HIGHLIGHT

Dendrimers and Other Dendritic Macromolecules: From Building Blocks to Functional Assemblies in Nanoscience and Nanotechnology

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ABSTRACT: Given their size, in the single-digit nanometer range, and the versatility of their functionality, dendrimers and other dendritic macromolecules are poised to make a significant contribution to the rapidly expanding fields of nanoscience and nanotechnology. This highlight focuses on nascent applications of dendrimers that take advantage of their structural features and polyvalent character. In particular, the concept of dendritic encapsulation of function, borrowed from Nature, can be applied to the design of a varied array of energy-harvesting, light-emitting, or catalytic macromolecules. Similarly, the compact size and hierarchical ordering of components within dendrimers make them ideal for exploring the limits of nanolithography. Finally, the presence of differentiated functionalities and the polyvalent character of dendrons and dendrimers constitute strong assets for their use in polymer therapeutics. © 2003 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 41: 3713–3725, 2003

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Born in France, Jean M. J. Fréchet moved to the United States in 1967 to pursue graduate work in carbohydrate chemistry at the State University of New York and Syracuse University under the outstanding mentorship of Conrad Schuerch. From 1971 to 1986, he taught chemistry, carried out polymer research, and assumed administrative functions at the University of Ottawa. In 1987, he joined Cornell University, where he remained for 10 stimulating years, first as the IBM Professor of Polymer Chemistry and then as the first holder of the P. J. Debye Chair of Chemistry. Having joined the Berkeley faculty in 1997, he currently holds the Henry Rapoport Chair of Organic Chemistry and a research appointment at Lawrence Berkeley National Laboratory. His research interests largely focus on functional polymers: their design, synthesis, properties, and applications.

INTRODUCTION

Benefiting from their unique architectural, structural, and functional features, dendritic macromolecules are poised to make significant contributions in several areas of the physical and biological sciences and engineering. Their nanometer size, globular shape, and multivalent character and the modularity of their assembly suggest and enable their use in a host of biomimetic and nanotechnological applications. This highlight does not attempt encyclopedic coverage; instead, it mostly focuses on our own work exploring early applications that exploit the unique nature of dendrimers and derived dendritic macromolecules. These applications include encapsulating media for nanoscale devices, unimolecular nanoreactors, antennae, and functional arrays for optoelectronics, energy harvesting and transduction, imaging materials and resists for molecular patterning, and nanosized carriers for diagnostics or therapeutic applications. As a result of the lack of general availability of most dendrimers, many of these applications are still distant, and it is likely that commercial acceptance of dendritic molecules will continue to involve only high-added-value applications for some time to come.

MOLECULAR FEATURES OF DENDRIMERS

Dendrimers are monodisperse and highly branched globular macromolecules that are typically 1–10 nm in size and carry a multiplicity of functional groups at their periphery. Their globular shape results from an internal structure[1–3] in which all bonds emerge radially from a central core or focal point with repeat units that each constitute a branch point and are arranged in a regular, layered, branching pattern. Most dendrimers are assembled through covalent bonds with a divergent[1] or convergent[4,5] synthetic strategy, although some may also be obtained through the self-assembly of mutually complementary molecular building blocks.[6–16] Figure 1 shows two stylized three-dimensional views of a dendrimer pointing to the connectivity of its various building blocks and the globular shape that it may achieve, along with a two-dimensional representation of an actual fourth-generation poly(benzyl ether) convergent dendrimer.

Numerous macromolecules possess some of the features of dendrimers, including the high degree of branching that leads to a multiplicity of reactive sites or chain ends. These include some naturally occurring polysaccharides, synthetic hyperbranched or comb-burst polymers, and hybrid dendritic–linear and dendronized polymers.[2,3] Yet none of these dendritic macromolecules is capable of matching the ultimate properties of dendrimers. Even with true dendrimers, the properties of the dendritic state,[3] such as core encapsulation[17,18] and unusual solution viscosity behavior,[19] are only accessed when globularity is achieved at a certain size threshold. The rigidity of dendrimers generally increases with the number of layers of repeat units or the generation of the dendrimer.[20,21] However, it is greatly affected by the choice, intrinsic flexibility, and branching multiplicity of the monomer repeat unit, the number and type of bonds between branches, and the degrees of freedom available to interbranch bonds. In general, dendrimers only achieve their globular, near-spherical shape in solution or at very high generations. Lower generation dendrimers are less rigid and, depending on their building blocks and the interactions (both intramolecular and intermolecular) that prevail, may adopt elongated and flattened ovoidal shapes when spread on a surface.[21–23]

As an artifact of the method by which they are drawn, two-dimensional representations of dendrimers (Fig. 1,
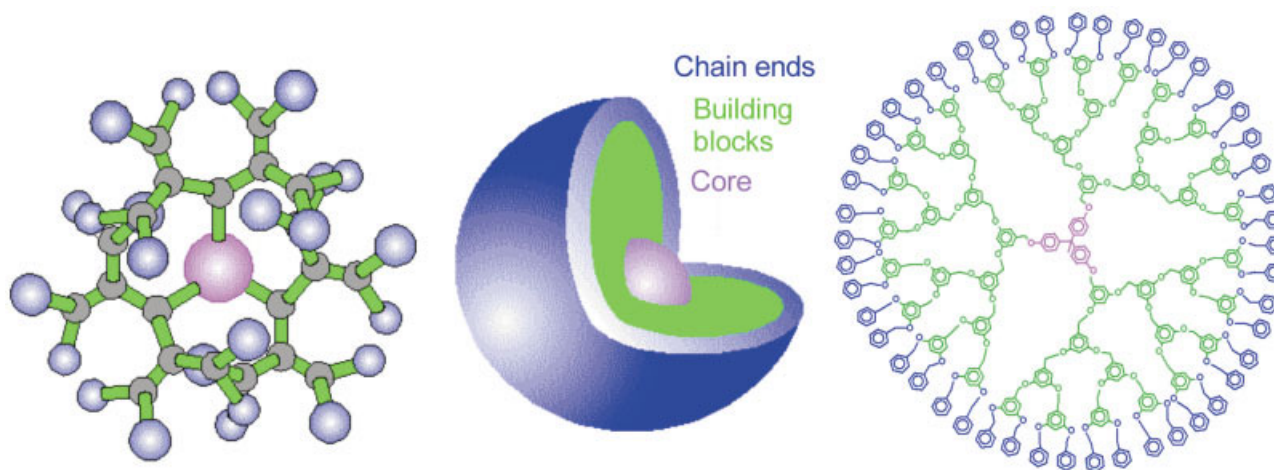

Figure 1.   Three dendrimer representations highlighting its major components.

right) suggest the existence of multiple cavities within the volume that they occupy. The possible existence of such cavities has remained a topic of some controversy. Unlike a micelle, which is a dynamic supramolecular assembly quite capable of incorporating a variable payload, covalent dendrimers are generally static structures with an internal volume that may be used to accommodate guest molecules,[24–29] particularly when they are enlarged by solvation with a good solvent. However, with the possible exception of very specialized structures such as shell-crosslinked dendrimers,[30,31] they do not possess a permanent and rigid cavity. Small guests, which can penetrate the volume of a dendrimers as a result of favorable enthalpic interactions, may remain encapsulated after the collapse of the solvated structure. Encapsulation may become permanent, as in Meijer et al.'s dendritic box,[29] if the peripheral density of the dendritic structure is increased to rigidify the whole macromolecule while guest molecules are located within the extended volume of a dendrimer. Such encapsulation may conceivably be used to prepare sensors, diagnostic beacons, or functional components of molecular machines.

CONCEPT OF DENDRITIC ENCAPSULATION

Nature is a wonderful source of inspiration, and our very fractional understanding of natural processes such as energy production, harvesting, and conversion, information storage, chemical synthesis, reproduction, and a myriad of other highly sophisticated processes can guide us in the design of functional molecular assemblies. Mimicry of Nature, combined with our enhanced abilities to mesh chemical structure and function, is responsible for many of the scientific and technological advances that have taken place over the past decades.

One area of natural mimicry of particular relevance to this highlight is that of function derived from site isolation.[18] Numerous biological systems make use of the concept of site isolation, by which an active center or catalytic site is encapsulated, frequently within a protein, to afford properties that would not be encountered in the bulk state. For example, the heme moieties of cytochrome C or hemoglobin would not be active and would not be able to perform their natural functions (catalysis and oxygen transport) were they not encapsulated in site-isolating proteins.

The dendritic shell is similarly capable of encapsulating functional core moieties to create specific site-isolated nanoenvironments, thereby affecting molecular properties. Taking advantage of the radially emanating architecture of dendrimers, researchers have placed ac-
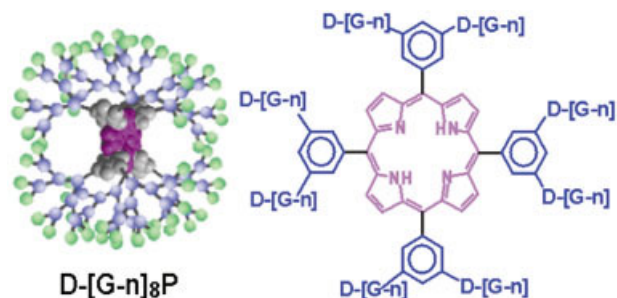

Figure 2. Two views of a porphyrin encapsulated in a dendrimer. The dendrons are marked [G-n], with n indicating the generation number in the structure on the right side.

tive sites that have photophysical, photochemical, electrochemical, or catalytic function at the core. For example, Figure 2 shows a dendrimer used to encapsulate a porphyrin moiety analogous to the hemes of many enzymes. Encapsulation is critical to function because it prevents the deactivation of catalytic activity that would result from intermolecular interactions if two porphyrin rings came close enough to each other to effect π-stacking. Applying the general concept of site isolation to problems in materials research is likely to prove extremely fruitful in the long term, with short-term applications readily accessed in areas such as the construction of improved optoelectronic devices.

DENDRIMERS AND LIGHT: FROM HARVESTING TO EMISSION

The self-assembly of dendritic carboxylate ligands around a single lanthanide ion serving as a core was used by Kawa[32,33] to improve the luminescence properties of the lanthanide metals, which are widely used as emitters in optical communications. In Kawa's work, three specially designed dendrons, each with an interacting carboxylate focal point, self-assemble around erbium(III), europium(III), or terbium(III) ions, leading in each case to an enhancement of luminescence efficiency with increasing generation because of site isolation of the lumophores, which drastically reduces the normally troublesomely high rate of self-quenching. Although it is of fundamental significance, this demonstration is also important for its implications in the context of fiber-optic applications. In such an application, an excellent match exists between the 1350-nm wavelength used to carry a signal through the fiber and the wavelength emitted by Er^{3+} after excitation by light at 980 nm being pumped into the amplifier module (Fig. 3). As the emission of the erbium(III) core dendrimers matches the wavelength used for signal transmission and dendrimer encapsula-
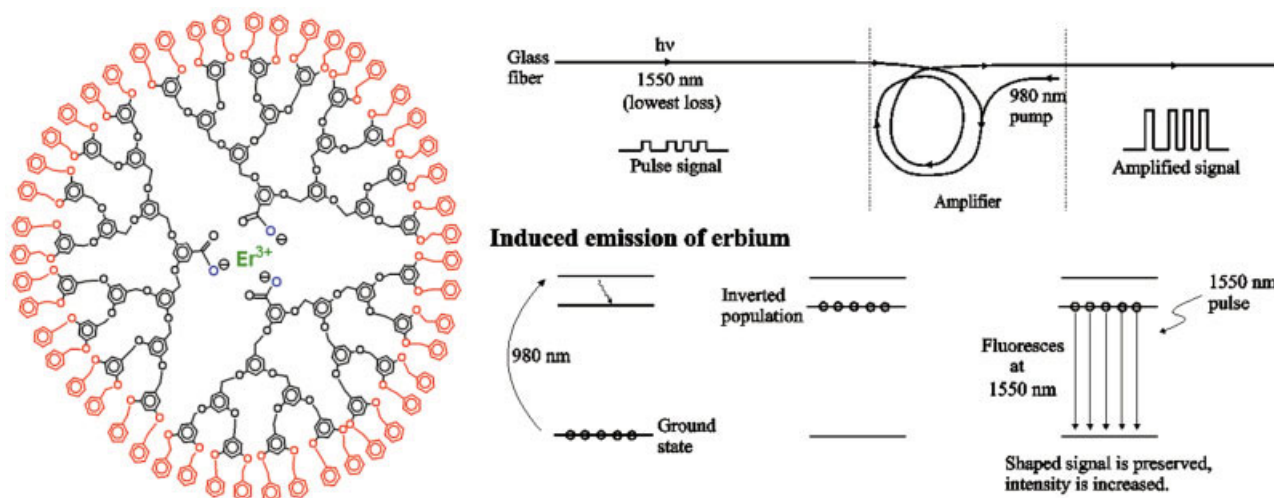
Figure 3. Encapsulation of an erbium ion in a self-assembled supramolecular dendrimer. The site isolation of the erbium ion negates self-quenching and enables its use in fiber optics as an optical signal amplifier.

tion eliminates self-quenching of the emission from Er^{3+}, they are extremely attractive for use in fiber-optic amplifiers and other optoelectronic devices.[34] Additional structure-related antenna effects attributed specifically to the Fréchet-type dendrons (Fig. 3) used for encapsulation have also been noted in the aforementioned systems and may lead to useful device applications.

In addition to steric protection, which is responsible for the site isolation used by Kawa et al.,[32–33] a dendrimer molecule is uniquely suited to arrange multiple peripheral functional groups around a single core unit. Through the introduction of an energy-transfer interaction or similar electronic link between the periphery and the core, the design of dendritic light-harvesting antennae becomes feasible.[35] In a dendritic antenna, an array of terminal donor chromophores collects many photons and transfers their energy through space (Förster energy transfer) to an acceptor unit located at the core or focal point of the dendrimer (Fig. 4). The acceptor, which can be excited independently of the periphery, also contributes to overall light harvesting. Because an emission is observed from the core only, the system serves as a spatial and spectral energy concentrator; in other words, it acts as a molecular lens.

Such light harvesting is important as it mimics the primary events in photosynthesis, in which the light-harvesting complex funnels its excitation energy to the special pair, leading to subsequent charge separation. Light-harvesting dendrimers can be used to effect several types of energy transformation: light into light (i.e., broad band into monochromatic, or upconversion of low-energy radiation into high-energy radiation with multiphoton processes), light into electricity with applica-

tions in a variety of novel photovoltaic systems, and light into chemical energy as done so masterfully in Nature.

In energy harvesting, two main types of systems can be envisioned: one involving the dendritic architecture solely as a scaffold[36–43] and another in which the dendrimer backbone itself participates in the energy-transfer event.[32,33,44–55] Using the former system, Gilat and Adronov[36–40] have shown that a useful form of light amplification can be achieved as the core acceptor moiety emits more light energy—transferred from the peripheral donor chromophores—than it ever could by its direct excitation. This amplification effect, which has its origin
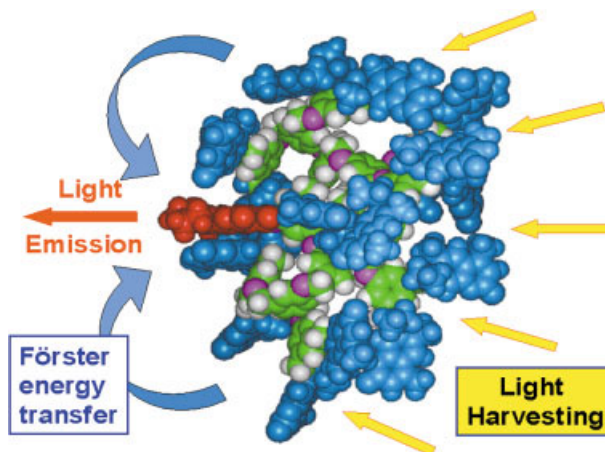

Figure 4. Light-harvesting antenna. Light harvested by all the chromophores (blue and red) is concentrated at the focal-point (red) acceptor chromophore and re-emitted as monochromatic radiation.
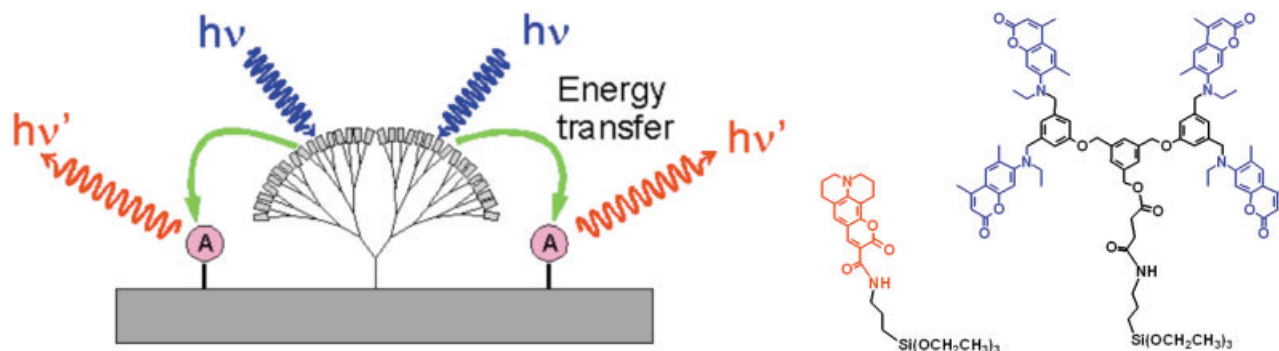
Figure 5. Multichromophoric light-harvesting antenna self-assembled on a surface such as silicon (right) and the donor (blue) and acceptor (red) chromophores used to prepare the light-harvesting monolayer (left).

in the enhanced donor absorption cross section and the extremely fast rate of through-space Förster energy transfer to the core, has been misunderstood by some. It is, therefore, useful to point out that, just as is the case for a classical audio amplifier, energy is not created out of thin air, but amplification simply involves the reprocessing of one form of energy into another.

Chrisstoffels et al.[56] extended our dendrimer antenna approach to a simpler self-assembled monolayer consisting of two components: a light-harvesting multichromophoric dendron and an isolated acceptor moiety. The self-assembly of these two components on a silicon surface with an optimized donor-to-acceptor chromophore ratio of 4:1 afforded the desired energy transfer and amplification of the acceptor emission (Fig. 5). We have also performed similar self-assembly of antenna molecules at the surfaces of other inorganic semiconductors used for photovoltaic cells.

Very recent work by Serin et al.[57] has further demonstrated that cascade energy transfer between three dendrimer-bound chromophores can be achieved with very high efficiencies (Fig. 6, right). A somewhat analogous cascade system was also reported recently by Müllen et al.[58] Similarly, Brousmiche, working in collaboration with the Prasad group (University at Buffalo), succeeded in achieving energy upconversion[59,60] through the use of two photon-harvesting chromophores[61] capable of direct energy upconversion or energy transfer to an acceptor moiety (Fig. 6, left).
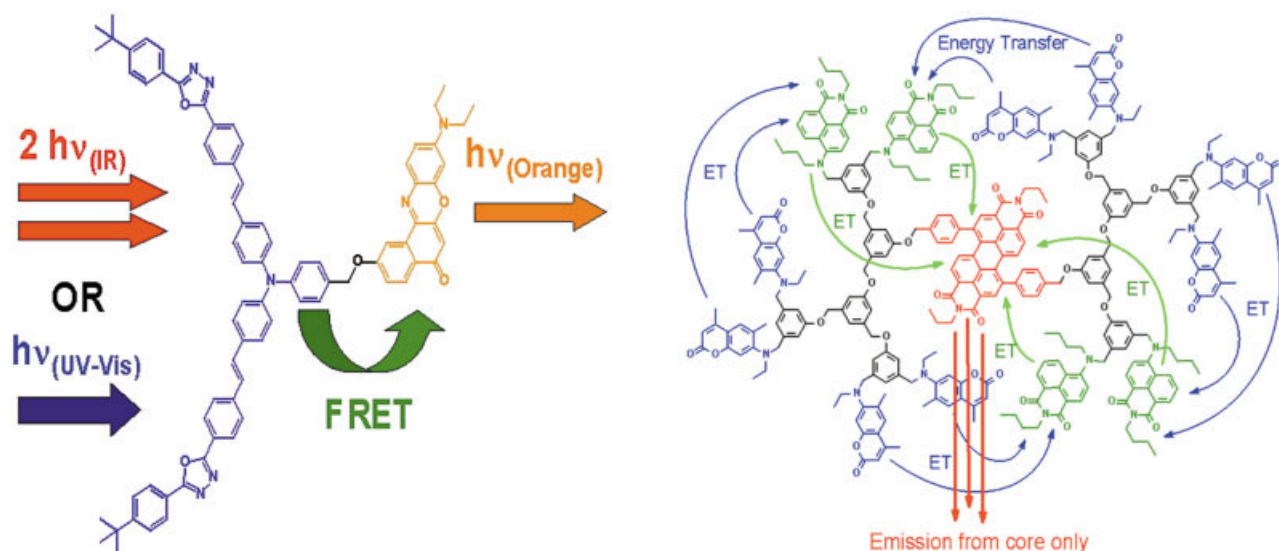

Figure 6. Two-photon energy-harvesting and upconversion process (left) and cascade energy transfer (ET) with relays between two types of donor chromophores leading to emission solely from the acceptor chromophore.
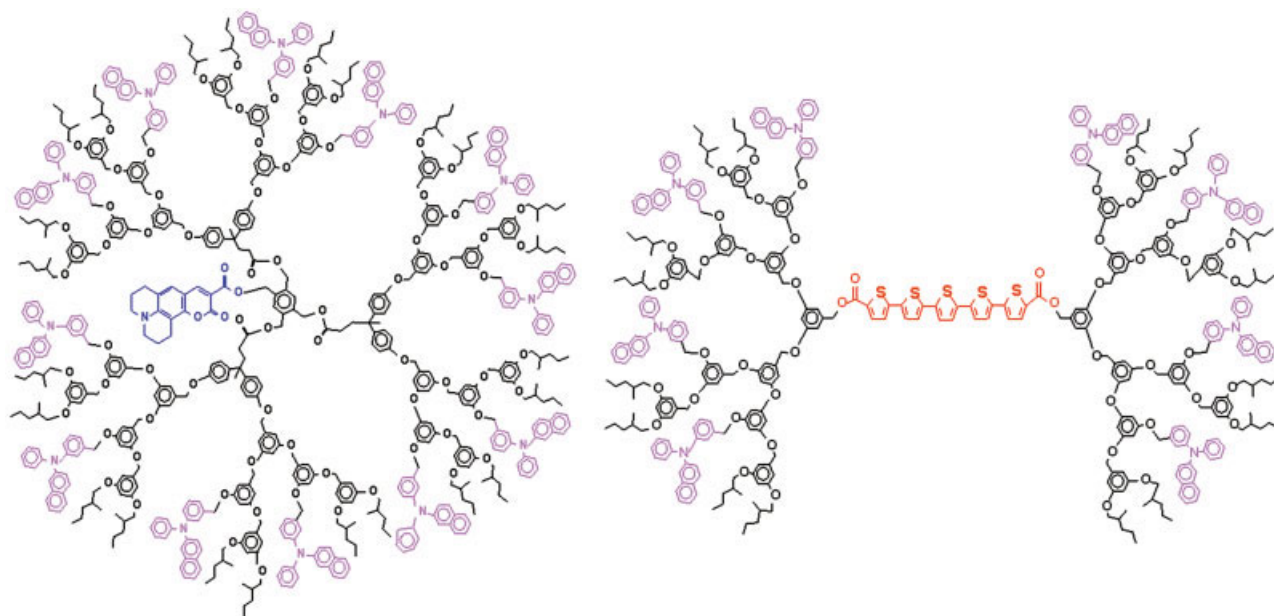
Figure 7. Two encapsulated chromophores used as a mixture capable of simultaneous emissions in an organic light-emitting diode. The coumarin moiety (the blue structure on the left) has been enlarged for clarity.

Among other key findings, Moore et al.[44] have shown that energy transfer is accelerated in dendrimers with an internal energy gradient, providing a stepwise decrease of the highest occupied molecular orbital/lowest unoccupied molecular orbital gaps of the branching units when progressing toward the acceptor core. In yet another approach relying on self-assembly, Balzani et al.[45] have constructed bipyridine-based polynuclear metal complexes capable of controlling the direction of energy transfer by altering the excited-state energies resulting from the introduction of appropriate metals.

Dendritic scaffolds have also been used to spatially arrange the different components necessary for the construction of organic light-emitting diodes. The excellent film-forming and unique encapsulation properties of many dendritic materials can be combined to create multicolor single-layer devices, as demonstrated in the recent fundamental work of Freeman and Furuta carried out in collaboration with the Thompson research group at the University of Southern California. In this work, naphthyl diphenylamine terminated poly(benzyl ether) dendrimers with a coumarin laser dye or a pentathiophene core were prepared (Fig. 7).[62,63]

These encapsulated emitters were then used to prepare two-component (i.e., two-color), single-layer devices consisting of dendrimers acting as both hole transporters and emitters, as well as an added oxadiazole serving as an external electron transporter. Although a mixture of the two dyes themselves only emitted light from the lowest bandgap pentathiophene chromophore, dendritic encapsulation enabled simultaneous emissions from the two dyes, demonstrating the value of the concept. The fabrication of the two-color light-emitting diode was facilitated by its single-layer design, and good matching of photoluminescence and electroluminescence was observed. The modular design of this approach, allowing the incorporation of both electroactive and solubilizing groups, along with the site isolation of the central dye by the larger dendritic frameworks[64] prepared by Furuta, allows for a combination of more than two dendrimers with differently emitting cores to be used, thus affording a color-tunable or white-light-emitting system. As of this writing, this approach remains one of only fundamental value because the lengthy preparation of the encapsulated dyes precludes their use in practical (i.e., potentially commercial) systems.

In the area of photovoltaic systems, dendrimers have excellent potential for increasing the light-absorbing cross sections of various systems for a better match with the solar spectrum.[65,66] Current research in this area is underway in our laboratory with dendrimers and several combinations of organic and inorganic materials.[67,68]

DENDRIMERS ON SURFACES: FROM FUNCTIONAL MONOLAYERS TO PATTERNING WITH NANORESISTS

More that a decade ago, we demonstrated that Fréchet-type poly(benzyl ether) dendrimers,[4,5] or more generally
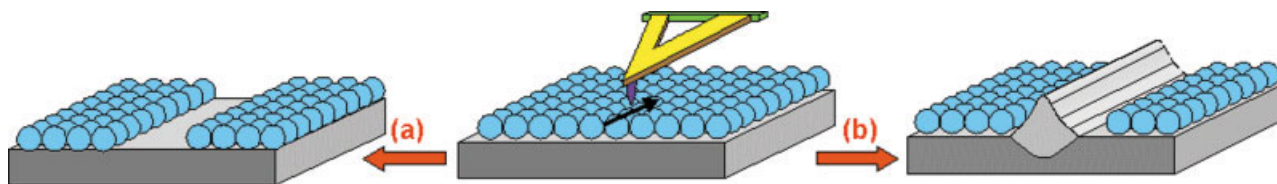
Figure 8. Two modes of imaging a dendrimer resist: (a) the removal of the dendrimer, leaving an area unprotected for subsequent etching, and (b) the oxidation of the dendrimer and underlying silicon, forming an image of SiO_2 that may be used in etching.

dendrons with a hydrophilic focal point and hydrophobic periphery, could be assembled into ordered monolayers at the air–water interface.[69] Neutron reflectivity studies also showed that the shape of the dendrons varied from spherical to ovoidal, depending on the degree of compression of the Langmuir film.[70] These early findings, coupled with the need for new, more performing resist materials, suggested that dendrimer monolayers might be used as resist materials or molecular pixels in nanolithography.[71] Because dendrimer molecules occupy a rather small volume, the opportunity for patterning molecule by molecule, possibly reducing the problems caused by line-edge roughness, exists if a suitable patterning tool with molecular resolution and sufficient throughput can be found.

Therefore, Tully and Trimble[72–74] investigated the preparation of ultrathin dendrimer films and monolayers self-assembled on silicon surfaces for their possible use as resist materials for scanning probe nanolithography. Modified poly(benzyl ether) dendrimers[4,5] that could serve as passivation resists in scanning probe lithography were covalently tethered to a silicon substrate through a spacer group attached to their focal point.[72,73] In the nanolithography experiments carried out in collaboration with Quate and Wilder (Stanford University), the conductive tip of the scanning probe microscope acted as the exposure source, degrading any organic monolayer located within the intense electric field created between the tip and the substrate [Fig. 8(a)]. At higher field strengths, the underlying silicon wafer could also be oxidized, and this resulted in the formation of raised oxide relief features on the substrate [Fig. 8(b)]. The latent image formed in the monolayer by this oxidation process could later be transferred into the underlying substrate by a selective wet-etching process.[72–74] In addition to covalently bound dendrimer self-assembled monolayers, we have also investigated the preparation of ionically bound dendrimer films by an acid–base self-assembly process. In this instance, the poly(benzyl ether) dendrons that we designed had a tethered carboxylic acid moiety at their focal point. A monolayer of dendrons could then be assembled onto an aminated silicon surface prepared by the pretreatment of a clean silicon wafer with (3-amin-

opropyl)triethoxysilane.[74] Although both types of dendrimers gave satisfactory performance, the exposure tool itself proved incapable of performing at the molecular level. The sizes of both the tip and the imaged features far exceeded the sizes of the individual dendrimer molecules.

The practical implementations of this technology will require a significant optimization of the tool and exposure method to reduce the sizes of the individual pixels achievable with scanning probe lithography tips. In addition, large-scale tip multiplexing will be required to compensate for the extremely slow exposure speed of each individual tip.

In related work carried out with the assistance of Angelopoulos and Medeiros of IBM (Yorktown Heights), we have demonstrated the imaging of dendrimer resists with e-beam lithography.[75]

We are currently studying several approaches to nanolithography with dendrimers; some still make use of a scanning tip as the exposure tool, whereas others involve the use of a nanowriter for the creation of a latent image.[76] In all cases, it is expected that the molecular makeup of the dendrimer itself, or of a novel anisotropic tubular dendronized structure[77] that we are starting to explore for use as a nanoscale resist, will be sufficient to provide the necessary etch resistance.

APPLICATION OF DENDRIMERS IN CATALYSIS: DESIGNING FREE-ENERGY-DRIVEN UNIMOLECULAR NANOREACTORS

Catalysis with highly branched macromolecules, primarily dendrimers, is well documented in the literature.[78–81] In one approach, the dendrimer merely acts as a support, displaying multiple copies of the catalyst at its periphery. In another approach, catalysis occurs within the dendrimer, offering possibilities of encapsulation of the reactive site to avoid its deactivation, or the creation of a special nanoenvironment that assists and enhances the catalytic process. Although several dendrimer catalysts in which catalysis occurs within the dendrimer have been described, only a few have performed better than a model

nondendritic system. The dendritic manganese porphyrins of Moore et al.[82] showed improved stability in solution in comparison with the free metalloporphyrin as a result of encapsulation by the surrounding polymer. The catalysts also provided some regioselectivity enhancements in the simple epoxidation of various dienes. Several other investigations of the effect of the dendritic superstructure on the catalytic activity of encapsulated sites have failed to uncover a dendrimer advantage.[83–86] However, a critical reading of some recently published work suggests that several of these approaches merely involved the incorporation of a well-known catalytic site in a dendritic superstructure. Because many of these designs did not provide for mass transport within the dendritic shell, product inhibition may well have been responsible for the relatively lackluster performance of several systems.

In view of our reading of these previous findings, we have taken a broader molecular system approach to the design of dendrimer catalysts. In this approach, instead of focusing only on the catalytic center and its immediate vicinity, we consider the overall environment of the catalytic site and its interaction with the surrounding medium (solvent) to incorporate not only the features responsible for catalysis but also the appropriate mass-transport machinery. Thus, the dendrimers should not only provide a shielded reaction center but also function, much like an enzyme, as a unimolecular, nanometer-size reactor, transporting and concentrating the substrate to the environment that best promotes the reaction, while also removing the product from the catalytic site as soon as it is produced.

This concept has now been reduced to practice in our laboratory[87,88] in an active collaboration with Hawker (IBM Almaden Research Laboratory). Therefore, Piotti used the chemical nature and structural features of the dendritic building blocks to generate a tailored nanoenvironment that assists in transporting the substrate and product and in stabilizing crucial intermediates and transition states. Transport is realized by the exploitation of free energy with a broadly applicable amphiphilic design that makes use of the contrasting polarity between the dendritic inner and outer environments, coupling it with a polarity difference occurring during the course of the catalyzed chemical transformation.

The amphiphilic design of the dendrimer catalysts is general: it leads to preferential accumulation of substrates and, in some instances, stabilization of transition states or intermediates in the interior, while the product is simultaneously expelled into the external medium, thereby preventing inhibition of the reactive site. An added feature of this free energy-driven mass transport is the fast kinetics that result from the comparatively high
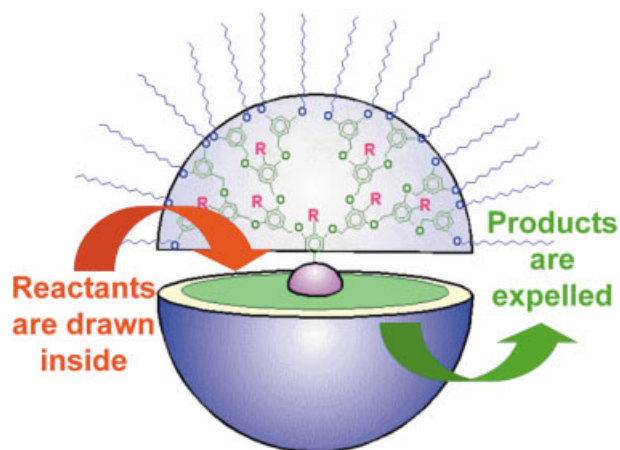

Figure 9. Dendrimer as a catalytic nanoreactor ensuring mass transfer in and out of the dendrimer interior in which the reaction takes place.

local concentration of the substrate that can be achieved near the catalytic site within the dendrimer.[87]

Piotti's initial demonstration involved a rather simple E1-type elimination reaction (Fig. 9) with a specially constructed dendrimer acting as a nanometer-size catalyst/reactor. The catalyst is designed with a radial gradient of polarity with a hydrophobic exterior and a hydrophilic interior that favors a low-energy transition state for the carbenium intermediate of the elimination reaction while also providing for preferential entry of the substrate. The peripheral alkyl chains provide solubility in nonpolar solvents, such as hexanes, helping to drive the starting alkyl halide reagent into the more polar dendrimer in which it concentrates. Because the elimination is a first-order reaction, its rate is greatly influenced by the ability of the dendrimer to concentrate the reagent inside its polar interior, and this translates into high turnover numbers (17,400) with almost quantitative conversions at very low catalyst loadings (<0.01 mol %).[87]

The generality of this concept was demonstrated by Hecht,[88] who reversed the polarities of the inner and outer zones of the dendrimer catalyst to carry out a bimolecular reaction that involved excited-state catalysis. A dendritic photocatalyst incorporating a triplet sensitizer as the core, relatively hydrophobic dendrons favorable for singlet oxygen reactions, and a hydrophilic periphery is assembled and used to perform a bimolecular [4+2]-cycloaddition between singlet oxygen and cyclopentadiene in a highly hydrophilic water–methanol mixture used as the solvent. The cyclopentadiene naturally concentrates within the hydrophobic dendrimer interior, and the reaction is started by the irradiation of the solution to create singlet oxygen through the action of the photoactive core of the dendrimer (Fig. 10).
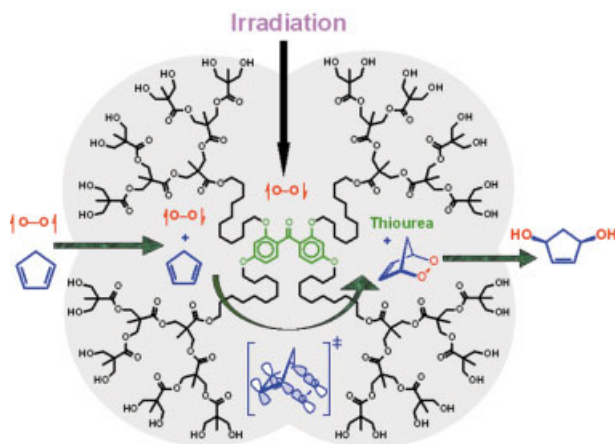
Figure 10. Dendrimer photocatalyst designed to produce singlet oxygen within the dendrimer while also ensuring mass transport.

The reaction leads to the rapid formation of a cycloadduct, which is immediately reduced *in situ* by the thiourea present within the dendrimer to afford the highly hydrophilic allylic diol product. The transformation of cyclopentadiene into a diol occurs with a very large increase in polarity and, given the relative polarities of the inner and outer portions of the dendrimer, leads to the expulsion of the product from the dendrimer (i.e., mass transport). Once again, the dendrimer acts as a nanoreactor providing for mass transport of the substrate into the reaction cavity and exclusion of the product from the reaction center, returning it to the surrounding solvent. A noteworthy feature of this system is that the bimolecular reaction benefits from both the high internal substrate concentration and the enhanced lifetime of singlet oxygen in the hydrophobic core environment. Although the choice of benzophenone as a core is convenient for this demonstration of a bimolecular reaction, a more robust sensitizing core is desirable, and Dichtel[89] is currently exploring the used of porphyrin-cored systems for analogous phototriggered transformations.

These initial findings clearly demonstrate the importance of a molecular system approach in general, and the amphiphilic motif in particular, for the rational design of catalyst nanoreactors. Current research is aimed at the exploration of a variety of reactions with different polymer architectures to gain further insight into important aspects of the roles of the architecture, molecular structure, and local environment as well as the possible cooperativity of multiple catalytic sites.

NANOMEDICINE: DENDRIMERS IN MACROMOLECULAR THERAPEUTICS

The targeted delivery of diagnostic and therapeutic agents is one of the great challenges of medicine today.

Recent work has shown that macromolecules such as poly(ethylene glycol) can be used to improve significantly the bioavailability and pharmacokinetics of known drugs.[90,91] A clear example, already a rousing commercial success, is Schering-Plough's PEG Intron, in which a short strand of monomethoxy poly(ethylene glycol) [PEG; molecular weight = 12,000 Da] is attached to interferon α-2b, a water-soluble protein (molecular weight = 19,271 Da) produced by recombinant DNA techniques.[92] The polymer–drug conjugate is much more effective that the parent interferon alone in the treatment of hepatitis C.

Today, the conjugation of drugs to PEG is being aggressively explored by numerous pharmaceutical companies as a means of improving the performance of both known and newly developed drugs. A significant hurdle of this approach when applied to low-molecular-weight drugs is that the conjugation of one or even two molecules of a drug to one molecule of PEG to form a prodrug leads to issues of low molar concentrations of the active ingredient or high viscosity of the solution of the drug conjugate.[93]

In contrast, polymers can be used for the conjugation of multiple copies of a drug onto a single polymer chain, as demonstrated by Kopeček and Duncan[94] using poly(N-2-hydroxypropyl methacrylamide) (HPMA) as the carrier. Although linear polymers such as HPMA will continue to be exploited successfully, the study of dendritic carriers is extremely attractive as they offer advantages such as high solubility, better bioavailability, lower polydispersity, and multivalency with enhanced access to numerous reactive sites of identical accessibility (Fig. 11, left).[95,96] Our current targets in macromolecular therapeutics include the development of microparticulates and nanoparticulates based on pH-degradable polymers[97] for the delivery of vaccines and genes and dendritic macromolecules for the conjugation and targeted delivery of drugs, diagnostic agents, or combinations of the two.[98–100]

Our design concepts include the use of nontoxic water-soluble carriers with high drug-loading capacities, as exemplified by our linear–dendritic hybrid stars based on aliphatic polyester dendrons (Fig. 11, right).[98–100] In our initial work, we used a passive targeting method that delivers the dendritic drug conjugate specifically to tumor cells with the so-called enhanced permeation and retention effect discovered by Maeda et al.[101] This targeting method, involving the relatively poorly defined and leaky vasculature that develops rapidly in the vicinity of tumors, requires rather long plasma residence times, a variable that is adjusted through the optimization of the size of the dendrimer–drug conjugate. As a result of their attachment to the macromolecular carrier, the drug conjugates have vastly reduced toxicity in compar-
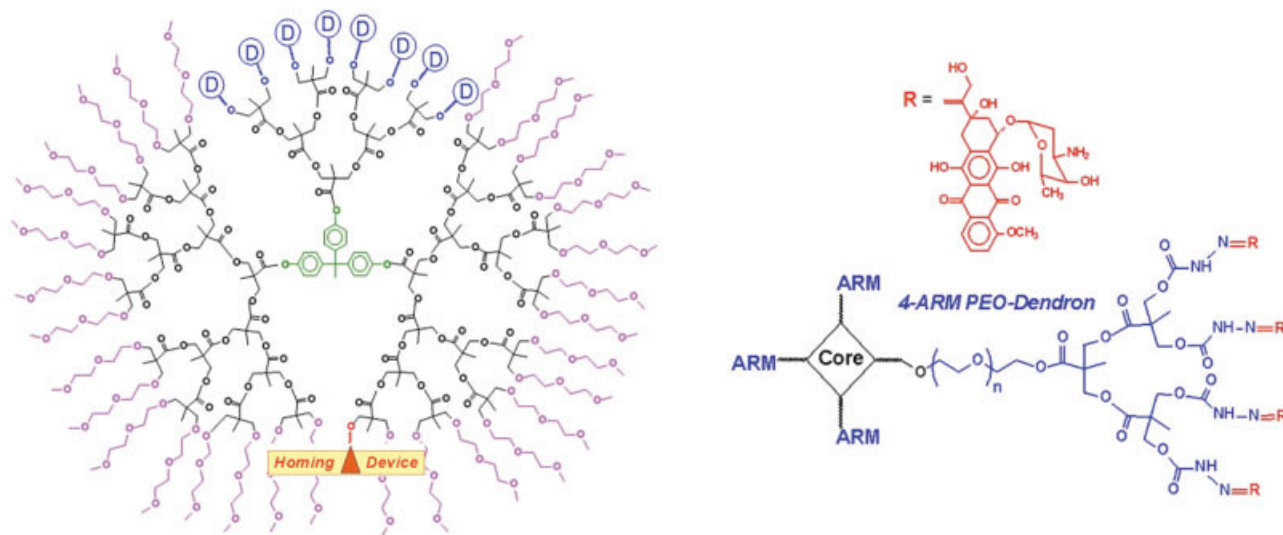
Figure 11. General concept of the targeted dendrimer–drug conjugate with multiple copies of the drug (D) attached to the dendrimer by a cleavable linkage (left) and a four-arm PEO dendron used for the delivery of the anticancer drug doxorubicin (right; refs. 98–100).

ison with the free drug (e.g., doxorubicin), and so deleterious side effects are therefore minimized. The release of the free drug from the multivalent dendritic conjugates is based on the low pH that prevails within tumor tissue, causing cleavage of the acid-labile linkages between the drug molecules and the dendritic carrier.[98–100] Biodistribution experiments carried out on a number of different dendritic architectures based on aliphatic polyester dendrons showed that the carrier molecules had no significant toxicity and could be eliminated through normal excretion mechanisms, mostly through the kidney. In the case of dendritic–linear doxorubicin conjugates, a slight accumulation of the drug in vital organs was observed, whereas the serum half-life of the doxorubicin conjugate was significantly higher than that of the free drug.[98–100] Thus, this and similar types of nanoscale drug carriers[102,103] exhibit promising characteristics for the development of new polymeric drugs.

As mentioned earlier, we have demonstrated in recent work that smart polymer carriers with controlled structures also have great potential for the effective delivery of vaccines and for gene therapy.[97,104] The role of dendrimers in such applications is still in infancy, but it is clear that the area of targeted delivery of therapeutic agents is one for which dendrimers and dendritic polymers in general show great potential.

Finally, it should be mentioned that one of the earliest medical applications of dendrimers was in the area of diagnostics: Wiener et al. and Bryant et al.[105–107] have explored the use of dendrimer–gadolinium (Gd^{3+}) complexes as contrast agents in magnetic resonance imaging. The molecular size, polyvalence, and solubility of the

dendrimers could be exploited to prepare diagnostic agents with high relaxivity and long residence times in the blood; this reduced the dose and the number of injections while providing maximum contrast.

Today, it appears that dendrimers and nanoparticles are poised to provide access to a future generation of delivery vehicles that will combine diagnostic function with the on-demand delivery of one or more therapeutic agents.

CONCLUSIONS

Dendrimers and dendritic polymers are important components of the developing areas of nanoscience and nanotechnology. Given their size, typically in the single-digit nanometer range, their remarkable architecture, and their multifunctional character, dendrimers are nearly ideal building blocks that may be assembled with other functional components either covalently or in a supramolecular fashion. Few other materials possess the internal organization, functional versatility, and excellent physical properties of dendrimers. There is little doubt that molecules possessing dendritic features and polyvalent character can provide valuable functions in areas as varied as optoelectronics, information storage, medical diagnostics and therapeutics, and catalysis. Whether or not these applications become commercial will depend in large part on the cost effectiveness of dendritic materials. As is the case with many new significant scientific developments involving novel materials, commercial implementation will require a long lead time, and the im-

patient critic should remember that the process of product development frequently extends 2 decades or more beyond the initial discovery. Meanwhile, science continues its forward progress, and the body of knowledge acquired through the study of dendritic materials is rapidly growing, stimulating further research and suggesting new areas of application.

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