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Dendrons/Dendrimers.

The convergence of quantized dendritic building blocks/architectures for applications in nanotechnology

ABSTRACT

Historically, the discovery of each traditional macromolecular architectural class, (i.e., (I) linear, (II) crosslinked and (III) branched polymers) has been accompanied by explosive growth in new structures, processes and enhanced properties that have enriched the human condition. A preponderance of these benefits was derived from a convergence of their diverse architectures, compositions and molecular weight distributions to produce new properties not found in natural materials. In the past five years, the advent of international nanotechnology initiatives has driven an unprecedented focus on novel synthesis strategies, structures and chemo/physical properties associated with specific parameters in the length scale of 1-100 nm. Although traditional polymer processes and architectures produce covalent nanostructures, most interesting nanoscale properties are impossible to isolate or are inaccessible by these strategies since they yield broad distributions of polydispersed products. This article will review the convergence of new architecturally driven "dendritic effects", offered by dendrons/dendrimers, with the ability to capture critical "nanoscale effects", by using bottom-up, dendritic synthesis strategies to produce precise covalent nanostructures as a function of size, shape and presentation of chemical functionality. New dendrimer based, commercial products emerging from these strategies will be briefly overviewed.

BACKGROUND

Beginning with Herman Staudinger's "macromolecular hypothesis" in the early 1900's (1), the past century has been referred to as the "polymer technology (plastics) age" (2). Since the introduction of Richard Feynman's nanoscale concepts in 1959 and formal commitment as a national initiative (NNI) by the USA. in 2003 (3), nanotechnology promises to become one of the most exciting emerging technologies of the 21st century. Presently there are four widely recognized nanotechnology platforms (4) that produce relatively precise nanostructures, namely; (a) dendrons/dendrimers, (b) fullerenes, (c) nanotubes and (d) quantum dots.

This review will focus on a new emerging, fourth major class of polymer architecture; the *"dendritic architectural state"*, and the implications of its convergence with nanotechnology (5, 6). In essence the confluence of new architecture driven properties derived from dendrons/dendrimers, (i.e., "dendritic effects"), with the ability to capture critical parameters (i.e. "nanoscale effects") by precisely controlling key nanoscale properties such as; size, shape and surface chemistries via "bottom-up" dendritic synthesis. The result has been the emergence of new products, therapies and diagnostics, many of which were recently reported at the "Fourth international dendrimer symposium" (IDS-4) (7), illustrated in Figure 1.

ARCHITECTURALLY DRIVEN PROPERTIES - "DENDRITIC EFFECTS"

Since Jacob Berzelius first proposed the concept of isomerism in 1825, the influence of molecular architecture on the properties and behavior of small molecules has

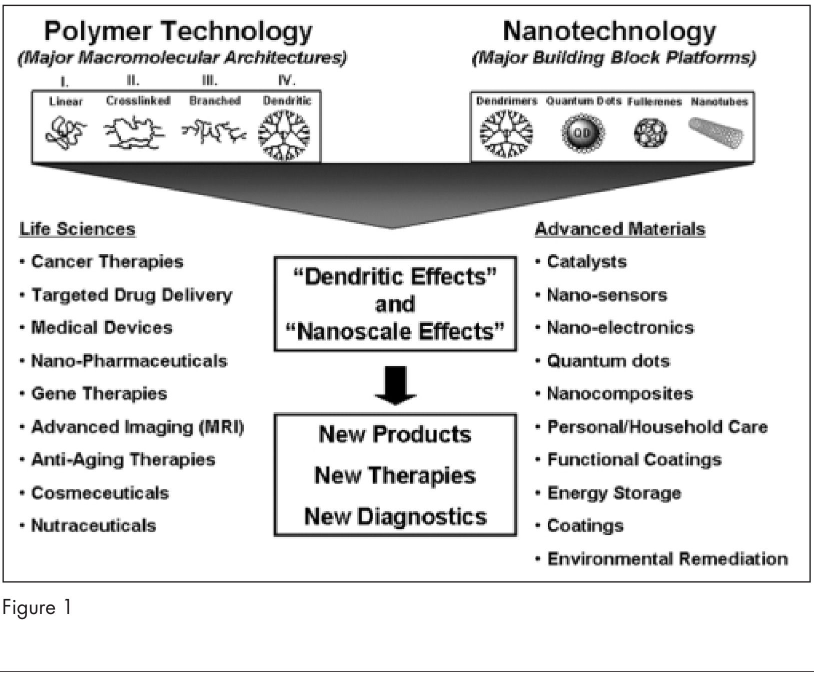


Figure 1

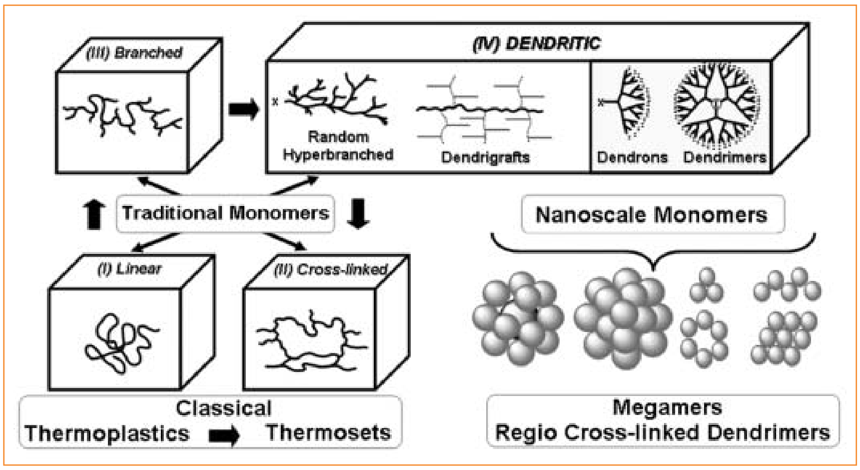


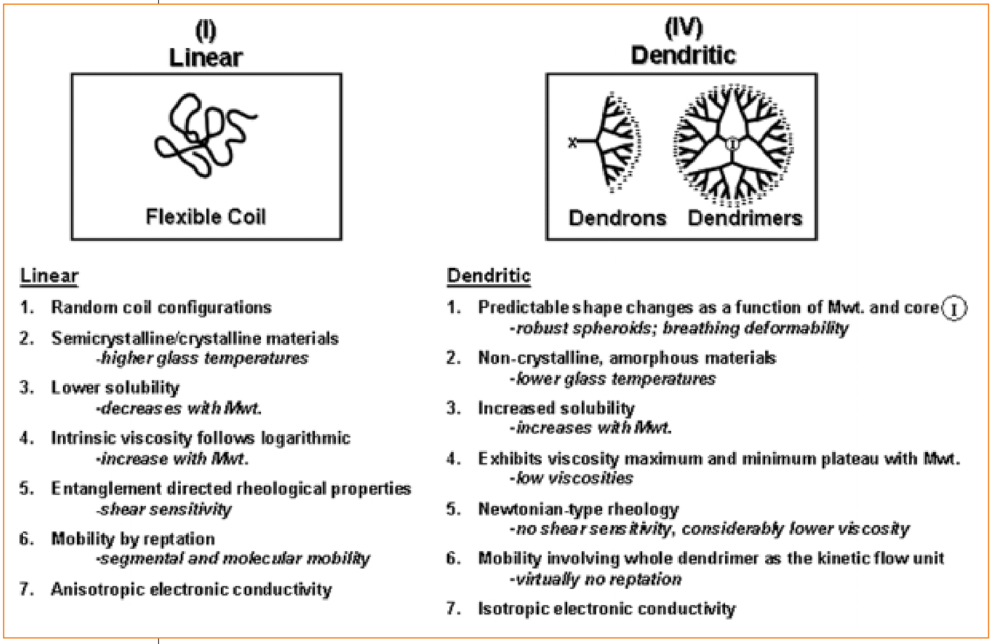
Figure 2

become one of the pillars of small molecule chemistry, (i.e. geometric/positional isomerism, optical stereoisomerism, tautomerism, etc). Such analogous architectural isomerism has been noted recently for property differences observed for the five known forms of carbon (8), involving structures that transcend from the nanoscale to the macro-scale level. More recently, the importance of “macromolecular isomerism” has been recognized (9). Prior to 1984 (10), only three synthetic polymer architectures were known, namely; *(I) linear (II) cross-linked and (III) branched type* configurations (Figure 2). These architectural discoveries have been characterized by the emergence of new syntheses, structures, phenomena, properties and products that have dramatically improved the human condition during this past century (11).

The “dendritic state” is a new, fourth class of polymer architecture (9) consisting of four subclasses: (a) random hyperbranched polymers, (b) dendrigrafts, (c) dendrons, and (d) dendrimers. The monodisperse nature of dendrons and dendrimers makes them important for nanoscientists. They are unlike traditional polymers in that critical nanoscale parameters, such as size, shape, and presentation of chemical functionality, can be precisely controlled through their architecture (i.e., their cores, interiors, and surfaces). The core may be thought of as the molecular information center. It determines the size, shape, directionality, and multiplicity of surface functionality. Within the interior, the branch cell amplification region is found. This defines the volume and type of containment space enclosed by the terminal groups, offering a variety of possible “guest-host relationships” (12, 13). Finally, the surface consists of reactive or passive terminal groups. These may serve as polyvalent nano-scaffolding, upon which new generations of dendrimers can be covalently attached for further growth. Alternatively, the surface groups may function as control gates for the entry and departure of guest molecules from the interior (12). The core, interior, and surface determine all the properties of dendrimers. With the exception of biological polymers, or perhaps fullerenes, no other covalent structure offers such ‘bottom-up’ control. Precise dendritic synthesis strategies (i.e. divergent/convergent) (14) for producing over 100 reported dendrimer/ dendron compositional families possessing over 1000 different surface /interior chemistries have been reported (5). These dendritic entities have been used as simple nanodevices or as nanoscale building blocks for the synthesis of more complex nano structures (5, 6).

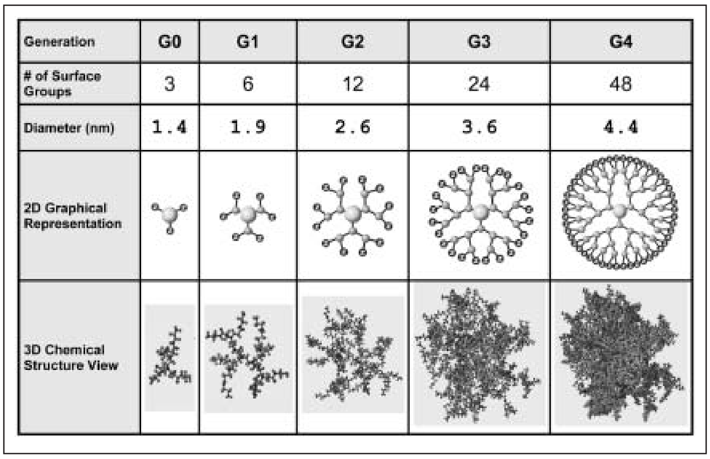
Certain statistical dendritic polymers (i.e., random hyperbranched) are now viewed as a penultimate topology in the continuum of architectures that reside between the two classical areas of “thermoplastic” and “thermoset” polymers (6, 11, 15, 16). Thermoset polymer pioneers such as Dusek, et. al. (6, 17, 18) conclude that “random hyperbranched polymers” (Figure 2) best represent the critical, penultimate thermoplastic architectural precursors that lead to the traditional thermoset state. In contrast, the quantized precision of dendrons/dendrimers allows these entities to be viewed as nanoscale monomer type building blocks, suitable for the construction of regio-cross-linked dendrimers referred to as; “megamers” (5, 19, 20) (Figure 2).

Polymer history has shown that independent of elemental composition, each new atom reconfiguration leading to the original three traditional architectural types has produced completely new and unexpected properties. This concept has validated the acceptance of “dendritic polymers” as the newest and fourth major class of macromolecular architecture. This is based on the fact that entirely new properties/behaviors, unprecedented in traditional polymer architectures, are clearly manifested by this macromolecular class (21). Since ordinary monomeric building blocks are used in the construction of these dendritic architectures, one cannot claim that new dendritic properties are predictable by simple extrapolation of the building block properties (22). A sampling of some well



Linear	Dendritic
1. Random coil configurations	1. Predictable shape changes as a function of Mwt. and core Ⓘ *-robust spheroids; breathing deformability*
2. Semicrystalline/crystalline materials *-higher glass temperatures*	2. Non-crystalline, amorphous materials *-lower glass temperatures*
3. Lower solubility *-decreases with Mwt.*	3. Increased solubility *-increases with Mwt.*
4. Intrinsic viscosity follows logarithmic *-increase with Mwt.*	4. Exhibits viscosity maximum and minimum plateau with Mwt. *-low viscosities*
5. Entanglement directed rheological properties *-shear sensitivity*	5. Newtonian-type rheology *-no shear sensitivity, considerably lower viscosity*
6. Mobility by reptation *-segmental and molecular mobility*	6. Mobility involving whole dendrimer as the kinetic flow unit *-virtually no reptation*
7. Anisotropic electronic conductivity	7. Isotropic electronic conductivity

Figure 3



Generation	G0	G1	G2	G3	G4
# of Surface Groups	3	6	12	24	48
Diameter (nm)	1.4	1.9	2.6	3.6	4.4
2D Graphical Representation					
3D Chemical Structure View					

Figure 4

recognized dendritic effects, relative to classical linear polymer architectures are as described in Figure 3.

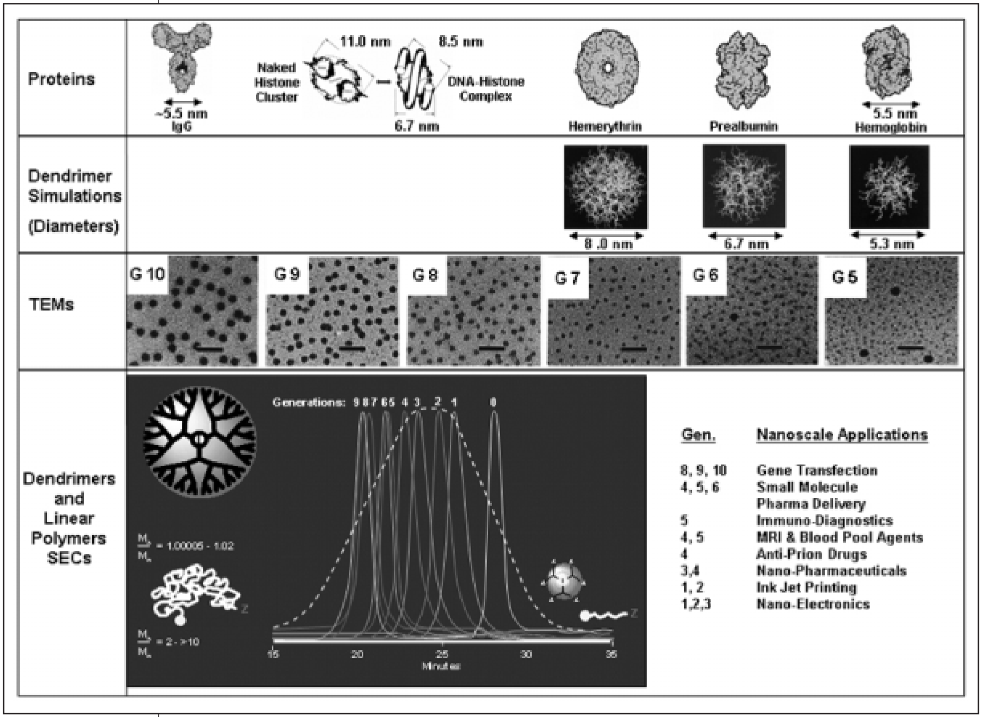
NANOSCALE EFFECTS

In the past five years, worldwide nanotechnology initiatives have created an international focus on new synthesis strategies, structures, phenomena, and properties associated with dimensional length scales residing between 1-100nm (23-28). These dimensions encompass those associated with many key biological building blocks (i.e., *life sciences;* protein, DNA, RNA, etc.), as well as nano dimensions in the electromagnetic energy spectrum (i.e. X- ray, UV) (5, 6) relating to critical abiotic application areas of interest (i.e. *advanced materials;* nano-photonics, nano-electronics).

Presently, an international focus is emerging on "nanotechnology." It has been described as the "ultimate scientific frontier" that will both define and lead the world into the next industrial revolution. New nano-physical/chemical properties related to precisely defined nano dimensions, shapes and functional group presentations are being reported on a regular basis (25-28). A critical key to advancing progress in synthetic nanochemistry/technology will dependent largely upon identifying appropriate quantized, nanoscale building blocks, much as were required for the development of the traditional chemistry (i.e., periodic elements) and polymer fields (i.e., monomers) (5, 29). The challenge is to develop critical structure-controlled methodologies to produce well defined nanoscale modules that will allow cost-effective synthesis and controlled assembly of more complex nanostructures in a very routine manner. Such nanostructures 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.

Nature solved these problems and shattered this nanoscale synthesis barrier several billions of years ago. These evolutionary events set the stage for nano dimensional scaling that today determines essentially all the significant molecular level structures and parameters dealing with life (i.e., proteins, DNA, RNA, etc.). These same parameters that include nanoscale sizes, nanosurfaces/ interfaces, nanocontainment, nanoscale transduction/amplification and information storage have important implications, not only in biology (30), but in critical abiotic areas such as catalysis (31), computer miniaturization, nano-tribology (28), sensors (28), and new materials (32). "Bottom-up" synthetic strategies that produce size-monodisperse, well-defined organic and inorganic nanostructures (dimensions ranging between 1-100 nm) will be of utmost importance. It is now well recognized, that dendritic 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 (31, 33).

The versatility of dendrons/dendrimers in such a role is becoming widely accepted. They are recognized as quantized nanoscale building blocks possessing precise nanometer sizes (nanoparticles), solvent filled interior void spaces for unimolecular encapsulation (nano-containers) and mathematically defined numbers of surface functionality (nano-scaffolding) as a function of generation as illustrated in Figure 4.



Gen.	Nanoscale Applications
8, 9, 10	Gene Transfection
4, 5, 6	Small Molecule Pharma Delivery
5	Immuno-Diagnostics
4, 5	MRI & Blood Pool Agents
4	Anti-Prion Drugs
3,4	Nano-Pharmaceuticals
1, 2	Ink Jet Printing
1,2,3	Nano-Electronics

Figure 5

Commercial Uses and Emerging Applications

The most extensively studied dendrimer families include the Tomalia-type (i.e., Starburst® poly(amidoamines) and Fréchet-type (i.e. poly(aryl ether)) dendrimers (5, 14). Their monodisperse nature has been verified extensively by mass spectrometry (20, 34), size exclusion chromatography (SEC), gel electrophoresis (35) and transmission electron microscopy (TEM) (36). Comparison of traditional linear polymer size distribution Mw/Mn=2-10 with PAMAM dendrimers (G=1-7) is illustrated by SEC and TEM (Figure 5) 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 (28, 37). Based on their systematic size scaling properties as well as their hydrophilic/hydrodynamic behavior (35, 38) they are referred to as "artificial proteins" (12, 20, 28). Substantial effort has been focused on the use of dendrimers for site-isolation mimicry of proteins (21, 39), enzyme-like catalysis (40), drug delivery (12, 41, 49), surface engineering (33), and light harvesting (32, 42) hybridization with fullerenes (43) or single strand DNA's (50) to produce a wide variety of nanoscale sizes, shapes, containers and scaffolding. These fundamental properties have, in fact, led to their well established commercial use as globular protein replacements for gene transfection(i.e. Superfect®, Qiagen, Inc.) (44, 45), immunodiagnostics (i.e., Status®, Dade-Behring) (46, 47), as a nanopharmaceutical for the prevention of HIV (i.e., Vivagel®; Starpharma Ltd.) (7, 48) and a variety of other biological applications. Interestingly, properties optimized for dendrimer applications have been found to be nanoscale size (generation)-dependent as indicated in Figure 5. In conclusion, these unique "nanoscale size effects" combined with the inherent architecturally influenced "dendritic effects" associated with dendrons/dendrimers offers a very powerful set of parameters to use in the quest for new properties and products in the nanoscale domain (7, 28, 33).

CONCLUSIONS

Dendrons/dendrimers, are expected to continue to offer unprecedented properties (i.e., dendritic effects) and play a key role as quantized, monodispered building blocks for nanoscale synthesis in the next century. Presently, this "enabling nano-platform" is allowing the routine assembly of a plethora of both simple and more complex commercial nanodevices/structures. Just as the first three traditional synthetic polymer architectures have so successfully fulfilled the critical material / functional property needs for society during the past century, it is appropriate to be optimistic about such a future role for the *dendritic* state.

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