In this regard, the role of the synthetic chemist in five of the above technological ages has been incalculable. Implicit in each of these events is the familiar pattern: advancement to a new covalent complexity level yields novel materials with behaviors that cannot be understood by simple extrapolation of the properties of their building blocks. These advancements generally produce entirely new structures (architectures) with properties that follow strange new rules and require unprecedented explanations, concepts, and generalizations. In essence, "new complexity is not only different, but always more than the linear summation of its components".[1] Such is the expectation as the field of synthetic nanochemistry emerges.

2. Covalent Complexity: Traditional Organic and Polymer Syntheses

As a synthetic and physical organic chemist, I reflect on a handful of profound breakthroughs that contributed so dramatically to our present understanding of synthetic, covalent complexity. My list[6,7] includes: the atom hypothesis (Lavoisier, 1789), the molecular hypothesis (Dalton, 1808), organic chemistry (Wöhler, 1828), architectural isomerism (Berzelius, 1832), and the macromolecular hypothesis (Staudinger, 1926).[8,9]

In 1808, Dalton described his "New System of Chemical Philosophy",[7] a provocative hypothesis for its time, that has since led to the synthesis of literally millions of small inorganic and organic structures of incalculable value. Based on his envisioned atom modules (bricks) and their propensity to form bonds (electronic mortar), an unlimited number of mathematically defined small-molecule compositions, architectures, and chemical functionalities have been combinatorially assembled at the picoscale or subnanoscale level.[10-13] These structures bear no similarity to the structures of their building blocks, exhibit profoundly different properties, and adhere to substantially different bonding rules. The well-known importance of architecture in the determination of properties, even within the same covalent complexity level, was amply demonstrated by Berzelius over 170 years ago with the simple rearrangement of identical elemental compositions into new architectural isomers, allotropes, etc.[7,11] Most noteworthy was the simple Wöhler isomerization of ammonium cyanate into urea, that ushered in the traditional era of organic chemistry in 1829.[7] The complexity of organic synthesis since that time has been steadily enhanced by utilizing the known hybridization states of carbon and specific heteroatoms to produce key molecular-level hydrocarbon building blocks (modules) and functional groups (connectors). These two construction parameters have been used to assemble literally millions of more complex structures. Relatively small (i.e., < 1

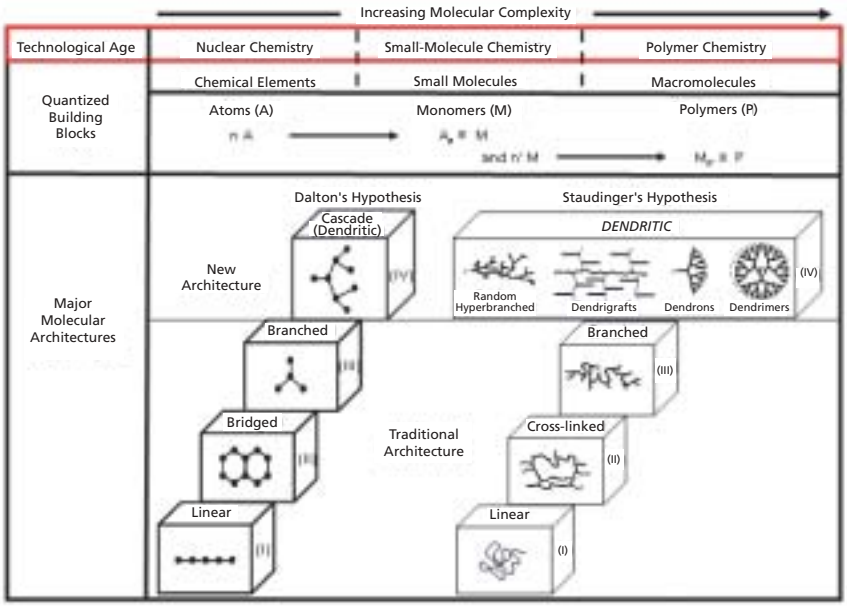


Figure 1. A Comparison of Complexity as a Function of Molecular Architecture, Strategy, Quantized Building Block, and Technological Age. (See Reference 3.)

nm) molecules were produced, the structures of which could be controlled as a function of their shape, mass, flexibility, and functional group placement. Based on the various hybridization states of carbon, at least four major carboskeletal architectures are known.[12,13] They are recognized as the (I) linear, (II) bridged (2D/3D), (III) branched and, more recently, the (IV) dendritic (cascade)[14] type. Consistent with the skeletal isomer principles demonstrated by Berzelius,[11] these major architectural classes exhibit very important differentiated physicochemical properties that are recognized as defining major areas within traditional organic chemistry (e.g., aromatic vs. linear, branched hydrocarbons, etc.). Such analogous macromolecular architectural classes have been recently defined together with their differentiated properties **(Figure 2)**.[13]

In 1926, Herman Staudinger[8] broke a second important complexity barrier—encountered by all synthetic organic chemists at the time—when he demonstrated his macromolecular hypothesis. This profound complexity breakthrough allowed the catenation (polymerization) of small, quantized monomer building blocks into megasized covalent structures (polymers) of nanoscale proportions, albeit with broad, statistical molecular-weight distributions. Three major macromolecular architectures have evolved from Staudinger's hypothesis. The first two architectural classes (i.e., linear and cross-linked)[15] literally defined the origins of traditional polymer science as well as major polymer property differences (i.e., thermoplastics vs. thermosets).[15] The third architectural class (i.e., branched)[16] is presently experiencing dramatic growth related to new polyolefin topologies derived from single-site, metallocene-type catalysts.[17] Historically, it has been widely recognized that macromolecular topologies significantly influence polymer behavior. The advent of each new architecture has invariably produced unique and important properties that have spawned many new products and industries, which have led to essentially all the significant benefits that have emerged from the plastics revolution.[9,18]

3. The Convergence of Nanotechnology and a New Macromolecular Architecture

3.1. The Quest for Quantized Nanoscale Building Blocks

Presently, an international focus is emerging on nanotechnology, which has been described as the "ultimate scientific frontier" that will both define and lead the world into the next industrial revolution.[2,3,19] While this description is surely exaggerated as today's challenges become tomorrow's routine accomplishments, nanotechnology still faces a very significant obstacle. In essence the growth and development of synthetic nanotechnology will be largely dependent upon successfully identifying appropriate quantized building blocks, much as was required for the development of the traditional fields of chemistry and polymer science. The challenge is to develop critical structure-controlled methodologies to produce appropriate nanoscale modules that will allow cost-effective synthesis and controlled assembly of more complex nanostructures in a very routine manner. Such structures will be macromolecular, require the controlled assembly of as many as 10^3–10^9 atoms, and possess molecular weights ranging from 10^4–10^{10} Daltons.

3.2. The Importance of Controlled Organic Nanostructures in Biology

All critical biological structures (e.g., cells) required for life have been based on the evolutionary development of quantized building blocks derived from controlled organic nanostructures. This evolutionary development occurred in two significant phases and involved bottom-up synthesis.[3,10,19,20] Clearly, critical parameters such as mass and dimensions had to increase in size to define the appropriate building modules. The first phase was abiotic and involved molecular evolution from atoms to small molecules. Nature dealt with this problem several billion years ago and shattered this nanoscale synthesis barrier with its evolutionary biological strategy for producing precise nanoscale modules such as DNA, RNA, and proteins. These modules were generally collections of precisely bonded atoms that occupied space with dimensions ranging from 1 to 10^2 nm. These building blocks set the stage for the synthesis of more complex nanostructures, and defined the dimensional (size) scaling that determines essentially all significant molecular-level factors required for initiating and sustaining life. These critical factors include: nanoscale sizes, nanosurfaces and interfaces, nanocontainment, nanoscale transduction and amplification, and information storage.[20] They have important implications, not only in biology, but also in significant abiotic areas such as catalysis, computer miniaturization, nanotribology, sensors, and new materials. Bottom-up synthetic strategies that produce size-monodispersed, well-defined, organic and inorganic nanostructures with dimensions between 1 and 100 nm will be of utmost importance. It will be essential that these strategies allow the systematic construction of nanoscale structures and devices with precise atom-by-atom control as a function of size, shape, and surface chemistry **(Figure 3)**.[19]

3.3. The Wet and Dry Worlds of Nanotechnology

The world of nanotechnology can be divided into two major areas: the wet and dry sides.[19,21] The former, of course, includes the biological domain, wherein the water-based chemistry of living entities is dependent upon hydrophilic nanostructures and devices that may function within biological cells. Dendritic nano-polymers, especially dendrimers, fulfill many applications in the wet world of nanotechnology. In contrast, the dry side includes those applications that derive from hydrophobic architectures. Progress in this second area is expected to enhance the tensile strength of materials, increase their electrical conductivity, or allow the reduction of computer chip size to levels unattainable with traditional bulk materials.

Although substantial progress has been made in the use of fullerenes and carbon nanotubes as nanomodules for dry nanotech

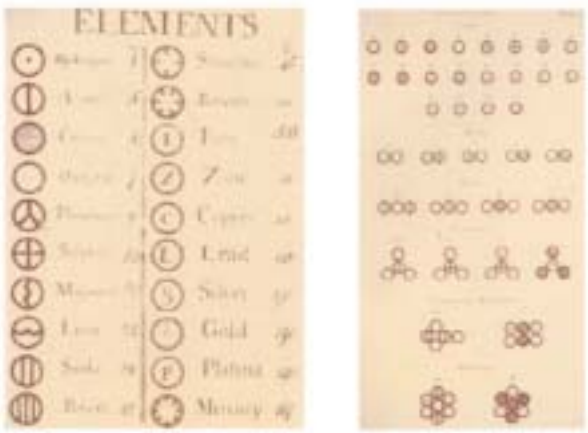


Figure 2. Dalton's Quantized Elemental Building Blocks and Their Combinatorial Possibilities That Led to His *New System of Chemical Philosophy* in 1808. (Reproduced from Reference 13 with Permission from VCH Publishers.)

applications, their use in biological applications has been hindered by the fact that they are highly hydrophobic and available in only specific sizes (i.e., usually approximately 1 nm).[22] However, recent advances have shown that a limited functionalization of fullerenes may be possible, and that these materials have a promising future in selected biological applications.[23]

4. The Dendritic State

4.1. Dendritic Polymers: A Fourth, Major New Class of Macromolecular Architecture

Dendritic architecture is one of the most pervasive topologies observed in nature at the macro- and microdimensional-length scales (i.e., m to μm). At the nanoscale (molecular level), there are relatively few natural examples of this architecture. 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.[5,24,25] The signature for such a distinction is the unique repertoire of new properties manifested by this class of polymers.[5,24,26–30] 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 (cascade) subclasses: (IVa) random hyperbranched polymers, (IVb) dendrigraft polymers, (IVc) dendrons, and (IVd) dendrimers **(Figure 4)**. The order of this subset, from (a) to (d), reflects the relative degree of structural control present in each of these dendritic architectures.[4,5]

All dendritic polymers are open, covalent assemblies of branch cells **(Figure 4a)**. They may be organized as very symmetrical, monodispersed arrays, as is the case for dendrimers, or as irregular, polydispersed 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 these assemblies, as well as by the branch-cell (BC) construction parameters. The BC parameters are determined by the composition of the BC monomers, as well as the nature of the excluded volume defined by the BC. The excluded volume of the BC is determined by the length of the arms, the symmetry, rigidity or flexibility, as well as the branching and rotation angles within each of the branch-cell domains. As shown in Figure 4a, these dendritic arrays of branch cells usually manifest covalent connectivity relative to some molecular reference marker (I) or core. As such, these branch-cell arrays may be very nonideal and polydispersed (e.g., $M_w/M_n \cong$ 2–10), as observed for random hyperbranched polymers (IVa), or very ideally organized into highly controlled core–shell-type structures, as noted for dendrons and dendrimers (IVc) and (IVd): $M_w/M_n \cong 1.0000$–1.05 and less. Dendrigraft polymers (IVb) reside between these two extremes of structure control, frequently manifesting narrow polydispersities of $M_w/M_n \cong$ 1.1–1.5, depending on their mode of preparation **(Figure 4b)**.

4.2. Random Hyperbranched Polymers

Flory first hypothesized dendritic polymer concepts,[15,31] 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.[4,5] This work was initiated nearly a decade before the first examples of random hyperbranched polymers were confirmed independently by Gunatillake[32] et al. and by Kim and Webster[33,34] 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 ABx monomers. When x is 2 or more, polymerization of such monomers gives highly branched

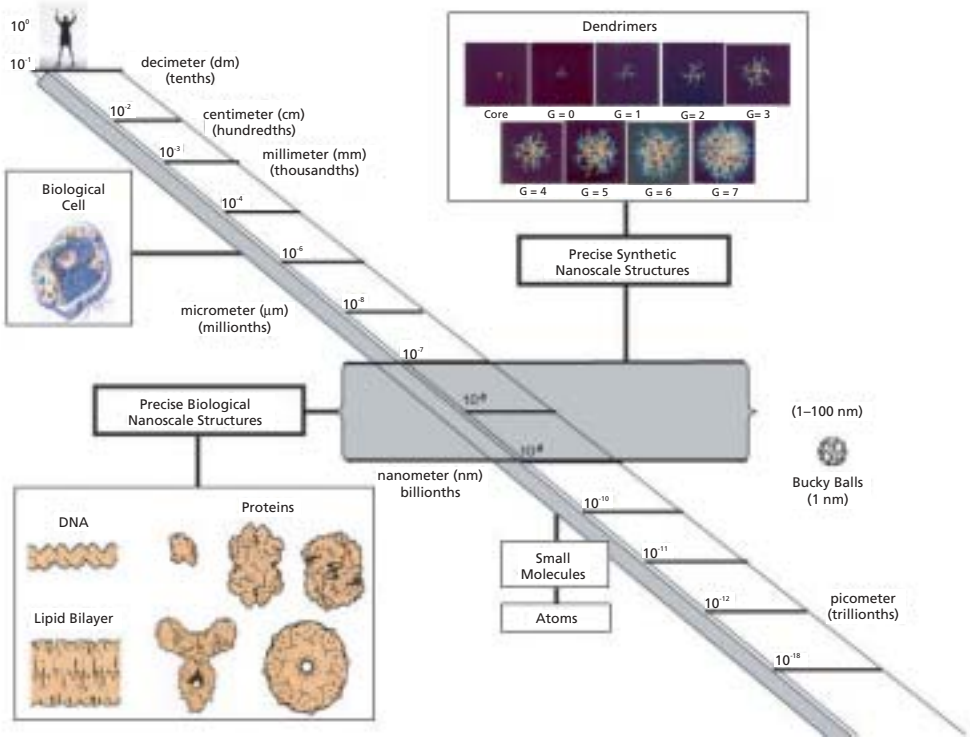


Figure 3. Nanoscale Dimensional Comparison of Poly(amidoamine) Dendrimers [NH_3 Core] (Gen = 0–7) with a Biological Cell, Proteins, DNA, Lipid Bilayer, Bucky Balls, Small Molecules, and Atoms. (Reproduced from Reference 19 with Permission from CRC Press.)

polymers (see Figure 4), 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 $[(x - 1)_n + 1]$ unreacted B terminal groups. In a similar fashion, copolymerization of A_2 and B_3 or other such polyvalent monomers can give hyperbranched polymers,[35,36] if the polymerization is maintained below the gel point by manipulating monomer stoichiometry or limiting polymer conversion.

Random hyperbranched polymers are generally produced by the 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, much as is 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 the Suzuki coupling;[33,34] poly(phenylacetylenes) prepared by the Heck reaction;[37] polycarbosilanes, polycarbosiloxanes,[38] and poly(siloxysilanes) by hydrosilylation;[39] poly(ether ketones) by nucleophilic aromatic substitution;[40] and polyesters[41] or polyethers[42] by polycondensations or by ring-opening polymerization.[43]

New advances beyond the traditional AB_2 Flory-type, branch-cell monomers have been reported by Fréchet and co-workers.[44,45] 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.[46] In addition, the use of enhanced processing techniques, such as pseudo chain growth by slow monomer addition,[47] allow somewhat better control of hyperbranched structures.[46]

4.3. 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.[48] and Gauthier and Möller.[49] 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. These 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 versus 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., $M_w > 10^4$ 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.[50] Further elaboration of these dendrigraft principles 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 were controlled independently.[51]

In general, the above methodologies have involved convergent-type grafting principles, wherein 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[52,53] and Hedrick[54,55] 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

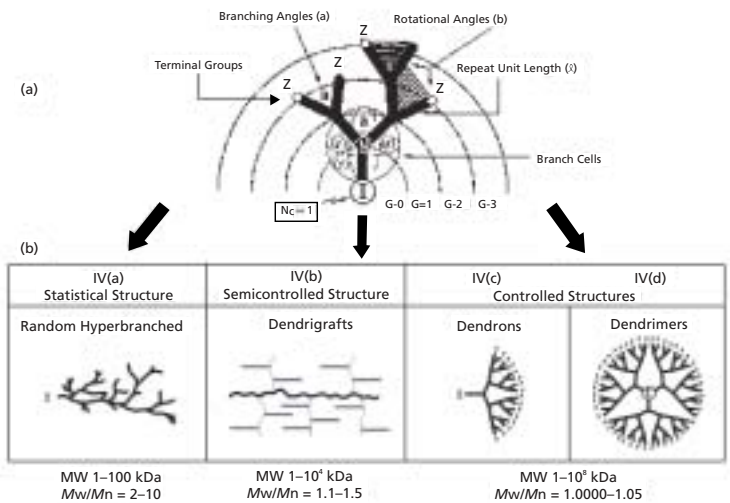


Figure 4. (a) Dendritic Polymers as Open, Covalent Assemblies of Branch Cells. (b) Dendritic Polymers: Subclasses of the Fourth Major New Class of Macromolecular Architecture.

of generation. Topologies produced by these methods are reminiscent of the dendrimer architecture. Since the branch-cell arms are derived from oligomeric segments, they are referred to as polymeric dendrimers.[56] These more flexible and extended structures exhibit unique and different properties as compared to the more compact traditional dendrimers. Fréchet, Hawker, and co-workers[57] have utilized the techniques of 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 has been the emerging role that dendritic architecture is playing in the production of commodity polymers. A recent report by Guan et al.[58] has shown that ethylene polymerizes to *dendrigraft*-polyethylene at low pressures in contrast to high-pressure conditions, which produce only branched topologies. This occurs when using late-transition-metal or Brookhart catalysts. Furthermore, these authors also state that small amounts of *dendrigraft*-polyethylene architecture may be expected from analogous early-transition-metal metallocene catalysts.

4.4. Dendrons and Dendrimers

Dendrons and dendrimers are the most intensely investigated subset of dendritic polymers. In the past decade, over 5000 literature references have appeared dealing with this unique class of structure-controlled polymers. 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.[59,60] 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.[4]

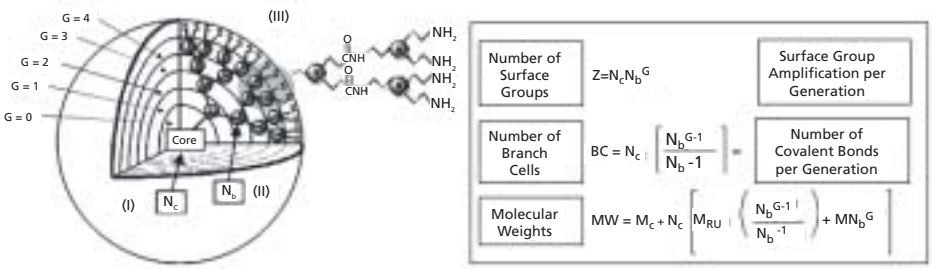
In view of the vast amount of literature in this field, the remaining overview will focus on PAMAM dendrimers. Its scope will be limited to a discussion of their critical properties and unique quantized nanomodule features that make these materials very suitable for nanoscale synthesis.

4.4.1. Dendrimer Synthesis: Divergent and Convergent Methods

In contrast to traditional polymers, dendrimers are unique core–shell structures possessing three basic architectural components **(Figure 5)**: a core (I), an interior of shells (generations) consisting of repeating branch-cell 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 methodology for branch-cell construction or dendron construction. Many of these issues, together with experimental laboratory procedures, have been reviewed elsewhere.[61–63]

PAMAM dendrimers are synthesized by the divergent approach. This methodology involves in situ branch-cell construction in stepwise, iterative stages around a desired core 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 reiterative, 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 G = 0 (i.e., the core branch cell), wherein 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 1 to 2 with the in situ creation of a branch cell at the anchoring site of the dendron that constitutes G = 1. Repeating these iterative sequences



Gen	No. of NH_2 Surface Groups	Molecular Formula	MW	Hydrodynamic Diameter (nm)
0	4	$C_{24}H_{52}N_{10}O_4S_2$	609	1.5
1	8	$C_{64}H_{132}N_{26}O_{12}S_2$	1,522	2.2
2	16	$C_{144}H_{292}N_{58}O_{28}S_2$	3,348	2.9
3	32	$C_{304}H_{612}N_{122}O_{60}S_2$	7,001	3.6
4	64	$C_{624}H_{1252}N_{250}O_{124}S_2$	14,307	4.5
5	128	$C_{1264}H_{2532}N_{506}O_{252}S_2$	28,918	5.4
6	256	$C_{2544}H_{5092}N_{1018}O_{508}S_2$	58,140	6.7
7	512	$C_{5104}H_{10212}N_{2042}O_{1020}S_2$	116,585	8.1

Z = monomer-shell-saturation level, N_c = core (cystamine) multiplicity, N_b = branch cell (BC) multiplicity, G = generation.

Figure 5. Mathematical Expressions for Calculating the Theoretical Number of Surface Groups (Z), Branch Cells (BC), and Molecular Weights (MW) for [Cystamine Core]-PAMAM Dendrimers as a Function of Generation. Approximate Hydrodynamic Diameters (Gen = 0–7) Based on Gel Electrophoretic Comparison with the Corresponding [Ethylenediamine Core]-PAMAM Dendrimers.

(see Scheme 2) produces additional shells (generations) of branch cells that amplify mass and terminal groups according to the mathematical expressions described in the box (see Figure 5).

It is apparent that both the core multiplicity (N_c) and branch-cell multiplicity (N_b) determine the precise number of terminal groups (Z) and mass amplification as a function of generation (G). One may view those generation sequences as quantized polymerization events. The assembly of reactive monomers,[27,64] branch cells[4,27,65] or dendrons[4,66,67] 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 branch cells as a function of generational growth stages (branch-cell shells)—to give discrete, quantized bundles of nanoscale mass—has been shown to be mathematically predictable.[68–70] Predicted molecular weights have been confirmed by mass spectrometry[71–74] and other analytical methods.[27,66,75,76] Predicted numbers of branch cells, terminal groups (Z), and molecular weights as a function of generation for a cystamine-core (N_c = 4) PAMAM dendrimer are shown in Figure 5. It should be noted that the molecular weights approximately double as one progresses from one generation to the next. The surface groups (Z) and branch cells (BC) amplify mathematically according to a power function, thus producing discrete, monodispersed structures with precise molecular weights and a nanoscale diameter enhancement as described in Figure 5. These predicted values are routinely verified by mass spectrometry for the earlier generations (i.e., 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.[27,77]

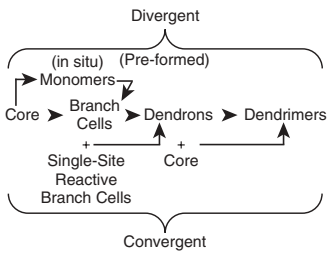
4.4.2. Dendrimer Features of Interest to Nanoscientists

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 these 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 the covalent connectivity to the outer shells. Within the *interior*, one finds the branch-cell 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. Branch-cell 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 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 periphery) 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, whereas 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, due to the steric crowding of the end groups. As a consequence, lower generations are generally open, floppy structures, whereas higher generations become robust, less deformable spheroids, ellipsoids, or cylinders—depending on the shape and directionality of the core (see Figure 3).

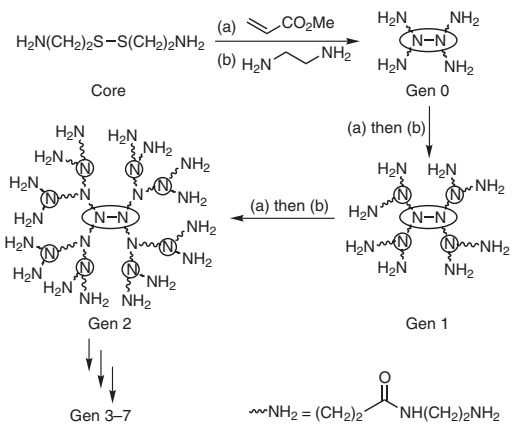
4.4.3. Dendrimers: Molecular-Level, Core–Shell Analogs of Atoms

4.4.3.1. Quantized, Core–Shell Modules as Building Blocks for Small-Molecule (Organic and Inorganic) Synthesis

We have compared the core–shell architecture of dendrimer-based, nanoscale modules to the core–shell architecture of subnanoscale atoms.[69,70] It is well recognized that the sequence of electron orbital filling of the elements occurs according to discrete, well-defined principles of quantum mechanics. Patterns for electron filling of the elements in the periodic table are defined by principal quantum numbers (i.e., n = 1, 2, 3, 4) associated with saturated electron shells leading to stable inert gas configurations (i.e., 2, 8, 8, 18, 32, etc.). Generally, the reactivity of the atom-based, small-molecule chemistry set is associated with the unsaturated electronic state of the atomic modules preceding the inert gas configurations in the respective periods. The inert gas configurations possessing filled shells are generally considered not to be highly reactive. It has been recognized since Wöhler



Scheme 1. Hierarchical Assembly Scheme Illustrating the Options for Constructing Dendrimers by Either Divergent (Tomalia-Type) or Convergent (Fréchet-Type) 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 Generations 3 to 7.

(1828) that elements in the second period (carbon in particular) may combine with first-period elements (hydrogen), second-period elements (oxygen, nitrogen, boron), and third-period elements (sulfur, silicon, etc.) to produce nearly all the compounds we classify today as organic. Essentially all other combinations are referred to as inorganic.

Approximately 50 years after Mendeleev published his traditional periodic table of the elements (1869), Niels Bohr introduced a nontraditional organization of the elements in a unique periodic table presentation in his Nobel lecture of 1922.[78] Coincidentally, in the same year, F. Aston was awarded a Nobel Prize for his invention of the mass spectrometer and his proof that the elements were precise bundles of mass that could be systematically organized and understood relative to both Mendeleev's and Bohr's periodic presentations. Bohr's representation provides the familiar electron configuration accounting system, as well as a facile visualization of several important periodic and quantized features associated with atoms **(Figure 6)**.[79] Bohr's unique periodic table displays the quantized electron space-filling features of atoms as a function of their atomic number and electron shell level. This clearly illustrates the systematic electron-filling rank of the respective, reactive elements possessing unfilled electron shells in each period. Moving to the end of each period leads to the saturated shell elements (i.e., noble gas configurations). Bohr's periodic table offers a visual appreciation of atomic module reactivity as a function of electron-shell saturation, and allows a very crude but relative size comparison of the respective elements (atoms) in the subnanoscale region (i.e., 0.01–1 nm).

It was from Bohr's periodic presentation of the elements that we were inspired to produce an analogous two-dimensional molecular display of the quantized, monomer-shell-filling features of dendrimers. It was hoped that such a presentation would allow a crude but, nevertheless, relative comparison of module size and perhaps reactivity in the nanoscale region (i.e., 1–100 nm) **(Figure 7)**.

By analogy to electron-saturation levels found in elemental atoms, dendrimers possessing unfilled monomer shells are very reactive at the molecular level via their terminal functional groups. *They may autoreact to form dendrimer multiples (i.e., dimers, trimers, etc.) or, in essence, nanoscale compounds called megamers by interdendrimer surface reactions.* Alternatively, they may simply undergo intramolecular reactions to produce macrocyclic sites. *In sharp contrast, dendrimer species possessing saturated monomer shells, mathematically defined by* $Z = N_c N_b^G$ *(see Figure 5), are not autoreactive,* nor do they react with reagents possessing a compatible surface functionality (i.e., either nucleophilic or electrophilic moieties, respectively)

4.4.3.2. Core–Shell Architectural Features of Core-Cleavable [Cystamine Core]-PAMAM Dendrimers

The core–shell architectural features of dendrimers have been described earlier in great detail.[69,70] Certain features of these dendritic architectures were shown to be quantized as a function of core (N_c) and branch-cell (N_b) multiplicity. The concentric monomer shells (generations) surrounding the nucleus (core) of the dendrimer were shown to have well-defined monomer-shell-saturation levels analogous to those observed for electrons at the atomic level, albeit at a Newtonian dimensional size scale. By analogy to electron shells in atoms, the parameters of certain quantized monomer shells surrounding a dendrimer core can be mathematically predicted. The maximum monomer content per generation is defined by the simple expression $Z = N_c N_b^G$.

More specifically, the divergent strategy involving the in situ branch-cell approach to PAMAM dendrimers may be described as a series of quantized, molecular-level "aufbau" events. Formally, such construction involves the covalent, self-assembly of *N*-(2-aminoethyl)acrylamide (2-AEA) monomer units. These structure-controlled, building events are completed by appropriate iterations of the familiar two-step sequence involving (a) alkylation of amino precursors with methyl acrylate, and (b) amidation of amplified ester-terminated intermediates using excess ethylenediamine. These amine (nucleophilic) and acrylate (electrophilic) reagents are assembled to produce a dendritic covalent connectivity consisting of β-alanine units. The *N*-(2-aminoethyl)acrylamide monomer degree of polymerization (DP_{RU}) for each generation (monomer shell level) of a perfect structure is discrete and quantized according to the expression in **eq 1**.

More recently, new synthetic options have been developed for dendrimers by introducing cleavable cores such as the one found in [cystamine core]-PAMAM dendrimers.[79] As such, the monomer

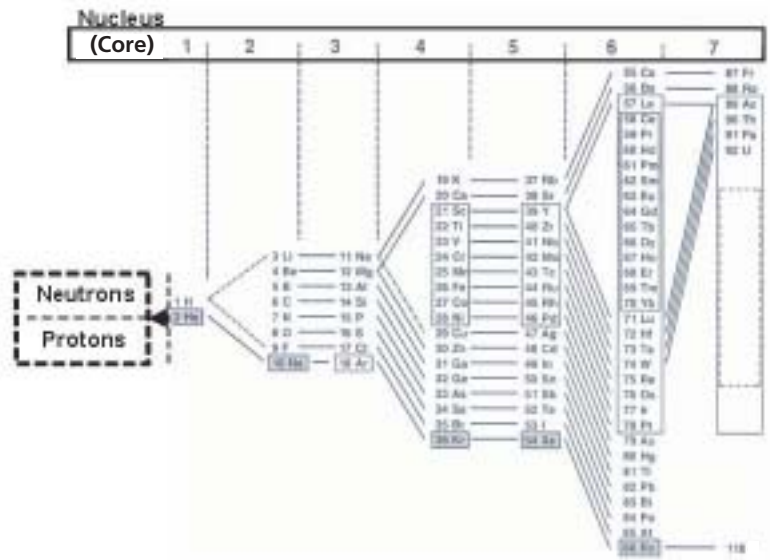


Figure 6. Core–Shell Representation of the Elements as a Function of Principal Quantum Numbers (Electron Shells) According to Niels Bohr (1922). (Reproduced from Reference 79 with Permission from Elsevier Science.)

shell level (G) and degree of polymerization (DP_{RU}) for the cleaved [cystamine core]-PAMAM dendrimer can be described relative to the new core or sulfhydryl focal point. This focal point resides at a terminus opposite to the surface groups and must be nonreactive toward the surface functionality on the hemiellipsoid as shown in **Figure 8**. Such a two-dimensional display illustrates the core, monomer shells, and crude coordinates for specific monomer units or terminal groups relative to the core. An abbreviated notation for these coordinates lists the monomer unit degree of polymerization (DP_{RU}) in bold sequential numbers as they appear in each principal shell or generation. These monomer units are associated with generation (monomer shell) levels and are designated by bold numbers in brackets. The superscript associated with each bracket indicates the number of monomer units in that shell. This serves as a monomer accounting system. In this manner, the monomer content is audited within a particular shell as each sequentially introduced monomer unit advances the shell toward a maximum quantized value. This saturation limit is defined by $Z = N_c N_b^G$. This monomer accounting system demonstrates how the monomer content per shell (generation) is quantized as a maximum value for each generational level. The total accumulation (DP_{RU}) of monomer units around the core can be predicted (see equation 1).

5. Unique Dendrimer Properties

5.1. Nanoscale Monodispersity

The monodispersed nature of dendrimers, as observed for atoms by Aston, has been verified extensively by mass spectrometry, size-exclusion chromatography, gel electrophoresis, and electron microscopy (TEM)[80]—as illustrated by TEMs for a Gen 5–10 series of PAMAM dendrimers **(Figure 9)**.[80] 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 utilized.

In general, convergent methods produce the most nearly monodisperse dendrimers as determined by mass spectrometry. This is because the convergent growth process allows purification at each step of the synthesis and eliminates cumulative effects due to failed couplings.[62] Appropriately purified, convergently produced dendrimers are probably the most precise synthetic macromolecules that exist today.

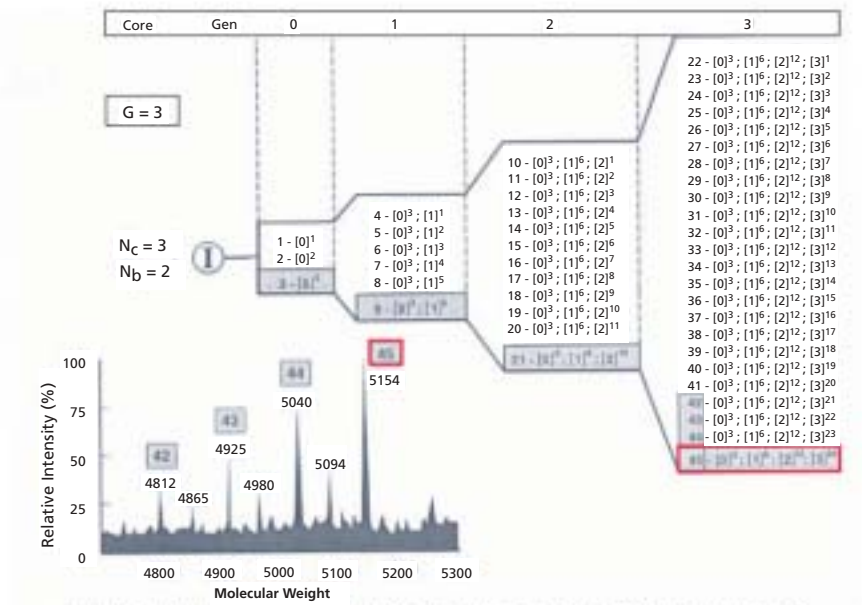
Mass spectrometry has shown that PAMAM dendrimers produced by the divergent method are remarkably monodisperse and have masses consistent with predicted values for the earlier generations (i.e., G = 0–5) (see Figure 7).[69,70,74] Even at higher generations, as one enters the De Gennes densely packed region, the molecular-weight distributions remain very narrow (i.e., 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.[19,77]

5.2. Nanoscale Container and Scaffolding Properties

Unimolecular container and scaffolding behavior appears to be a periodic property that is 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 **(Figure 10)**.[19] 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 Figure 10.

The earlier generations (i.e., G = 0–3) do not exhibit any well-defined interior characteristics, whereas interior development related to geometric closure is observed for the intermediate generations (i.e., G = 4–7). Accessibility and departure from the

$$DP_{RU} = N_c \left[\frac{N_b^{G+1} - 1}{N_b - 1} \right] \qquad \text{eq 1}$$



The shaded boxes refer to saturated-shell, nonautoreactive dendrimers. The rest of the listings refer to unsaturated-shell, autoreactive dendrimers.

Figure 7. Core–Shell (Niels Bohr Type Representation) of [Ammonia Core]-PAMAM Dendrimer (Gen 3) as a Function of Principal Monomer Shell Levels (Generations). Mass Spectrometry Data Illustrating Mass Corresponding to a Nonautoreactive Saturated-Shell Structure (i.e., DP = 45; M_r = 5154) Accompanied by Autoreactive Unsaturated-Shell Structures (DP = 44, 43, and 42; M_r = 5040, 4295, 4812, Respectively).

interior is determined by the size and gating properties of the surface groups. At higher generations (i.e., 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,[81] Hecht and Fréchet,[26] and Weener et al.[82]

5.3. Amplification and Functionalization of Dendrimer Surface Groups

Dendrimers within a generational series can be expected to present their terminal groups in at least three different modes, namely as a *flexible, semiflexible, or rigid functionalized scaffolding* (see Figure 10). Based on mathematically defined dendritic branching rules (i.e., $Z = N_c N_b^G$), 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 **(Figure 11)**. The ability to control and engineer these parameters provides an endless list of possibilities for utilizing dendrimers as modules for nanodevice design.[69,83,84,85] Recent reviews have begun to focus on this area.[26,27,85–87]

5.4. 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 **(Figure 12)**.[19] Based on their systematic, size-scaling properties and electrophoretic and hydrodynamic[75,76] behavior, they are referred to as artificial proteins.[79,81,83] Substantial effort has been focused recently on the use of dendrimers for site-isolation mimicry of proteins,[27] enzyme-like catalysis,[88] as well as other biomimetic applications,[83,89] drug delivery,[81] surface engineering,[90] and light harvesting.[91,92] These fundamental properties have in fact led to their commercial use as globular protein replacements for gene therapy, immunodiagnostics,[93,94] and a variety of other biological applications.

6. Importance of Dendrons and Dendrimers for Synthetic Nanochemistry

6.1. Nanostructure Control Within a Dendrimer

6.1.1. Size- and Shape-Designing Features of the Single-Site, Mercapto-Core, Functionalized Dendrons

We recently reported the synthesis of [cystamine core]-PAMAM dendrimers and their facile cleavage under reducing conditions to give single-site, mercapto-functionalized didendrons.[79] A general strategy for the facile synthesis of both

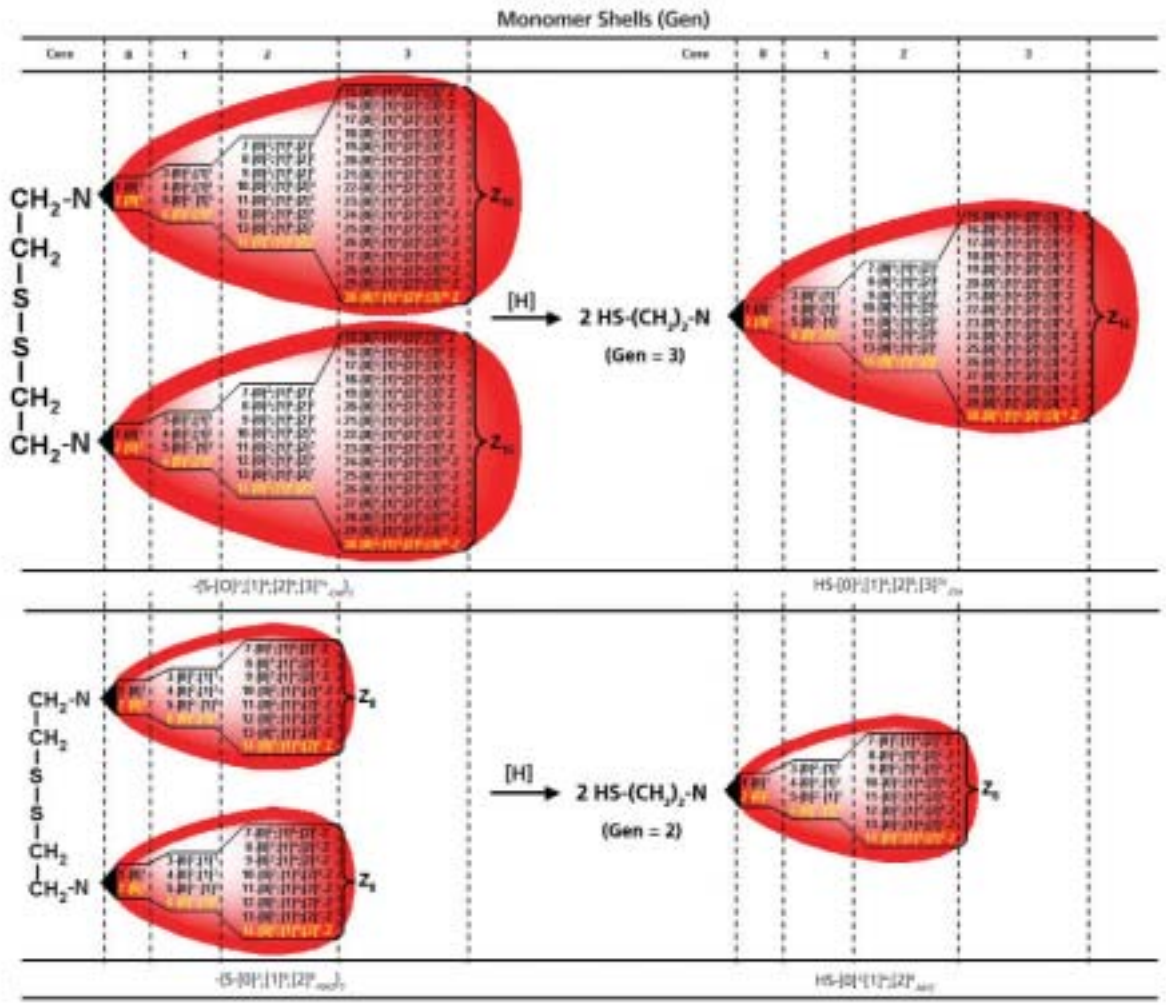


Figure 8. Niels Bohr Type, Core–Shell Representation of Gen 2–3 [Cystamine Core]-PAMAM Dendrimers in Their Oxidized and Reduced Forms.

surface- and generation-differentiated PAMAM dendrimers was demonstrated by hybridizing two different core-functionalized, mercapto-dendron reagents **(Figure 13)**.[79]

[Cystamine core]-PAMAM dendrimers (Gen 0–3) are displayed vertically as coupled spheres above the bucky ball **(Figure 14)**. They are represented with abbreviated notations in brackets to designate the generation level of the respective sulfur-bonded didendrons attached to the core before cleavage (i.e., Gen 3 [CYS]-PAMAM is designated as [3]:[3]). By cleaving these homodimers, performing subsequent oxidative coupling reactions on the mercapto-core, functionalized didendrons (i.e., [G]–SH), and utilizing various generation levels and surfaces, a wide variety of size-, shape-, and chemo-differentiated homo- and heterodimer-type nanoscale modules are possible (see Figure 13). A brief catalogue of size- and shape-differentiated products that are possible by hybridizing various combinations of homo-functionalized (Gen 0–3) cystamine precursors are shown in Figure 14. Two experimentally demonstrated examples of size-, shape-, and regiochemically differentiated hybridization products are illustrated by structures [0]:[1] and [1]:[3]. To the right of these hybridized dendrimers are two well-known globular proteins, namely insulin (diam 3.0 nm) and *Cytochrome c* (diam 4.0 nm). It should be noted that not only do the overall dimensions of these proteins scale closely to those of these two dendrimers, but the ability to synthesize nanoscale clefts and cusps, defined in the hybridized dendrimer architectures, is an important step toward mimicking unique and important differentiated shapes and surfaces found in these biostructures.[20,70,83]

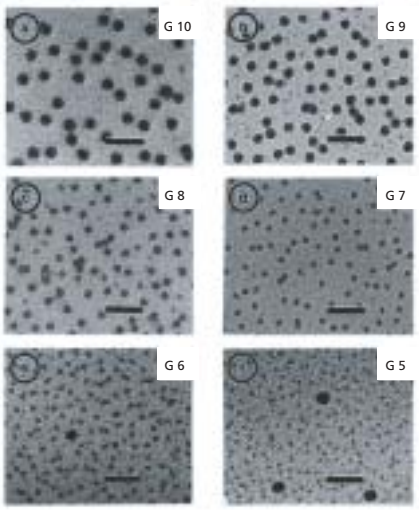


Figure 9. Transmission Electron Micrographs (TEMs) of Gen 5–10 PAMAM Dendrimers. Sample ⓕ Contains Three Molecules of Gen 10 Dendrimer for Comparison. Bar Length = 50 nm. (Reproduced from Reference 80 with Permission from ACS.)

6.1.2. Size Comparison of Dendrimers with Buckminsterfullerene and Small Molecules

The variety of sizes, shapes, and chemically differentiated surfaces that are possible by the combination of atoms to form molecular orbitals is staggering. A sampling and comparison may be visualized, to a crude first approximation, as space-filling objects represented by Corey–Pauling models. Such models are arranged in ascending complexity from right to left, as shown at the bottom of Figure 14. The importance of these parameters in defining the central dogma (size, shape, and functionality) of traditional chemistry cannot be overstated. A scaled comparison of these small-molecule parameters with buckminsterfullerene, a reference structure that defines the entry into the nanoscale region, reveals several interesting features. Glucose has a diameter of approximately 0.5 nm. Although it is about half the size of a bucky ball, it possesses surfaces which are richly decorated with chemically differentiated primary and secondary hydroxyl groups, as well as ether domains whose molecular orbitals define subnanoscale cusps and clefts in space. In contrast, the bucky ball symmetry presents an undifferentiated spheroidal surface with a dimension of approximately 1 nm.

Buckminsterfullerenes (diam ≅ 1 nm) are precise, quantized nanostructures consisting of 60 or 70 carbon atoms, which have been polymerized into the familiar soccer-ball-type structures.[22] In contrast, nanotubes derived from carbon and other elements[95] are available in various lengths, but with only several discrete

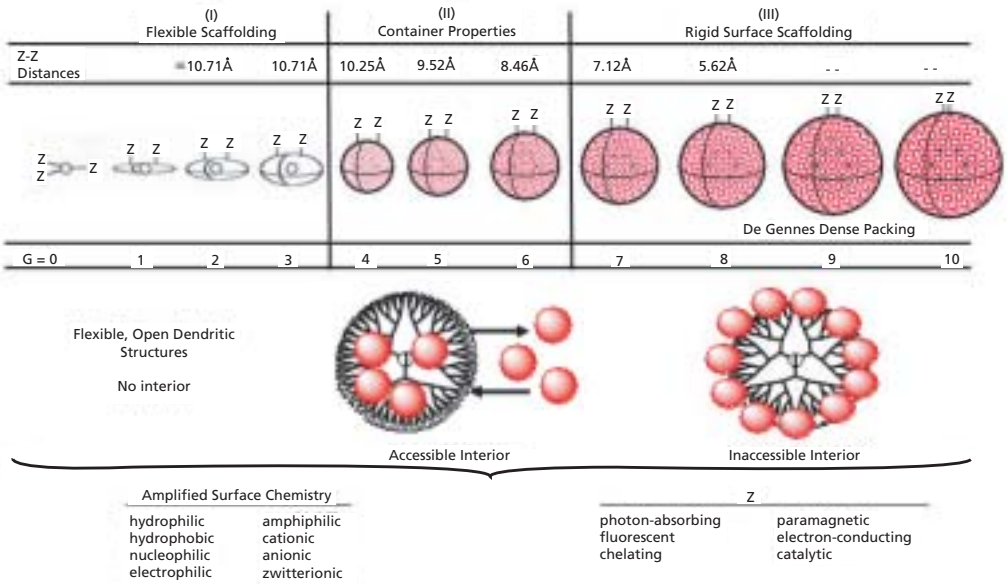


Figure 10. Periodic Properties of PAMAM Dendrimers as a Function of Generation. Various Chemophysical Dendrimer Surfaces Amplified According to $Z = N_c N_b^g$, Where N_c = Core Multiplicity, N_b = Branch-Cell Multiplicity, and G = Generation. (Reproduced from Reference 19 with Permission from CRC Press.)

diameters. Bucky balls and carbon nanotubes are some of the most intensely studied modules for abiotic nanoscale device design.[96,97] As nanoscale building blocks, these modules allow very limited opportunity to control structure relative to size, shape, and compositional or functional group design. It should be apparent that the above dendrimer-based strategies offer promising new alternatives for controlling these parameters.

6.2. Nanostructure Control Beyond the Dendrimer

Dendrimer-synthesis strategies now provide virtual control of macromolecular nanostructures as a function of size,[80,98] shape,[99] and surface or interior functional groups.[27] These strategies involve the covalent assembly of hierarchical components such as reactive monomers (A),[64] branch cells (B),[65,68] and dendrons (C)[67] around atomic or molecular cores according to divergent or convergent dendritic branching principles **(Figure 15)**.[4,68,100] Systematic filling of space around a core with shells (layers) of branch cells (i.e., generations) produces discrete core–shell dendrimer structures. Dendrimers are quantized bundles of mass that possess amplified surface functionality and are mathematically predictable.[68] Predicted molecular weights and surface stoichiometry have been confirmed experimentally by mass spectrometry,[68,69,71] gel electrophoresis,[75,76] and other analytical methods.[80,98] It is now recognized that empirical structures such as B, C, and D may be used to define these hierarchical constructions. Such synthetic strategies have produced traditional dendrimers with dimensions that extend well into the lower nanoscale region (i.e., 1–20 nm).[101] The precise structure control and unique new properties exhibited by these dendrimeric architectures have yielded many interesting advanced-material properties.[26,102,103] Nanoscale dendrimeric containers[102,104,105] and scaffoldings[27] have been used to template zero-valent-metal nanodomains,[86,106] nanoscale magnets,[107–109] electron-conducting matrices,[110,111] as well as provide a variety of novel optoelectronic properties.[112,113]

However, the use of such traditional strategies for the synthesis of precise nanostructures (i.e., dendrons (B) and dendrimers (C)) larger than 15–20 nm has several serious disadvantages. Firstly, it is hampered by the large number of reiterative synthetic steps required to attain these higher dimensions (e.g., Gen 9; PAMAM dendrimer, diam ≅ 10 nm, requires 18 reaction steps). Secondly, these constructions are limited by the De Gennes dense-packing

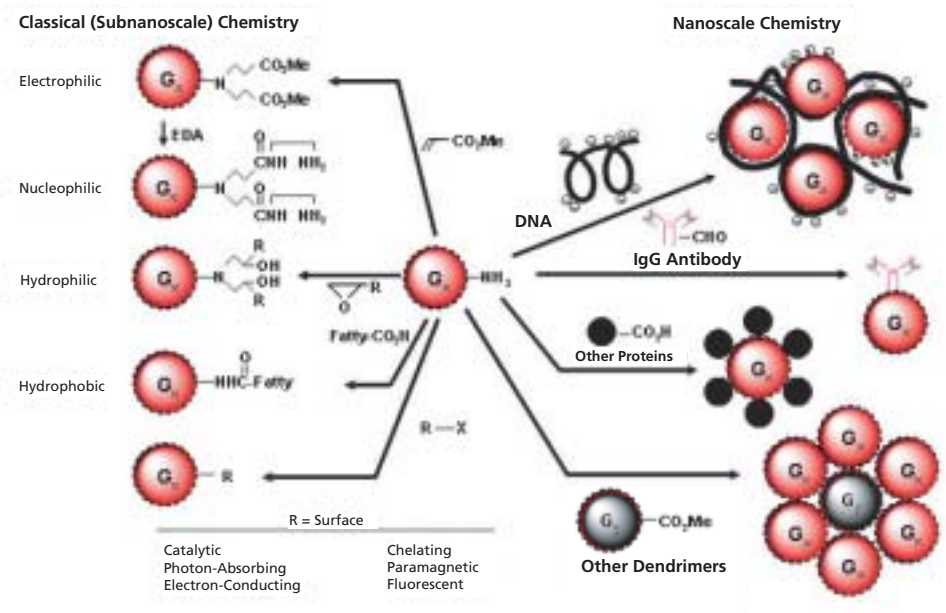


Figure 11. Options for Modifying Amine-Terminated Dendrimers by Utilizing Classical Subnanoscale and Nanoscale Reagents.

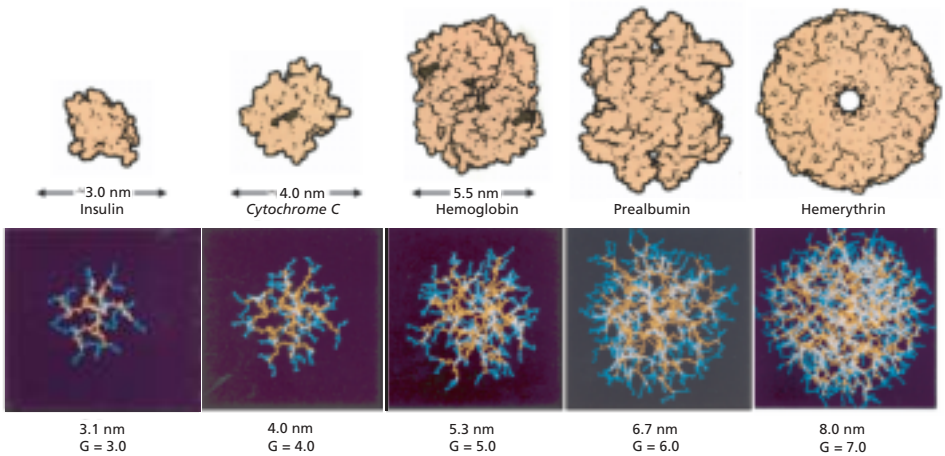


Figure 12. The Close Dimensional Size (nm) of Selected Proteins to Respective Generations of [Ammonia Core]-*dendri*-PAMAM Dendrimer. (Reproduced from Reference 19 with Permission from CRC Press.)

phenomenon, which precludes ideal dendritic construction beyond certain limiting generations.[68,114] 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*.[118] Both randomly assembled megamers,[115] as well as structure-controlled megamers,[116–118] have been demonstrated. Recently, new mathematically defined megamers (dendrimer clusters) or core–shell tecto(dendrimers) have been reported.[103,116,119,120] The principles of these structure-controlled-megamer syntheses mimic those used for the traditional 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 spheroid target core surface with covalently bonded spheroidal megamer-shell reagent. Since the diameters of the megamer-core and shell reagents are very well defined, it is possible to mathematically predict the number of megamer-shell molecules required to saturate a targeted core dendrimer.[121]

These core–shell relationships have been analyzed mathematically as a function of the ratio of core (r_1) and shell (r_2) radii.[121] At low r_1/r_2 values (i.e., 0.1–1.2), very important symmetry properties emerge as shown in **Figure 16**. It can be seen that, when the core reagent is small and the shell reagent is larger, only a very limited number of shell-type 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 a general expression that is described by the Mansfield–Tomalia–Rakesh equation (see Figure 16).

6.3. Dendrimers as Reactive Modules for the Synthesis of More Complex Nanoscale Architectures (Megamers)

6.3.1. 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., G = 5–7; NH_2-terminated PAMAM dendrimer) with an excess of a carboxylic acid terminated (e.g., PAMAM) dendrimeric shell reagent.[119] These two charge-

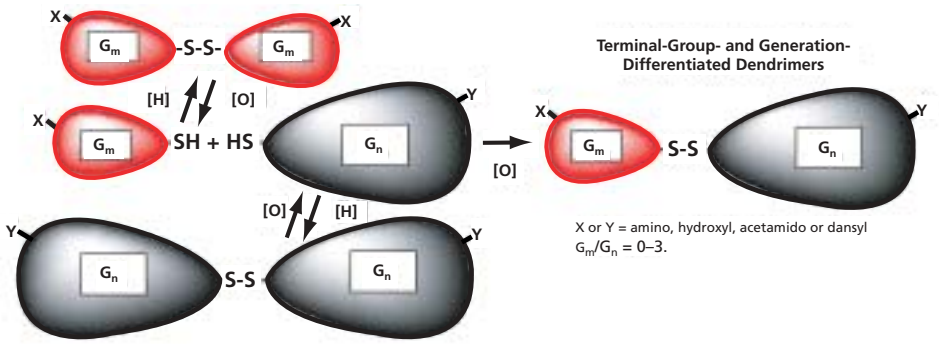


Figure 13. Reduction and Re-Oxidation of Cystamine-Core Dendrimers Possessing Different Surface Groups and Generational Levels to Produce Terminal-Group- and Generation-Differentiated Hybrid Dendrimers. (Reproduced from Reference 79 with Permission from Elsevier Science.)

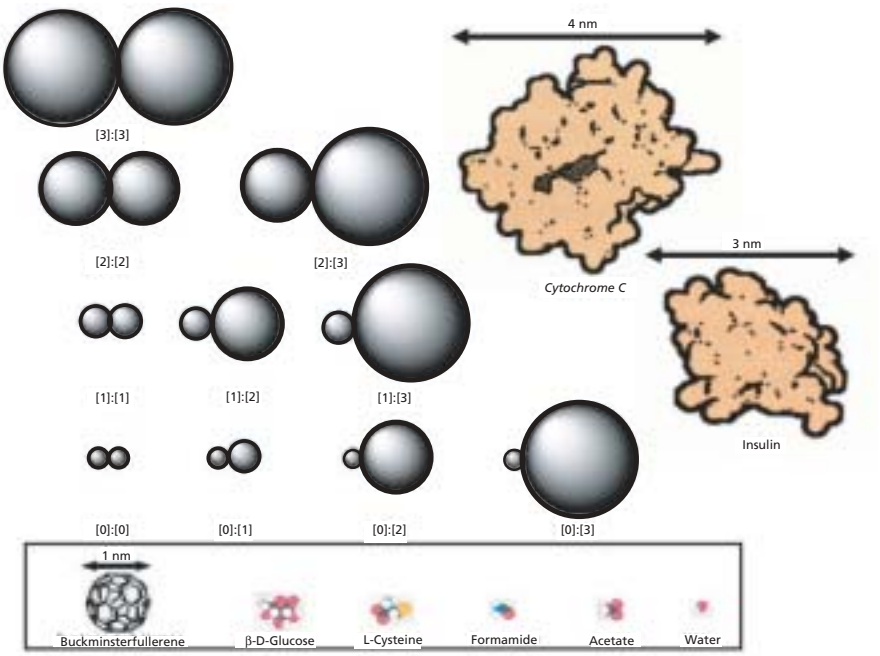


Figure 14. Scaled Space-Filling Models Comparing Small Molecules (Corey–Pauling) to Buckminsterfullerene and Various [Cystamine Core]-PAMAM Dendrimers (Represented as Spheres). Bold Numbers in Brackets Indicate the Generation Level of the Respective Dendrimer Hemiellipsoids. These Size-Scaled Synthetic Structures Are Compared to Two Globular Proteins: Insulin and *Cytochrome C*.

differentiated species are allowed to self-assemble into the 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 **(Figure 17)**.[119,120]

The carboxylic acid terminated shell-reagent dendrimers (e.g., G = 3 or 5) were synthesized by ring opening of succinic anhydride with the appropriate amine-terminated PAMAM dendrimers.

All reactions leading to core–shell tecto(dendrimers) were performed in the presence of LiCl at room temperature as dilute solutions (~ 0.5 wt %) in water. Equilibration times of 16–20 h were 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, was added to covalently bond the assembly of dendrimeric shell reagents 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.[118,119]

Remarkably monodispersed products were obtained by performing the core–shell self-assembly reactions in the presence of LiCl. In the absence of LiCl, these reactions yielded bimodal or trimodal product-mass distributions (as observed by SEC). Core–shell products formed in the absence of LiCl are multimodal, and are presumed to be due to clustering of the amine-terminated core reagent into various domain sizes. Such clustering of amine-terminated PAMAM dendrimers has been noted in earlier work.[80] Attempts to subsequently charge-neutralize these polydispersed domains with anionic dendrimeric shell reagent produced a broad product distribution. Reversing the terminal functional groups on the core and shell reagents, respectively (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, did not yield the desired product. The reason for this is not evident from our studies so far.

6.3.2. Unsaturated-Shell-Architecture Approach

The second method, the direct covalent-bond-formation method, produces semi-controlled, partially filled shell structures.[83,118] It involves the reaction of a limited amount of a nucleophilic dendrimeric core reagent with an excess of electrophilic dendrimeric shell reagent as illustrated in **Figure 18**.[120] 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-shell architectures.[119] 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) were each allowed to react with an excess of an appropriate PAMAM dendrimeric shell reagent. The reactions were performed at 40 °C in methanol and monitored by FT-IR, ^{13}C NMR, size-exclusion chromatography (SEC), and gel electrophoresis. Conversions in Step A (see Figure 18) were monitored by SEC and confirmed by observing the formation of shorter-retention-time products, consistent with higher-molecular-weight structures. Additional evidence was 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 displayed a much shorter migratory band position on the electrophoretic gel. In fact, the molecular weights of the resulting core–shell tecto(dendrimers) could 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.[75]

It was 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 were either 2-aminoethanol or tris(hydroxymethyl)aminomethane (TRIS).[83]

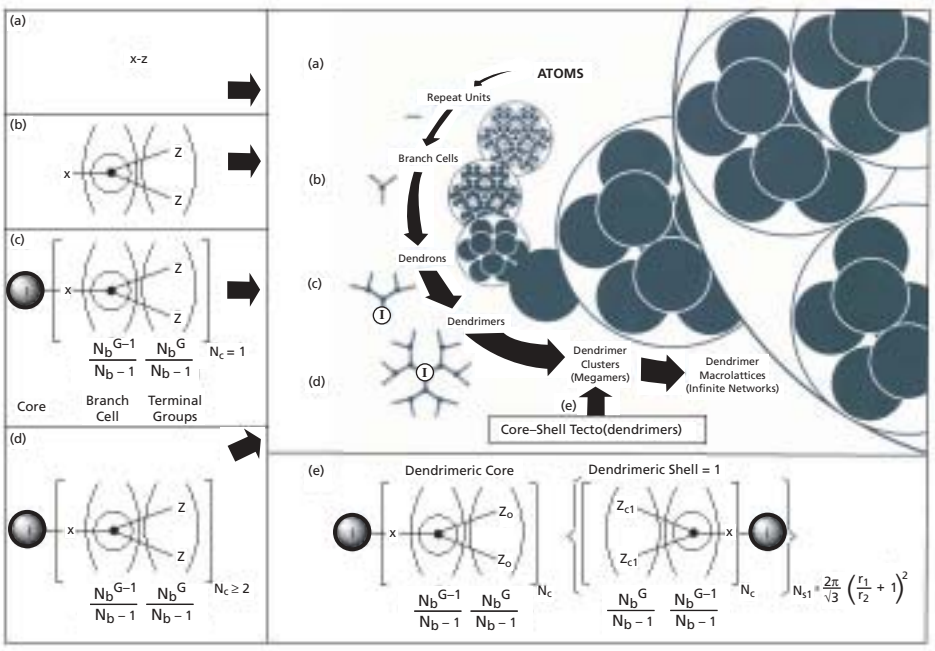


Figure 15. Hierarchy of Empirical Construction Components: Monomers (a), Branch Cells (b), Dendrons (c), and Dendrimers (d) Leading to Core–Shell Tecto(dendrimers) (e).

7. Core–Shell Patterns Influencing the Modular Reactivity of Dendrimers

Dendritic species, possessing an unsaturated outer monomer shell consisting of ester and amine domains, exhibited autoreactive behavior. They were often encountered, if a completely saturated state of either ester or amine groups was not attained. These species, which included missing-branch structures, led to the formation of monodendrimers containing macrocyclic terminal groups as well as moderate amounts of megamers (i.e., dimeric, trimeric, etc. species). Ideal dendrimer structures (i.e., saturated-outer-monomer-shell products) could, however, be separated from these side products by silica gel column chromatography and preparative TLC isolation techniques. Ideal dendrimer structures that exhibited mathematically predictable masses, as well as unsaturated-monomer-shell products exhibiting mass defects, were readily characterized by electrospray (ESI) and MALDI-TOF mass spectrometry.[71–74]

Recently, we have reported work that offers additional evidence that unfilled-outer-monomer-shell species are autoreactive intermediates that do indeed lead to megamer formation. In general, saturated-shell PAMAM dendrimers (i.e., all-amine- or all-ester-group-saturated surfaces) are very robust species (i.e., are 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 (i.e., amine and ester group domains on the dendrimer surface) are notorious for exhibiting autoreactive properties leading to terminal looping (i.e., macrocycle formation) and megamer formation.[69,70]

Remarkably, these autoreactivity patterns are also observed for the dimensionally larger core–shell tecto(dendrimer)

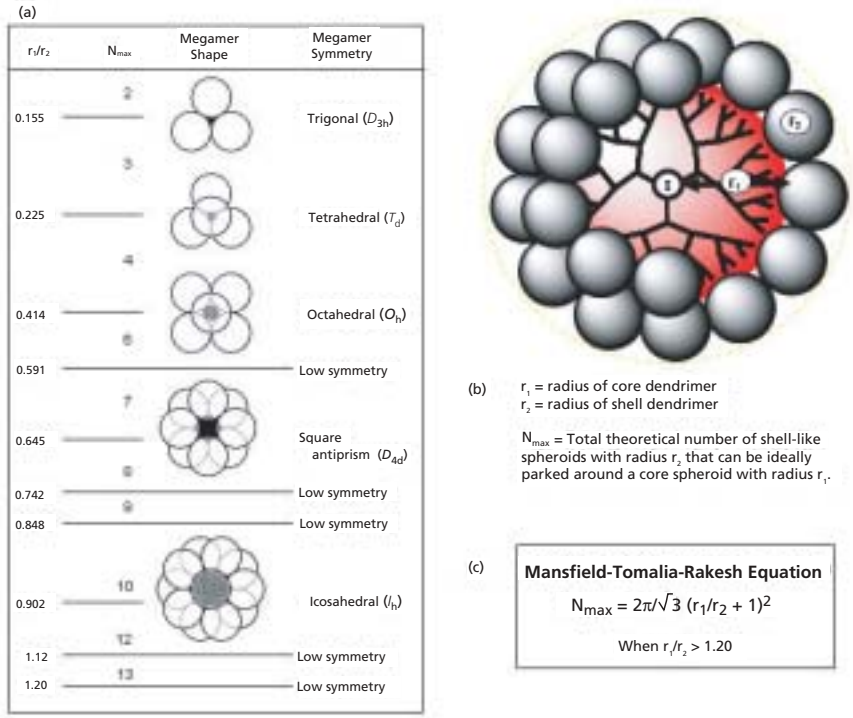


Figure 16. (a) Symmetry Properties of Core–Shell Structures, Where $r_1/r_2 < 1.20$. (b) Sterically Induced Stoichiometry (SIS) Based on the Respective Radii of Core and Shell Dendrimers. (c) Mansfield–Tomalia–Rakesh Equation for Calculating the Maximum Shell Filling When $r_1/r_2 > 1.20$.

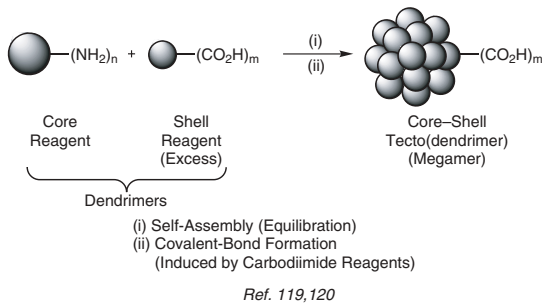


Figure 17. The Saturated-Shell-Architecture Approach to Megamer Synthesis. All Surface Dendrimers Are Carboxylic Acid Terminated.

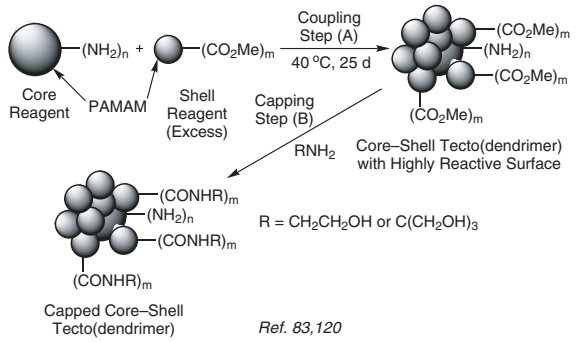


Figure 18. Step A: The Unsaturated-Shell-Architecture Approach to Megamer Synthesis. Step B Describes Surface-Capping Reactions.

architectures. For example, saturated-shell, core–shell tecto(dendrimer) architectures *exhibit no autoreactivity*; whereas partially filled shell, core–shell tecto(dendrimers) *exhibit profound autoreactivity*, unless pacified by reagents possessing orthogonally reactive functionalities. This behavior is comparable to that of atoms and basic dendrimers **(Figure 19)**.[83,120]

8. An Overview of New Nanosynthetic Strategies for the Organic Chemist

An overview of the hierarchical complexity that leads to precise, controlled nanostructures clearly illustrates the importance of quantized building blocks for viable bottom-up synthetic strategies **(Figure 20)**.[19] The importance of atom modules (0.1–0.6 nm) for the small-molecule (traditional chemistry) age and monomers (0.5–1.0 nm) for the macromolecular (polymer) age clearly hints at the significant role that dendrimers (1.0–20 nm) are expected to play as appropriately length-scaled, quantized building blocks for the synthesis of well-defined, more complex nanostructures. Experimental work has already demonstrated the ability to control size, shape, and chemical functionality within a wide variety of dendrimer structures. The first steps have been taken to demonstrate the use of these designed dendrimeric structures as fundamental building blocks for the synthesis of well-defined nanostructures beyond dendrimers (i.e., megamers), specifically the recent new class of core–shell tecto(dendrimers).[83,118,119,120]

9. From Atom-Based (Classical) to Dendrimer-Based (Nanoscale) Chemistry

Historically, it is well recognized that Dalton's proposed use of atom modules for the synthesis of higher chemical complexity in his *New System of Chemical Philosophy* (1808)[7] and Staudinger's catenation of monomers to create macromolecules[8] provided the critical enabling building blocks, and hence the synthetic platforms, for the very important fields they pioneered. These historical events encountered resistance at their inception and, in some cases, these individuals faced severe peer criticism.[8] It is from this perspective and in view of recent concept demonstrations that I am compelled to make the bold proposal that "what atoms have been to traditional chemistry and monomers to polymer chemistry, dendrimers should be to the emerging science of synthetic nanochemistry" **(Figure 21)**.[69,70] The future use of dendrimers as fundamental, reactive building blocks is expected to provide the enabling platform required for the routine synthesis of broad classes of well-defined synthetic organic, inorganic, and hybridized biomolecular nanostructures (see Figure 11). The significant role that synthetic organic and polymer

	Atoms	Dendrimers	Core–Shell Tecto(dendrimers)
Dimensions	0.05–0.6 nm	1–15 nm	5.0 to ≥ 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)

Figure 19. 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.

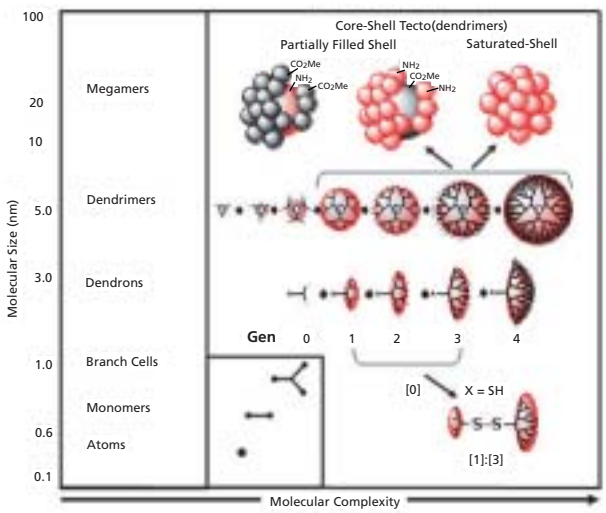


Figure 20. Approximate Nanoscale Dimensions as a Function of Atoms, Monomers, Branch Cells, Dendrons, Dendrimers, and Megamers.

chemists are presently playing in the development of this new field is readily apparent from a recent issue of *Tetrahedron Symposia-in-Print*.[122]

10. Conclusions

Dendritic polymers are expected to play a key role as enabling building blocks for nanotechnology during the 21st century, just as the first three traditional architectural classes of synthetic polymers have so successfully fulfilled critical material and functional needs in the plastics age during 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 amongst 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*.

11. Acknowledgements

This work was funded by the Army Research Laboratory (ARL), Dendritic Polymer Center of Excellence (Contract DAAL-01-1996-02-044). I would like to express my sincere appreciation to Ms. L. S. Nixon for preparing the manuscript.

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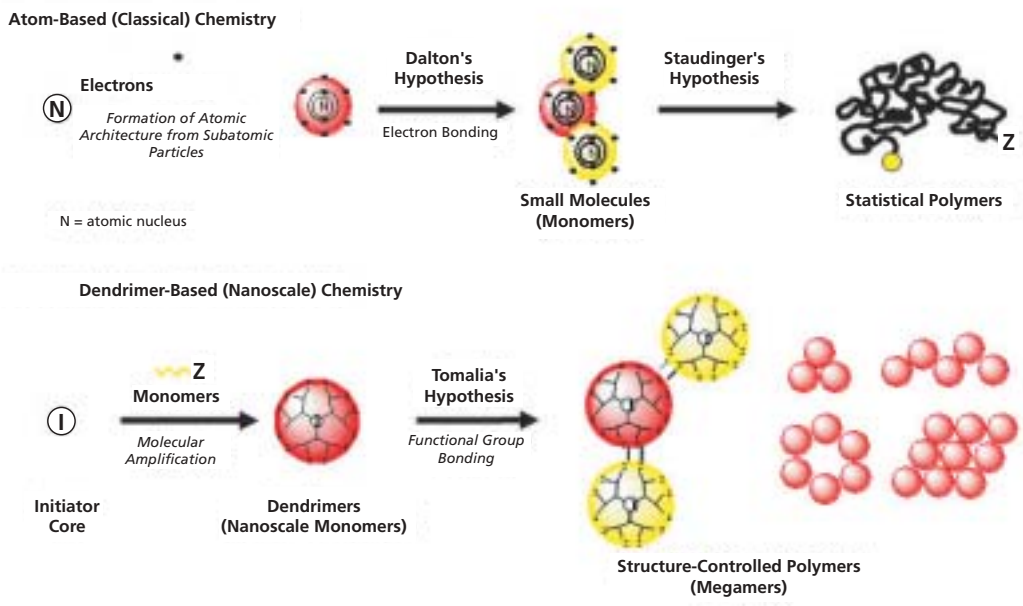

Figure 21. A Comparison of Atom-Based Classical Chemistry (Dalton and Staudinger Hypotheses) with Dendrimer-Based Nanoscale Chemistry (Tomalia Hypothesis) for Synthesizing Higher-Complexity Structures.

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Note Added in Proof

Silicon- and gallium-based nanowire components have been used recently to construct unique nanoscale dendrigraft structures (Wang, D.; Qian, F.; Yang, C.; Zhong, Z.; Lieber, C. M. *Nano Lett.* **2004**, *4*, 871).

About the Author

Donald A. Tomalia received his B.A. in chemistry from the University of Michigan and, while at the Dow Chemical Company (1962–1990), completed his Ph.D. in physical organic chemistry at Michigan State University (1968) under Professor Harold Hart. His discovery of the cationic polymerization of 2-oxazolines led to two international industrial research awards (R&D–100) in 1978 and 1986. His discovery of dendrimers (dendritic architecture) in 1979 led to a third R&D–100 award in 1991 and the Leonardo da Vinci Award (Paris, France) in 1996. He has recently received the Society of Polymer Science Japan (SPSJ) Award for Outstanding Achievement in Polymer Science (2003).

In 1990, he joined the Michigan Molecular Institute (MMI) as Professor and Director of Nanoscale Chemistry & Architecture, and served in that capacity until 1999. He cofounded Dendritech, Inc., the first commercial producer of dendrimers, and served as its founding President and Chief Scientist from 1992 to 2000. He became Vice President of Technology for MMI (1998–2000), while simultaneously serving as Scientific Director of the Biologic Nanotechnology Center, University of Michigan Medical School (1998–2000).

Dr. Tomalia founded Dendritic NanoTechnologies, Inc. (DNT) in 2002 as a joint venture with Starpharma Ltd. (Melbourne, Australia). He currently serves as President and C.T.O. of DNT with production and laboratory facilities located at Central Michigan University, Mt. Pleasant, Michigan. Dr. Tomalia was recently appointed Director of the National Center for Dendrimer Based Nanotechnology located on the Central Michigan University campus (2003). He was recently appointed Principal Investigator for DNT's participation in MIT's Institute for Soldier Nanotechnologies (MIT/ISN) (2003). Other positions currently held by Dr. Tomalia include Distinguished Visiting Professor (Columbia University) and Distinguished Research Scientist/Professor (Central Michigan University).

He is listed as the inventor on over 110 U.S. patents, and is author or co-author of more than 185 peer-reviewed publications. Over 155 papers are focused in the dendrimer or dendritic polymer field, including a monograph entitled *Dendrimers and Other Dendritic Polymers* that was co-edited with J. M. J. Fréchet (Wiley, 2001). Dr. Tomalia serves on the editorial advisory boards of *Bioconjugate Chemistry* (1999–present) and *Nano Letters* (2000–present).