

Dendrimers Designed for Functions: From Physical, Photophysical, and Supramolecular Properties to Applications in Sensing, Catalysis, Molecular Electronics, Photonics, and Nanomedicine

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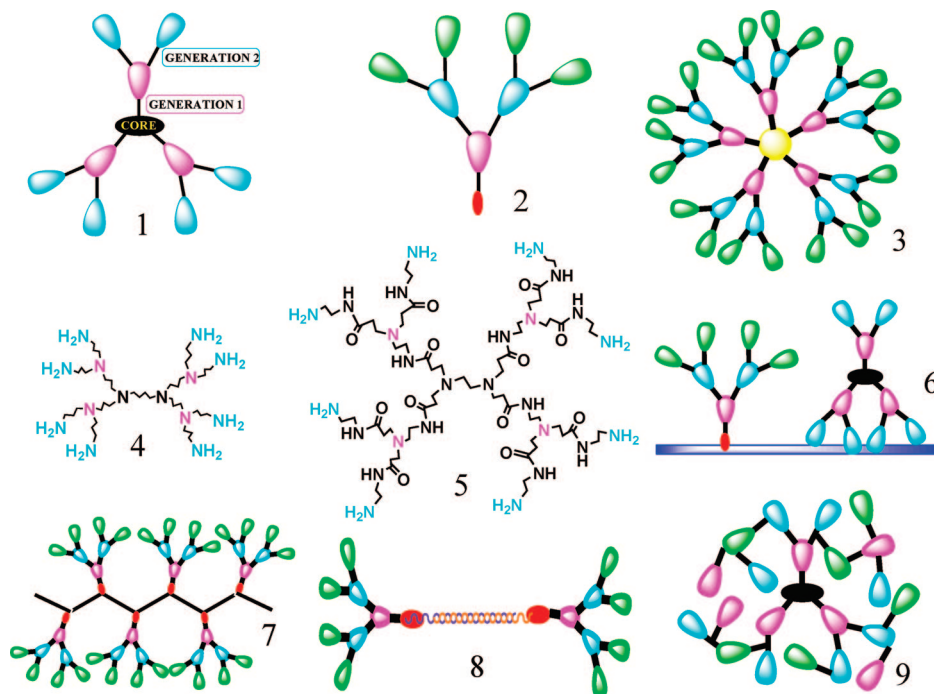
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1. Introduction, Scope, and Organization of the Text

Dendrimer chemistry^{1,2} largely relies on supramolecular properties.³ Since the pioneering work on iterative reaction sequences^{4,5} and dendrimer syntheses,^{6–8} the supramolecular dendritic aspects^{8–10} have been extended to the macromolecular nanoscale.⁹ In this review, we focus on the functions and applications of dendrimers resulting from supramolecular and physical properties. We will not address the synthetic aspects that have been the subject of many reviews.^{9–46} During the early days, the properties of dendrimers were first examined with Tomalia's PAMAM dendrimers^{7,9,17} and Newkome's arborols (unimolecular micelles),^{8,14–16} then with Meijer's poly(propylene imine) (PPI dendrimers)^{10,12,13,22} that are commercial, as are the PAMAM dendrimers, and with Fréchet's polyether dendrimers.^{23–26} The spectrum of dendrimer families is now very broad,^{10–27} so that there are numerous possibilities for molecular engineering in order to obtain a desired function. Books on dendrimers have been published,^{1,2,11–13} and the dendrimer literature is huge.^{9–46} Topics of synthetic interest have already been addressed early on and continuously reviewed during the past 20 years of dendrimer chemistry. Thus, the synthetic aspects will not be covered here, but in this concern let us only point out the crucial importance of the purities of dendrimers that may vary from one family to the other and significantly influence the adequate achievement of the functions. We will concentrate our attention on the most powerful concepts of

dendrimer chemistry in terms of functions and potential applications. We will especially emphasize dendritic effects whenever they are known. We will quote the seminal reports and the review articles and will review essentially the most

Chart 1. Schematic Representations of Dendritic Structures: 1, Dendrimer; 2, Dendron; 3, Dendritic Nanoparticle; 4, PPI Dendrimer; 5, PAMAM Dendrimer; 6, Dendronic and Dendritic Surface; 7, Dendronized Polymer; 8, Dendriplex; 9, Dendrigraft



recent work even if the major concepts will be recalled. Dendrons bonded to polymers were called dendronized polymers,⁴⁷ and they disclose properties relevant to those of dendrimers and will be discussed whenever a specific function or application is involved. Branched or hyper-branched polymers, pioneered by Flory,⁴⁸ are useful alternatives to dendrimers that are commercially of great interest and can sometimes show closely related properties for functions. They are not included here unless they fall in the dendrimer context, but reviews are available,^{48,49} and Chart 1 represents the major types of dendritic frameworks. Most applications of the physical and photophysical properties (section 3) of dendrimers are in catalysis (section 5), nanomedicine (section 6), and sensing (sections 3.16, 4.12, and 6.9), but optoelectronic applications also appear throughout section 3.

2. Dendritic Structures and Physical Properties

2.1. Simulation Versus Experiment: Localization of the Terminal Groups

The well-known de Gennes dense-packing model has dominated the attention for about two decades. It predicted that surface congestion occurs at the periphery of a dendrimer after a certain generation. The surface area A_Z is given by eq 1 in which Z is the number of terminal groups, A_D is the total surface of the dendrimer, N_Z is the number of surface groups per generation, r is the radius of the dendrimer, N_C is the number of core branches, N_b is the number of branches at each generation, and G is the number of generations.

$$A_Z = A_D N_Z (r^2 / N_C N_b G) \quad (1)$$

This means that A_Z decreases as the number of generations increases. The dense-packed generation G_1 is reached

when A_Z reaches the cross-sectional area corresponding to the van der Waals radii. A simple equation was provided for PAMAM dendrimers having a branch-cell segment P :

$$G_1 = 2.88(\ln P + 1.5) \quad (2)$$

According to this equation, the dense-packed generation is reached between 10 and 11.⁵⁰ This appears to be impressively large, but imperfection in this dendrimer series, as in others, starts in early generations. Other theoretical studies have concluded differently. For instance, it has been suggested that the most probable conformation has its maximum density in the center of the dendrimer.⁵¹ Indeed, the “dense-core” approach appeared since 1990.⁵² Such an overall structure is an average of a large number of possible conformers. Such theoretical calculations are in agreement with the fact that flexible dendrimers would be characterized by a surface and internal holes. A survey of a large number of theoretical studies has recently appeared, converging toward this latter analysis.⁵³ This implies that the end groups of dendrimers backfold toward the center. For PAMAM dendrimers, such backfolding has been considered despite the interchain H-bonded termini that contribute to minimizing this back-bonding. ¹³C NMR relaxation studies (G_0 – G_{10}) suggest that the chain termini are not densely packed at the surface of G_{10} bearing a theoretical number of 3072 terminal branches. Examination of CPK models¹⁰ shows a maximum radius of 71 Å, whereas the SEC experiments indicate an actual radius of 62 Å. At full extension, each terminal group needs a surface area of 21 Å, but only 16 Å is available, which suggests some backfolding.⁴⁴ The dynamics of PAMAM dendrimers was recently made available by the use of dielectric relaxation spectroscopy (DSR) showing different relaxation behavior below and above the glass transition temperature T_g , which is around -30 °C.⁴⁵ Until recently, the syntheses of dendrimers did not overtake the de Gennes dense-packing limit, however. Syntheses of dendrimers far

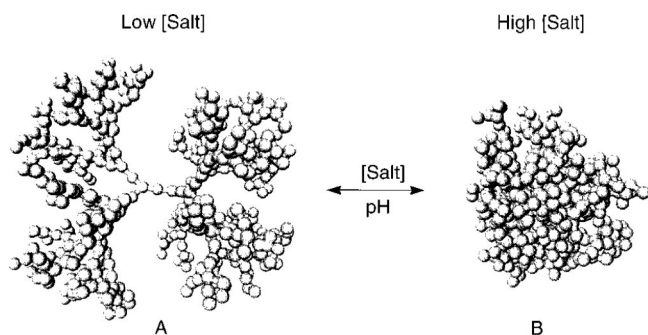


Figure 1. (A) Hollow core, “dense shell” picture. (B) “Dense core” picture. These are representative snapshots from the statistical ensembles generated in this study for the sixth generation with two springs between branch points. Reprinted with permission from ref 65 (Muthukumar’s group). Copyright 1998 American Chemical Society.

beyond the de Gennes “dense-packing” limit have been reported in 2003 until the ninth generation⁵⁴ with a theoretical number of $3^{11} = 177\,147$ allyl branch termini using a Newkome-type $1 \rightarrow 3$ connectivity.^{7,10} At the ^1H NMR accuracy (i.e., approximately 97%), all the reactions appeared to be completed, whereas the de Gennes dense-packing limit was below generation 6 ($3^8 = 6561$ termini). AFM and TEM experiments for the highest generations showed a steady growth with increase of the generation number. Since these giant dendrimers have small methylene termini, severe backfolding is necessary, so that the limit of construction is dictated by the dendritic volume rather than by the surface of the de Gennes model.

Computer-assisted molecular modeling initially showed that the PAMAM dendrimers are spherical above generation 4 but have hemispherical domes below this generation. The surface congestion was confirmed by viscosity and refractive index experiments that reflected the reduced interaction between the surface groups and the solvent above generation 4.⁸ The only experimental tools available to analyze the spatial structure of dendrimers in solution are scattering methods such as small-angle neutron scattering and small-angle X-ray scattering,⁵⁵ but the information obtained is limited.^{56–59} The combination of scattering and theoretical simulation methods converged to satisfying conclusion, however.^{56–61} A common feature of all generations is the strong backfolding of the terminal groups, a tendency that grows with increasing generation number. As noted early on,⁸ most of the surface of high-generation dendrimers lies inside the dendrimer, and construction beyond the dense-packing limit proceeds in the dendritic interior, which is confirmed by slow kinetics.⁵⁴ The size of the end groups plays a key role in termini backfolding, with the ability to backfold being all the more reduced as the termini are larger.⁶⁴ Charged dendrimers expand with maximum size occupancy compared to uncharged ones (Figure 1),^{8,65} although this trend has also been controversial.^{62,63,66,67}

For instance, SANS studies of the counterion effects on the molecular conformation and structure of charged G_4 -PAMAM dendrimers in aqueous solutions show that strong repulsion is introduced by protonation of the amino groups deeply modifying the internal dendrimer structure, although the gyration radius R_G only changes by about 4% when the pD value varies from 10.25 to 4.97.⁶⁰ The solvents also influence R_G ; for instance with $\text{D}(\text{CD}_2)_m\text{OD}$, R_D of G_8 -PAMAM is reduced by 10%, changing the solvent from m

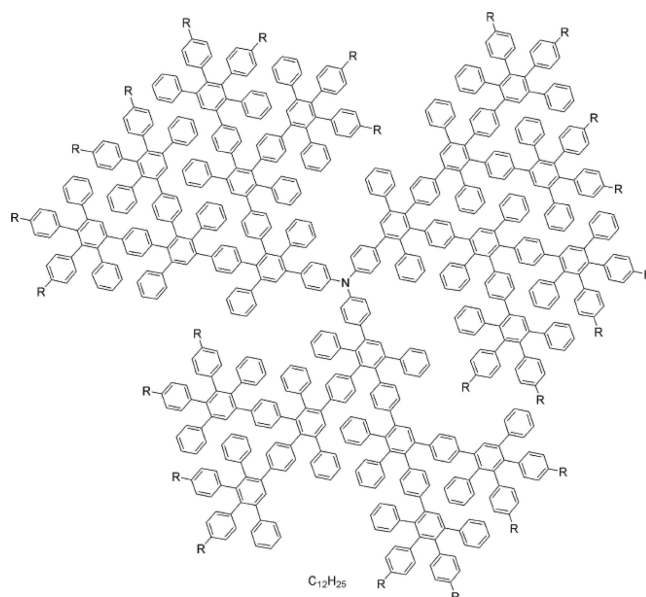


Figure 2. Third-generation dendrimer with a triphenylamine core. Reprinted with permission from ref 411 (Müllen’s group). Copyright 2005 American Chemical Society.

$= 0$ to $m = 4$.^{60,61} With Newkome-type dendrimers containing carboxylate termini, SANS studies showed that addition of a salt suppressed the interdendrimer interactions and that accumulation of tetramethylammonium counterions occurs around the surface with a counterion thickness between 4 and 6 Å.⁶² Capillary electrophoresis studies showed that the effect of an electric field increased the mobility of these dendrimers.⁶³

Local dendrimer dynamics including local motion has been compared to supercooled liquids and linear polymers,⁶⁸ including glass transition aspects.⁶⁹ A hybrid approach involving both a single-chain Monte Carlo simulation and DFT calculation of the Helmholtz energy allowed insight into the microscopic dendrimer properties.⁷⁰ The shape of dendrimers was related to the shear viscosity using nonequilibrium molecular-dynamics simulations.⁷¹ Atomistic molecular dynamics simulations were applied to negatively charged PAMAM dendrimers with sodium counterions, indicating that the charge effect on conformations is more pronounced for low generations than for large ones.⁷²

A Brownian dynamic study indicates how the adsorption of charged dendrimers can be tailored by changing various parameters.⁷³ The rigid polyphenylene dendrimers (Figure 2) do not present the possibility of backfolding terminal groups, contrary to the flexible dendrimers.³⁵

This remarkable family has been the subject of recent simulations using atomistic molecular dynamics,⁷⁴ molecular modeling,⁷⁵ and polymer reference interaction site model integration theory.⁷⁶ The effect of repeat dendrimer unit flexibility on conformation was studied by atomic molecular dynamic simulations, which showed that all dendrimers are radially distributed throughout their interiors due to backfolding of the flexible dendrimers or to branching angle effects for stiff-chain polyphenylene dendrimers.⁷⁷

In azobenzene-terminated dendrimers, UV irradiation causes changes in the shape and size of the dendrimers due to the chromophore units that reversibly photoisomerize $E \rightarrow Z$.^{12,13} In ferrocenylazobenzene-terminated dendrimers, this reversible photoisomerization provokes a generation-dependent size change that could be monitored by cyclic voltam-

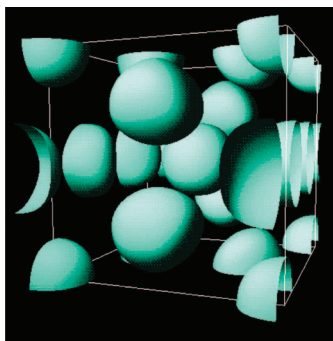


Figure 3. 3D electron density distribution of the $Pm\bar{3}n$ Cub phase ($a = 79.2 \text{ \AA}$ at $80 \text{ }^\circ\text{C}$) of the spherical supramolecular dendrimers self-assembled from 16 monodendrons. These isoelectron surfaces were generated from XRD by Fourier synthesis with the structure factor phases determined by TEM. Reprinted with permission from ref 89 (Percec's group). Copyright 1997 American Association for the Advancement of Science.

metry, because the diffusion-coefficient dependent intensity increases upon $E \rightarrow Z$ irradiation due to dendrimer size decrease. This effect is all the more obvious as the generations increase.⁷⁸

A strong correlation was established between the solvent polarity and the mean radius of gyration.⁷⁹ For instance, simulations with dendritic polyelectrolytes indicate a dramatic contraction upon increasing the ionic strength of the solvent,⁸⁰ and a similar effect was demonstrated with PPI dendrimers upon addition of a salt.²²

Experimentally, backfolding of the dendritic tethers was initially shown in the flexible Fréchet-type polyarylether dendrimers using SEC coupled with differential viscosimetry (viscosity reaches a maximum as a function of generations),⁸¹ rotational-echo-double-resonance NMR (REDOR),^{82,83} spin relaxation (T_1) with a paramagnetic core,⁸⁴ and fluorescence depolarization using rubicene cores.⁸⁵

On the other hand, Percec-type dendrimers containing perfluorinated⁸⁶ or perhydrogenated^{87,88} tethers were shown by X-ray diffraction to present solid-state assemblies precluding backfolding (Figure 3).⁸⁹

Many studies carried out with PAMAM dendrimers (SEC, viscosity, ^{13}C NMR relaxation, ^2H NMR, SAXS, SANS, photophysical, and ESR), reviewed elsewhere,^{8,19} have shown that the interbranch terminal H-bonded groups preclude backfolding (confirming the validity of the de Gennes model in this case) to a certain extent, with the conclusions being variable among the studies.^{90–93} Likewise, the degree of interbranch H-bonding in PPI dendrimers was shown to grow with increasing generation numbers, and these studies (IR and NIR)⁹⁴ have been reviewed.²²

PPI dendrimers terminated with CN and palmitoyl groups were studied by translational diffusion and viscosimetry. Their volumes was shown to increase proportionally with the number of end groups, meaning that these end groups were predominantly located at the dendrimer periphery (due to H-bonding between CN and NH groups and possible repulsion between the palmitoyl groups and the core).⁹⁵ The translational diffusion coefficient D is a hydrodynamic characteristic sensitive to the dendrimer size, with a linear correlation, $M[\eta] \approx D^{-3}$, where $[\eta]$ is the intrinsic viscosity and the hydrodynamic radii R can be calculated from D according to the Stokes–Einstein equation,

$$R_D = kT/6\pi\eta_0 D$$

or from viscosimetric data and molecular weight according to the following equation:⁹⁶

$$R_\eta = (3/10\pi N_A)^{1/3} (M[\eta])^{1/3}$$

The comparison between the physical properties of dendrimers and polymers shows the specific structure and behavior of large dendrimers, with trends clearly demonstrated in the pioneering work by Hawker and others.^{81,97–101} For instance, large dendrimers are most often globular (except specifically designed Percec dendrimers), and the influence of terminal groups is crucial on the physical properties, whereas this influence decreases with increasing molecular weight for linear polymers. Thus, contrary to linear polymers, the intrinsic viscosity of large dendrimers is very dependent on the nature of the end groups and is not increasing with molecular mass, but has been reported for the main dendrimer classes to reach a maximum at a certain generation.^{8,22,81} Polyester dendrimers were shown to be soluble in a large variety of organic solvents, contrary to linear polymers. The reactivity of the end groups is enhanced with large dendrimers, because they are more numerous and not so shielded as in linear polymers, and because dendrimers are more soluble than polymers. The hydrodynamic volume of large dendrimers is smaller than that of linear analogues, because dendrimers are more compact (with backfolding of termini) than polymers (Figure 4).^{97–101}

Self-folding of charged dendronized polymers was shown for G_2 - and G_3 -polyamide–polyether dendronized polymers with aminopropoxybenzoic methacrylate cores and neutral and negatively charged peripheral groups.^{99,100}

In conclusion, the specificity of dendrimers compared to linear polymers appears at high generation, with severe change of the properties above a certain generation.^{8,22,97} This trend also clearly appears from photophysical studies that are the subject of the forthcoming section. Molecular dynamics and mean field theory studies also indicate that, in polyelectrolyte dendrimers, electrostatic interactions are strongly screened and the dendrimer core is filled, with very weak conformation dependence on ionic strength.⁹⁸ Conformational changes in dendrimers were shown by bare Coulomb interactions to be induced by charges. The presence of charges leads to an increase in the dendrimer size due to the combined effect of electrostatic repulsion and the presence of counterions within the dendrimer. Accordingly, the bond lengths near the dendrimer center increase to facilitate a more effective usage of space in the region of the dendrimer periphery.^{99,100} G_3 and G_4 -poly(aryl ether) dendrimers containing a naphthyl group as the core were shown by fluorescence measurements in dichloromethane–acetonitrile to form an intramolecular exciplex between the naphthyl core and benzyloxy backbone units (resulting from photoelectron transfer) that validate exciplex formation enhancement by backfolding conformation of the dendrimers.¹⁰¹

2.2. Gelation of Dendrimers

From the initial publication, Newkome-type arborols were designed as water-soluble dendritic micelles with hydrophobic interiors and water-solubilizing alcohol termini.^{7,102} Such structures or closely related structures are susceptible to gelation as shown with the [9]-10-[9] dendrimer, for which negative-staining TEM revealed the presence of fibers.^{103,104} In these dendritic structures, the core is a polymethylene

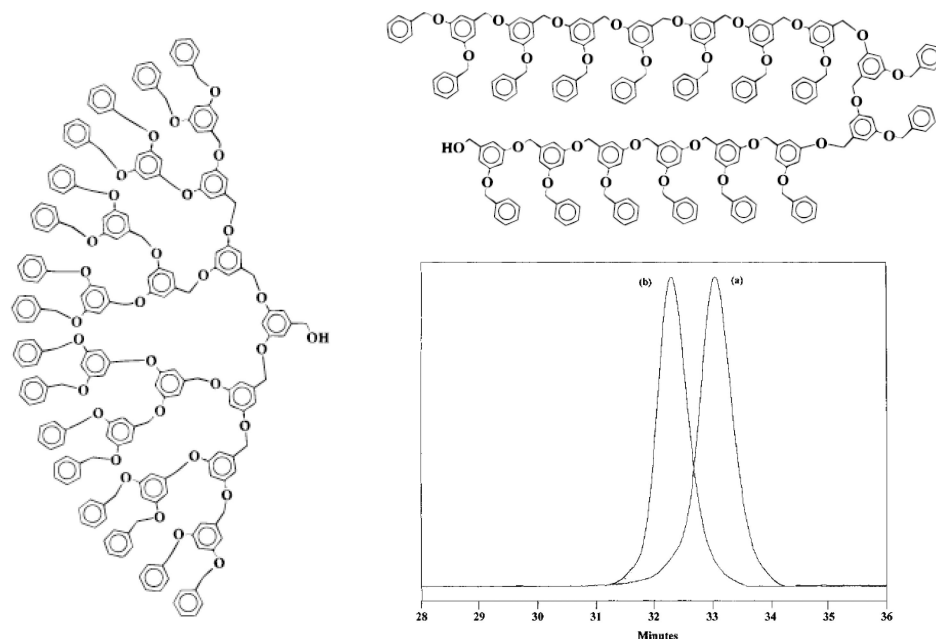


Figure 4. Comparative structures of the fourth-generation dendritic alcohol and its exact linear analogue; gel permeation chromatography (GPC) traces for the (a) fifth-generation dendritic alcohol and (b) the corresponding exact linear analogue. Reprinted with permission from ref 97 (Fréchet's group). Copyright 1997 American Chemical Society.

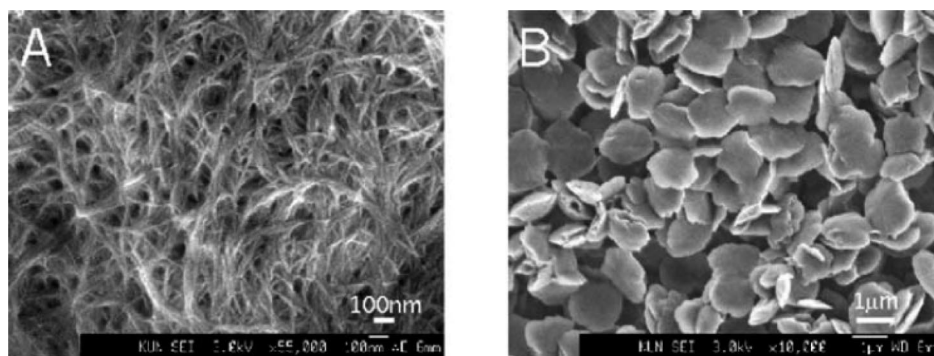


Figure 5. Nanoscale morphology observed using SEM for the two-component gelation system: (A) 2:1 dendron/diamine ratio and (B) = 1:4.5 dendron/diamine ratio. Reprinted with permission from ref 108 (Smith's group). Copyright 2005 American Chemical Society.

chain of variable length. The gel is dried, then coated with phosphotungstic acid solution prior to TEM visualization. Static and dynamic light scattering and viscosimetry were also used to study gelation of these dendrimers.¹⁰⁵ Gelation usually requires 5–10 min and can be reversed by heating. Differential scanning calorimetry shows the transition point, and freeze-fracture TEM of the arborols shows the fiberlike texture.¹⁰⁶ A variety of gelating dendritic structures were subsequently synthesized based on Newkome's concept of linear chain (which sometimes is a polyethylene glycol chain or a molecular wire¹⁰⁷) separating two covalently bound dendronic units, sometimes called “two-component” dendritic gels (Figure 5).¹⁰⁸

On the other hand, other dendritic gels with a polymeric and dipeptide component bound to a dendron were reported by Stupp's group¹⁰⁹ and Aida's group,¹¹⁰ respectively. In the latter case, dipeptide rather than mono-peptide, ester functionalities on the dendron surface, and higher-generation dendrons favored gelation. In a recent study, glycine and L-glutamic acid have been used as cores to form dendritic gels, with gelation properties increasing from the first to the third generation. Hydrogen bonding and π - π stacking were

the main driving forces to form the fibrous networks at low concentrations (0.5%), as shown by TEM, AFM, fluorescence, IR, circular dichroism, ¹H NMR, small-angle X-ray scattering (SAXS), and wide-angle X-ray diffraction.¹¹¹ Altogether, dendritic gels benefit from strong fibrous assemblies resulting from multiple dendronic branch interactions, a steric role in the formation of one-dimensional assemblies, and multiple-site cross-linking units for cross-linked dendronized polymer gels.¹⁰⁸ Butyl-terminated poly-(amidoamine) dendrons with either a Boc group or a carbonyl group at the focal point formed dendronic gelators with lamellar structures of 30–100 nm size as shown by TEM, WAXD, SAXS, NMR, and FTIR spectroscopy. The nature of the focal group impacted greatly on the gelation ability, and dendron generation increase favored gelation. Hydrogen-bonding and hydrophobic forces were shown to be the main driving forces for the fibrous assembly.^{112,113} Dumbbell-shaped dendrimers with a *p*-terphenylene core with bulky dendronic wedges self-assembled, forming gels with elastically interpenetrating 1-dimensional nanostructures in several organic solvents through cooperative π - π stacking, hydrogen bonding, and van der Waals forces.¹¹⁴

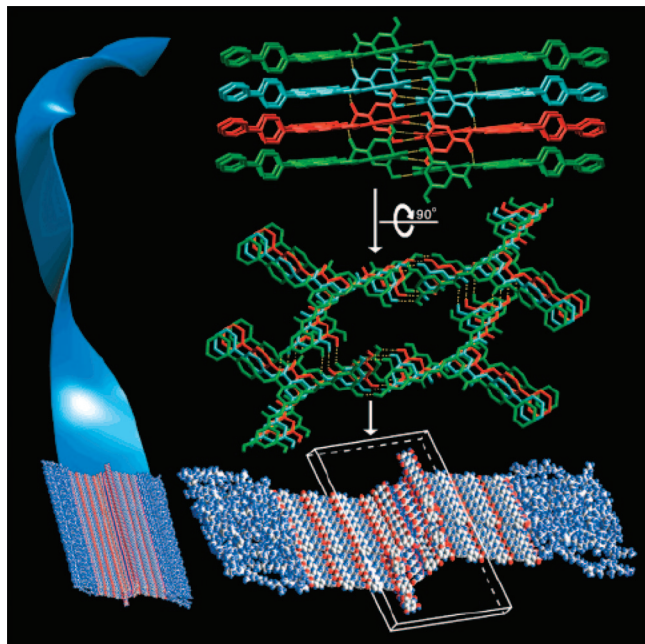


Figure 6. Side view of the ribbonlike structure taken directly from the crystal structure of a dendrimer shows color-coded hydrogen-bonded tetramers (upper right) stacked on top of each other along the direction of the crystal (top view is shown in the middle right). Schematic (left and bottom right) representation of the proposed structure for a DRC nanoribbon. Reprinted with permission from ref 124 (Stupp's group). Copyright 2001 American Chemical Society.

2.3. Dendrimer–Polymer Blends and Aggregates

Promising possibilities of coupling the physical properties of polymers and dendrimers led to studies of blended materials such as dendrimer-hyperbranch polymers,^{115,116} polystyrene–polyphenylene hyperbranched structures,¹¹⁷ aryl ester dendrimer–bisphenol polycarbonate,¹¹⁸ and 12-*tert*-butyl ester dendrimer–poly(methyl methacrylate) (PMMA).¹¹⁹ Glass transition temperatures (T_g) are found between those of the components. The methods used for these studies are viscosity, refractometry, UV–vis and FTIR spectroscopies, DSC, and DEA.¹¹⁹ Copolymers based on polyether dendrimers and polyethylene glycol (PEG) form micelles in methanol/water.¹²⁰ Polystyrene–PPI dendrimers are amphiphilic and aggregate in water, forming vesicles, micellar rods, or spherical micelles depending on the dendritic generation.¹²¹ Block copolymers assembled from polyether dendrimers and thermoresponsive polar poly(*N*-isopropylacrylamide) self-assemble in aqueous solution into bilayer spherical aggregates.^{122,123} Dendrimer–rod–coil incorporating a dendritic block at the end of a rod segment formed self-supporting gels in dichloromethane at concentrations down to 0.2 wt %, observed by TEM and AFM. They self-assemble into flat or helical ribbons, can incorporate electronically conductive groups, and can be mineralized with inorganic semiconductors (Figure 6).^{124–127}

2.4. TEM, AFM, and Studies on Surfaces

The behavior of dendrimers on surfaces and in amphiphilic materials was reviewed in 1999.²² PAMAM (most frequently),⁸ Newkome-type,¹²⁸ phosphorus,¹²⁹ carboxiloxane¹³⁰ and polyphenylacetylene^{131,132} dendrimers have been examined by TEM or cryo-TEM with the observation of aggregation when intermolecular H-bonding occurs (carboxylic acid

or hydroxy end groups).^{10,14–16,22} Spherical shapes were observed for large dendrimers, as expected. Sodium phosphotungstate was used for amine-terminated large PAMAM dendrimers (15 nm radii for G_{10}).¹³³ Gold phosphine-terminated dendrimers with up to a theoretical number of 3072 end groups were observed with up to 15 nm diameter.¹²⁹ Monolayers are usually observed on surfaces, but multilayer films of oppositely charged PAMAM ($-\text{NH}_3^+$ and CO_2^- termini) were also shown.¹³⁴ Wetting of mica surface was observed when hydroxyl groups preferentially adsorb on the surface. Flexible dendrimers, such as the PAMAMs, flatten on surfaces.¹³⁵ AFM observation of the PPI dendrimer G_2 -DAB hydrophobically modified with dodecanoyl end groups deposited on mica by adsorption from solution shows that, after 20 s, the dendrimer formed a submonolayer thin film that contained many fractal aggregates that were larger than 1 μm and 0.8 nm thick. After longer time, the initial fractal aggregate transformed into disks and other less-branched shapes with average heights of the domains of 0.6 and 0.4 nm, respectively (Figure 7).¹³⁶

Fréchet-type polyether,^{137,138} PAMAM,¹³⁹ PPI,¹⁴⁰ and dendrimers functionalized with various groups have been examined at the air–water and Langmuir–Blodgett interfaces, resulting in deformation of the dendrimers at the interfaces. With mesogenic functionalities, liquid crystalline (nematic or smectic) properties were obtained with sheetlike conformations.^{141,142}

Polyallyl dendrimers of fourth generation with a theoretical terminal olefin branch number of 729 were functionalized to glycolate metalocycles by vaporization of OsO_4 under a well-ventilated hood, which showed individual dendrimers by HRTEM with about 5 nm diameter, and the ninth generation with a theoretical terminal branch number of 177 047 was functionalized by hydrosilylation using $\text{HSiMe}_2\text{CH}_2\text{Cl}$. The corresponding iodomethylsilyl-terminated dendrimers were observed by HRTEM on a graphite support, showing the globular shape with a diameter of 13 nm.⁵⁴ Atomic force microscopy (AFM) also is a useful analytical tool, because it provides high-resolution imaging and measurement of surface topology.^{143–145} The layer-by-layer deposition technique has been monitored herewith,¹⁴⁶ surface morphologies of high-generation PAMAM dendrimers have been studied,¹⁴⁷ and assembled films of dendrimers in monolayers or multilayers have been investigated.¹³⁴ The series of polyallyl-terminated dendrimers with 3^{n+2} end allyl groups (n = generation number) were also observed by AFM on highly oriented pyrolytic graphite (HOPG) support from the first to the ninth generation, which showed a steady size increase of the height of the flattened dendrimers up to 25 nm, probably resulting from double or multiple layers in the highest generations.⁵⁴ PAMAM dendrimers were imaged by AFM, and the molecular weights and volumes calculated for G_5 – G_8 were in agreement with theoretical values. G_5 – G_{10} PAMAM dendrimers could be imaged by tapping-mode AFM, although single G_4 dendrimers could not be imaged.¹⁴⁸

Adhesion forces could be quantified, and dendrimer distortions have been revealed upon physisorption.^{148–151} Increasing charge on the PAMAM dendrimers at low pH resulted in volume expansion^{149,150} and delocalized stack formation.¹⁵¹ High-generation PAMAM dendrimers have also been characterized at the interface between an aqueous solution and a hydrophobic or hydrophilic substrate, and for instance, G_5 gives large aggregates on the HOPG surface when water is used as a solvent.¹⁵² Müllen's rigid polyphene-

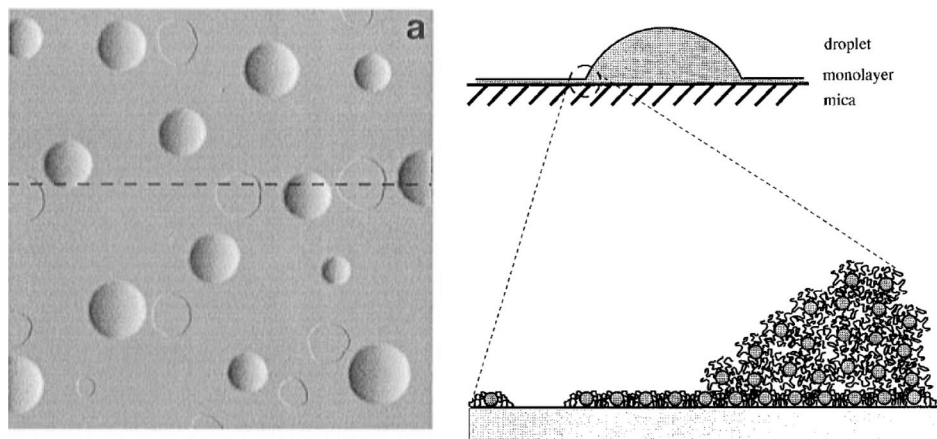


Figure 7. Amplitude (a) micrograph demonstrating autophobic wetting of the mica surface by the carbosilane dendrimer with hydroxyl end groups. Fluid droplets with a contact angle of about 8.7° were observed. Two-dimensional sketch of the autophobic spreading of the carbosilane dendrimer on mica. Because of the preferential adsorption of the end OH-groups on the surface of mica, the hydrocarbon core gets exposed to air. The picture is consistent with scanning force microscopy studies and molecular dynamic simulation of the dendrimer on mica. Reprinted with permission from ref 135 (Sheiko's group). Copyright 1997 American Chemical Society.

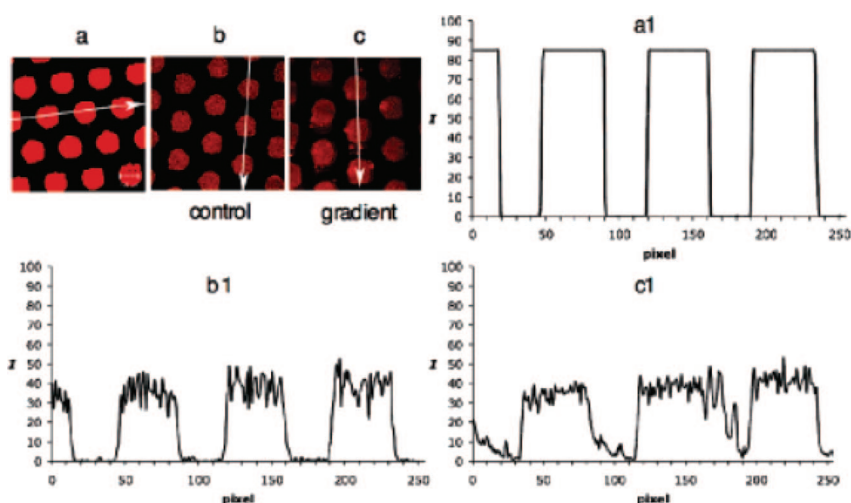


Figure 8. Averaged fluorescence profiles and their corresponding confocal microscope images of dendrimers (a) before immersion and (b) control and (c) gradient substrates, after 16 h of immersion. Reprinted with permission from ref 157 (Reinhoudt's group). Copyright 2007 American Chemical Society.

nylene dendrimers were also examined on various surfaces by noncontact AFM (NCAFM) and pulse force mode AFM (PFM-AFM), which showed either individual dendrimers or aggregates, globular clusters, and monolayers with long nanofibers.^{153,154} Monolayers of dendritic polymers were prepared by covalent attachment to a silicon wafer surface, and these ultrathin dendrimer films served as effective resists for high-resolution lithography using a scanning probe microscope.^{155,156}

PPI dendrimers labeled with rhodamine B and attached to glass substrates via imine bonds were able to move on the surface by hydrolysis and reformation of these imine bonds as shown on confocal microscopy images. In the presence of a gradient, it was suggested that the dendrimers move in one direction with the gradient (Figure 8).¹⁵⁷

The morphology of immobilized first-generation PPI-salicylaldiamine dendritic ligands was examined by AFM and related to the electrochemical behavior of surface-confined films.¹⁵⁸

Brownian dynamic simulations were used to study the structure and transport properties of dendrimers in dilute solutions, the diffusivity, and the zero-shear-rate intrinsic viscosity. Incorporation of hydrodynamic interactions was

sufficient to reproduce the maximum in the intrinsic viscosity versus molecular weight observed experimentally.¹⁵⁹

3. Photophysical Studies: Light-Harvesting and Light-Driven Processes

3.1. Concepts and Pioneering Studies

This aspect probably is the most presently studied field of dendrimer science together with nanomedicine, because solar light harvesting is an essential way to capture the energy necessary for living organisms including both the biosphere¹⁶⁰ and human activities.¹⁶¹ Biosphere activities have produced, over millions of years on earth, fuel that is being consumed overall in only a few decades; thus, future generation will need to return to solar light to capture energy for human activities. Many photosynthetic organisms in the biosphere, the most important of which are purple bacteria, are models for the design of artificial light-harvesting devices. The photosynthetic unit shows that the reaction center is surrounded by light-harvesting complexes such as a ring-shaped assembly of chlorophyll and carotenoid forming an antenna in which collected photons are transferred to the

reaction center with a remarkable unit efficiency.¹⁶⁰ Mimicking Nature is relevant to supramolecular photochemistry.^{1-3,162-168} It is obvious that molecular trees, i.e., dendrons (rather than dendrimers), are topologically framed to potentially model natural photosynthetic centers. Indeed, once the photons are collected by the photon absorbers located at the periphery of the dendronic device, they must reach the reaction center at the dendron focal point that needs to be connected to the reaction center (the root of the tree).^{10,11,39}

Besides light harvesting, photophysical studies of dendrimers are also important from both a fundamental viewpoint (theoretical studies on energy-transfer processes,¹⁶⁴ studies of fluorescence anisotropy giving information on the dendrimer structure, motion, and aggregation,^{165,166} fluorescence at the single-molecule level¹⁶⁷) and an applied one (changing the color of light, sensing with signal amplification, quenching and sensitization processes).

There are two mechanisms that allow the photoexcited state of a chromophore D (donor) to transfer energy to another chromophore A (acceptor) in its ground state located at the focal point near the reaction center. The first one is the short-range (<10 Å) through-bond (Dexter) mechanism involving simultaneous electron exchange between the S_1 states of D and A and between the S_0 states of D and A, thus requiring strong D–A orbital overlap with an interaction that exponentially decreases with the D–A distance (rigidity and conjugation between the D and A chromophores are key parameters). The second one is the relatively long-range (10–100 Å) through-space (Förster) mechanism that only involves dipole–dipole interactions (the intrinsic properties of the D and A chromophores: transition dipole moments and spectral overlap of D emission with A absorption are the key parameters).¹⁶⁹ The first approach to light-harvesting using a photoactive dendritic antenna that undergoes intramolecular energy transfer was reported by Balzani's group in 1991 with a series of polypyridyl Os–Ru complexes as ligands that allowed the construction of luminescent dendrimers containing up to 22 metal-based units with 1090 atoms with an estimated size of 5 nm. Ligand-dependent bandgap energies were controlled by the location of Ru and Os atoms at the different sites of the dendrimers.¹⁷⁰⁻¹⁷³ In the heterobimetallic Ru–Os complexes, Dexter-type energy migration occurs from Ru to Os¹⁷⁴⁻¹⁷⁷ (either from the dendritic core to the periphery or the opposite depending on the respective locations of Ru and Os atoms). This work has been the subject of several reviews.¹⁷⁸⁻¹⁸⁵ Xu and Moore designed rigid polyacetylene dendrons linked to an energy-sink perylene at the focal point. The conjugated phenylacetylene units that act as peripheral energy donors show a strong absorption around 250–300 nm whose intensity doubles for each additional dendritic generation. Excitation of the periphery at 312 nm yielded only perylene core emission with almost complete quenching of the dendron emission.^{130,187-189} Further analogous dendronic synthesis using phenylacetylene linkers induced the formation of an energy gradient that increased the energy-transfer rate by 2 orders of magnitude.¹⁹⁰ Theoretical work confirmed that such a directional multistep process is more productive than the random walk.^{191,192} Fréchet's group designed dendrimers based on a lanthanide ion core (Er^{3+} or Tb^{3+}) surrounded by three benzoate Fréchet-type dendrons (polybenzyl ethers) in order to inhibit the self-quenching of these ions when they were clustered in the solid state, diminishing their effectiveness as signal amplifiers for optical fiber communication.

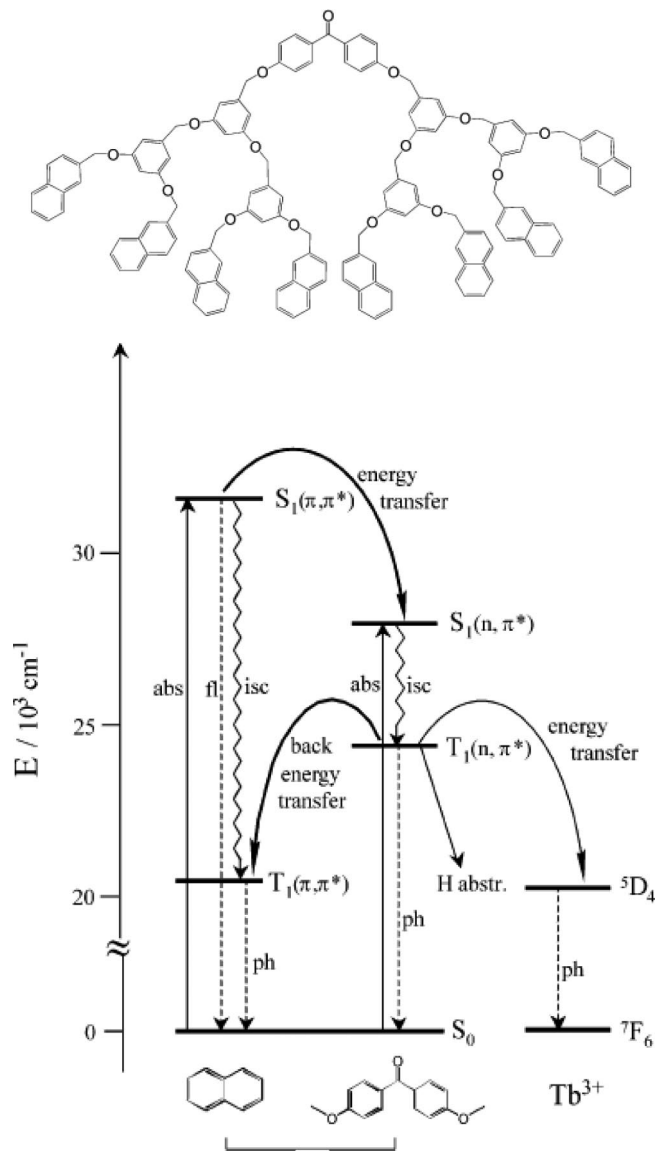


Figure 9. Energy level diagram showing the excited states involved in the photochemical and photophysical processes of the dendrimer. Reprinted with permission from ref 205 (Balzani's and Vögtle's groups). Copyright 2004 Royal Society of Chemistry.

Irradiation of the dendrimer dendrons near 280–290 nm resulted in strong luminescence from the lanthanide ion core. The postulated Förster mechanism was more efficient for Tb^{3+} than for Er^{3+} due to better overlap of dendrimer emission with Tb^{3+} absorption.¹⁹³⁻¹⁹⁷ Several groups also observed similar antenna effect with energy transfer from Fréchet-type dendrons or 1,3,5-phenylene-based dendrons to a porphyrin core.¹⁹⁸⁻²⁰² Jiang and Aida reported acceleration of *cis-trans* isomerization of azobenzene-cored G_4 and G_5 poly(benzylether) dendrimers under the influence of either IR (2500 or 1155 cm^{-1}) or UV (280 nm) light. Both isolation of the chromophore from energy dissipation (similar to Fréchet's lanthanide-cored dendrimer) and harvesting antenna effects were invoked to rationalize the observations. The latter effect was justified by the fact that the energy corresponding to 4.9 IR photons was required for the rate acceleration.¹⁹⁹ Fréchet's group also designed dendrimer-independent energy transfer involving through-space (Förster) interaction between chromophores located at the core and periphery using coumarin-type and oligothiophene chromophores. Large spectral overlap between donor emission

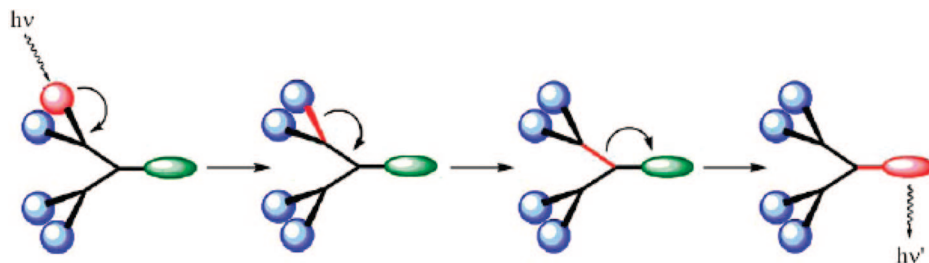


Figure 10. Schematic illustration of a dendron as an antenna. The excitation energy $h\nu$ (shown in red) migrates along the dendrimeric framework until it reaches the core, where the energy is used for some purpose such as a chemical reaction. Reprinted with permission from ref 210 (Flomembom's group). Copyright 2005 Elsevier.

and acceptor absorption is required for efficient energy transfer as shown by time-resolved experiments at subpicosecond time scales. This through-space energy transfer has also been experimented with dendrimers containing peripheral naproxen units as donors and a naphthalene acceptor.²⁰² Dendrimer-based light-emitting diodes (LEDs) were also designed using such coumarin and oligothiophene chromophores. The principle consists of isolating the chromophores in a dendronic structure in order to inhibit energy transfer and favor the function of single-layer LEDs.^{195–197} Thin films based on rigid dendrimers exhibited modest electroluminescence due to solid-state aggregation.²⁰³ NLO properties of DAB dendrimers functionalized up to the fifth generation with the typical NLO chromophores 4-dimethylaminophenylcarboxamide as end groups were investigated using the hyper-Raleigh technique, providing sensitivity to molecular symmetry, and the measurements showed that the dendrimers in solution formed globular structures with the 32- and 64-armed DAB dendrimers.²⁰⁴ Forward (singlet–singlet) and backward (triplet–triplet) energy transfer have been demonstrated in a dendrimer containing peripheral naphthalene units and a benzophenone core (Figure 9).²⁰⁵

The photochemical and photophysical properties are broad and varied, and specific studies are often connected to specific dendrimer families, as shown later.

3.2. Dendrimers with $[\text{Ru}(\text{bpy})_3]^{2+}$ Core

Luminescent dendrimers have largely been used as ligands for transition-metal and lanthanide ions. The resulting properties are (i) shielded excited states from quenching processes, (ii) light harvesting, (iii) conversion of incident UV light into visible or infrared emission, and (iv) metal ion sensing with signal amplification.^{178–183} The Balzani group studied the photophysics of dendrimers that exhibit interactions of luminescent units within dendrimers, quench dendrimer luminescence by external species, sensitize luminescent metal ions, and sensitive and quench dye luminescence. Examples of such photoactive dendrimers include dendrimers based on a metal-complex core, dendrimers with metal complexes at the branching centers, and dendrimers containing fluorescent organic units. A series of dendrimers whose photophysical studies were carried out by the Balzani group have a $[\text{Ru}(\text{bpy})_3]^{2+}$ core (bpy = 2,2'-bipyridine) that exhibited photophysical (luminescence) and redox properties (Figure 10).^{179–184,206–212}

It was shown that the rate of quenching reactions by nearby acceptor systems such as dioxygen, tetrathiafulvalene (TTF), and methylviologen (MV^{2+}) was slower when the $[\text{Ru}(\text{bpy})_3]^{2+}$ complex was buried in the dendrimer core than in the free (nondendritic) complex. A contrario, such dendrimers can also be supramolecular hosts for quenching reactions

due to guest molecules. The Stern–Volmer equation gives the rate constant k_q of a quenching process taking place by a diffusional mechanism, and luminescence studies showed that the quenching process obeys this equation:

$$\tau^0/\tau = \phi^0/\phi(1 + k_q\tau^0[Q]) \quad (3)$$

In $[\text{Ru}(\text{bpy})_3]^{2+}$ -cored dendrimers containing dimethoxybenzene- and naphthyl-type units on the branches, antenna effects were observed, i.e., very efficient (90%) energy transfer takes place from the fluorescence of these units to the orange core whose phosphorescence is sensitized ($\lambda_{\text{max}} = 610 \text{ nm}$). As a result, these dendrimers exhibit a strong emission in the visible region upon UV excitation of the branch groups.^{179–184,211} An unusual lanthanide complex, exploiting a dendrimer and a $[\text{Ru}(\text{bpy})_2(\text{CN})_2]$ moiety as ligand, exhibits luminescence in the near-IR region. In the absence of the ruthenium component, the dendrimer is unable to transfer energy to the Nd^{III} ion, despite direct coordination.²¹²

3.3. Ionic Dendrimers Electrostatically Bound to $[\text{Ru}(\text{bpy})_3]^{2+}$ on Their Surface

In early studies, Tomalia and Turro investigated the quenching of $[\text{Ru}(\text{bpy})_3]^{2+}$ by PAMAM dendrimers terminated by carboxylate groups that were not covalently bound to the photoactive probe but only electrostatically connected with interactions that depended on the dendrimer generation. It was concluded that efficient quenching was mostly due to interactions at the dendrimer surface, and this study also confirmed that the PAMAM dendrimer structure undergoes change at about $G_{3.5}$.²¹³ Later, in a careful although less conclusive study, it was shown that, at high generations, the dendritic backbone acted as the solvent.²¹⁴ Similarities of dendrimer and micelles structures were also revealed based on the dynamics of electron-transfer quenching of photoexcited $[\text{Ru}(\text{bpy})_3]^{2+}$ by methyl viologen that was investigated using the luminescence decay of the metal-based chromophore.²¹⁵ Quenching studies of $[\text{Ru}(\text{bpy})_3]^{2+}$ electrostatically bound to the carboxylate PAMAM dendrimer surface by $[\text{Co}(\text{phen})_3]^{2+}$ showed that the quenching process was intradendritic.²¹⁶

3.4. Poly(propylene imine) PPI and Polyamide Dendrimers with Dansyl Chromophores Attached to the Periphery

The photophysical studies of PPI dendrimers of generations G_1 – G_5 containing 2^{n+1} terminal dansyl groups show that these groups behave independently from one another. They exhibit intense absorption that is characteristic of the

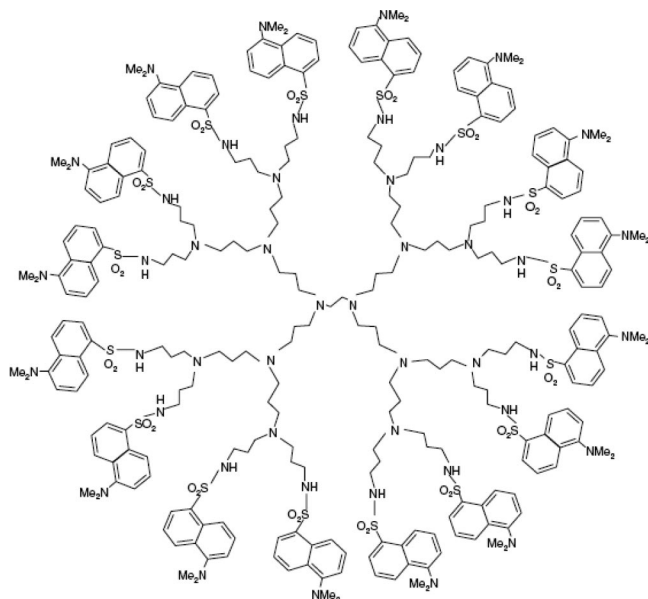


Figure 11. Structural formula of third-generation dansylated POPAM dendrimer (G_3). Reprinted with permission from ref 221 (Aumanen's group). Copyright 2006 Elsevier.

dansyl chromophores ($\lambda_{\max} = 252$ and 339 nm; $\epsilon = 12\,000$ and $3\,900$ mol $^{-1}$ cm $^{-1}$, respectively, for each dansyl unit in acetonitrile/dichloromethane 1:1 v/v solution) and a strong fluorescence band in the visible region ($\lambda_{\max} = 500$ nm). If a Co^{2+} salt is added, fluorescence quenching takes place due to coordination of the Co^{2+} ion in the dendrimer interior, and this quenching is all the more pronounced as the generation number increases. The coordination is also shown to be fully reversible. The fluorescence of all the dansyl groups of the periphery is quenched when a single Co^{2+} ion enters the dendrimer,^{217–219} whereas in polyamide-cored dendrimers fewer dansyl units are quenched.²²⁰ Ultrafast energy transfer between dansylated PPI dendrimers and eosin was monitored by femtosecond transient absorption spectroscopy, and the time constants (1 and 6 ps) were found to be independent of the dendrimer generation. Relaxation processes in eosin were faster with these dendrimers than in solution due to both eosin–dendrimer and intradendritic eosin–eosin interactions (Figure 11).^{221,222}

With polylysine cores instead of PPI cores, the lanthanide ions (Nd^{3+} , Eu^{3+} , Gd^{3+} , Tb^{3+} , Er^{3+} , Yb^{3+}) quenched the dansyl fluorescence, and with Nd^{3+} , Er^{3+} , and Yb^{3+} , a sensitized near-infrared emission of the lanthanide ion was observed.²²³

Highly efficient photoinduced energy transfer was observed for adducts between G_1 , G_3 , and G_4 -dansylated PPI dendrimers and anthracene clips. The coordination properties of Zn^{II} therein have been exploited in the self-assembly of complex structures in which Zn^{II} mediates the dansyl–anthracene interactions.²²⁴

3.5. Dendrimers with Cyclam Cores

Dendrimers with a 1,4,8,11-tetraazacyclodecane (cyclam) core, dimethoxybenzene branches and naphthyl termini exhibit emission bands of the naphthyl excited states ($\lambda_{\max} = 337$ nm), naphthyl excimers (λ_{\max} ca. 390 nm), and naphthyl–amine exciplexes ($\lambda_{\max} = 480$ nm).^{225,226} The two successive protonations using trifluoroacetic acid prevent exciplex formation and cause rearrangements affecting excimer formation between the peripheral naphthyl units.

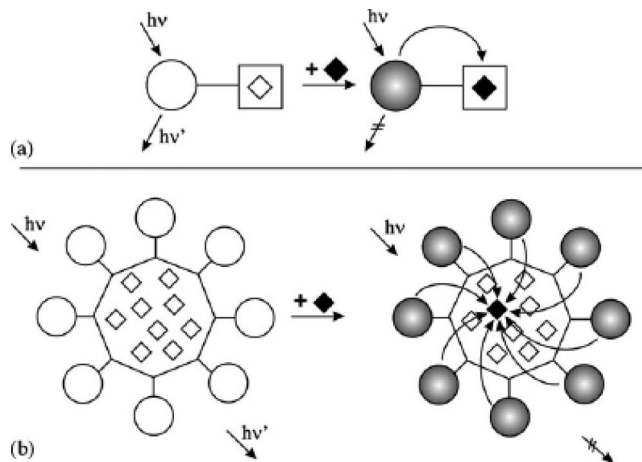


Figure 12. Schematic representation of (a) a conventional fluorescent sensor and (b) a fluorescent sensor with signal amplification. Open rhombi indicate coordination sites, and black rhombi indicate metal ions. The curved arrows represent quenching processes. In the case of a dendrimer, the absorbed photon excites a single fluorophore component, which is quenched by the metal ion, regardless of its position. Reprinted with permission from ref 232 (Balzani's group). Copyright 2007 Royal Society of Chemistry.

Coordination of the cyclam core with Zn^{2+} forms bicyclam complexes $[\text{Zn}(\text{dendrimer})_2]^{2+}$, which also prevents exciplex formation, with a resulting increase of the naphthyl fluorescence. The photophysical studies also provide information on the relative conformation of the dendrimers.^{227,228} Similar photophysics results were obtained with complexes of lanthanide ions (Nd^{3+} , Eu^{3+} , Gd^{3+} , Tb^{3+} , Dy^{3+}), but emission data were best fitted with 1:3 and 1:2 complexes.²²⁹ Dendrimers containing two covalently linked cyclams as a core exhibited photophysical data suggesting that the two cyclams did not behave independently upon protonation but formed a sandwich structure. Upon titration with $[\text{Zn}(\text{CF}_3\text{SO}_3)_2]$ or $[\text{Cu}(\text{CF}_3\text{SO}_3)_2]$, the emission spectral changes showed evidence for the formation of a 1:1 complex, then replaced by a 2:1 complex, although the results were different both in absorption and emission spectra for these two metal ions.²³⁰ An adduct between $[\text{Ru}(\text{bpy})(\text{CN})_6]^{2-}$ and a dendrimer metal–cyclam core was shown to form when the dendrimer was appended with 12 dimethoxybenzene units and 16 naphthyl termini. The photophysical data show that this dendrimer plays the role of a light-harvesting second coordination sphere that transfers the collected energy to $[\text{Ru}(\text{bpy})(\text{CN})_6]^{2-}$. Moreover, the adduct can be disrupted by addition of either acid or base exhibiting two distinct optical outputs according to an XOR and an XNOR logic, respectively (Figure 12).^{231–234} In europium–cyclen-cored dendrimers formed by “click” reaction between a tetravalent cyclen core containing four alkyne groups and dendrons containing an azido group at the focal point, the photophysical results showed that the proximate triazoles acted as sensitizers, transferring their singlet–singlet excitation in the UV region (270–290 nm) to the partially filled luminescent lanthanide 4f shell. An increase of luminescence decay time from the lanthanide $5d^0 \rightarrow 7f^2$ emission was observed with increasing dendrimer size, indicating that the shielding effect of the dendron wedges is important for the relaxation of the photoexcitation and energy transfer.²³⁵

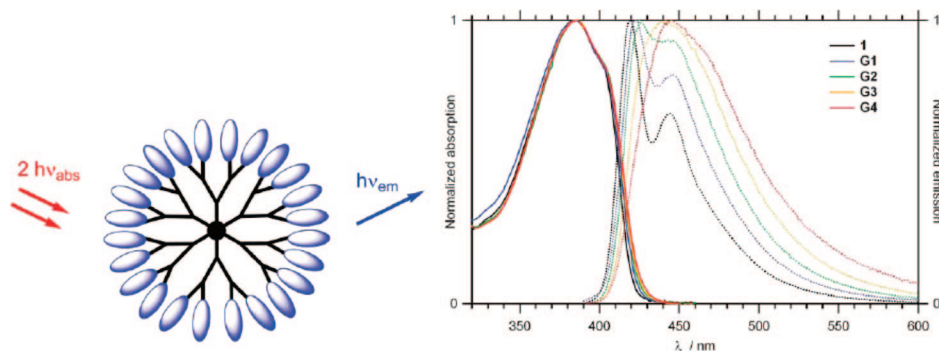


Figure 13. Schematic representation of dendrimeric two-photon absorbing fluorescent organic “nanodots”. Normalized absorption and emission spectra in toluene of dendrimers G_1 – G_4 and model chromophore noted 1. Reprinted with permission from ref 276 (Blanchard-Desce’s group). Copyright 2006 Royal Society of Chemistry.

3.6. Porphyrin Dendrimers

Since the first example with Fréchet-type dendron units,²³⁶ Aida has investigated the photoactivity of bioinspired porphyrin-cored and other porphyrin dendrimers as artificial hemoproteins^{236–239} such as cytochrome C mimics^{240,241} and for photodynamic cancer therapy.^{242–245} Another porphyrin-centered dendrimer with PAMAM units mimicking hemoproteins was reported by Diederich, Collman, and co-workers.²⁴⁵ Vectorial excitation energy transfer was achieved using porphyrin-cored dendrimers,^{246–249} and such a process was efficiently achieved using a multiporphyrin array with energy donating zinc–porphyrin dendrimer units to a metal-free porphyrin dendrimer core yielding enhanced core emission.^{250,251} In a dendronic analogue having a metal-free porphyrin acceptor at the focal point, energy transfer from peripheral Zn–porphyrin units appeared to be less efficient.^{252,253} Stern–Volmer analysis was used to investigate the access of benzyl viologen to the porphyrin core in several generations of dendrimers containing Fréchet-type dendrons. No fluorescence quenching inhibition was found for generations 1–3, but only a slight rate enhancement for G_4 . The study also suggested that the periphery does not interfere with the photophysics of the porphyrin core.²⁴⁴ The dynamics of electronic energy transfer was investigated for porphyrin-terminated poly(propylene imine) dendrimers using time-resolved fluorescence anisotropy in a glass environment. Depolarization of fluorescence was observed for all the generations studied compared to monoporphyrin model compounds.²⁴⁵ With porphyrin-cored dendrimers containing carbazole chromophores on the branches, the fluorescence observed indicated that the light collected by the peripheral chromophores was quantitatively transferred to the core.²⁴⁶ Snowflake-shaped dendrimers containing a Zn porphyrin core and anthraquinonyl peripheral groups provided highly efficient (100%) intramolecular singlet energy transfer. Electron transfer in this system was more efficient than with linear analogues, showing that covering of the conjugated chain enhanced electron transfer partly due to charge-transfer interaction.²⁴⁹ In phthalocyanine dendrimers, fast carrier movement is dominated by polaron hopping and tunneling charge-transfer mechanisms.²⁵⁴

3.7. Two-Photon Absorption (TPA) Using Porphyrin-Cored Dendrimers

“Two-photon absorption” (TPA) involves the simultaneous absorption of two photons by the same molecule, and nonlinear dependence on light intensity leads to various optical and imaging applications.^{255,256} The efficient section

of the absorber is a key parameter that must be optimized, because it is related to the probability of absorption of two photons. Branched or dendritic molecules are useful in this respect.^{257–266} The groups of Fréchet and Prasad examined the generation of cytotoxic singlet oxygen for photodynamic therapy to subcutaneous tumors by fluorescence resonance energy transfer (FRET) using porphyrin sensitizers as dendritic cores of dendrimers containing two-photon donor chromophores such as the complex polyaromatic AF-343 at the periphery.^{267–269} Whereas much work is involved in decreasing the band gap energy to shift the porphyrin absorbance to the near-infrared,^{270,271} the advantage of two-photon chromophores (TPA) is that they absorb 750–1000 nm light (near-infrared) where tissues are more transparent, which allows deeper light penetration with reduced risk.^{272–274} TPI of dendrimers containing a stilbene core and benzyl ether dendrons showed that the quantum yield of stilbene core radical cation during the 308 nm TPA was independent of dendrimer generation, whereas the 266 nm TPI disclosed generation dependence. Since both the stilbene core and benzyl ether dendrons were ionized, it was suggested that the dendrons acted as hole-harvesting antennae.²⁷⁵ TPA was also studied with two-photon chromophores located at the periphery of nonporphyrinic dendrimers (Figure 13).^{276–278}

In another TPI study with porphyrin-cored dendrimers, Fréchet’s group showed that TPA also displays quadratic dependence on laser intensity, providing better spatial resolution of treatment. Tetraethylene glycol termini provided water solubility of some of these dendrimers, allowing generation of singlet oxygen in water using this strategy.²⁶⁸ Some systems involving both porphyrin and fullerene chromophore units have been reported and are detailed in the following fullerene dendrimer section.

3.8. Fullerene Dendrimers

Fullerenes (C_{60}) were introduced at the termini of star-shaped^{279,280} and dendritic^{281,282} structures for electrochemical and photophysical purposes. The alternative strategy consists of the introduction of the fullerene at the dendrimer core (Figure 14).^{283–290}

It was indeed shown that the lifetime of the first triplet excited state of such fullerodendrimers is very sensitive to the solvent, which could be used to evaluate the degree of isolation of the fullerene core.^{283–293} Electrooptical properties, such as Kerr constants determined in the pulsed electric field, which depend on the polarity and anisotropy of optical polarizability determined for several fullerodendrimer families were shown to be generation dependent.²⁹⁴ Whereas

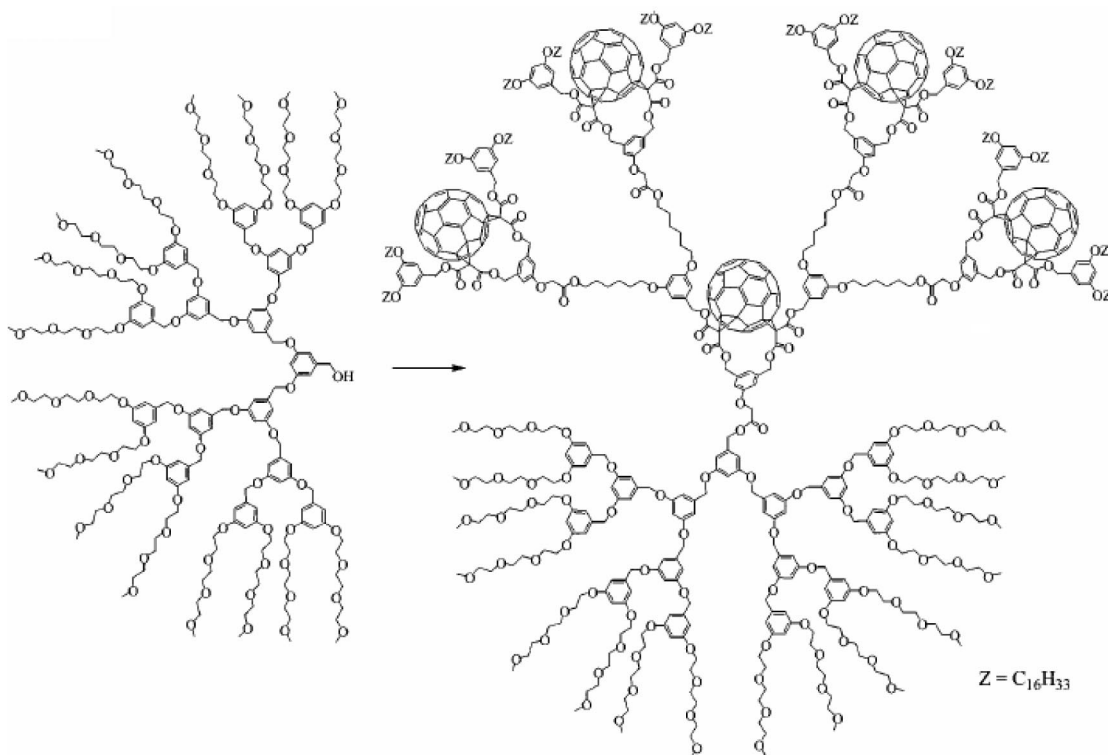


Figure 14. Fullerodendrimers. Reprinted with permission from ref 285 (Nierengarten's group). Copyright 2001 American Chemical Society.

photophysical studies of chromophore-containing dendrimers mostly focused on energy transfer from a donor to an acceptor (light-harvesting with antenna effect and phototherapy), photophysical studies on fullerodendrimers often involve photoinduced electron transfer from a donor chromophore to the C_{60} fragment that also is an electron acceptor. Indeed, the reduction potential of C_{60} and its derivatives to C_{60}^- is low, only about -0.9 V versus the ferricinium/ferrocene redox couple that is most usually used as the reference.^{295–298} Thus, covalently linked porphyrin– C_{60} dyads integrated in a dendritic frame are photoinduced electron-transfer units involving charge separation ($P^+–C_{60}^-$ state) from the porphyrin P to C_{60} . Dendrons containing Zn–porphyrin units (P_{Zn}) on the branches and C_{60} at the focal point exhibit a Soret band that becomes broader from $1P_{Zn}–C_{60}$ and $3PPZn–C_{60}$ to $7P_{Zn}–C_{60}$ (difference in the full-width at half-maximum of $+54$ cm^{-1}), i.e., as the generation increases, suggesting electronic interaction among the P_{Zn} moieties in $7P_{Zn}–C_{60}$. Fluorescence quenching was found to arise from the P_{Zn} unit to the focal half point, with formation of the ion pair $P_{Zn}^+–C_{60}^-$ being confirmed by means of picosecond time-resolved spectroscopy. The back-electron-transfer process was also shown to be retarded.²⁹⁹ Fullerodendrimers with peripheral ferrocenyl units disclose steady-state emission intensities that were quenched relative to the *N*-methylfulleropyrrolidine model, nanosecond transient absorption revealing efficient charge separation in both systems with longer lifetimes of the (ferrocenyldendron $^+–C_{60}^-$) state.³⁰⁰ Dendrimers with fullerene units at the periphery have been assembled either by electrostatic²¹⁹ or covalent binding,^{290,300–302} and some of them disclose unique luminescence properties.^{287,290,300,302} Multiple porphyrin– C_{60} dyads have been successfully constructed at a dendrimer surface,^{303,304} and a remarkable dendrimer containing a Zn–tetraphenylporphyrin core rigidly linked and conjugated to four C_{60} peripheral units was reported to show a dendrimer effect on the singlet energy

transfer.³⁰⁵ Dendrimers containing up to 16 fullerene peripheral units designed by the Nierengarten and Vögtle groups showed enhanced absorption in the region between 360 and 500 nm by increasing the generation number and disclosed a size-dependent trend in decreasing singlet lifetime and fluorescence quantum yields.³⁰⁶

3.9. Carbon Nanotube-Based Dendrimers

Very few nanotube-dendrimer composites are known.^{307–310} Single-wall carbon nanotubes, functionalized by 1,3-dipolar cycloaddition of $HO_2CCH_2NHCH_2OCH_2CH_2OCH_2CH_2–NHBOc$ and *para*-formaldehyde at 120 °C in DMF followed by solid-phase PAMAM dendrimer synthesis and tetraphenylporphyrin linking, were studied by steady-state and time-resolved spectroscopy. The fluorescence kinetics provided evidence for a very short-lived transient decay (0.04 ± 0.01 ns) and a long-lived one (8.6 ± 1.3 ns), indicating that the porphyrin presumably does not interact with the nanotube.³¹⁰

3.10. Rigid Dendrimers with Conjugated Poly(Arylene) Units

Moore elegantly pioneered the area of rigid dendrimers that contained poly(phenylene ethynylene) backbones with photophysical properties (vide supra).^{131,132} Another remarkable family including giant dendrimers were reported by Müllen's group with poly(arylene) scaffolds.^{311–318} First-generation dendrimers containing a triarylamine core *para*-substituted with three Müllen-type dendrons, one of which was covalently attached to a peryleneimide chromophore at the rim, were investigated by steady-state and time-resolved spectroscopic techniques in different solvents of medium and low polarity. Single-photon counting experiments revealed a fast charge separation and a thermally activated back

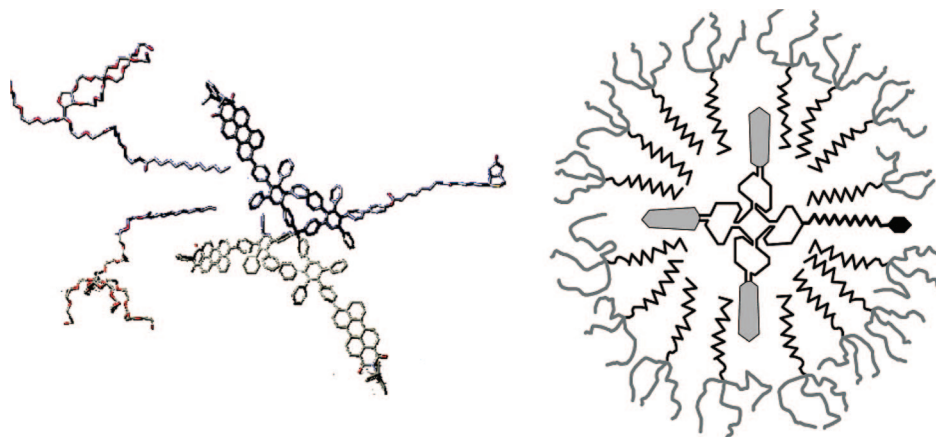


Figure 15. (a) Visualization of the dendrimer–detergent complex obtained via force field calculations. (b) Scheme of the dendrimer–detergent complex. Reprinted with permission from ref 323 (Müllen’s group). Copyright 2003 American Chemical Society.

reaction from the charge-separated state to the locally excited state. A through-space electron-transfer mechanism was suggested. At 77 K, the recombination luminescence is long-lived.³¹⁵ Multichromophoric dendrimers containing peripheral perylenecarboximide units were studied by far-field fluorescence microscopy, which underlined the dynamic character of the interactions among the chromophores.^{311,312} Intramolecular Förster-type excitation energy transfer (FRET) was investigated in polyphenylene dendrimers with peripheral peryleneimide chromophores.³¹⁸ Poly-*p*-phenylene macromolecules (PPP) have large HOMO–LUMO energy gap giving rise to blue emission that has been the subject of intense research to make full-color organic displays. Since it is necessary to solubilize these materials without hampering conjugation and to prevent aggregate formation, Fréchet-type³¹⁹ and Müllen-type^{320–322} dendrons have been successfully used to end-cap polyfluorene materials. An OLED using such a polyfluorene containing 9,9-diaryl substituents produced blue emission with onset voltages below 4 V.^{320–322} A polyphenylene dendrimer carrying three perylenemonoimide dyes and one biotin group exhibited stability in the presence of serum proteins, and specific binding to the protein streptavidin was demonstrated using a magnetic bead assay (Figure 15).³²³

A rigid 1,3,6,8-tetraethynylpyrenyl-cored dendrimer with a polyphenylene shell could encapsulate pyrene, this material presenting high quantum efficiency and good film-forming properties for applications in electronic devices.³²⁴ Terphenyl-cored dendrimers containing oligosulfonimide dendrons exhibited high steady-state anisotropy. In these dendrimers, energy transfer from the dendronic chromophores to the terphenyl core does not occur, and the terphenyl core shows a very high fluorescence quantum yield (ca. 75%) and a short emission lifetime (0.8 ns), allowing investigation of the fluorescence depolarization caused by the rotation of the dendrimers.³²⁵ Polyphenylene dendrimers are promising OLEDs, especially because they can reach up to 28 nm at 271.6 kD (Figure 16).^{326,327}

Energy transfer in wire-type dendrimers having oligophenylene peripheries as light-harvesting antennae proceeds from these peripheries to the backbone polymers, and in solid dendrimer films, red shifts of this backbone photoluminescence bands were observed.³²⁸ Polytriphenylene dendrimers were designed for blue-light-emitting materials with high photoluminescent quantum yields, with stiff dendritic backbones preventing intermolecular fluorescence quenching.³²⁹

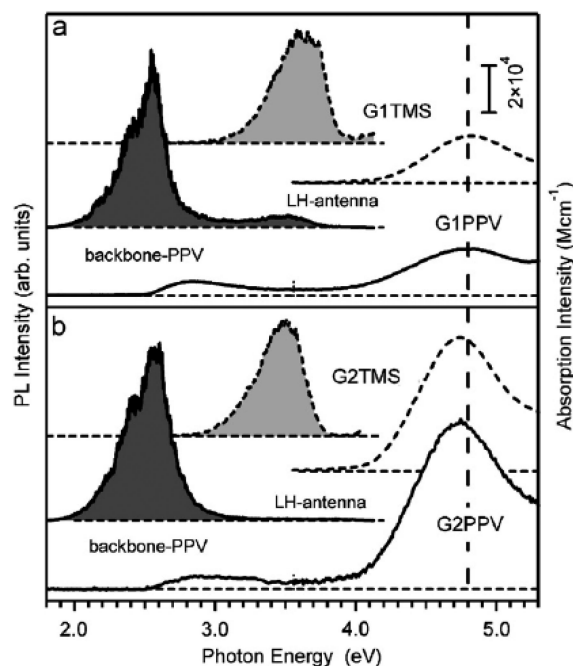


Figure 16. Absorption and PL spectra of G_n PPVs (G_n PPV: n th-generation dendrimer with poly(phenylene vinylene) backbone; $n = 1, 2$) and G_n TMSs (G_n TMS: n th-generation dendrimer with trimethylsilyl group backbone; $n = 1, 2$) in solutions. PL spectra are displayed with grayish shadow. Vertical broken line marks the energy of the excitation. Reprinted with permission from ref 328 (Akai’s group). Copyright 2008 Elsevier.

3.11. Azobenzene and Azomethine Dendrimers

Azobenzene derivatives undergo an efficient and fully reversible photoisomerization, and it is a photochrome system that has been used in photoswitchable devices.^{162,330} Thus, azobenzene-terminated poly(propylene imine) dendrimers have been studied^{331–342} and used as photoswitchable dendritic hosts. For instance, with eosin, the quenching is most likely due to an electron-transfer reaction between the singlet excited state of eosin and the tertiary amine unit, and quenching from the Z form is more efficient than quenching by the E form. The E \rightarrow Z and Z \rightarrow E photoisomerization reactions of the azobenzene units are sensitized by eosin via a triplet–triplet energy-transfer mechanism.^{331–333} Transmission microscopy and confocal fluorescence microscopy images have shown that azobenzene-terminated (polypropyleneimine) dendrimers assemble (by H-bonding at pH <

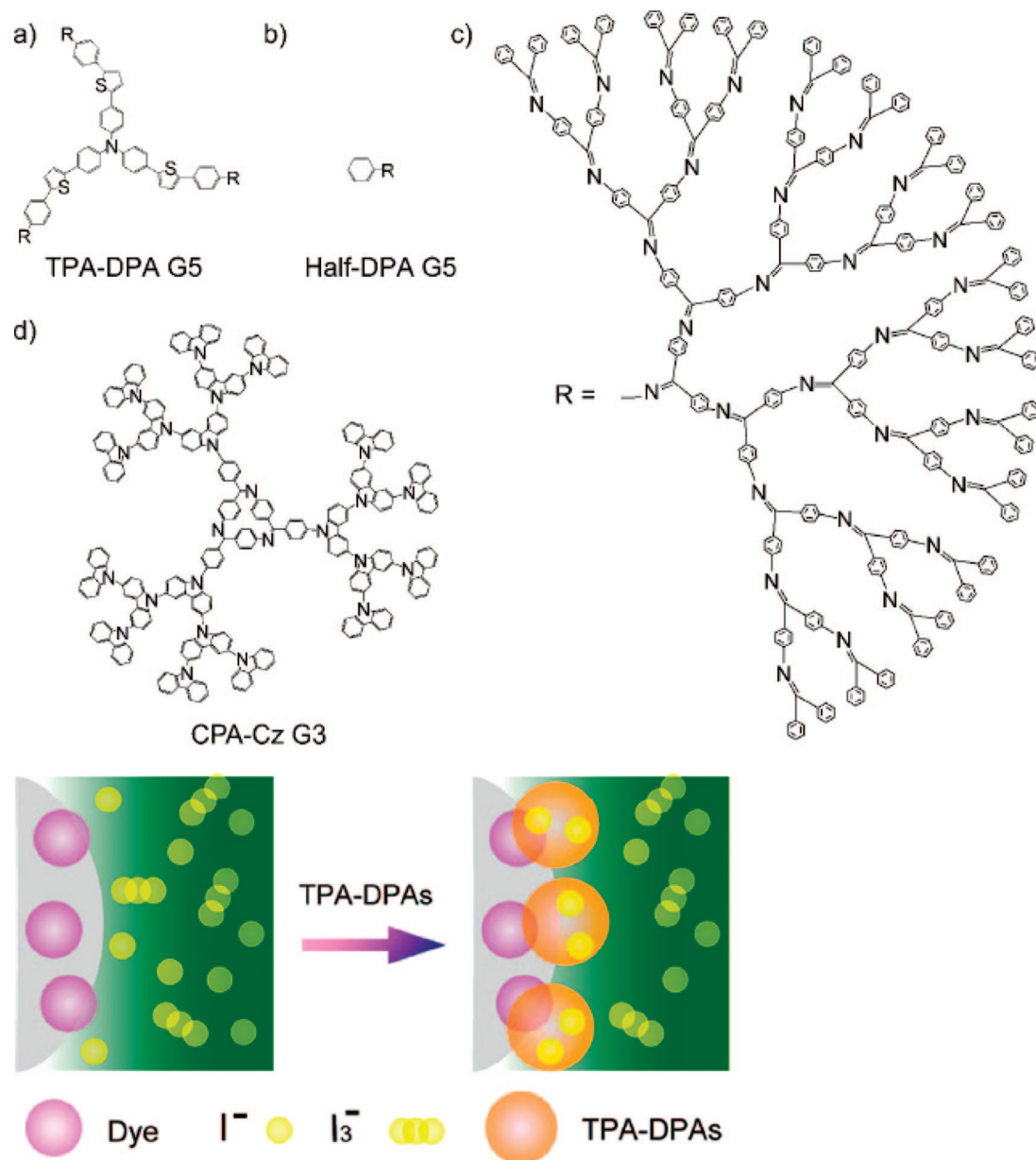


Figure 17. Structure of the dendrimers: (a) triphenylamine (TPA) core- G_5 , (b) half-dendritic phenylazomethine core (half-DPA G_5), (c) generation 5 of DPA dendron units, (d) carbazole dendrimer containing cyclic phenylazomethine of generation 3 (CPA-Cz G_3); interface modification by dendrimers on TiO_2 electrode. Reprinted with permission from ref 349 (Yamamoto's group). Copyright 2008 American Chemical Society.

8 and π - π stacking) to form giant vesicles in aqueous dispersions.³³⁹ Yamamoto's group has designed remarkable phenylazomethine dendrimers,³⁴³⁻³⁴⁷ and the electroluminescence of these dendrimers as double-layer organic light-emitting diodes (OLEDs) has been demonstrated using tris(8-hydroxyquinoline) aluminum as an emitter.³⁴⁸⁻³⁵⁰ Moreover, upon complexation of the dendrimer nitrogen ligands by $SnCl_2$, the properties of the hole-transporting layer were improved, and the luminance and electroluminescence (EL) efficiency were drastically increased by comparison with the dendrimers alone. Dendritic effects were also observed, with G_3 being the optimal generation among the G_1 - G_5 phenylazomethine dendrimer series.³⁴⁸⁻³⁵⁰ Quantum size effects were observed in TiO_2 nanoparticles prepared by finely controlled metal assembly on such phenylazomethine dendrimer templates (Figure 17).³⁴⁹

3.12. Polythiophene Dendrimers

Oligo- and polythiophene derivatives have been extensively investigated and used as organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs), and in photovoltaic (PV) applications. These organic materials exhibiting large electro-optic response have the potential for use in telecommunications, digital signal processing, phased-array radar, THz generation, and other photonic devices.³⁵¹⁻³⁵⁶ For OLEDs, light is emitted upon application of a few volts to a thin layer of these materials. Red, green, and blue colors can be obtained, and such colored components may be assembled to provide vivid color displays. Organic compounds are cheap and easy to process and integrate in devices, and they have low dielectric constants and high bandwidth. For instance, solar power conversion efficiencies of up to 4.8% have been

certified at the National Renewable Energy Laboratory for devices based on blended polymer–fullerene assemblies.³⁵⁷ High-quality films formed by π -conjugated dendrimers make this dendritic approach a privileged one, because self-order and crystalline ordering on several nanometer-length scales are essential to success.³⁵⁸ Dendrimers offer the possibility of introducing multichromophores in EO materials for the control of interchromophore electrostatic interactions, and thiophene-containing dendritic EO chromophores were found to exhibit more stable EO properties as compared to the corresponding isolated chromophores.^{359,360} Oligo- and polythiophenes are the most common units that take part in these devices, but other units discussed in the following sections such as poly(phenylene vinylene), carbazole, and triaryl amines are also used (vide infra).

Phenyl-cored polythiophene dendrimers have been blended with [6,6]-phenyl C₆₀ butyric acid methyl ester (PCBM) for the fabrication of bulk heterojunction PV devices.³⁶¹ A significant increase of fluorescence quantum yield in dendrimers with an increasing number of bithiophenesilanes was obtained compared to linear analogues.³⁶² Encapsulating individual chromophores inside a dendritic structure greatly enhances their optical properties due to reduced self-quenching. For instance, electroluminescence studies in OLED devices confirmed that color tuning could be achieved by mixing both encapsulated dyes (pentathiophene and coumarin 343 interacting via Forster energy transfer) in a single layer, even if selective trapping by one of the dyes dramatically modifies the efficiency of the others.³⁶³ OLEDs involving dendrimers as both hole-transporting and electron-transporting components as well as emitters have been designed,^{363–373} but the requirement of site isolation in relatively large dendrimers is crucial.³⁶³ There are only a few reports on the applications of dendrimers in organic solar cells.^{374–377} With oligothiophene-centered dendrimers containing bistriarylamine-substituted carbazole tethers, the absorption and fluorescence emission peaks red-shifted with increasing oligothiophene core length. Thus, the conversion efficiencies of the solar cells using the composite of this dendrimer and PCBM also increased with increasing the oligothiophene core length from 0.04% with a dithiophene core to 0.13% with a pentathiophene core under AM 1.5 simulated solar illumination at an irradiation of 100 mW/cm².³⁷⁷ In addition, rigid, terthiophene-terminated Müllen dendrimers were found to be good conductors due to the hopping process in the 3D network as a result of the small distances between the planarized wings of different cores.³⁷⁸ Ultrafast energy transfer (200–300 fs) to the longest dendrimer branch and superlinear increase of 2-photon absorption section due to increased excitation delocalization were disclosed in thiophene dendrimers (Figure 18).³⁷⁹

In such oligothiophene dendrimers, the excitation is delocalized over a large number of thiophene units in the dendrimer, and there is ultrafast energy transfer (200–300 fs) to the longest dendrimer branch. A superlinear increase of 2-photon absorption was observed with an increase in thiophene dendrimer generation.³⁸⁰ Thiophene dendrimers with aryl cores and thiophene termini were modified by introduction of ethynyl spacers, with a decrease of bandgap for the four-arm dendrimer due to the reduction of interactions between the arms and the congested 1,2,4,5-arrangement around the core.³⁸¹ Dendritic oligothiophene (DOT)–perylene bisimide hybrids showed optoelectronic properties, indicating that the perylene core and dendritic oligothiophene

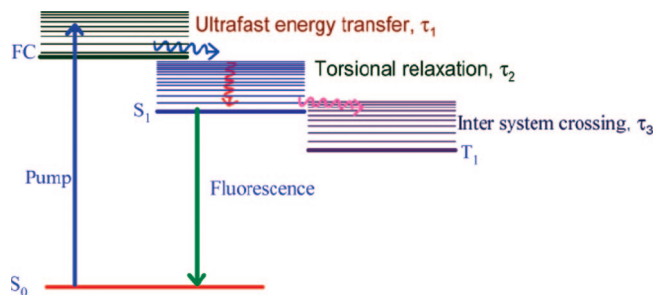


Figure 18. Mechanism of excited state deactivation of higher-generation thiophene dendrimers. Reprinted with permission from ref 379 (Goodson III's group). Copyright 2008 American Chemical Society.

units were electronically decoupled. Photoinduced electron transfer was facilitated with increasing DOT generation and donor strength, and electropolymerization led to cross-linked donor–acceptor conducting films.³⁸²

3.13. Poly(phenylene vinylene) Dendrimers

Distyrylbenzene is fluorescent blue in solution, but in the solid state, the fluorescence is suppressed due to aggregation. A dendrimer protection of a distyrylbenzene core could form processable films for a working device. Excimer formation causes the presence of a red tail that is all the more reduced as the dendrimer generation increases.^{383,384} A distyrylbenzene core was used to obtain blue emission, a distyrylanthracene core gave green, and a *meso*-tetraarylporphyrin core provided the red, yielding OLED materials for these colors consisting of a single dendrimer layer between ITO and calcium contacts. Nondendritic units with these structures are inefficient, however, because strong interchromophoric interactions quench the luminescence.³⁸⁵ Likewise, in tris-(distyrylbenzyl) amine-cored dendrimers, aggregate-excimer emission responsible for a red tail in the zeroth generation progressively disappears as the generation increases.³⁸⁶ Quantum chemical calculations were helpful in providing an accurate description of the measured absorption data and understanding the observed fluorescence dynamics.³⁸⁷ Another important factor in an OLED is the charge-transport properties. In triarylamine-centered dendrimers, charge mobility due to the amine photooxidation decreases as the generation increases, and determination of mobility using gel-permeation chromatography showed that the mobility was proportional to $D^2 \exp(-D/D_0)$, where D is the molecular diameter and D_0 is a characteristic hopping parameter. The results showed that the conjugated dendrons did not participate in charge mobility that entirely proceeded from core to core.³⁸⁸ Low mobility enhances charge capture and quantum efficiency, but it should not be too low or power efficiency would decrease. Thus, a number of oligo(*p*-phenylenevinylene) dendrimers have been reported as candidates for OLED materials,^{389–391} including crystalline phases and copolymers (Figure 19).^{392–397}

Oligo(*p*-phenylenevinylene)-decorated PPI dendrimers were synthesized, extensively studied, and coated on films by the Meijer group.³⁹⁸ Dendron-containing copolymers with high molecular weights show that both quantum efficiency and hole injection are significantly enhanced by increasing the dendron generation. Double-layer light emitting devices including these copolymers were fabricated whose performances benefited from dendron generation increase.^{399,400} Prolonged irradiation of PPI dendrimers functionalized with

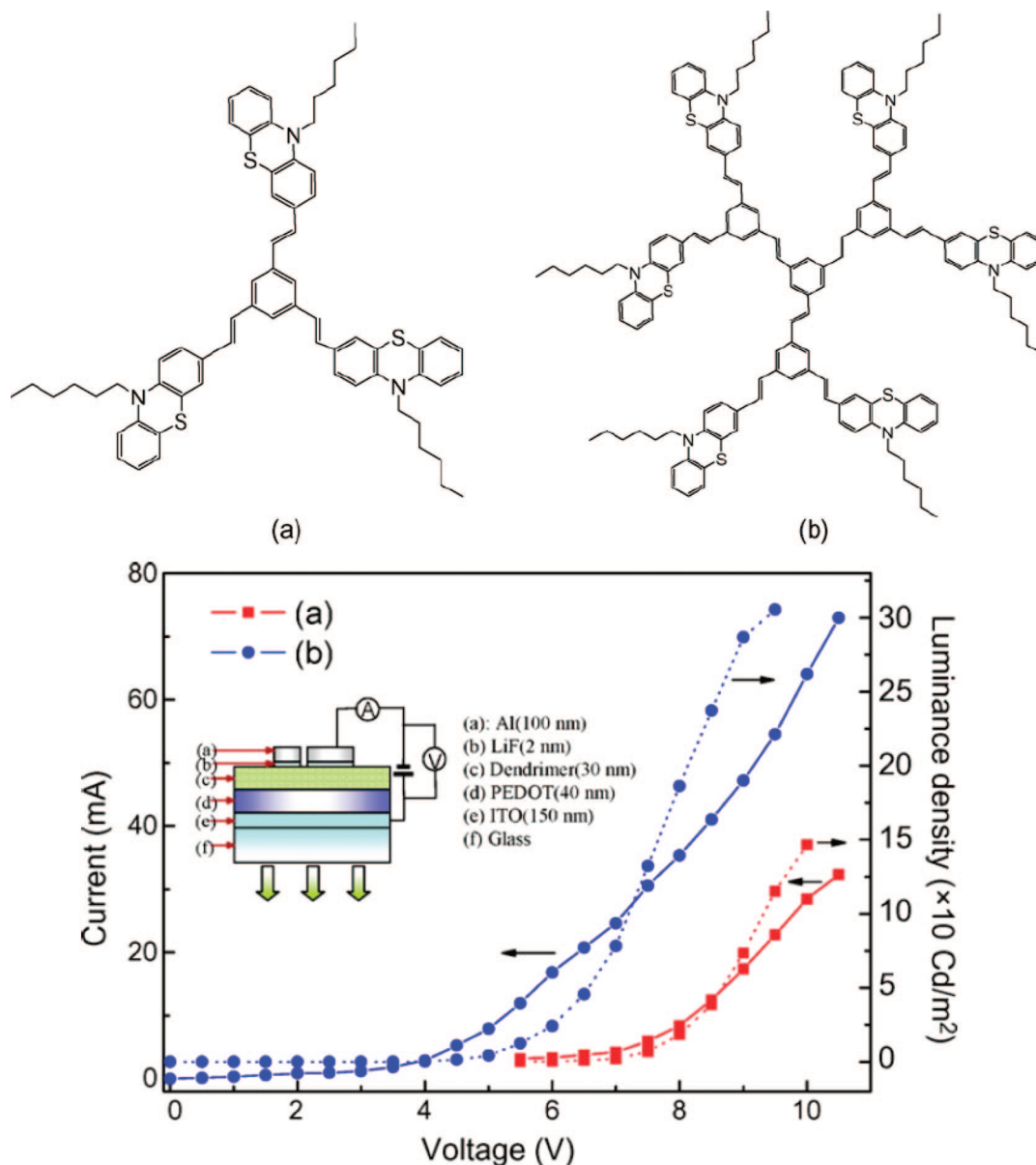


Figure 19. Current–voltage–luminance curves for two LEDs made of dendrimers. Reprinted with permission from ref 397 (Choi's group). Copyright 2007 Elsevier.

stilbene or 1,4-distyrylbenzene chromophores led to the destruction of the chromophores upon oligomerization (cross-linking).⁴⁰⁰ With the dendrimers, the efficiency remains low (up to 0.1%), however. Indeed, this efficiency is proportional to the number of excitons formed by charge recombination, the fraction of excitons generating light (PL quantum yield), the fraction of singlet excitons (fluorescence = 0.25 due to spin statistics), and the fraction of light that escapes from the device (usually 0.2). In poly(phenylene vinylene) dendrimers, these factors are not optimized, although the increase in dendrimer generation is favorable in phenothiazine-terminated dendrimers containing phenylene-vinylene cores and dendrons. Highly efficient dendritic OLED optimizing all these factors involved phosphorescent dendrimers (thus utilizing both the singlet and triplet formed in the devices) with polyphenylene, carbazole, triarylamine, and/or oligothiophene units (rather than poly(phenylene vinylene) ones), and a *fac*-tri(2-phenylpyridyl)iridium(III) core (vide infra).

3.14. Highly Efficient Dendritic OLEDs with a *fac*-Tri(2-phenylpyridyl)iridium(III) Core and Polyphenylene, Carbazole, Triarylamine, and/or Oligothiophene Units

The Burns and Samuels groups have developed green phosphorescent dendrimers providing highly efficient OLEDs with high PL quantum yields of up to 70% in dilute solution (with the highest generation) using the *fac*-tri(2-phenylpyridyl)iridium(III) core.^{401,402} This core provides a fast radiative decay rate (or shorter excitation lifetime). Charge is injected into this Ir^{III}-centered core as shown by electrochemical data.⁴⁰³ PL quantum yields were lower in the solid state, and the dendritic effect was positive, i.e., the first dendrimer generation gave a higher PL quantum yield than a nondendritic film and a lower PL quantum yield than the second dendrimer generation. Another crucial parameter for these highly efficient dendritic OLEDs was the use of biphenyl units and 2-ethylhexyloxy surface groups.^{404,405} Blending these dendrimers with 4,4'-bis(*N*-

carbazolyl)biphenyl, which spaces the dendrimers, was highly efficient. For instance, a 20:80 wt % dendrimer/4,4'-bis(*N*-carbazolyl)biphenyl blend film showed a PL quantum yield of 78%.^{401,402} Small structural variations in the Ir^{III} ligand substituents and linkers also provided red^{406,407} and blue⁴⁰⁸ phosphorescent dendritic OLEDs. The peripheral groups have an important influence, and solubilizing alkyl groups located at the periphery of Ir^{III}-centered dendrimers provided good device efficiencies in bilayer devices upon blending with 4,4'-bis(*N*-carbazolyl)biphenyl.^{409,410} Peripheral groups such as Müllen-type units yielded good results for arylthiophene OLEDs.^{411,412} A strategy involving charge-transporting groups such as oxadiazole or carbazole units used in conjunction with perylenes led to the preparation of devices. An example with eight carbazole units had a quantum efficiency of 0.1% at a brightness of ca. 6 cd m⁻². Another one included oxadiazole or triarylamine charge-transporting peripheral units, leading to three-layer devices that gave red emission with quantum yield of 1.5–1.9% and power efficiencies of 1.0–2.1 lm W⁻¹.^{413,414} Fully conjugated systems also gave blue emissions for bilayer devices.^{415,416} *fac*-Tri(2-phenylpyridyl)iridium(III)-cored dendrimer containing carbazole groups gave very good devices, especially upon blending with 2-(4-biphenyl)-5-(4-*t*-butylphenyl)-1,3,4-oxadiazole.^{415–418} An europium-centered dendritic OLED with carbazole groups at the periphery is also known with white emission (resulting from several emissions).⁴¹⁹ The advantage of dendrimer devices (containing only a dendrimer/host blend, a light-emitting layer, and an electron-transport layer) is that they lead to a simplification of the device compared to other OLEDs having five or six components in four or five layers. Such simple dendritic device structures are highly efficient, because (i) the light-emitting processes from solution lead to possible variation of colors and (ii) the exciton diffusion length in the dendrimer is much smaller in the dendrimer film than in devices containing small molecules.^{410–426} Highly efficient light-harvesting systems based on a blue Ir^{III}-centered phosphorescent dendritic acceptor coupled with dendronic carbazole-based donors via singlet–singlet (efficiency greater than 90%) and triplet–triplet (efficiency greater than 90%) energy transfer were recently reported.⁴²⁷ PPI dendrimers decorated with *E*-stilbene termini have been subjected to photoisomerization and fluorescence studies; comparison with the monomer shows a decrease of the fluorescence quantum yield in the dendrimer.^{430,431} Photoluminescence and triplet–triplet exciton annihilation in a neat film of a *fac*-tris(2-phenylpyridyl)iridium(III)-cored dendrimer and its blend with a 4,4'-bis(*N*-carbazolyl)biphenyl host were recently observed in the temperature range 77–300 K.⁴²⁸ Triplet–exciton hopping was shown to be controlled by electron-exchange interactions and could be over 600 times faster than phosphorescence quenching in films of Ir^{III}-centered phosphorescent dendrimers.⁴²⁹ A double-layer dendrimer with carbazole as the outer layer and phenylazomethine as the inner layer of the dendrons was shown by Yamamoto and his Keio group to be an excellent hole transporter in an OLED device, with performances increasing with generation increase.⁴³²

Newkome's group has delineated the general concepts, design criteria, and physical parameters such as component placement and electroluminescence, which relate to the construction of OLED devices, and illustrated and discussed these key electroluminescent elements with dendritic ex-

amples, calling for more research efforts in this attractive field of dendrimer design.⁴³³

3.15. Miscellaneous Photophysical Studies

Triarylamine dendrimers are excellent energy-donor cores (compare with triaryl amines as electron-donor cores upon photoexcitation³¹⁵), and energy migration was shown to be due to a coherent excitonic mechanism for which the exciton was delocalized in multichromophoric branched systems.⁴³⁴ On the other hand, trialkylamines, which are much better reductants than triaryl amines, could be used to quench, by electron transfer, the excited state of the anthracene chromophore that was located at the core of dendrimers of various generations. These trialkylamines including several diamine and triamine quenchers gave lower Stern–Volmer bimolecular quenching rate constants with increasing dendrimer generations, consistent with greater site isolation with increased dendrimer generations. Shape selectivity was observed as well, with rigid amines being shown to approach the anthracene core more easily than flexible ones.⁴³⁵ The fluorimetric titration technique could be successfully used for quantitative analysis of binding cationic PAMAM dendrimers with anionic fluorescent probes.⁴³⁶ Fluorescence anisotropy was revealed to be a very useful tool to investigate dendrimer structures and energy-migration processes as recently illustrated with four distinct luminophores, terphenyl, dansyl, stilbenyl, and eosin, which showed distinct fluorescence depolarization mechanisms in PPI dendrimers.⁴³⁷ Electro-optics effects were analyzed in multichromophore dendrimers from joint theory and experimental viewpoints, and a reasonably linear relationship between chromophore number density and electro-optic activity was disclosed.⁴³⁸ The photoluminescence of poly(methyl methacrylate) was doped with fluorescein and carbosilane dendrimers, and lasting effect was obtained herewith from a simple photonic band gap resonance cavity.⁴³⁹

Dendrimer-based multilayer films that incorporate redox and/or photoactive sites have been shown to exhibit photocurrent flow from the dendrimer to an electrode.^{440–446} Stepwise assembly of dendrimers containing covalently bound [Ru(bpy)₃]²⁺ termini and tris-viologen core on ITO surface using the layer-by-layer approach led to the disclosure of dendrimer generation effect by UV–vis, AFM, and electrochemistry. Anodic and cathodic photocurrents were observed upon visible irradiation and were attributed to light-harvesting properties.⁴⁴⁶ PAMAM dendrimers of generations 2.5, 3.5, and 4.5 have been shown to drastically accelerate the crystallization of fluorescent dyes upon reprecipitation in water, a process whose kinetics was monitored by UV–vis absorption spectroscopy.^{447,448} Nonconjugated dendrimers including diarylaminopyrene energy- and electron-donor termini and a benzyl ether-based backbone with a benzothiadiazole moiety were subjected to electron-transfer quenching of the photoexcited state or a prevalent sequential energy-transfer + electron-transfer pathway.⁴⁴⁹ Theoretical methods have been developed to test and evaluate the electronic structures and physical properties of polyacenes, polypyrroles, polyfurans, polyphenylenes, polyvinylene, and PAMAM dendrimers (Figure 20).⁴⁵⁰

A strong charge-transfer interaction between an electron-accepting guest, diazapyrenium dication, and a third-generation electron-donating amine-containing dendrimer was shown with 1:1 stoichiometry and monitored by strong changes in the absorption and emission spectra.⁴⁵¹ Static

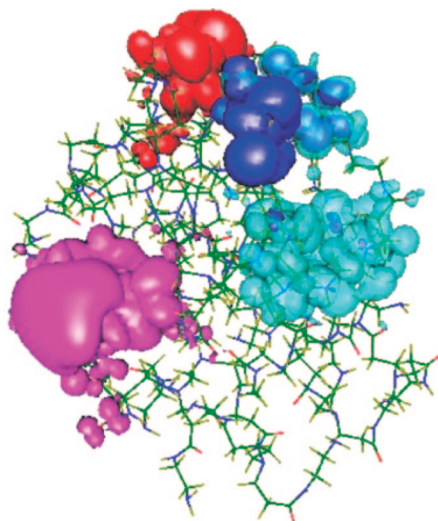


Figure 20. Probability density of the HOMO-1 (light blue), HOMO (dark blue), LUMO (red), and LUMO+1 (pink) orbitals of the generation 3 PAMAM dendrimer. The isosurfaces correspond to the probability of finding an electron inside the surface of 90%. Reprinted with permission from ref 450 (Vukmirović's group). Copyright 2008 American Institute of Physics.

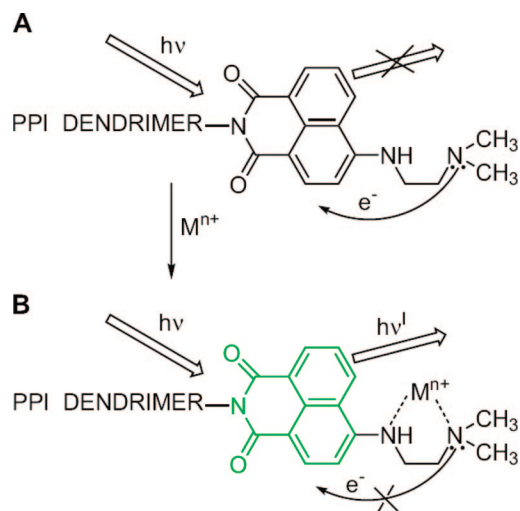


Figure 21. Proposed mechanism of fluorescence enhancement of 4-*N,N*-dimethylaminoethylamino-1,8-naphthalimide-labeled PPI dendrimer. Reprinted with permission from ref 454 (Grabchev's group). Copyright 2008 Elsevier.

fluorescence of a series of 10 perylene-cored dendrimers with anthracene termini revealed that excitation of the anthracene groups led to the core emission, indicating efficient energy transfer.⁴⁵² Cyclic phosphazene-cored dendrimers with aminopyrene groups are processable blue fluorescent systems used as emissive layers in OLEDs that reach current efficiencies of 3.9 cd/A at brightness levels near 1000 cd/m². Depending on the bridge between the core and fluorescent dendrons, the emissive wavelength varies between 470 and 545 nm due to the stacking of the aminopyrene units.⁴⁵³ The green fluorescence intensity of first-generation PPI dendrimers containing 1,8-naphthalimide fluorophores increases in the presence of protons and a variety of transition-metal cations (Figure 21).⁴⁵⁴

Hydroxy-terminated poly(propyl ether imine) dendrimers of generations 1–5 were reported to absorb in the region of 330 nm, in methanol and aqueous solutions, which led to an emission near 390 nm whose intensity increased under acidic pH and in more viscous solvents.⁴⁵⁵

The photochemistries of organic guests included within water-soluble dendrimers terminated by carboxylate groups were conducted with 4-methyl dibenzyl ketone, benzoin ethyl ether, and acenaphthylene photodimerization, and the cage effect was involved. Other prototypical reactions were photo-Fries reactions of 1-naphthyl benzoate and 1-naphthyl phenyl ether. It was found that the dendritic environment restricts the mobility of the radical intermediates and strongly inhibits leaking of substrate, intermediate, and products outside the dendrimers.^{456,457} Rapid energy transfer was reported in a stilbenoid phthalocyanine dendrimer having π -conjugated light-harvesting antennae.⁴⁵⁸ The dendrimer generation-dependent fluorescence properties of poly(ester amine) dendrimers with focal 4-amino-*N*-benzylphthalimide were used for switchable proton sensing.⁴⁵⁹ Excellent energy-funneling ability (over 95%) was disclosed by time-resolved fluorescence spectroscopy for π -conjugated dendrimers with 5,5,10,10,15,15-hexahexyltruxene as the node and oligo(thienylethynylene)s with various lengths as the branching units.⁴⁶⁰ Dendrimers consisting of a *p*-pentaphenylene core branched to two G_2 - or G_4 -sulfonimide dendrons, and two *n*-octyl chains showed pentaphenylene fluorescence ($\lambda_{\text{max}} = 410$ and 420 nm in fluid solution and solid state, respectively) without energy transfer from the chromophoric groups of the dendrimer branches.⁴⁶¹ Ir^{III} organometallic supramolecular core-shell dendrimers were characterized as phosphorescent emitters, and these host-guest materials were applied as luminophores in OLED devices.⁴⁶²

3.16. Dendritic Fluorescent Sensors

The majority, if not all, of the studies carried out with fluorescent dendritic materials reviewed in this section (section 3) can either involve or be directly applied to sensing, especially if they are or can be integrated in an adequate device. As an example from the St. Andrew group, sensing of 1,4-dinitrobenzene, a model of the explosive substance 2,4,6-trinitrotoluene (TNT), used bisfluorene dendrimer-distributed feedback lasers. Indeed, fluorescence quenching of a G_1 -dendrimer conjugated with 2,2'-bis(9,9-di-*n*-hexylfluorene) core was obtained with much greater sensitivity by using the material as such a surface-emitting distributed feedback laser. The slope efficiency of the laser is very convenient to detect the analyte, as it decreased by 50-fold in its presence.⁴⁶³ Immunosensing is an alternative for trace TNT detection (Figure 22).⁴⁶⁴

The $G_{4,5}$ -PAMAM-CO₂Na dendrimer was found to be a fluoride sensor in methanol, based on the intensely decreased fluorescence (blue, $\lambda_{\text{max}} = 445$ nm) with fluoride ion, but not with the other halides.⁴⁶⁵

3.17. Nonlinear Optical Properties

With three-branched dendritic nonlinear optical (NLO) chromophores, it was shown that the NLO activity could overtake the sum of the three noninteracting single-stand subunits, when the dendrimers show nearly parallel or helical alignments of the single-stranded subunits. Because of this conformational situation, the NLO activity can be enhanced up to nine times the value of the "independent chromophores".⁴⁶⁶

Cubic NLO properties were determined for phenyl- and ferrocenyl-terminated resorcinarene-cored dendrimers in which these end groups were joined to the core by vinyl moieties with *trans*-configuration. The $\chi(3)$ values estimated

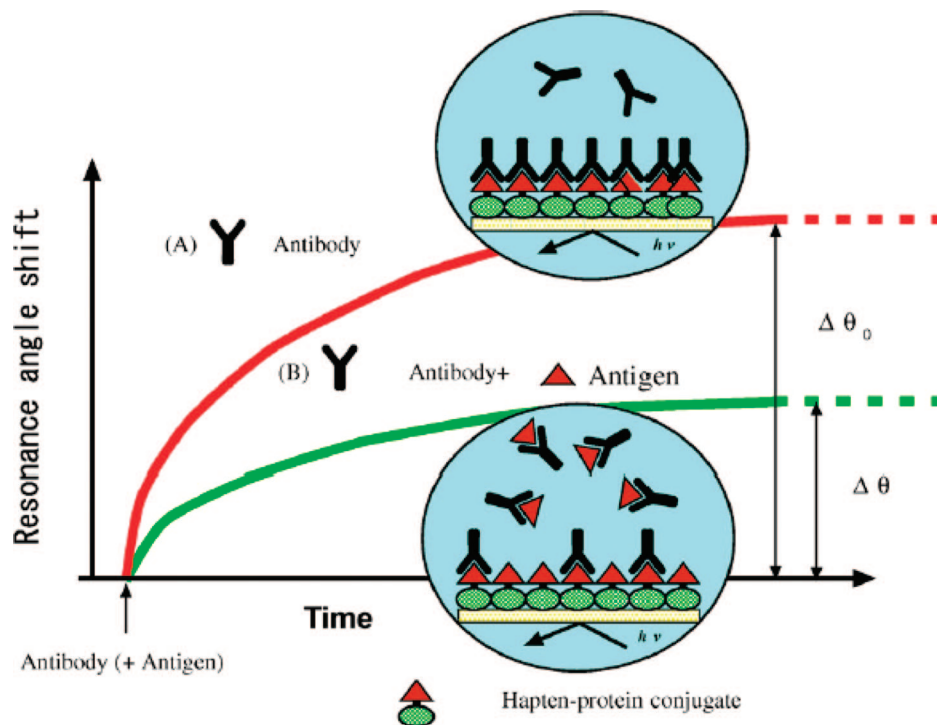


Figure 22. Principle of competitive inhibition assay on surface plasmon resonance immunosensor. Reprinted with permission from ref 464 (Singh's group). Copyright 2009 Elsevier.

from the THG Maker-fringe technique for these dendrimers dispersed in thin solid films are of the order of 10–13 esu.⁴⁶⁷ Dispersion of the NLO properties was observed for triphenylamine-cored alkynylruthenium dendrimers. The NLO performances of these inorganic dendrimers are one order of magnitude greater than those of similar organic dendrimers, demonstrating the key role of the incorporation of metal centers at appropriate positions and with adequate bridging ligands in the molecular architecture.⁴⁶⁸ Increasing the generations of thiophene dendrimers increased the cross section for both entangled and random two-photon absorption cross sections, suggesting that the thiophene groups within the dendrimer nonlinearly absorb in a cooperative manner.⁴⁶⁹

4. Supramolecular Properties

4.1. Concepts and Pioneering Studies

Supramolecular chemistry, defined by Lehn as “Chemistry beyond the Molecule”,³ is strongly involved in dendritic structures. Dendrimers can encapsulate guest substrates in their interior and interact through supramolecular interactions (H bonding, ionic bonding, coordination) of their many branch termini with substrates at the dendrimer periphery. This most important supramolecular property^{1,2} of dendrimers, their ability to encapsulate guest molecules or ions, was underlined at the very beginning of dendrimer chemistry by the pioneers when, in 1985, Newkome coined the term “*unimolecular micelle*”.⁷ Tomalia also reported, in 1987, experimental evidence for covalently fixed unimolecular micelles⁹⁰ as well as, at the end of the 1980s, the encapsulation of several molecular guests.⁸ Subsequently, a variety of supramolecular interactions in- and with dendrimers were shown to contribute, eventually in synergy, to guest encapsulation by dendrimers and interdendritic (or dendronic) interactions for the formation of more complex dendritic nanoassemblies. Newkome promoted the concept of “*unimolecular micelles*” with his dendritic arborols encapsulating

inter alia phenol blue as shown by dynamic light scattering, fluorimetry, fluorescence microscopy, and UV–vis spectroscopy.¹²² The study of the encapsulation of acetylsalicylic acid in PAMAM dendrimers was carried out by Goddard and Tomalia using spin–lattice relaxation times.⁴⁷⁰

Supramolecular interactions with guests inside the dendrimers included hydrophobic dendrimer cavities, hydrogen bonding, metal–ligand coordination, and physical encapsulation (such as Meijer's dendritic box encapsulating Rose Bengal),⁹ whereas supramolecular interactions at the periphery involved electrostatic or H-bonding interactions, peptide–protein interactions for the production of peptide antibodies and synthetic vaccines,⁴⁷¹ and carbohydrate–protein interactions⁴⁷² for cell recognition and infection.^{473,474}

Newkome also pioneered the bolaamphiphiles that have two hydrophilic, water-soluble polyol dendrons linked by a variety of hydrophobic chains at the dendrimer interior and form gels.⁴⁷⁵ Large dendritic micelles and vesicles were subsequently synthesized.^{476–478} Self-organization of dendrimers led Percec to prepare spectacular liquid crystalline phases with sharp transition peaks and low degrees of supercooling. Enantiotropic nematic mesophases and a smectic mesophase were formed with increasing phase-transition temperatures as the generation number increased.^{479,480} Carbosilane-based liquid crystalline dendrimers were also synthesized.⁴⁸¹ Stoddart assembled dendrimers using the π – π interaction between a π -donor and a π -acceptor, including rotaxanes with stoppers that could eventually also be dendritic.^{482–486}

Finally, various ligands were installed at the periphery of dendrimers to form classic coordination complexes including dendritic transition-metal catalysts that will be dealt with in section 5. The supramolecular properties of dendrimers were systematically reviewed, besides in Tomalia's early reviews,^{8,17,18} in other early reviews on dendrimers^{7–22} and in the excellent reviews that appeared in the late 1990s, including the reviews by Newkome's group,^{10,15,16} Zeng and Zimmermann,⁴⁷³ and

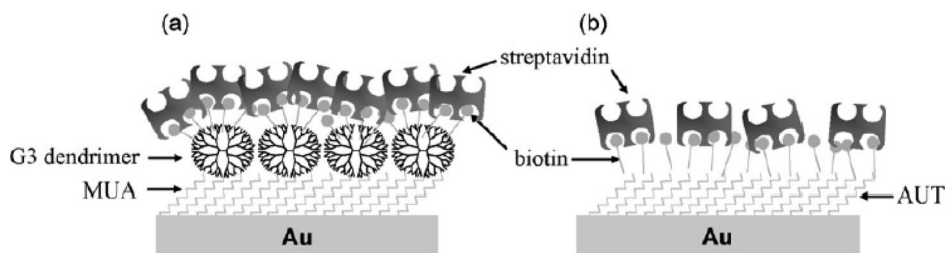


Figure 23. Schematic of streptavidin immobilized on a (a) G_3 PAMAM dendrimer monolayer and (b) self-assembled monolayer of 11-amino-1-undecanethiol (AUT) onto gold. Reprinted with permission from ref 474 (Lee's group). Copyright 2008 Elsevier.

Meijer's group.²² Thus, we will now focus on more recent supramolecular properties of dendrimers that were reported during this decade. Obviously, this section largely overlaps with the photophysical section for the characterization of the supramolecular properties, with the catalytic section for the approach of the coordination sites of the metals, and with the biomedical section, because biological and drug–biological–substrate interactions are essentially supramolecular.

4.2. H-Bonding

H-bonding is common in Nature with the two complementary strands of DNA and with proteins. Thus, H-bonding in dendrimers may be more or less biomimetic, because dendrimers can be of sizes close to those of biomolecules. A typical biomimetic example is the supramolecular interaction between avidin and biotin on dendrimers, for instance, on surfaces and SAMs that was quantified by time-of-flight secondary ion mass spectrometry (Figure 23).⁴⁷⁴

The best known example of H-bonding in dendrimer chemistry is Zimmermann self-assembly of dendrons that has been reviewed.^{473,474} Supramolecular assemblies based on H-bonding between diaminobutane (DAB)-cored dendrimers with dendronic phenol were shown by ¹H NMR and cyclic voltammetry to reversibly form. The dendritic framework was sufficient on the electrochemical time scale (0.1 s) to recognize the H_2PO_4^- anion whose sensing requires such a dendritic exoreceptor structure. Moreover, titration of the anion occurred with a sudden intensity drop at the equivalent point. This was taken into account by a drop of the diffusion coefficient due to the supramolecular formation of a larger framework incorporating the H_2PO_4^- anion bridging amidoferrocenyl groups.^{487–491} Dendrons with other functional groups such as the redox-active 4,4'-bipyridinium showed that the redox potential can be influenced by the dendron size.⁴⁹⁰ Self-assembled dendrimers have been reported since 2002. In particular, Zimmerman's supramolecular dendrimers involved complementary H-bonding motifs in the core.^{492,493} Other self-assembled supramolecular dendrimers involved other types of H-bonded arrangements.^{494,495} More recently, whole dendritic assemblies were built up, shell-by-shell, in a self-assembly process. Such assemblies are based on a single complementary pair of H-bonding motifs A and B forming an AB assembly. Self-assembly dendrimers are formed by mixing a tripodal core A_3 with a branched linker BA_2 and a capping unit B in the required ratio.⁴⁹⁶ Uniform self-assembled dendritic architectures were subsequently reported using tri- and tetraurea-derived calixarenes including ¹H DOSY NMR studies (Figure 24).⁴⁹⁷

Meijer introduced transient supramolecular dendritic networks based on H-bonding of termini with guest substrates. The dynamic supramolecular interaction was studied by

dynamic light scattering showing concentration-dependent association.⁴⁹⁸ Porous networks were formed by attaching multiple hydrogen-bonding sites to dendritic cores based on pentaerythrityl tetraphenyl ether. This concept creates links between crystal engineering involving tectons and dendrimers whose cores are not too flexible.⁴⁹⁹ DAB dendritic tectons have been used in crystal engineering upon halogen bonding between DAB– $(\text{NHC}_6\text{F}_4)_{22}$ and (*E*)-1,2-bis(4-pyridyl)ethylene in a 1:2 supramolecular adduct.⁵⁰⁰

4.3. Electrostatic Binding

Classic examples are dendrimers whose tethers are terminated by ionic groups such as carboxylate groups that are well-known in Newkome,^{10,14–16} Tomalia,^{9,17,18} and Fréchet's dendrimers.^{26–30} These ionic interactions play a key role in the binding between dendrimers with cationic termini and DNA or oligonucleotides (see sections 6.2.3 and 6.9). When a dendron is functionalized at the focal point with a 4,4'-bipyridinium (viologen) residue, noncovalent complexation with a crown ether (that encircles the viologen unit) can be followed by the variations of the stability constant that is very sensitive to the dendron generation. Indeed, it decreases as the size of Newkome-type dendrons increases because of steric hindrance. For Fréchet-type dendrons that are quite rigid, such an effect is not observed. The electrochemistry of these dendrons shows electrochemical reversibility, i.e., fast electron transfer between the redox site and the electrode (Figure 25).^{501–505}

On the other hand, note that, in dendrimers, buried redox centers disclose irreversibility (slow electron transfer) that increases as the dendrimer generation increases, because the distance between these redox centers and the electrode increases as the generation increases.^{506,507} The focal point of a dendron can more easily reach the electrode surface within a small distance, because it is more exposed to the outside, and the cationic charge of viologen is electrostatically attracted by the negatively charged electrode. In connection with these electrochemical studies, the diffusion coefficients were determined using the NMR technique of pulse-gradient stimulated echo (PGSE)^{508,509} and compared with the cyclic voltammetry peak currents that are proportional to the square root of the diffusion coefficient.^{501–504,509,510} Interactions of this kind with ferrocenyl and other redox dendrimers containing β -cyclodextrin³⁵⁶ and cucurbit[7]uril⁵¹¹ hosts were also reported. Electrochemistry is a current method to generate charges, and measure electrochemical redox potentials gives indications on the stabilization of these charges by the medium.⁵¹² Specially interesting types of ionic dendrimers are those that include their ion pairing deeply buried inside the dendrimer interior, because such ion pairs are shielded by the peripheral group and can even be solubilized in hexane, when the terminal groups are apolar.

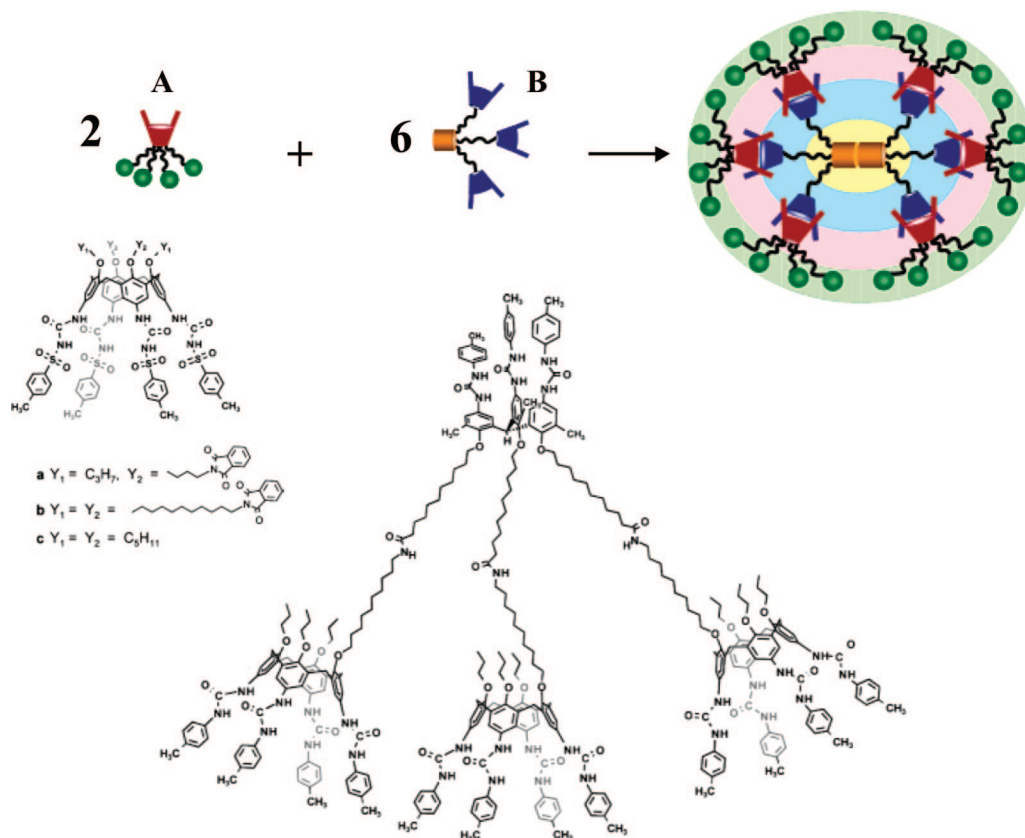


Figure 24. Schematic representation of a dendrimer self-assembled of two molecules of A and six molecules of B. Reprinted with permission from ref 497 (Böhmer's group). Copyright 2005 American Chemical Society.

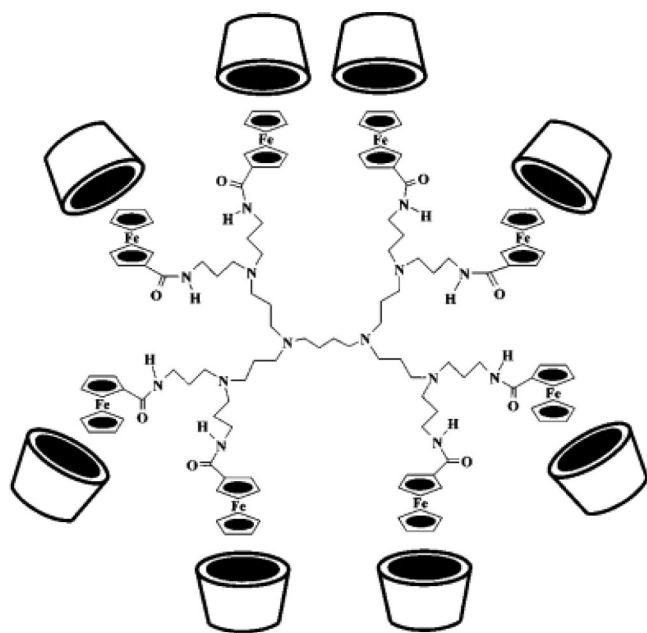


Figure 25. Dendrimer serves as a three-dimensional template to organize the CD receptors in the periphery of the dendrimer structure, giving rise to large supramolecular assemblies. Reprinted with permission from ref 501 (Kaifer's group). Copyright 1997 American Chemical Society.

For instance, dendrimers with polyammonium cores solubilize the dye methyl orange in organic solvents.^{513,514}

It was shown that fluorescent dyes such as eosin, fluorescein, and rose Bengal are extracted from water solutions as their neutral aryl carboxylic acid forms by dichloromethane solutions of dansyl-decorated DAB dendrimers, forming

ammonium–carboxylate bonds in the dendritic framework upon protonation of the DAB amino groups.⁵¹⁵ Likewise, cationic dendrimers containing viologen units form ionic bonds with eosin, completely quenching the eosin fluorescence, but these ionic bonds can be destroyed by the addition of chloride, then re-established upon chloride precipitation with Ag^+ .⁵¹⁶ With cationic polylysine dendrimers, ionic interactions were probed with the fluorescent anion 8-aniline-1-naphthalene sulfonate (ANS), but the interaction was also shown by ANS fluorescence studies to rely on additional aromatic–aromatic interactions between the dendritic host and the ANS guest.⁵¹⁷ In these cases, the polarity is opposite to that used in a seminal study for PAMAM dendrimers functionalized with terminal carboxylate groups, with these later dendrimers being able to host cationic dyes such as methylene blue, acridine orange, pyronine G, and phenosafranine.⁵¹⁸ Applications of G_5 -DAB have appeared for pH-dependent rapid perchlorate water depollution.⁵¹⁹ The ionic bond can also be that of the guest rather than that of the dendrimer. For instance, Shriver studied ion transport of $Li[CF_3SO_2)_2N]$, a well-known electrolyte for batteries in DAB and PAMAM dendrimers. It was shown that G_5 -DAB-64 forms more-conducting electrolytes with this salt than PAMAM-64 dendrimers. At low salt doping, the ionic conductivity and glass transition of DAB-64 are more favorable than those of the standard branched polymer, which was attributed to the reduced motion of the dendrimer upon coordination of the lithium cation to the nitrogen atoms at the DAB–dendrimer periphery.⁵²⁰ Electrostatic interactions with guests such as 5-aminosalicylic acid, pyridine, mefenamic acid, and diclofenac within citric-acid-terminated PEG dendrimers have been proposed to be responsible for solubility enhancement.^{521,522} Other assemblies of two den-

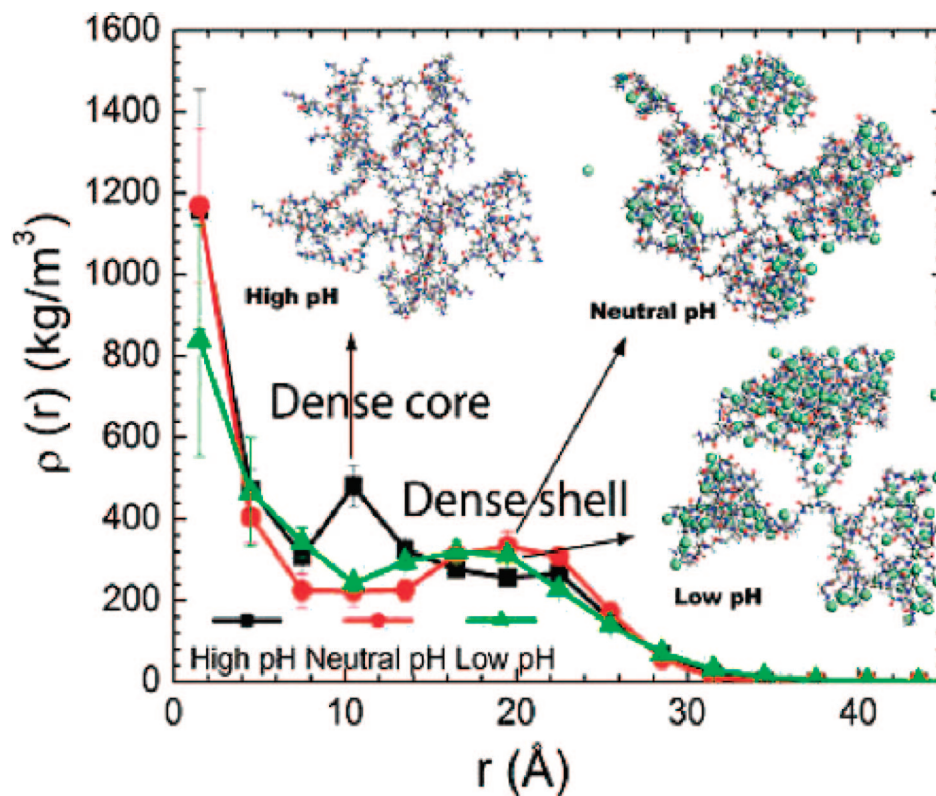


Figure 26. Radial density distribution of G_4 -NH₂ PAMAM dendrimer at various pH values (using the center of mass of the dendrimer as the reference and averaged over 200 ps). Snapshots from molecular dynamics (MD) simulations are shown in the insert. Reprinted with permission from ref 524 (Goddart III's group). Copyright 2009 American Chemical Society.

drons through focal point interactions around ammonium units also lead to dendritic assemblies.⁵²³

Atomistic molecular dynamics simulations of a G_4 -PAMAM-NH₂ dendrimer carried out in aqueous solutions with explicit water molecules and counterions predicted that the gyration radius changes little between pH 10 and pH 5 (126 protons), agreeing with small-angle neutron-scattering experiments. Dramatic conformational change was found, however, with ion pairing at low pH leading to a locally compact dense shell, contrasting with a dense core at high pH, which is useful information in view of guest encapsulation and release using the pH trigger (Figure 26).⁵²⁴

The Newkome group has reported dendrimer–metallomacrocyclic composites that form nanofiber by multion pairing. Ion-promoted, automorphogenic, and stoichiometric self-assembly of a hexameric, Ru-based macrocycle and a dodecarboxylate-terminated dendrimer produced a stable nanofiber. These polyanionic dense-packed counterions led to ion-pair superstructures in which the randomness of single-charged counterions has been eliminated.⁵²⁵

4.4. Combined H-Bonding/Ionic Bonding

Polycationic dendrimers terminated by redox-active groups that are bonded to an amido group providing H-bonding with anions of environmental or biological interest give rather strong binding with this anionic guest that can be monitored by cyclic voltammetry. These redox-active dendrimers such as polycobaltocenium^{526–528} or polyferrocene–ferricinium dendrimers^{487–490,529,530} are thus excellent sensors, especially because electrode derivatization is easy and strong, which makes it possible to wash and reuse the electrochemical sensors.^{529,530}

Meijer and his group have designed PPI dendrimers whose tethers are terminated by ureid groups and whose internal tertiary ammonium groups are electrostatically bound to anionic guests also containing an ureido group or a peptide. In this way, the ureid groups of two dendritic branches provide H-bonding with the ureid or peptide group of the anion. Protonation of the internal tertiary amines of the dendrimer was best achieved using phosphonic or sulfonic acid groups. Binding constants, which are high, were determined by using fluorescence titrations and optimized by fitting the appropriate length of the anionic ureido guest. The stability of these dendritic host–guest assemblies was confirmed by collision-induced dissociation mass spectrometry (CID-MS), ¹H, ¹³C, and ³¹P NMR, nuclear Overhauser enhancement NMR, T₁-relaxation, IR, and dynamic light scattering.^{531–534} The interaction of various ammonium cations with benzoate-terminated dendrimers containing 9, 27, 81, or 243 tethers in water was studied by ¹H and ¹³C NMR in D₂O including DOSY experiments that allowed access to the diffusion coefficients. The lack of significant size change upon cation binding indicated intradendritic encapsulation of the cationic guest and backfolding of the host terminal carboxylates, and deshielding of the benzoate proton signals showed the intimate guest–host contacts. In the case of dopamine as a guest, combined ionic/H-bonding induced a much stronger bonding (characterized by the association constants) than with the guests that only involved ionic bonding. Positive dendritic effects upon cation binding by the polyanionic dendrimers were observed as the generation increased from 0 to 2, and nondendritic benzoates provided almost no ¹H NMR perturbation upon association in D₂O (Figure 27).^{535,536}

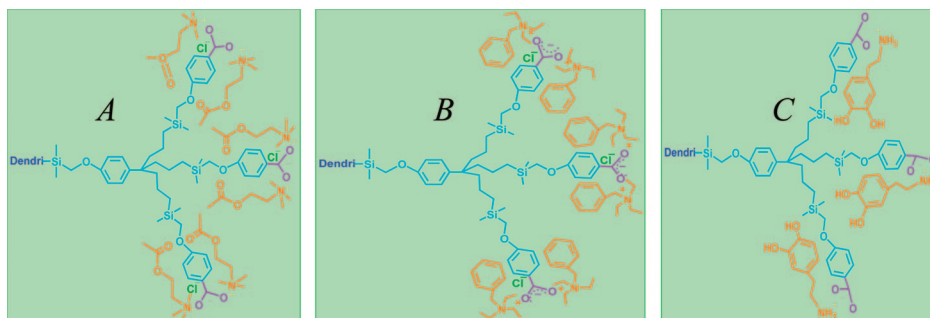


Figure 27. Representation of the ionic aggregates of carboxylate dendrimers with two acetetylcholine, two benzyltriethylammonium, and one dopamine. Reprinted with permission from ref 536 (Astruc's group). Copyright 2008 Royal Society of Chemistry.

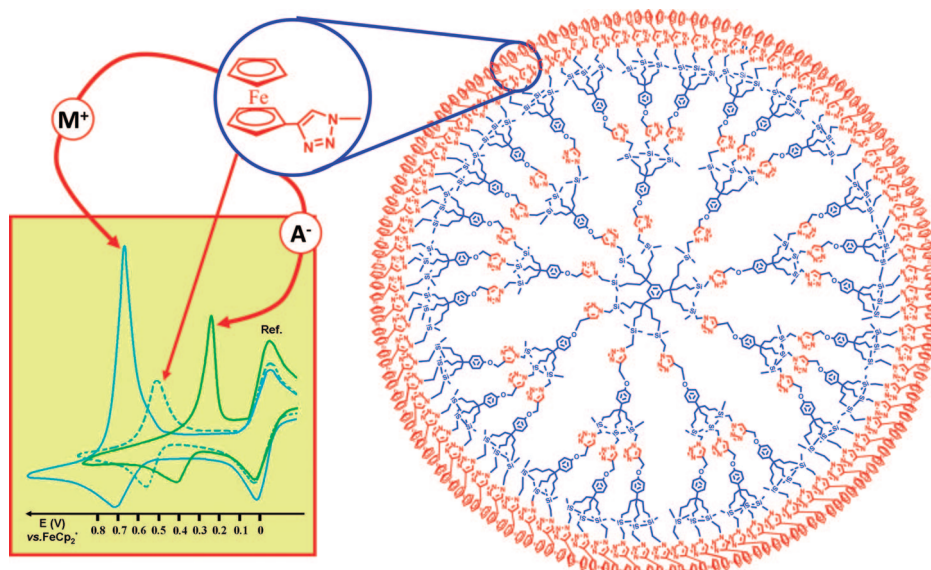


Figure 28. “Click” ferrocenyl dendrimers serving as electrochemical sensors for the recognition and titration of both oxo-anions such as ATP^{2-} and late transition-metal cations with positive dendritic effects. The pointed dashed cyclovoltammogram shows the dendrimer alone. The green voltammogram (cathodic shift, to the right) shows anion (ATP^{2-}) recognition whereas the blue voltammogram (anodic shift, to the left) shows Pd(II) recognition (Astruc's group).

4.5. Coordination of Metal Ions

The incorporations of metal ions in dendritic architectures involves an essential part of dendritic chemistry and has been the subject of numerous reviews,^{10–22} including recent ones.^{537–542} The metal ions are found at the dendritic core, dendritic focal point, tether termini, branching points, and sometimes on other places of the tethers. Pioneer work in inorganic dendrimers is found in Balzani's ruthenium polypyridine complexes,^{170–186} whereas the first organometallic dendrimers were those of iron sandwich complexes.^{4,19} Applications are found with the luminescent and other photophysical properties of the ruthenium polypyridine and metalloporphyrin complexes (see section 3); catalysis with V, Fe, Co, Ni, Cu, Ru, Co, Rh, and W-based complexes (see section 5); PAMAM gadolinium complexes as NMR contrast agents (see section 6); and sensors and molecular electronics materials (see section 3). The supramolecular aspects are involved in all these domains of metallodendrimer chemistry and physics and are discussed in the appropriate sections. Here, we just recall that metal–dendritic ligands interactions are intimate parts of supramolecular chemistry whereby the supramolecular aspects are more or less involved from dendrimer assembling (for instance Fréchet's Europium-cored dendrimers¹⁹⁵ and Newkome's terpy-metal-ion building

blocks⁵⁴⁴) to various functions and applications indicated above (Figures 28, 29, 30). Applications are also found in electrochemical sensors (see sections 4.4 and 6.9).⁵⁴³

4.6. Intradendritic π – π Interactions

A well-known case of intradendritic π – π interaction is found in Stoddart's rotaxanes with dendritic stoppers, the so-called “threading” approach, in which the thread based on electron-poor bipyridinium dication is terminated by Fréchet-type dendrons and encircled by the electron-rich aromatics of the bis(tetraethylene glycol phenylene) ring (Figure 31).^{20,545}

Another remarkable example is the π – π interaction between dendritic cyclohexatrienes for which Nierengarten showed that the binding association constant with C_{60} increased together with the increase of the dendrimer generation, reaching 340 M^{-1} for G_4 in CH_2Cl_2 .^{293,546–548} In Fréchet's seminal polyarylether dendrimers functionalized with water-solubilizing carboxylate groups, the unimolecular micelle behavior was demonstrated by pyrene solubilization, but possible π – π interaction was invoked, because twice as much of the electron-deficient compound 2,3,6,7-tetranitrofluorenone was solubilized as pyrene. It is likely that many cases of less clear-cut examples may involve inter alia such interactions in dendritic encapsulation of guests containing aromatic

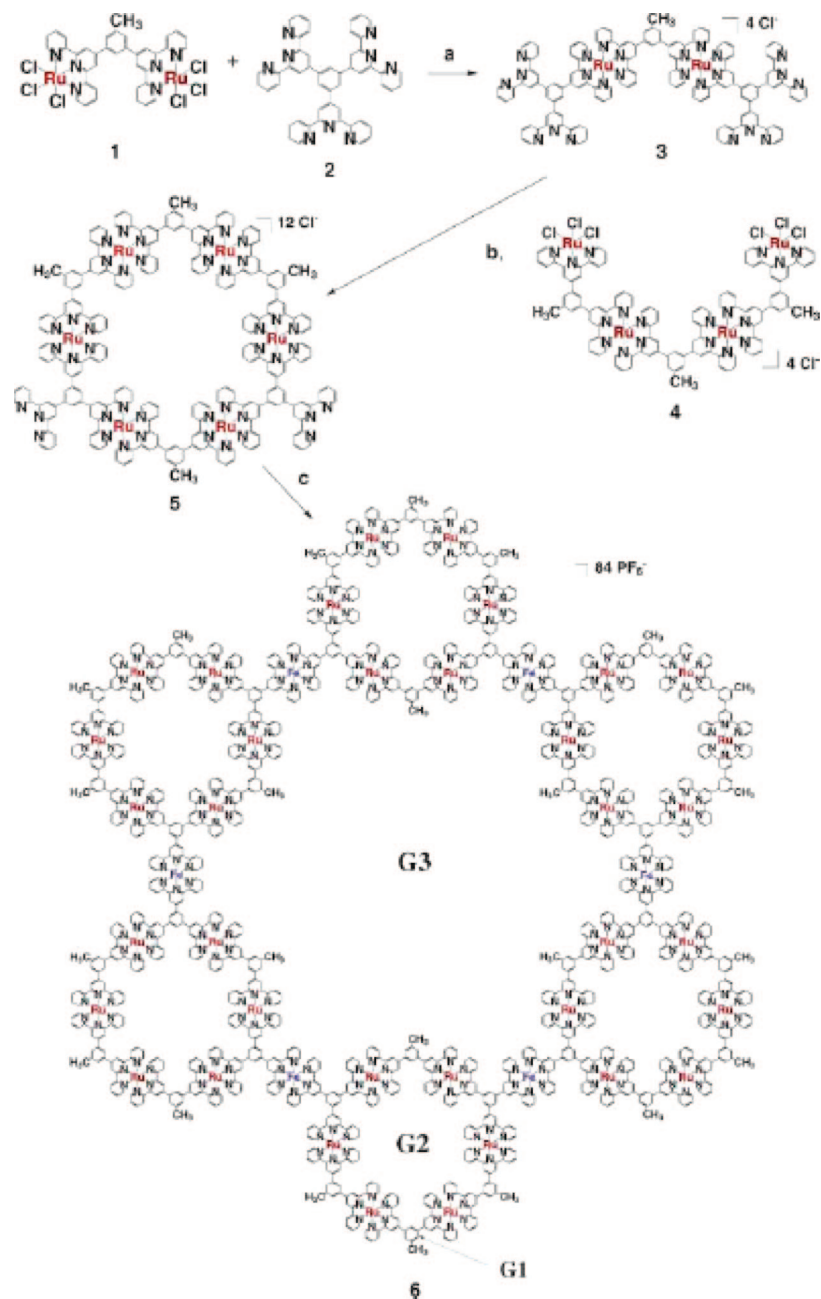


Figure 29. Reaction scheme for the synthesis of trimer **3**, hexamer **5**, and the fractal gasket **6**. Reaction conditions were as follows: (a) **1** and **2** were mixed with *N*-ethylmorpholine in refluxing $\text{CH}_3\text{OH}/\text{CHCl}_3$ (2:1 v/v), for 20 h. (b) **3** and **4** were stirred in refluxing CH_3OH with added *N*-ethylmorpholine for 12 h. (c) First, hexamer **5** was refluxed in CH_3OH in the presence of 1 equiv of $\text{FeCl}_2 \cdot 6\text{H}_2\text{O}$ for 20 h. Then, to a CH_3OH solution of $\mathbf{5}(\text{Cl}^-)_m(\text{NO}_3^-)_n$ was added a solution of NH_4PF_6 to obtain the desired gasket **6** as a precipitate. G_1 – G_3 indicate generations 1–3 that can be envisioned for this fractal-based construct. Reprinted with permission from ref 544 (Newkome's group). Copyright 2006 American Association for the Advancement of Science.

residues in dendrimers. In a recent review of weak aromatic interactions, yet containing a dendrimer section, the paucity of other reported studies of intradendritic interaction appears in spite of the frequent occurrence of these interactions,⁵⁴⁹ in contrast with studies of interdendritic assemblies.

4.7. Encapsulation of Neutral Guest Molecules

Since the seminal proposal of dendrimers as unimolecular micelles by Newkome in 1985,⁸ guest encapsulation by dendrimers has appeared as one of the major dendritic properties, because of the potential applications for drugs.⁵⁵⁰ A well-known example is Meijer's dendritic box, a PPI dendrimer for which the dendrimer–guest complex is capped by reaction of the terminal amino groups with Boc- or Fmoc-

protected amino acids for permanent guest encapsulation or subsequent release upon deprotection using formic acid.⁴⁷⁷ Studies by various authors of neutral guest encapsulation have involved simple molecules such as iodine, pyridine or benzoic acid,⁵⁵¹ 2,6-dibromo-4-nitrophenol,⁵⁵¹ dyes (Reichart's dye,⁵⁵² Bengal Rose,⁵⁵³ orange OT,⁵⁵⁴ 4,5,6,7-tetrachlorofluorescein⁵⁵³), other molecules of photophysical interest (anthracene,⁵⁵⁵ pyrene^{550,556–558}), and many drugs⁵⁵⁹ (see section 6.2.1). A large majority of studies have concerned PAMAM dendrimers, because they are commercially available, water-soluble, can be functionalized with terminal groups, and work very well for a variety of encapsulations. Most often, the PAMAM dendrimers were used with further functionalization by means of their terminal NH_2 groups, but

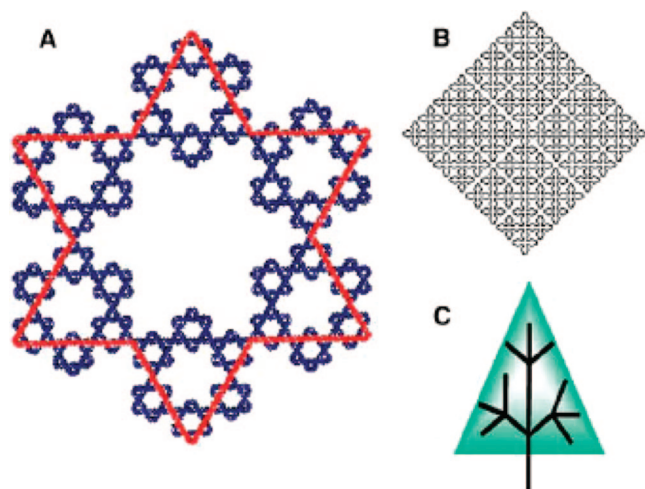


Figure 30. Sierpinski's hexagonal gasket (A) incorporating the Star of David and the Koch snowflake motifs. Images of (B) the snakelike "kolam" pattern and (C) the 1 \rightarrow 3 branching pattern of a tree. Reprinted with permission from ref 544 (Newkome's group). Copyright 2006 American Association for the Advancement of Science.

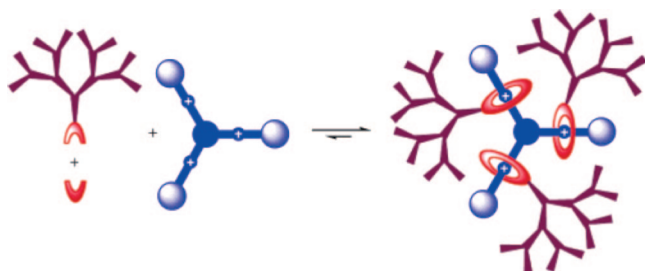


Figure 31. Graphical representation of the template-directed synthesis of mechanically interlocked dendrimers. Reprinted with permission from ref 545 (Stoddart's group). Copyright 2005 American Chemical Society.

sometimes the PAMAM hosts were terminated by OH or PEG groups and occasionally by other groups such as esters,

citric acid, or lauroyl.⁵⁵⁹ Many other dendrimers have also been used such as PPI, polyether, and PEG dendrimers. Following Newkome's concept,⁸ dendrimers with hydrophobic core and hydrophilic periphery exhibited micelle-type behavior and showed the marked property to act as molecular containers. The guest-encapsulating property of dendrimers goes together with their solubilizing properties. The water-insoluble molecules can be encapsulated by water-soluble dendrimers (owing this property to water-solubilizing termini) that have hydrophobic interiors. The property of guest solubilization by encapsulation increases as the dendrimer generation increases. This has been shown by all the precise studies with various guests and dendrimers (Figure 32).^{521–525,557,560,561} G_4 -PAMAM dendrimers functionalized with phenylalanine or γ -benzylglutamate moieties were terminated with PEG₂₀₀₀, which enhanced their nanocontainer properties, for instance with Rose Bengal, and indicated their potential capacities for drug delivery (cf. section 6.2).⁵⁶² Up to 50 Rose Bengal molecules could be encapsulated in PEGylated PEI dendrimers. The encapsulation capacities were dependent linearly with the degree of the PEG shell, either as PEG length or degree of functionality, confirming that the PEG chains play a predominant role in the encapsulation process.⁵⁶³ As an example, PAMAM dendrimers having both PEG and β -cyclodextrin termini could solubilize 2 μ M C₆₀ in water.⁵⁶⁴

The dendrimers have open shapes for low generations, and the dendrimer shapes progressively become globular as the generation number increases, which has been related to the concomitant increase of guest solubilization. It has also been shown that small guests are more easily encapsulated and solubilized than larger ones.^{521–525} Amphiphilic dendrimers, first reported by Fréchet's group, produce emulsions in dichloromethane/water.⁵⁵⁵ Recently, it was shown that amphiphilic dendrimers having both hydrophilic (carboxylic acid) and hydrophobic (decyl) groups in the dendrimer repeat unit and 3,5-dihydroxybenzyl alcohol termini solubilize both hydrophobic and hydrophilic guest molecules.⁵⁵⁸ Another variation is hydraamphiphiles, so-called when the dendrimer

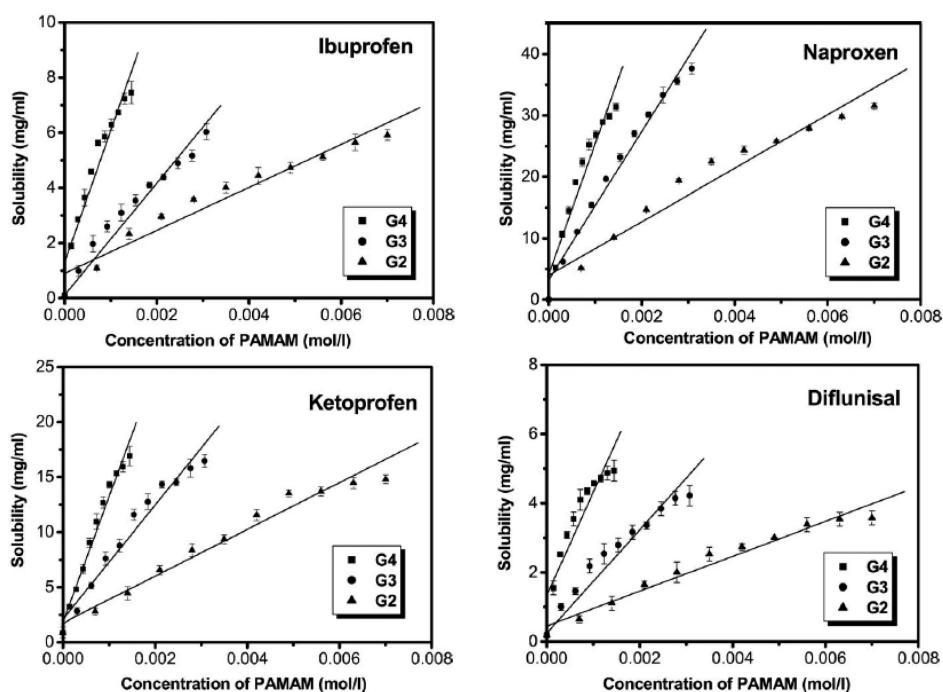


Figure 32. Solubility of ibuprofen, naproxen, ketoprofen, and diflunisal in the presence of increasing concentration of PAMAM dendrimers. Reprinted with permission from ref 561 (Yiyun's group). Copyright 2005 American Chemical Society.

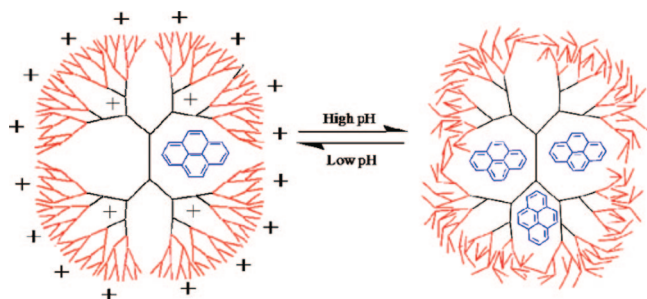


Figure 33. Schematic representation of pyrene encapsulation in PPI-core/PAMAM-shell dendrimers at acidic and basic pH. Reprinted with permission from ref 567 (Imae's group). Copyright 2009 American Chemical Society.

contains hydrophilic, hydrophobic, and central polar groups. The solubility of the dye Orange OT increased linearly with the concentration of such a dendrimer that could be useful as well in the solubilization of both polar and hydrophobic substrates.⁵⁵⁴ Dendrimers can be used as surfactants.⁵⁶⁵ In a seminal example, PPI dendrimers functionalized with a fluorine-group-containing CO_2 -philic shell extracted the hydrophilic methyl orange, a CO_2 -insoluble dye, from an aqueous CO_2 solution.⁵⁶⁶ Dendrimers consisting of PPI core and PAMAM dendrons encapsulated pyrene all the more as the pH and generation number were higher, with solubilized pyrene being located in the hydrophobic PPI cavities of the core (Figure 33).⁵⁶⁷

4.8. Interdendritic Supramolecular Associations

4.8.1. Liquid Crystals

In the preceding sections, we discussed interdendritic supramolecular associations involving the dendron focal point by coordination around a central template that can be a metal ion or an organic or inorganic core by H-bonding and/or electrostatic interactions. Interdendritic supramolecular interactions reach a higher level of organizational sophistication with Percec's work in which the termini are three or four C_{12} – C_{14} alkoxy chains on gallic-acid-based aryl groups, and the dendronic focal point is carefully designed to supramolecularly direct shape-specific assemblies that have liquid crystalline properties ("dendromesogens"). Globular dendrimers self-assemble from conical or other conformers that represent a fragment of a sphere,^{568,569} and chiral assemblies from conical dendrons were reported to form hollow globular assemblies (Figure 34).⁵⁷⁰

Columnar thermotropic supramolecular assemblies formed from conical dendrons.⁵⁷¹ Hydrophobic interactions are responsible for the formation of libraries of such dendrons.⁵⁷² Dendrimers centered on cyclohexatriene cores self-assemble into helical pyramidal columns and cubic and tetragonal lattices.^{573,574} Percec's group^{568–581} and Jain's group^{582,583} have recently reported a number of examples of such dendrimers that self-assemble into supramolecular lattices or ensembles. In particular, the cylindrical phases of supramolecular

dendrimers have attracted attention because of their potential applications as optoelectronic materials,^{584–586} selective membranes,^{569,587} and nanopatterning templates.^{588,589} The degree of control and selectivity in the orientation of fan-shaped supramolecular cyclinders has been dramatically improved by applying magnetic fields to perfluorinated dendrimers.⁵⁹⁰ As pointed out by Tomalia, "fluorine makes the difference", as fluorination of a self-assembling dendrimer enhanced the ability of Percec's dendrimer to self-assemble compared to its nonfluorinated analogue,⁵⁹¹ despite some counterexamples.⁵⁸⁴

The area of dendritic liquid crystals is indeed broad and rich and has recently been the subject of an excellent review by the Donnio–Guillon group.⁵⁹² Classic dendrimers such as PAMAM, PPI,^{593–596} and carbosilane dendrimers^{597–601} have been decorated with side-chain liquid crystalline groups. An example is known with H-bonding with G_1 – G_4 pyridine-terminated PPI dendrimers to which 3-cholesteryloxycarbonyl propanoic acid was added. These liquid crystals form birefringent glasses at room temperature and viscous smectic A phases at higher temperatures.⁶⁰² Amphiphilic polyether dendrons containing a polyethylene oxide chain connected to the focal point form crystalline lamellar, micellar cubic, continuous cubic phases upon increasing the length of the polyethylene oxide chain and the temperature. In this case, the microphase separation between the hydrophobic dendron and the hydrophilic chain is responsible for mesomorphism.^{582,583} Amphiphilic polyester dendrimers terminated with chiral mesogenic calamitic groups form ferroelectric liquid crystals exhibiting smectic C and smectic A phases. The liquid-crystal design was also introduced as a main chain such as in willowlike dendrons and dendrimers based on terphenylene units forming enantiotropic N and smectic phases.⁴⁷⁹ The Donnio–Guillon group reported octopus-shaped dendrimers terminated with aliphatic chains adopting a prolate conformation and exhibiting remarkable smectic A and B phases resulting from parallel disposition of the mesogenic groups on both sides of the core.^{604,605} Subsequently, a wide range of mesogenic structures were elaborated with homolytic and heterolytic dendrimers based on octopus cores.^{601–606} Ferrocenyl- and C_{60} -terminated dendrimers and other fullerene-containing dendrimers were also shown to form smectic A phases (Figure 35),^{286,607–613} but only very few other metallomesogens are known, with nitrogen ligand–metal complexes.^{614,615}

On the other hand, Moore's rigid-cored dendrimers¹³⁰ terminated with oligo(ethylene oxide) chains formed columnar discotic liquid crystals with clearing-point temperatures that were dramatically generation-dependent.⁶¹⁶ Photosensitive ionic nematic liquid crystalline complexes were designed based on dendrimer and hyperbranched polymers and a cyanobenzene carboxylic acid. High and stable values of the in-plane order parameter up to 0.67 have been reached.⁶¹⁷ PAMAM and PPI dendrimers modified by decanoic, 4-octylbenzoic, and 1,3,5-trioctyloxybenzoic acid termini generated dendritic liquid crystals of smectic and columnar phases that were luminescent with blue emission at 370 nm, which

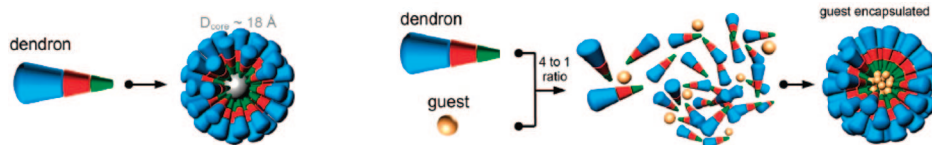


Figure 34. Schematic representation of encapsulation of LiOTf and RbOTf guests in the hollow core of the supramolecular sphere assembled from the dendron. Reprinted with permission from ref 570 (Percec's group). Copyright 2008 American Chemical Society.

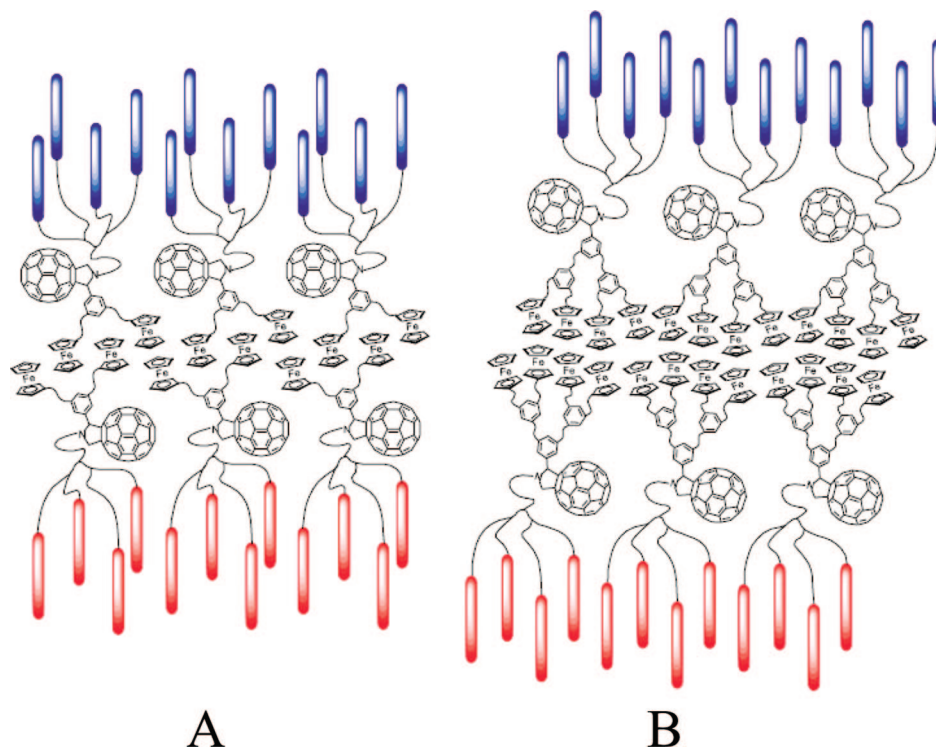


Figure 35. Postulated supramolecular organization of A (left) and B (right) within the smectic A phase. Reprinted with permission from ref 610 (Deschenaux's group). Copyright 2006 Elsevier.

shows that PAMAM- and PPI-based mesogenic structures exhibit intrinsic emission in the visible region without additional chromophores.⁶¹⁸

4.8.2. Other Dendritic Self-Assemblies

The self-assembly mechanism and molecular dynamics for poly-L-lysine-terminated polyphenylene dendrimers were examined using X-ray, solid-state NMR, calorimetry, and dielectric spectroscopy by Florence et al. Poly-L-lysine length dependence, packing restriction, and glass transitions related to the rigid polyphenylene cores were shown.⁶¹⁹ Monolayers at the solid/air, solid/water, or air/water interface represent interacting structures,^{619,620} and these dendrimers self-associate in aqueous media to form micellar aggregates.⁶²¹ The self-assembly pattern takes the form of micelles and turns to vesicles called “dendrisomes” upon increasing the lipophilicity of dendrons.⁶²² Incorporation of cholesterol affected the morphology, size, and thermal transition of these dendrisomes.^{622,623} Dendrimers terminated with hydrophobic groups spontaneously aggregate in aqueous media and form nanoparticles whose size and stability depend on the packing characteristics of the dendrimers (Figure 36).⁶²⁴

Müllen and his group have shown how to self-assemble a second-generation polyphenylene dendrimer into nanofibers. 1*H*,1*H*,2*H*,2*H*-perfluorodecyltrichlorosilane was grafted in the gas phase onto a silicon substrate in order to guide the formation of the dendrimer fibers into well-defined patterns.⁶²⁵ The self-assembly of amphiphilic dendrons with homopolymer polystyrene at the focal point and poly(acrylic acid) periphery produced micelles of uniform size (14–18 nm) with 43 dendrons per micelle.⁶²⁶ Designed dendronized supramolecular nanocapsules are pH-independent with water-soluble, deep-cavity cavitands that assemble via the hydrophobic effect around a range of molecular guests.⁶²⁷ Helical supramolecular dendrimers were generated by Percec's group from self-assembling dendrons and dendrimers and from self-

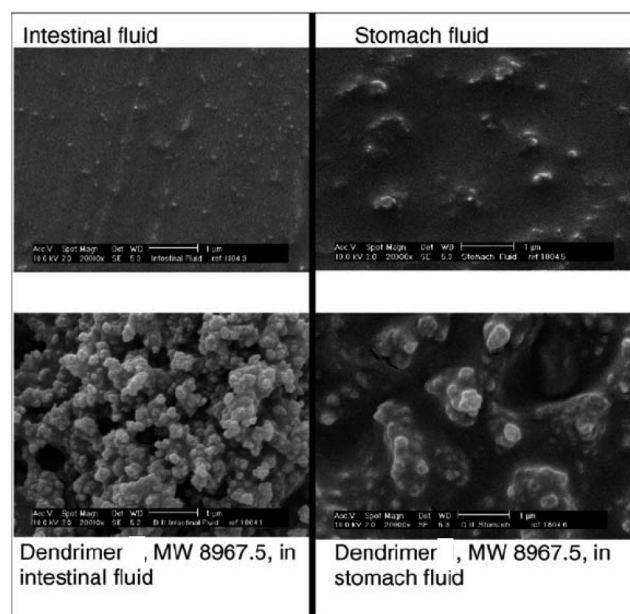


Figure 36. SEM pictures of purified intestinal and stomach fluid with and without dendrimer (1.71 mg/mL) after 3 h of incubation. Reprinted with permission from ref 624 (Florence's group). Copyright 2005 Elsevier.

organizable dendronized polymers, as indicated by the X-ray diffraction pattern of their oriented fibers. Hundreds of samples were screened until a library containing 14 supramolecular dendrimers and dendronized polymers provided a sufficient number of helical structures.⁶²⁸ Amphiphilic dendrimers, which contain both hydrophobic and hydrophilic groups in every repeat unit, exhibit environment-dependent assemblies both in a hydrophilic solvent, water, and in a lipophilic solvent, toluene. In a mixture of immiscible solvents, these dendrimers were kinetically trapped in the solvent in which they are kinetically assembled. This property

has been exploited to extract peptides from aqueous solution into an organic phase, where the peptides bind to the interior functionalities of the dendritic inverse micelles.⁶²⁹ Large π -extended dendrimers self-assemble in the gas phase, in solution, and on a mica surface (from DLS, AFM, and SEM experiments), and encapsulate C_{60} .⁶³⁰ G_5 -PAMAM-OH dendrimers were hydrophobically modified with varying amounts of dodecyl moieties or cholesteryl moieties, which caused aggregation and molecular interactions between dendrimers that are absent in unmodified G_5 -PAMAM-OH dendrimers. The cholesteryl moiety being a rigid lipid found in abundance in biological system did not cause toxicity increase of these dendrimers (cf. section 6.6).⁶³¹

4.9. Supramolecular Assemblies between Dendrimers and Surfactants or Polymers

Such assemblies transform the physical and solubility properties of dendrimers.^{619,620} They were pioneered by Tomalia's studies of the interaction between PAMAM and dodecylammonium bromide, leading to generation-dependent surfactant aggregates.⁶³² Surface activity and hydrophobicity of the surfactants are enhanced upon interaction with PAMAM dendrimers, and the apparent dendrimer diameter considerably increases with such interactions. Largely improved capacity of hydrophobic guest solubilization, such as pyrene, results.⁶³³⁻⁶³⁵ The techniques used to study these assemblies are fluorescence correlation spectroscopy and dynamic light scattering.^{619,620} The nonionic surfactants polysorbate 20 and polysorbate 60 exhibit dendrimer-solubilizing properties, which were taken into account by the flexibility of the hydrophobic tail of the surfactant that penetrates into the hydrophobic dendrimer interior.⁶³⁶ Assembly properties were also reported for phosphorus dendrimers with galactosylceramide analogues.⁶³⁷ Electrostatic interactions were used to create a template-assisted supramolecular assembly consisting of a polymeric dendrimer at the core and amphiphilic substrates on the periphery. The positioning of guest molecules within the supramolecular complex could be modulated with dendrimer generation, surfactant chain length, and dendrimer/surfactant concentration ratio.⁶³⁸ Competitive interactions in ternary systems including a slightly cross-linked polyanionic hydrogel, a protonated PPI dendrimer, and an ionic surfactant indicated that the direction of the substitution reactions in systems containing cationic surfactants depended on the length of the aliphatic radical in the surfactant molecule as well as on the dendrimer generation number.⁶³⁹

Emulsions can also be stabilized by dendrimers. Emulsion polymerization of styrene was carried out using dendrimer DAB-dendr-(NH₂)₆₄ as seed, and the nanosized dendrimer/polystyrene polymer emulsion particles obtained were monodisperse in the range of 26–64 nm in diameter. The size and size distribution of emulsion particles were influenced by the contents of dendrimer, emulsifier, and initiator, as well as the pH value.^{640,641} With dodecylsulfate, latexes are formed,⁶⁴² and comparable results were obtained with PPI dendrimers.⁶⁴³⁻⁶⁴⁵ The geometry and surface chemistry of PPI dendrimer assemblies can be varied through the addition of surfactants, and these dendrimer/surfactant aggregates can be tuned to template the formation of the different phases of calcium carbonate.⁶⁴⁶ "Catanionic" surfactants were prepared with dendrimers using unprotected lactose or lactobionic acid, and these amphiphilic dendrimers bearing

sugar polar heads are of interest for their biological applications as mimics of natural ligands of proteins.⁶⁴⁷

The effect of ionic binding on the self-diffusion of anionic dendrimers and hydrophilic polymers in aqueous systems was studied by pulsed-gradient NMR techniques and was shown to have a most significant effect on dendrimer diffusion.⁶⁴⁸ Covalent dendrimer-polymer assemblies are dealt with in section 2.3, and dendrimer-biomolecule interactions, in particular with DNA, are discussed in section 6.

4.10. Dendrimer Encapsulation and/or Stabilization of Metal Nanoparticles and Quantum Dots

Metal nanoparticles (MNPs) can be stabilized either by encapsulation^{649,650} within dendrimers or by interdendrimer stabilization.⁶⁵¹ Crooks demonstrated that PAMAM dendrimers that have protonated amine termini or are terminated by OH groups can complex metal ions such as Cu²⁺, Pd²⁺, Pt²⁺, Ni²⁺, Fe²⁺, Mn²⁺, Au³⁺, and Ru³⁺ inside the dendrimers. Subsequent reduction by NaBH₄ of various PAMAM dendrimers complexed by Cu²⁺ and Pt²⁺ leads to dendrimer-encapsulated MNPs.^{649,652,653} For several ions for which the complexation was not strong enough, such as Ag⁺, it was possible to form dendrimer-encapsulated MNPs by redox reaction from CuNP-encapsulated PAMAM dendrimers:



The redox displacement method also works to form dendrimer-encapsulated MNPs with Au³⁺, Pt²⁺, and Pd²⁺, because the standard reduction potentials (E°) of these ions are more positive than that of Cu²⁺/Cu. This method can also be extended to the synthesis of heterobimetallic metal NPs if a substoichiometric amount of such oxidizing ion Pd²⁺, Pt²⁺, Au³⁺, or Ag⁺ is used with G_6 -OH (Cu_n) PAMAM dendrimer, yielding dendrimer-encapsulated PdCuNPs, PtCuNPs, AuCuNPs, or AgCuNP, respectively. Dendrimer-encapsulated heterobimetallic NPs can also be prepared by simultaneous cocomplexation followed by a single reduction step. It is also possible to form dendrimer-encapsulated metal NPs such as G_6 -PAMAM-OH-PtPdNPs sequentially, because after the formation of a monometallic MNP, the complexation sites are free for the complexation of another metal. It has been pointed out that one disadvantage of PAMAM dendrimers is their thermal instability above 100 °C due to retro-Michael reactions. PPI dendrimers are stable up to 470 °C, however, allowing PPI dendrimer-encapsulated MNPs to be used for applications at high temperature.^{655,656} Monodisperse MNPs have applications in catalysis, optoelectronics, magnetism, and chemical sensing, and the MNPs synthesized by dendrimer encapsulation are relatively monodisperse as observed by the various TEM and HRTEM histograms reported. Their sizes range from 1 to 4 nm depending on the dendrimer type, dendrimer generation, and dendrimer/metal ion ratio. The terminal dendrimer groups allow one to solubilize them in a variety of solvents, and the dendrimer periphery serves as a nanofilter whose filtration power depends on the dendrimer generation.⁶⁵⁴ Evidence of encapsulation is provided by compared NMR spectra in the presence and absence of PdNP showing more perturbation of the intradendritic methylene group signals.⁶⁵⁷ "Click" metallodendrimers have been designed to coordinate metal ions in their interior at each

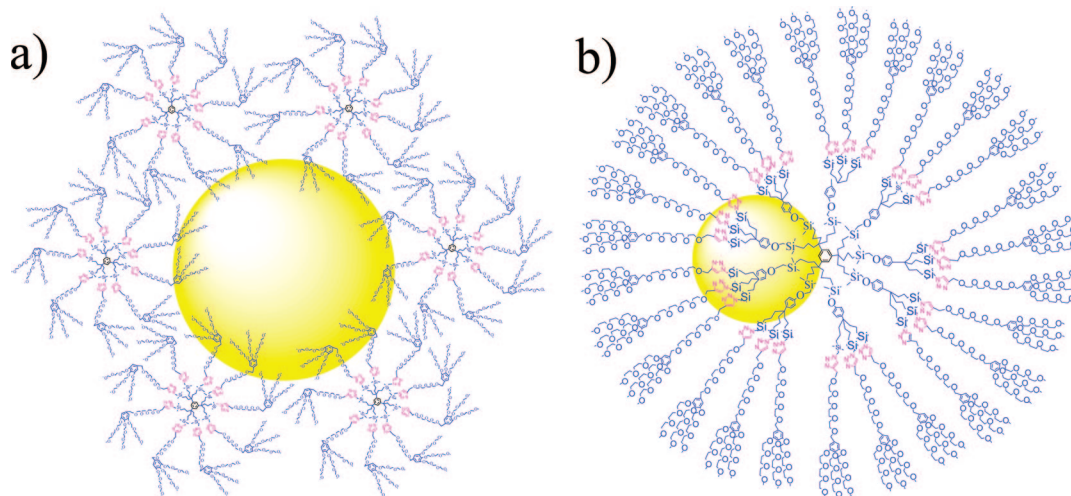


Figure 37. (a) AuNPs stabilized by several G_0 dendrimers; (b) G_1 dendrimer-encapsulated AuNPs. Reprinted with permission from reference 663 (Astruc's group). Copyright 2008 Royal Society of Chemistry.

1,2,3-triazolyl layer.^{530,658,661} Such dendrimers can electrochemically sense both anions such as ATP^{2-} and metal cations such as Cu^+ , Cu^{2+} , Pd^{2+} , and Pt^{2+} , using the ferrocenyl termini that are directly bonded to a terminal triazolyl recognition site. Further reduction for instance of Pd^{II} -click-dendrimer complexes yields dendrimer-encapsulated (G_1 and G_2) or dendrimer-stabilized PdNPs (G_0), with the latter being obtained when the dendrimer is too small.^{657,658} Using PEG-modified click metallodendrimers, dendrimer-encapsulated- and dendrimer-stabilized AuNPs could also be obtained upon reduction of their 1,2,3-triazolyl-Au^{III} intradendritic complexes, yielding various AuNP sizes depending on the Au^{III} loading (Figure 37).⁶⁶³

Various syntheses and studies of other dendrimer-encapsulated AuNPs and AgNPs have recently expanded the interest in this area.⁶⁶⁴⁻⁶⁷⁴ Ag-CuNPs having various shapes were prepared by cocomplexation in the presence of PAMAM dendrimers. Small and evenly sized spherical Ag-CuNPs were obtained with $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ as reductant, whereas long, rod-shaped bimetallic NPs were prepared using NaBH_4 as the reductant.⁶⁷⁴ The synthesis of heterobimetallic NPs (such as AuPdNPs) encapsulated in dendrimers has been achieved for catalytic applications (cf. section 5.5.2). The Yamamoto group designed rigid azomethine (imine) dendrimers incorporating Sn^{II} and Ti^{IV} ions that could be reduced to dendrimer-encapsulated SnNPs and oxidized to dendrimer-encapsulated TiO_2 NPs, respectively.⁶⁷⁵ These dendrimer-encapsulated nanomaterials served as catalysts, high-intensity light-emitting devices, efficient organic solar cells, and metal delivery systems.⁶⁷⁵ AuPs covered with thiolate ligands terminated by carboxylic acid groups were supramolecularly bound to PAMAM dendrimers of generation 1-4 via their terminal amino groups, leading to mixed thiolate-AuNP-PAMAM dendrimer assemblies that precipitated all the more slowly as the generation was higher. SAXS was used to quantify the interparticle spacing that ranged from 0.6 nm for G_0 to 1.9 nm for G_4 (edge-to-edge), indicating dendrimer constriction upon assembly (compare G_4 , 4.5 nm). The interparticle spacing increase observed upon increasing dendrimer generation shifted the AuNP plasmon absorption in these assemblies from 592 nm for G_0 to 538 nm for G_4 .⁶⁷⁶ Quasi-alloy PdAu G_6 -PAMAM DENs rearrange upon oxidation in air to yield core-shell configurations.^{677,678} Polymer-cored DAB-dendrimer-shelled NPs in 15-20-nm size range could trap more than 900 Cu^{2+} ions per NP-DAB16, and external amine

groups could be covalently linked to up to 1000-1500 azobenzene chromophores per NP through aza-Michael addition in aqueous suspension.⁶⁷⁹ CoNPs were stabilized by G_5 -PAMAM-NH₂ dendrimers (approximately 38 Co atoms per dendrimer), and investigation of the magnetic properties indicated superparamagnetism with a blocking temperature of 50 K.⁶⁸⁰

Similarly, various dendrimers have been used for the stabilization of other NPs, in particular CdS and CdSe, the best characterized semiconductors that are of great interest for the fabrication of nanoelectronic devices.⁶⁸¹⁻⁶⁸⁵ Finally, dendrimers, such as PPI dendrimers modified with long alkyl chains, can serve as templates to direct the formation of biomaterials such as calcium carbonate, the main constituent of mollusk shells. It was found that Ca^{2+} -induced assemblies of dendrimer/surfactant aggregate into giant spherical particles.⁶⁸⁵ On the other hand, PAMAM dendrimers ($G_{5.5}$) with surface carboxylate groups inhibited the crystal formation of hydroxyapatite nanorods and affected the crystal morphology and particle size during the preparation.^{686,687} AgNP dispersions were obtained via a dendrimer-polymer template approach, which allowed their use as antibacterial surface treatment.⁶⁸⁸

4.11. Interactions of Dendrimers on Surfaces: Self-Assembled Monolayers (SAMs) and Surface Patterning

Self-assembled monolayers (SAMs) are an essential part of nanoscience.^{689,690} Reinhoudt's group has shown that ferrocenyl-terminated dendrimers⁶⁹¹⁻⁶⁹³ and biferrocenyl-terminated dendrimers^{694,695} bind cyclodextrin⁵⁰¹⁻⁵⁰⁴ attached to gold or silicon oxide surfaces ("molecular printboard") and are removed upon oxidation to ferricinium.⁶⁸⁹⁻⁶⁹⁴ For high-generation dendrimers, only a determined fraction of the ferrocenyl groups are bound.⁶⁹³ A coarse-grained molecular-dynamics model was developed to study the multivalent or multisite binding of small functionalized dendrimers to β -cyclodextrin SAMs, the molecular printboard.⁶⁹⁵ Dendrimers that encapsulate MNPs can be immobilized on surfaces,⁶⁹⁶ and polycationic PPI or PAMAM dendrimers encapsulating MNPs can also be immobilized on surfaces using the well-known layer-by-layer technique⁶⁹⁷ by alternating their deposition with that of polystyrenesulfonate anion.⁶⁹⁸ Alternatively, the negatively charged layers can consist of

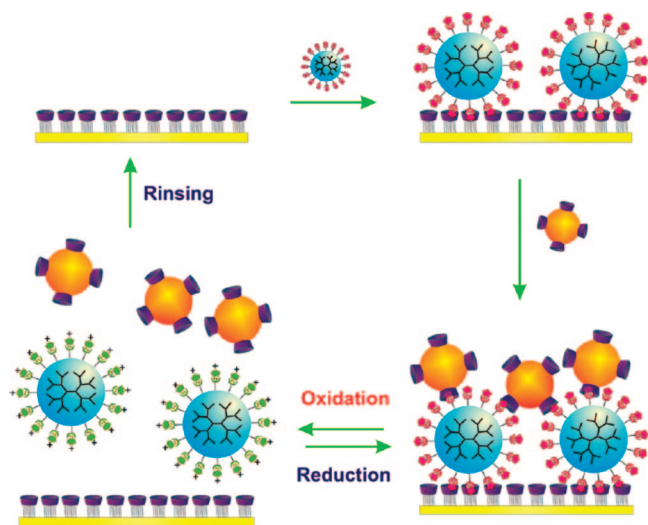


Figure 38. Illustration of the adsorption and desorption of β -CD-functionalized NPs onto and from β -CD SAMs with Fc dendrimers as a reversible supramolecular glue. Reprinted with permission from ref 714 (Husken's group). Copyright 2008 American Chemical Society.

hydroxy-PAMAM dendrimers encapsulating AgNPs.^{699,700} Microshells can also be coated in this way by dendrimer-encapsulated AuNPs.⁷⁰¹ Layer-by-layer assembled thin films composed of PAMAM-CO₂H dendrimers could be used as a pH-sensitive nanodevice.⁷⁰² AuNP-centered dendrimer terminated by silylferrocenyl termini strongly adsorb on Pt electrodes, which allows ATP²⁻ anion sensing using the modified electrodes, and washing the ATP²⁻ substrate allows reuse of these AuNP-dendrimer-modified electrodes.^{487-490,529}

Soft-lithography patterning has been applied to dendrimers using the inkjet printing technique,⁷⁰³⁻⁷⁰⁶ and PAMAM-dendrimer-adsorbed Pd²⁺ ions can be microcontact printed (μ CP) and then guide Co or Pd metal plating by electroless deposition.^{707,708} Adamantyl- and ferrocenyl-terminated dendrimers have also been used for such microcontact printing.⁷⁰⁹⁻⁷¹¹ Application of surface-adsorbed dendrimer-metal ion has been used to form Fe₂O₃ NPs and catalyzed the growth of carbon nanotubes using the plasma-enhanced chemical-vapor-deposition technique.⁷¹² PPI dendrimers with ferrocenyl termini were used with cyclodextrin-coated surfaces to contact two gold electrodes with supramolecular junction by metal transfer printing.⁷¹³ A combined surface plasmon resonance spectroscopy and electrochemical set up was used to monitor the in situ adsorption and desorption of ferrocenyl dendrimers and β -CD-functionalized AuNPs (approximately 2.8 nm) onto and from the molecular printboard. With larger silica NPs (approximately 60 nm), ultrasonication was used to reduce the desorption time (Figure 38).⁷¹⁴

In conclusion, nanofabrication using surface supramolecular coating of ferrocenyl-, biferrocenyl and adamantyl-terminated dendrimers as well as dendrimer-encapsulated metal nanoparticles is a productive and promising area, as shown in particular by the Reinhoudt group.⁷¹⁵ Recent dendrimer-mediated transfer printing of DNA and RNA microarrays also gives a biomedical direction (cf. section 6.9.1, Figure 39).⁷¹⁶

The work function of indium-tin-oxide (ITO) anodes has been modified by adsorption of cationic PAMAM dendrimers. Kelvin probe characterization of these PAMAM-functionalized ITO films and electroadsorption measurements on polymer LEDs incorporating poly(9,9-dioctylfluorene)

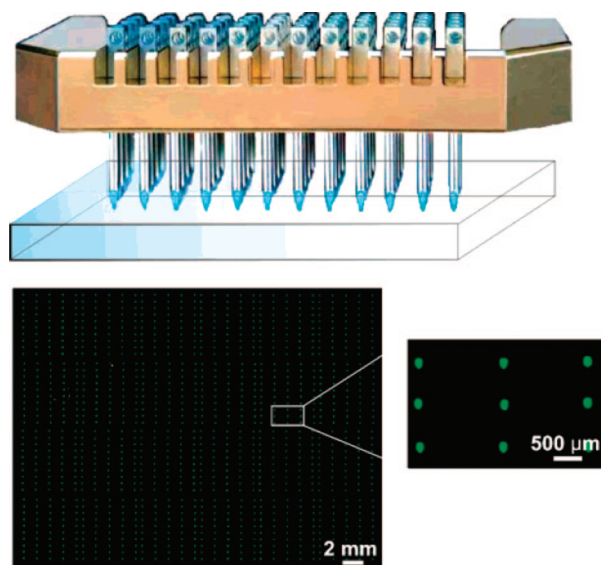


Figure 39. Robotic contact printing of DNA onto a flat dendri-stamp. Fragment of a fluorescence image of an aldehyde-terminated glass slide with an array of 400 spots of oligonucleotide labeled with fluorescein printed using a dendri-stamp. Reprinted with permission from ref 716 (Reinhoudt's group). Copyright 2007 American Chemical Society.

active layers revealed an abrupt lowering (0.55 eV) of the effective work function upon addition of the adsorbed layer and a weak dependence on PAMAM generation.⁷¹⁷ The TiO₂ electrode interface was modified by Yamamoto and his Keio group using various dendrimers including G₃-phenylazomethine dendrimers with a triarylamine core in dye-sensitized solar cells.⁷¹⁸

4.12. Application of Dendrimer Films, Membranes, and Surface Interactions to Gas Sensors

Most dendritic sensors are biosensors, an area reviewed in section 6.9. Sensors are based on photophysics^{230,719-724} or electrochemistry,⁷²⁵⁻⁷³¹ for which the reader is also referred to the photophysical and electrostatic sections, respectively. Here we mention gas sensors using composite dendrimer films and membranes. Thin films of dendrimer-containing AuNPs were fabricated by layer-by-layer assembly, and they were efficiently used as resistors with conductivity measurements (relative resistance change $\Delta R/R$) for sensing vapors of toluene, 1-propanol, and water.⁷³² Membranes based on PAMAM dendrimers were used for CO₂ separation with high CO₂/N₂ selectivity.^{733,734} Arrays of carbon black-dendrimer composites could detect volatile organic amines and carboxylic acids.⁷³⁵ Hyaluronic acid in a chitosan gutter layer was added to PAMAM dendrimer composite membrane to improve its CO₂ separation performance, because it improved the swelling degree of the membrane.⁷³⁶ A siloxane dendrimer-AuNP composite served as CO sensor, with CO concentration proportional to the current.⁷³⁷ G₀-G₈ PAMAM dendrimer films were found to sense volatile organic compounds with different functional groups by sequentially dosing dendrimer-modified surface acoustic wave (SAW) mass balance. It was found that G₄ was the optimal generation, which was tentatively attributed to the fact that it is the smallest spheroid generation with accessible interior. CO₂ adsorbents based on melanine-terminated dendrimers were designed by functionalizing SBA-15.⁷³⁸

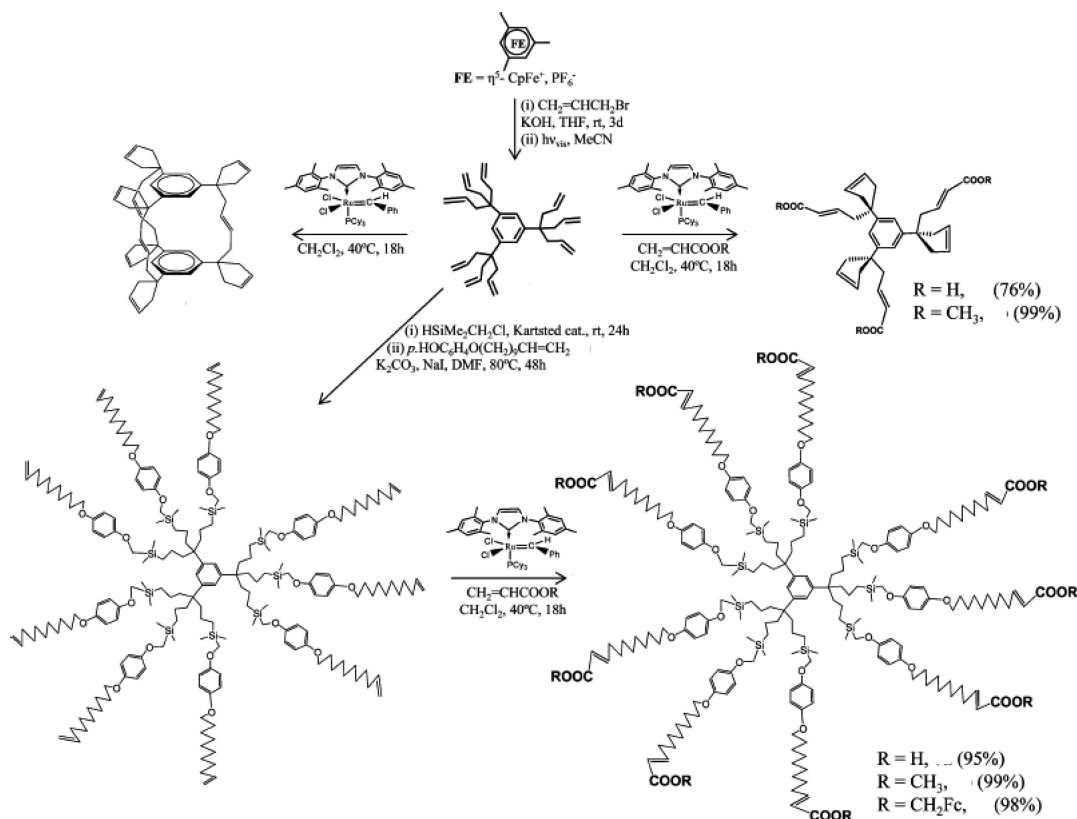


Figure 40. Bifunctionalization of the nonallyl core, lengthening of the dendrimer tethers, and efficient monofunctionalization by cross metathesis for the dendrimer solubilization in water. Reprinted with permission from ref 745 (Astruc's group). Copyright 2008 American Chemical Society.

4.13. Molecular Imprinting Inside Dendrimers

Zimmerman designed an imprinting strategy based on the synthesis of cored dendrimers, attachment of dendrons, then removal of the core for selective binding of the remaining hollow macromolecular host to specific guest substrates.^{739,740} This molecular imprinting methodology involved porphyrin cores whose large sizes were appropriate for large guest substrates. Peptide-type coupling was carried out between *meta*-dihydroxyphenylporphyrin *meso*-substituents and buten-oxo-terminated Fréchet-type dendrons bearing a carboxylic acid group at the focal point. Thus 1-buten-oxo-terminated dendrimers were synthesized, and olefin metathesis using first-generation Grubbs catalyst yielded only intramolecular ring-closing metathesis producing dendritic spheres,^{739,740} despite the tendency of olefin-terminated dendrimers to cross-metathesize (Figure 40).^{745–750}

It appears that this process is entropically controlled and forms the single thermodynamic product following the primary formation of many kinetic products that slowly rearrange by metathesis.^{744–747} Hollow dendritic architectures were then formed upon ester hydrolysis. The cleaved porphyrin groups could be replaced by pyridyl derivatives as guest substrates that were hydrogen-bonded to the carboxylic acid groups of the hollow cavities.^{739–743} The concept was further extended to (trifluoroacetyl)azobenzene as a chromogenic reporter for amines and diamines.^{750,751} Other new applications of this dendrimer coring/hollowing research were the formation of organic nanotubes^{752–754} and organic nanoparticles.⁷⁵⁵ In a related strategy, Peng's group covered CdSe particles with olefin-terminated dendrimers with [dendr-CH(allyl)]₂ branches. Olefin metathesis using Grubbs catalyst produced a dendritic box by cross-metathesis between the olefin termini of the dendrons in spite of the

very favorable ring-closing metathesis producing cyclopentenyl rings in a few minutes under ambient conditions with such branches.^{746,747} The CdSeNP core was removed from dendrimer boxes using concentrated HCl, producing a dendritic hollow sphere whose mass spectrum showed Gaussian mass dispersities between 10 000 and 12 000 Da.^{756–759}

4.14. Electron-Transfer Processes in Dendrimers

With dendrimers, this topic is involved inter alia in the photophysical aspects (section 3), redox sensing,^{50–60} redox catalysis (glucose sensors, section 6.9.3; oxygen electroreduction, section 5.5.3.2; and other redox-catalyzed processes, section 5.3.4), and electron-transfer-chain catalysis (section 5.3.4).⁷⁶⁰ Gorman's group has extensively studied iron-cluster-cored dendrimers as metalloprotein mimics,⁷⁶¹ and the Diederich and Gross groups have reported electron-transfer studies in metalloporphyrin-centered dendrimers as hemoprotein models.⁷⁶² In both cases, the dendron shielding modifies the redox-potential values and considerably slows down electron-transfer processes.

Our group has long been interested in redox-system-terminated stars and dendrimers with ferrocenyl and other transition-metal sandwich units with various redox-potential regions whereby the redox systems are chemically and electrochemically reversible.⁷⁶³ The interest of these latter systems is that only one reversible cyclic voltammetry (CV) wave is observed, which is of interest for redox sensing, modified electrodes, electrocatalysis, electron-transfer-chain catalysis, and molecular batteries. The fact that only one wave is observed does not mean that all the redox systems, which are equivalent, are active at exactly the same standard

potential, although all the potentials are almost the same and look identical. In fact, all these standard redox potentials are statistically distributed around a mean value according to a binomial law as indicated in a seminal article by Bard and Anson.⁷⁶⁴ Dendrimers with 9 and 21 viologen groups were reported by the Balzani and Stoddart groups, in which only the peripheral redox viologen sites are active, not the inner ones.⁷⁶⁵ A very interesting aspect is that this CV wave is electrochemically reversible, indicating that electron transfers are fast between all the redox systems and the electrode, even for metallodendrimers containing up to 14 000 ferrocenyl or cobaltocenyl groups at the dendrimer periphery.^{766,767}

Two mechanisms have been proposed to take this phenomenon into account: (i) electron hopping among the flexible redox termini^{768,769} and (ii) fast rotation of the dendrimer,⁷⁷⁰ although the latter cannot proceed if the dendrimer is attached to a modified electrode. Interdendrimer electron-transfer processes are also fast, and their kinetics has been determined.^{771,772} Finally, the molecular-battery concept has been raised for these systems that include an enormous amount of charging capacity in a minuscule volume (for instance, 14 000 electrons for a G_7 -dendrimer that has a volume of $13.4 \times 10^4 \text{ nm}^3$).^{766,767,773}

5. Dendritic Catalysts: Dendritic Effects, Efficiency, and Recycling

5.1. Introduction: Basic Concepts and Seminal Studies

The most important problems in catalysis are the cost related to the catalyst efficiency (turnover number of the catalyst, TON, and turnover frequency, TOF) and the recovery of the catalyst from the reaction mixtures for both economical (catalyst recycling) and ecological reasons (prevent contamination of the reaction product by the catalyst). Selectivity is another important aspect related to efficiency: chemoselectivity, regioselectivity, stereoselectivity, enantioselectivity, and diastereoselectivity, and these selectivity factors are always optimum with homogeneous catalysts. Most often, however, these catalysts cannot be removed from reaction media, because separation is too difficult due to their small sizes. Supported, biphasic, and heterogeneous catalysts have brought possible solutions for catalyst separation, but these solutions are somewhat limited by lack of selectivity, metal leaching, and poisoning, respectively.^{774,775} Dendrimer catalysis has appeared since the early 1990s as an interesting possibility to explore, because homogeneous catalysts could be bound to the periphery or interior of dendrimers, providing homogeneous catalysts for a tailored, well-controlled definition of the molecular environment of the catalytic site and solubility. Moreover, such metallodendritic catalysts are nano-objects that can be easily separated, as macromolecules, from the reaction products by precipitation or ultrafiltration and industrially by using membranes. The extreme variety of dendritic definition for a catalyst environment in metallodendrimers renders the outcome intellectually challenging, and indeed a large body of data is now available after two decades of dendritic catalysis research.

Initial results were obtained at Shell by van Leeuwen who patented in 1992 catalysis of CO/alkene polymerization upon comparing mononuclear and star-shaped hexaphosphine-palladium catalysts. The star-shaped catalyst gave 3%

fouling whereas the monopalladium catalyst gave 50% fouling, which was already a dendritic effect.⁷⁷⁶ In 1993–1994, five research groups reported catalysis by metallodendrimers, those of Brunner (dendrisymes for Cu^{I} -catalyzed enantioselective styrene cyclopropanation and Rh^{I} -catalyzed acetamidocinnamic acid hydrogenation, with the latter reaction providing a positive dendritic effect),^{777–780} Du Bois (palladodendrimer for electrocatalytic reduction of CO_2 to CO),⁷⁸¹ Ford (catalysis by ammonium-terminated dendrimers of decarboxylation and phosphonate hydrolysis),⁷⁸² and van Koten together with van Leeuwen (Ni^{II} -catalyzed anti-Markovnikov Kharash addition of CCl_4 to methacrylate).⁷⁸³

An important conceptual advance in dendrimer catalysis was the metallodendrimer recycling that was pioneered by Reetz in 1997 with PPI dendrimers terminated by $\text{N}(\text{CH}_2\text{PR}_2)_2$ groups whose Pd complexes catalyzed the Heck reaction between bromobenzene and styrene. More than 98% of the catalyst with 16 peripheral Pd groups was recovered by precipitation, and the recovered catalyst (with an uncertain structure) displayed comparable activity and selectivity. This catalyst had a TON three times higher than that of the monometallic catalyst, showing a positive dendritic effect.⁷⁸⁴ We now know, however, that PdNPs form in the Heck reactions of bromobenzene, because they require high temperatures, leading to catalytically active PdNPs.^{785–787} Thus, we believe that the higher reactivity of the metallodendrimer in this case was due to the fact that such PdNPs formed were stabilized by the dendrimer (vide infra), which could not occur when the monometallic catalyst was used in the absence of dendrimer (Pd black formation).

Another very important technological improvement was that involving nanofiltration with membranes. Membrane nanofiltration was pioneered by the groups of Kragl and Reetz, when they described in 1999 the retention of Meijer's diaminopropyl-type dendrimers modified with palladium phosphine termini by such ultra- or nanofiltration membranes. These groups used the dendritic catalysts for the allylic substitution in a continuously operating chemical membrane reactor. Retention rates were higher than 99.9%, resulting in a 6-fold increase of the total turnover number for the dendritic Pd catalyst of generation 3 bearing 16 diphosphine-Pd groups at the periphery.⁷⁸⁸

The heterogenization of metallodendritic catalysts, for which the seminal work by Alper's group appeared in 1999 and was steadily continued later, is a concept involving dendritic catalysis with both advantages of molecular design on support and easy removal of the catalyst by simple filtration. Thus, initially Alper et al reported hydroformylation with Rh^{I} catalysts supported on PAMAM-dendronized silica gel support, i.e., the dendron was constructed on the silica support in a divergent way and terminated by catalyst binding.⁷⁸⁹

A breakthrough in dendrimer catalysis was the use of dendrimer-encapsulated PdNPs in catalysis by Crooks' group with PAMAM dendrimers that was reported in 1999 and successfully continued further on. This approach was previously carried out with other polymers, ligands, or surfactants in order to control the size and prevent agglomeration. Dendrimers have a better-defined shape than ordinary polymers or surfactants, however, and were chosen because they were hoped by Crooks to function as "nanoreactors" and nanoporous stabilizers. The catalytic reactions were carried out in organic solvents, water, supercritical CO_2 (sc CO_2), or fluorous/organic biphasic solvents, exploiting the

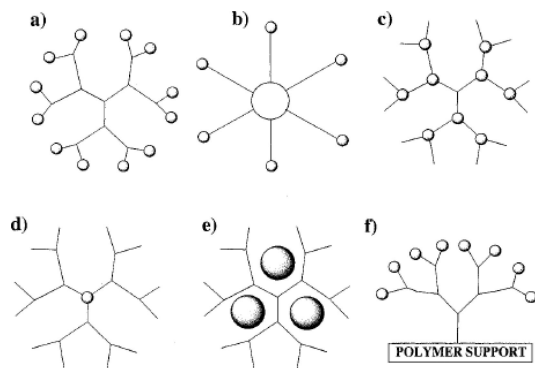


Figure 41. Various metallo-dendritic assemblies efficient for metallo-dendritic catalysis: (a) Reetz, Heck reaction 1st recycle in 1997; (b) redox catalysts kinetics shows no steric congestion; (c) Kakkar's phosphine–Rh at focal points; (d) Van Leeuwen, ferrocenyldiphosphine–Pd-centered; (e) Crooks, PAMAM inserted Pd nanoparticles; (f) Alper's Pd-phosphine dendrons anchored on polystyrene. Reprinted with permission from ref 799 (Astruc's group). Copyright 2001 American Chemical Society.

large flexibility of dendrimer solubilization provided by the nature of the branch termini.⁷⁹⁰

A rather general trend in catalyst-terminated dendrimers that are the majority of reported metallo-dendritic catalysts is the bulk provided at the periphery upon increasing the dendrimer generation, restricting access of the substrate to the catalytic metal center. Thus, the Astruc group reported in 1997 that star metallo-dendrimers do not suffer from such steric constraints. Metallostars with electron-reservoir iron-sandwich termini were shown to be redox catalysts for nitrate and nitrite reduction to ammonia in water without kinetic loss compared to monometallic catalysts, whereas similar bulky monometallic iron-sandwich catalysts are kinetically limited by the bulk.^{791–797}

Localization of the catalyst at the dendrimer core is a powerful concept, because it recalls enzymatic catalysis. The catalytically active metal center can in this way be fully protected by the surrounding dendrimer. Kinetic restrictions are an obvious drawback in this situation, but the stability and protection of the metal center can be decisive and dominant factors, as shown in various examples of dendrimer catalysis reports. The first examples were those reported in 1996 by Suslick's group with manganese–porphyrin-centered dendritic catalysts providing enhanced selectivity⁷⁹⁴ followed in 1999 by van Leeuwen group's report of 1,1'-diphenylphosphinoferrocene-centered dendrimers providing enhanced stability of Pd catalysts.⁷⁹⁵ Dendrimer-encapsulated catalysis was also encountered with Crooks' PAMAM dendrimer-encapsulated PdNPs⁵⁴⁵ and in organic catalysis, as shown first by Fréchet's group in 2003 with 4-(dialkylamino)pyridine-containing dendronized polymers that catalyzed acylation reactions using sterically demanding tertiary alcohol substrates. In these catalysts, the nanoenvironment played the dominant role in determining the catalytic activity.⁷⁹⁶

Altogether, various locations have been reported for catalytically active centers in dendritic architectures: dendritic and supported dendronic branch termini, core, branch intersection, and between the branches (NPs).

The first general reviews on dendritic catalysis were published in 2001 by the groups of van Leeuwen⁷⁹⁸ and Astruc (Figure 41).⁷⁹⁹ Since then, a large number of specialized reviews have appeared on the various aspects of this field that has become very large.^{800–819} The most

important problems that are presently addressed are those of the dendrimer recovery/recycling^{801,819} and the dendritic effects. We will thus focus our attention in this review essentially on these efficiency aspects and the results that were reported during the second half of this decade.

5.2. Methods of Separation/Recycling

5.2.1. Classic Laboratory Method: Precipitation

This method is the most widely used one, as it already was in Reetz' seminal examples.⁷⁸⁴ It takes advantage of the macromolecular nature of metallo-dendrimers. As biomolecules and polymers, the nanoscopic size allows separation. Because the desired solubility of a dendrimer can be easily adjusted by the choice of the terminal groups, systems can be designed for separation between the metallo-dendrimer and products after the catalytic reaction. For instance, Fréchet-type dendrons with an Ir–BINAP species at the focal point up to G_4 catalyzed the hydrogenation of quinolines under H_2 atm in THF with TON of 43 000 at 0.0002 mol % catalyst, whereas a nondendronic diphosphine complex was much less active, and with higher enantiomeric excess (ee) (90% vs 74%). Interestingly, the activity increased from 43% conversion for G_0 to >95% for G_4 , also with higher TOF for the latter ($3\,450\ h^{-1}$). The G_3 catalyst was reprecipitated from hexane and reused six times with similar ee's, but with relatively lower activities.⁸²⁰

In another study, chiral dendronized diamine–Ru^{II} and –Rh^{III} complexes catalyzed asymmetric transfer hydrogenation of ketones and activated olefins using HCO_2H or HCO_2Na as the hydrogen source with about the same efficiency as the nondendronized catalyst. The catalytic activity dropped, however, for high-generation metallo-dendritic catalysts, which was attributed to site wrapping by dendron tethers. Recovery of the G_2 catalyst was carried out by reprecipitation using methanol, and 10% catalyst was lost due to leaching after each run, but the ee remained high (97%).⁸²¹ Aqueous conditions were used with high efficiency (99% conversion and 96% ee) for the G_1 – G_3 Rh–diamine–dendron-catalyzed reduction of acetophenone. In water, down to 0.01 mol % catalyst loading yielded 61% conversion and 95% ee for G_2 . Upon precipitation with hexane, the recovered dendronic Rh catalyst worked similarly for six runs.⁸²²

After a seminal example by Newkome and Hill of tetrabranch POM-catalyzed tetrahydrothiophene oxidation,⁸²³ it was shown in our group that cationic dendrimer- or dendron-protected polyoxometallate (POM) catalysts, which were active for olefin epoxidation as well as sulfide oxidation to sulfones and secondary alcohols to ketones in biphasic $CDCl_3$ /aqueous mixtures using H_2O_2 as the oxidant, were recyclable by precipitation upon addition of ether, as shown by ³¹P NMR.

This contrasted with nondendritic tetraalkyl ammonium salts that were not recyclable due to decomposition. The dendron-protected POM catalysts were slightly more air-stable than the dendrimer-protected catalysts, although both could be used several times without loss of activity, but the activity of the dendron-protected catalyst decreased upon increasing the dendron generation and bulk.^{824–828}

The $Pd(OAc)_2$ complexes of PPI dendrimers terminated with 4, 8, and 16 $N(CH_2PR_2)_2$ chelating ligands were shown in our group to be efficient for the Suzuki coupling of inactivated chloroarenes (best medium: $NaOH/THF/H_2O$, $R = Cy$, $65\ ^\circ C$)⁸²⁹ and the copper-free Sonogashira coupling

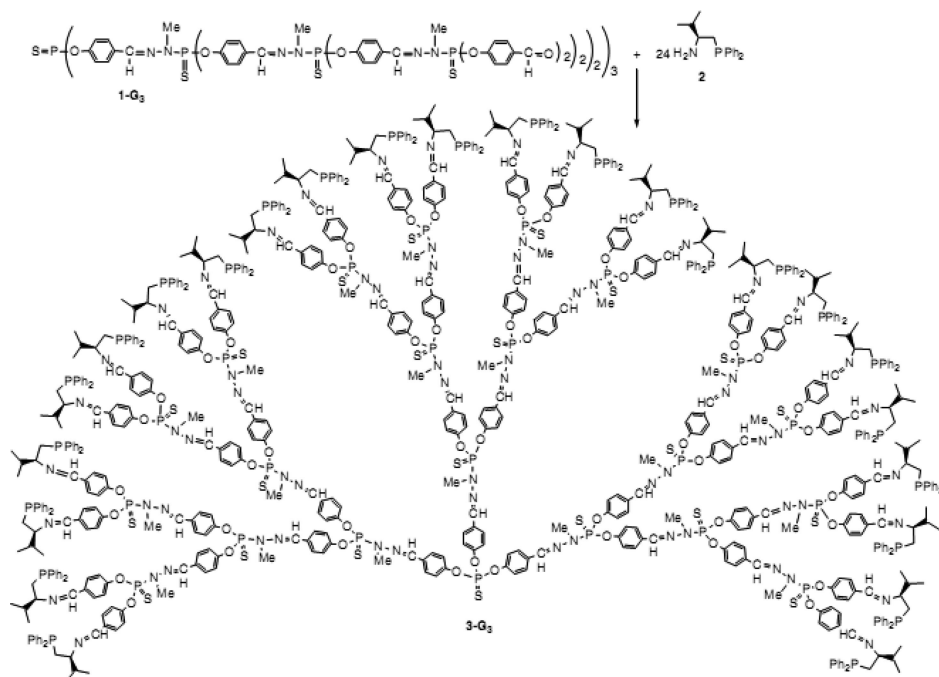


Figure 42. Synthesis of a chiral dendrimer. Reprinted with permission from ref 835 (Majoral's group). Copyright 2005 Elsevier.

of halogenoarenes including activated chloroarenes (NEt₃, 80 °C for bromo- and chloroarenes, −20° to 20 °C for iodoarenes, R = *tert*-Bu).^{830–833}

The cyclohexylphosphine dendrimers were more active than the *tert*-butylphosphine dendrimers for the Suzuki reactions, but the opposite was found for the Sonogashira reactions, showing the change of the stereoelectronic balance for the Pd complexes from one reaction to the other. The dendritic effect was negative for both reactions, i.e., the G₃ catalysts were less active than G₁ and G₂ (the kinetics decreased upon increasing generation number). The dendritic catalysts were precipitated with pentane for recovery with R = Cy (but not with R = *tert*-Bu, because they were too soluble). The best efficiency after recovery was for G₂, for which practically no loss of efficiency was observed contrary to G₁ and G₃. By comparison, the monopalladium complex gave palladium black under the reaction conditions, which prevented recycling. With star complexes containing six Pd-Buchwald-type phosphine termini, chloroarene with one or two *ortho* methyl substituents could couple to arylboronic acids containing one or two *ortho* methyl groups in yields higher than 90% under Suzuki conditions, an efficiency equal to that of the monomer, and the catalyst could be recycled five times with progressively decreasing yields.⁸³⁴

Asymmetric allylic alkylation of racemic *trans*-1,3-diphenyl-2-propenyl acetate with pivalate was catalyzed by iminophosphorane-terminated Majoral-type dendrimers combined with [Pd(allyl)Cl]₂ with similar activity to that of the nondendritic complex, but the enantioselectivity was improved with the dendrimer (90% ee) compared to the nondendritic complex (80% ee, Figure 42).⁸³⁵

The dendritic catalyst was recovered by precipitation using ether and reused with practically the same efficiency. Azabis(oxazoline)-terminated phosphorus dendrimers bound to Cu^{II} catalyzed asymmetric benzylation of diols in good yields and excellent enantioselectivities (up to 99%). The catalyst was recovered by precipitation from CH₂Cl₂ with hexane and reused three more times with quite the same efficiency.⁸³⁶

Fréchet-type dendrons-functionalized 2,2'-bipyridine-Cu(OTf)₂ complexes catalyzed the Mannich condensation of aldehydes, *o*-anisidine, and a silyl enolate or triethyl phosphite nucleophile in CH₂CH₂, a solvent in which the catalyst was recyclable, and in water. The catalyst was poorly soluble in water but gave a 3-fold better yield than in CH₂Cl₂. The yield increased with increasing catalytic generation, which was taken into account by a favorable hydrophobic environment provided by the dendrons for the catalyst.⁸³⁷

5.2.2. Solid Supports

After his seminal work on silica gel-supported metallo-dendronic catalysis of olefin hydroformylation with Rh^I,⁷⁸⁹ Alper's group developed this field with polystyrene supports and hydrogenation, hydroesterification, carbonylation, oxidation, and carbon–carbon coupling reactions.^{838–844} Further work in the area was carried out by the Portnoy group, in particular for carbon–carbon coupling reactions with studies of the influence of the generation^{847–850} on effects and influence of the backbone structure.^{812,845,846} The influence of silica pore size and coordinative ability of the dendrimer backbone were investigated.⁸⁴⁵ Organocatalysis of the aldol reaction with proline dendronic endings has also been carried out on polystyrene-supported dendron, and the first- and second-generation catalysts showed yields and selectivities that were comparable or better than in solution.⁸⁵¹ Magnetic separation of NPs is a well-developed field in supported catalysis that has been extended to supported dendrons. Silica-supported magnetic NPs were indeed dendronized with PAMAM and bound to Rh^I for catalysis of styrene hydrogenation with good recycling properties.⁸⁵²

Subsequent to the design of dendrimer-encapsulated NP catalysts by Crooks,^{652–654} supported metal–NP-containing dendrimers were shown to be active and recyclable catalysts, and this field has been reviewed by Chandler et al., who brought an important contribution (vide infra).^{853–856}

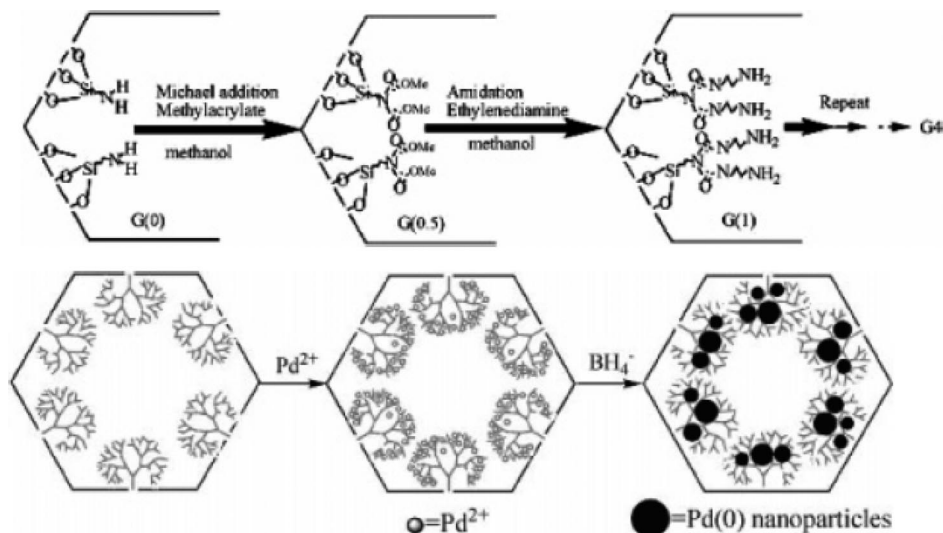


Figure 43. Preparation of SBA-15 supported dendrimers; formation of nanoparticles. Reprinted with permission from ref 958 (Detty's group). Copyright 1999 American Chemical Society.

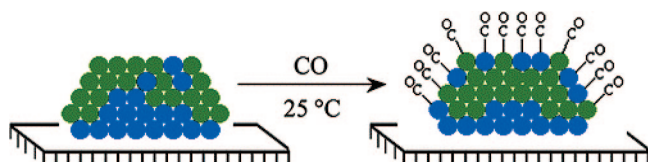


Figure 44. Bimetallic dendrimer-stabilized nanoparticles (DSNs) used to prepare supported Pt–Au catalysts within the bulk miscibility gap for a binary system. Reprinted with permission from ref 861 (Chandler's group). Copyright 2004 American Chemical Society.

Two approaches were used. In the first one, metal NPs were generated in SBA-15-supported dendrons (Figure 43),^{857,858} whereas in the other one, the dendrimer containing the NPs was deposited onto a solid support followed by thermal removal of the dendrimer (Figure 44).^{853–856,859–863}

Finally, in another approach, cross-linking of scandium-based dendrimers yielded insoluble catalysts that were active in various reactions.⁸⁶⁴

5.2.3. Biphasic Catalysis

Dendrimers are easily amenable to biphasic catalysis, because the solubility can be designed by an appropriate choice of terminal endings (tails). In particular, this property has been astutely used with dendrimer-encapsulated NPs that have been solubilized in water,^{652–654,865,866} and in fluorosolvents^{867,868} for fluorosolvent/organic biphasic catalysis.^{652–654}

Thermotropic mixtures of two solvents, such as dimethylformamide and heptane, are homogeneous at relatively high temperatures, whereas they form two phases at lower temperatures, which allows both homogeneous reaction conditions and the possibilities of separation upon cooling. This principle has been applied to dendritic catalysis by Kaneda's group. The dendritic catalyst in the DMF phase can be recycled, because the organic products remain in heptane. The terminal amino group of PPI dendrimers was functionalized with decanoyl chloride, providing the possibility for the Pd catalyst to bind the nitrogen atoms inside the dendrimer. Such systems are active for the Heck and allylic amination reactions.⁸⁶⁹ A positive dendritic effect was observed for the Heck coupling between iodobenzene and *n*-butyl acrylate in which the polyammonium dendrimer cores obtained by protonation of DAB dendrimers terminated by

long alkyl chains bind the Pd catalyst via a triarylphosphine bearing a *para*-carboxylated phenyl substituent. Indeed, the reaction rate increased with increasing dendrimer generation, whereas the nondendritic catalyst was unreactive. In the same reaction with 1,4-diiodobenzene, the dendritic catalyst selectively yielded monosubstitution, whereas the analogous nondendritic catalyst showed little selectivity (mono/di = 45:55). On the other hand, the dendritic effect was negative for the allylic amination with these dendritic catalysts, although the dendrimer nanoenvironment improved the linear/branch selectivity.⁸⁶⁹ Further reactions that were carried out using the thermotropic property of this solvent mixture included amination of cinnamylmethyl carbonate with piperidine and then the hydrogenation of dienes by dendrimer-encapsulated PdPtNPs.⁸⁷⁰ A metal-free dendritic pyridine has been used with recovery and reused in a thermotropic DMF/cyclohexane mixture (homogeneous at 60 °C) in the catalysis of the Baylis–Hillman coupling reaction of unsaturated ketones and aromatic aldehydes.⁸⁷¹

With nonthermotropic solvent mixtures such as hexane/ethanol or hexane/butanol/acetonitrile that are miscible, the addition of water after the catalytic reaction provokes phase separation, which allows separation of the catalyst and recycling. For instance, a dendritic OsO₄–glycolate complex with alkyl termini was soluble in nonpolar solvents. It was used for olefin dihydroxylation reactions yielding polar diol products that were retained in the polar phase after addition of water, whereas the hexane-soluble catalyst was successfully recovered (99%) in hexane and reused 10 times.⁸⁷²

5.2.4. Membrane Nanofiltration

Membrane technology, based on size-exclusion filtration, is a fast-growing area, and solvent-resistant commercial membranes allow a cutoff of molecular weights between 200 and 1000 Da (Figure 45).⁸⁷³

Continuous-flow membranes reactors (CFMRs) were already efficiently used by Kragl and Reetz in their seminal study of the dendrimer separation of catalyst terminated with third- and fourth-generation PPI dendrimers. Later studies involved Ni^{II}–catalyst-terminated dendrimers for atom-transfer radical addition reaction.⁸⁷⁴ These dendrimer–Ni^{II} and –Pt^{II} complexes of NCN-pincer ligands have been used extensively with membrane filtration in the early 2000s, and

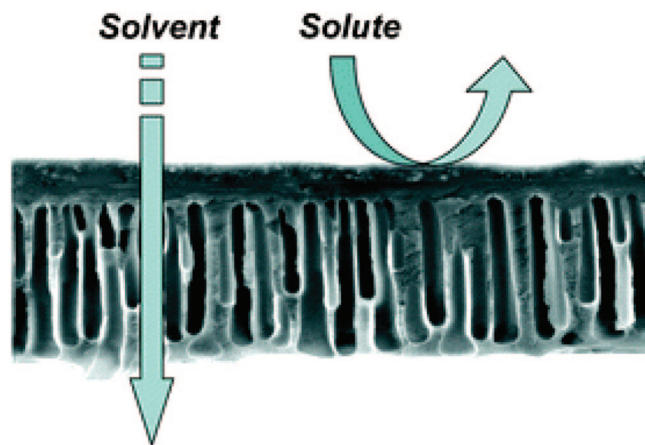


Figure 45. Solvent-resistant nanofiltration: separating on a molecular level. Reprinted with permission from ref 873 (Vankelekom's group). Copyright 2008 Royal Society of Chemistry.

this work has been reviewed.^{46,514,800,803,875} van Leeuwen's Pd complexes 1,1'-bis(diphenylphosphino)ferrocenyl-centered dendrimers were found to be much more stable in a CFMR than when the Pd^{II} groups are located on the dendrimer periphery.⁸⁰⁴ A fifth-generation dendrimer in which the peripheral part containing the Pd^{II} catalyst is strongly bound to the PPI core by combined ionic bonding and multiple hydrogen bonding (cf. section 4.4) showed retention rates of 99.4–99.9% in a CFMR.⁸⁷⁶ Star-shaped dodecanuclear NCN pincer Lewis acid catalysts for double Michael addition of ethyl cyanoacetate to methyl vinyl ketone were found to be retained with very high efficiency (>99.9%) in a CFMR under continuous reactions conditions, with a very small yield decrease occurring with time. The rigidity was also considered to be a favorable factor.⁸⁷⁷ This indicated that high-generation dendrimers are not necessary for efficient recovery and confirmed that star-shaped catalysts may work better than sterically congested catalyst-terminated dendrimers.⁷⁴

5.3. Catalysis with Metallo-dendritic Complexes

5.3.1. Palladium Complexes

The role of palladium complexes in catalysis is of considerable importance, because it deals with the key carbon–carbon bond formation and oxidation reactions.^{878–886} Thus, it is not surprising to observe that, among dendritic organometallic catalysts, palladium complexes have been the first ones studied,⁷⁷⁶ are by far the most numerous, and have been the subject of excellent reviews.^{539–542,819}

5.3.1.1. Pd-Catalyzed Carbon–Carbon Bond Formation: Heck, Suzuki, Sonogashira, and Stille Coupling. The

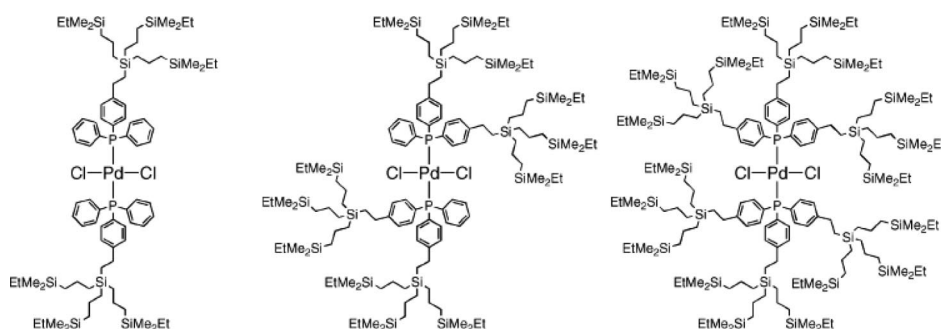


Figure 46. Palladium complexes. Reprinted with permission from ref 892 (de Jesus' group). Copyright 2006 American Chemical Society.

Heck reaction, being one of the essential C–C coupling reactions, has been researched with dendritic catalysts for years.^{784,798–819,869} Heck reactions between iodobenzene and various alkenes using diphosphine that were supported by poly(ether imine) dendrimers selectively yielded the *trans* compounds.⁸⁸⁷ Recycling was observed to proceed with a decrease of activity. With iminophosphorane G_4 dendrimers, Pd black formed extensively,⁸⁸⁸ but with pyridylimine ligands, higher rates, conversions, and stability were found.⁸⁸⁹ Tris- and hexanuclear (star-shaped) *N*-heterocyclic carbene complexes⁸⁸⁶ have been shown to catalyze Heck coupling between iodobenzene or activated bromobenzenes with acrylates, although truly dendritic complexes are not known.^{890,891} Heck reactions between iodobenzene and methyl acrylates, which were not productive with $[\text{PdCl}_2(\text{PPh}_3)_2]$ as the catalyst in scCO_2 , became possible with 40% conversion when $(\text{CH}_2)_3\text{SiMe}_2\text{Et}$ tails were introduced in the *para* position of the phenyl rings of the ligands (Figure 46).⁸⁹² Negative dendritic effects upon increasing dendron generation in catalysis of bidentate phosphine–Pd-dendronized support for the Heck reaction have been reported.⁸⁹³

Suzuki coupling has become recently very important, because boron reagents are now widely available and expected to be mostly nontoxic, whereas analogous Stille coupling uses toxic tin derivatives. In addition, Suzuki coupling can be catalyzed by palladium complexes under relatively mild conditions, for instance, at a temperature much lower than that in the Heck reactions.^{879–886} Suzuki reactions catalyzed by recyclable palladium-catalyst-terminated dendrimers have been discussed in section 5.2.1. Recently, palladium complexes have been heterogenized by cross-linking homogeneous star-shaped catalysts with oxime palladacycles, and good activity and recyclability were observed.^{894–896} Suzuki reactions between aryl bromides and aryl boronic acids were carried out at 80 °C with high frequencies (2586 h^{-1}) and TONs (59 000) using *N*-heterocyclic carbene palladium complexes branched on water-soluble polyglycerol containing 65 peripheral metal centers that were recycled five times without loss of activity.⁸⁹⁵ Triarylphosphanes with dendritically arranged tetraethylene glycol moieties at the dendrimer periphery were efficient ligands for the Pd-catalyzed Suzuki–Miyaura coupling reaction of aryl chlorides.⁸⁹⁶

The Sonogashira reaction is of high interest, because it avoids synthesizing organometallic *trans*-alkynylating complexes by direct use of a mixture of palladium and copper catalysts, or sometimes even with the palladium catalyst alone.⁸⁸⁶ Copper-free Sonogashira coupling using dendritic catalysts, showed, as for Suzuki reactions, that the rates and conversions to reaction products decreased upon increasing

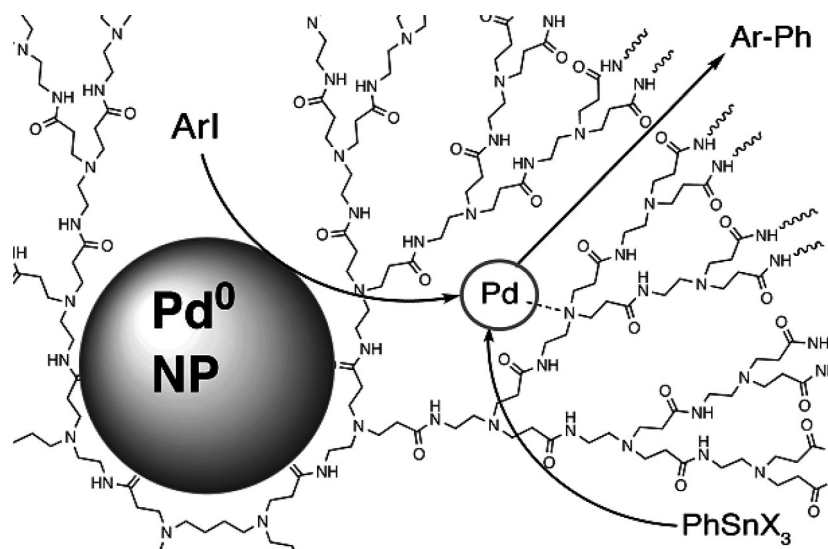


Figure 47. Suggested mechanism for the Stille reaction in water using the Pd DEN precatalyst 2. The reaction is catalyzed by palladium species leached from the nanoparticle and coordinated to the dendritic interior. Reprinted with permission from ref 898 (de Jesus' group). Copyright 2009 American Chemical Society.

the generation number of Pd–diphosphine-terminated PPI dendrimers (i.e., with negative dendritic effect). With the most active low-generation bis(*tert*-butylphosphine) ligands, reactions with iodoarenes could even be carried out under ambient conditions in the absence of copper.^{829,831} With phosphorus dendrimers containing bis(diphenylphosphinoethyl)amino ligand termini, the conversion increased with the generation number,⁸³² contrary to other studies.^{813,829}

No report has appeared on Stille coupling subsequent to publications on cross-coupling of aryl iodides with thienyl or vinyl organostannanes catalyzed by bis(diphenylphosphanyl)methylamine or iminophosphane palladium-terminated dendrimers that could be recycled for three runs with only slightly decreased reactivity.⁸⁹⁷ Pd PAMAM DENs were compared to PdAc₂ as precatalysts for the Stille coupling reaction between SnCl₃Ph and PhI in water, and a similar reactivity was observed, but the DEN suppressed the formation of homocoupling products and allowed catalytic recycling. The leaching mechanism seems to operate, with the PdNP remaining bound to the dendrimer (Figure 47).⁸⁹⁸

5.3.1.2. Hydrogenation, Hydrovinylation, Polymerization, and Copolymerization of Olefins. Carbosilane-cored aminopropyl palladium-terminated dendrimers catalyzed the reduction of C=C and C=O bonds, and these palladodendrimers were shown to be recyclable.⁸⁹⁹ Palladocatalysts prepared in situ from hemilabile P,O-ligand-terminated carbosilane dendrimers catalyzed the styrene–ethylene coupling to 3-phenyl-2-butene (styrene hydrovinylation) in a CFMR with high regioselectivity (no formation of oligomers) and minimization of the subsequent isomerization reaction at low conversion. Deactivation with formation of Pd black was observed after 10 h, however, which limited the catalyst efficiency and practical use. The dendrimer was less stable than the monomer under batch conditions, which could be taken into account by the flexibility of the dendrimer tethers.⁹⁰⁰ Similar results were obtained with diphenyl-⁹⁰¹ or phenyl(aryl)phosphine-terminated carbosilane dendrimers,⁹⁰² with the dendrimers being less active than the monomer, although these catalysts were more active than those with the P,O ligands above. Interestingly, with a P-stereogenic phosphine, the cationic catalyst, as a BF₄[−] salt, produced an excess of the (*S*)-3-phenyl-1-butene enantiomer (ee =

63–68%) at 35% conversion. The activity, chemoselectivity, and enantioselectivity of the cationic catalyst were even improved for G₁ with the BARF counteranion. Even better results (73–82% ee) were obtained with the P-stereogenic phosphine (*S*)-MePPh(2-biphenyl) located at the focal point of carbosilane dendrimers.⁹⁰³

The Pd-initiated polymerization has been recently examined with dendrimers. A MAO-activated tetrabranched alkylpyridylimine–palladium complex catalyzed ethylene polymerization. Remarkably, this tetranuclear initiator was more active than the mono- and binuclear analogues and yielded high-molecular-weight linear polyethylene.⁹⁰⁴ Cationic arylpyridylimine–palladium dendrimer catalyzed the alternating copolymerization of CO and 4-*tert*-butylstyrene with an activity that increased with increasing dendrimer generation, although the half-lives were similar for the monomer and the dendrimers. Generation increase also resulted in lower and broader distributions of molecular weights and in a constant decrease of the stereoregularity of the syndiotactic polyketone polymers. These results were taken into account by steric enhancement of chain-transfer processes that inhibited the polymer chain-end control and lengthening (Figure 48).⁹⁰⁵

5.3.1.3. Allylic Substitution. Following Kragl and Retz who pioneered the CFMR technology with palladodendrimer-catalyzed allylic substitution,⁷⁸⁸ further work was carried out in CFMR with phosphine-terminated carbosilane dendrimers with a reactivity that was rather analogous to that of monomeric Pd catalysts. Allylic amination of crotyl acetate and piperidine yielded mixtures of branched and linear *trans* products, and dendritic tether lengthening by addition of a methylene spacer improved the yields and catalyst stabilities.⁹⁰⁶ The amination of *trans*-cinnamyl acetate with morpholine was catalyzed by PPI dendrimers terminated by diphosphino–palladium groups, and the linear vs branch selectivity (90:10) was unchanged from monomer to dendrimers. In sharp contrast, the reaction of *cis*-3-acetoxy-5-carbomethoxycyclohex-1-ene proceeded with a *cis* product selectivity, whereas this stereoselectivity increased up to 94% with the G₅ catalyst. This strong dendritic effect was attributed to steric shielding of the π-allyl–Pd species from *endo* attack.⁹⁰⁷ The seminal introduction by Togni's group

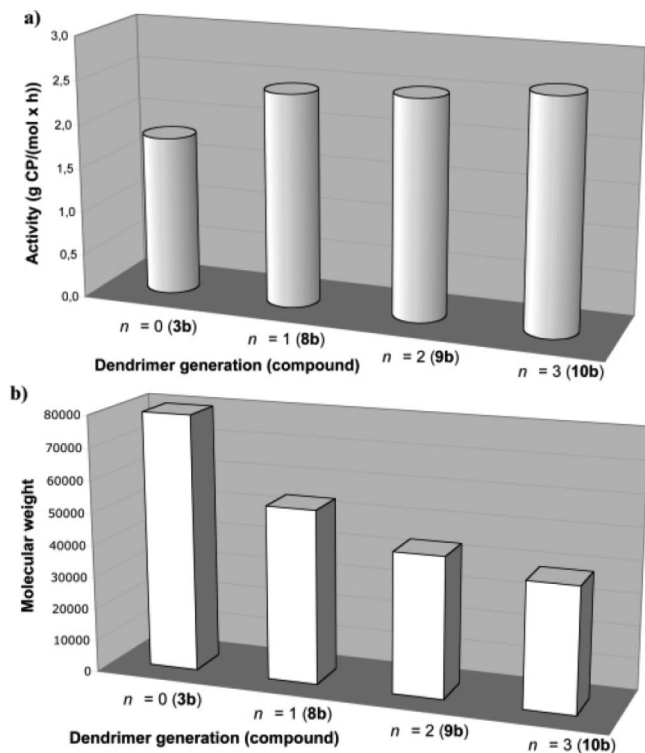


Figure 48. (a) Activities for G_n -ONNMe₂[Pd(MeCN)Me⁺] and (b) copolymer M_w values obtained using neat 4-*tert*-butyl styrene as a solvent. Reprinted with permission from ref 905 (Flores' group). Copyright 2006 American Chemical Society.

of the asymmetric version with the reaction between racemic *trans*-1,3-diphenyl-2-propenyl acetate and dimethyl malonate resulted in 89–91% ee using a dendrimer terminated by chiral ferrocenyl phosphines, which was slightly less than that using the parent mononuclear ligand complex (93% ee).⁹⁰⁸ Recently, Majoral-type phosphorus dendrimers produced a higher ee (90%) than the mononuclear analogue (ee = 80%), and the dendrimer showed good stability and recovery/reuse with an efficiency that was almost completely preserved. Optimized conditions yielded an ee of 95%.⁹⁰⁹ The dendritic effect was spectacular on the enantioselectivity of the allylic amination of *trans*-1,3-diphenyl-2-propenyl

acetate with morpholine reported by Gade's group. The ee was only 9% for the monomer and regularly increased with generation increase up to 40% for G_5 pyrphos-terminated PPI dendrimer and up to 69% for G_5 pyrphos-terminated PAMAM dendrimers. These results were taken into account by a conformational change of the aryl substituents of the phosphine ligands upon steric increase at the dendrimer periphery concomitant with increasing generations.^{805,806,910}

5.3.1.4. Other Pd^{II}-Catalyzed Reactions. The catalysis by a variety of dendritic Pd^{II}-cyanometalated and pincer–NCN complexes of aldol-type condensation between benzaldehyde and ethyl isocynoacetate yielding an oxazoline has been extensively reported and reviewed by van Koten et al.^{46,800,803,809,875,911–914} In short, the reaction rates of monomers and dendrimers were comparable but were diminished when the dendritic tethers bearing the catalyst suffered from bulk at the periphery. Interestingly, a first example of hyperbranched polymer instead of a dendrimer was reported in collaboration with Frey's group, showing the same diastereoselectivity (*trans/cis* = 2) and only slightly decreased activity compared to the monomer.⁹¹⁴

The Michael addition between ethyl cyanoacetate and methyl vinyl ketone was the subject of several reports by van Koten et al. using pincer–Pd complexes (Figure 49) that gave comparable yields for mononuclear catalysts and dendrimers (except when lower solubility resulted in poorer yields).⁹¹⁵

In this context, it was surprising to observe the case of a star-shaped dodecanuclear complex providing a 3-fold increase in activity that was taken into account by a positive cooperation between the peripheral metal centers.⁹¹⁶ This complex was very efficient in a CFMR.⁹¹⁷

5.3.2. Rhodium Complexes

Rhodium(I) catalysts are mostly studied for hydroformylation (linear vs branch regioselectivity), asymmetric hydrogenation, and (more rarely) hydrosilylation reactions,^{918,919} at least in their metallodendritic versions. Following the seminal work by Reetz et al. with Rh^I-diphosphine-terminated PPI dendrimers⁷⁸⁴ including the first CFMR in collaboration with Kragl,⁷⁸⁸ and by Alper et al. with Rh^I

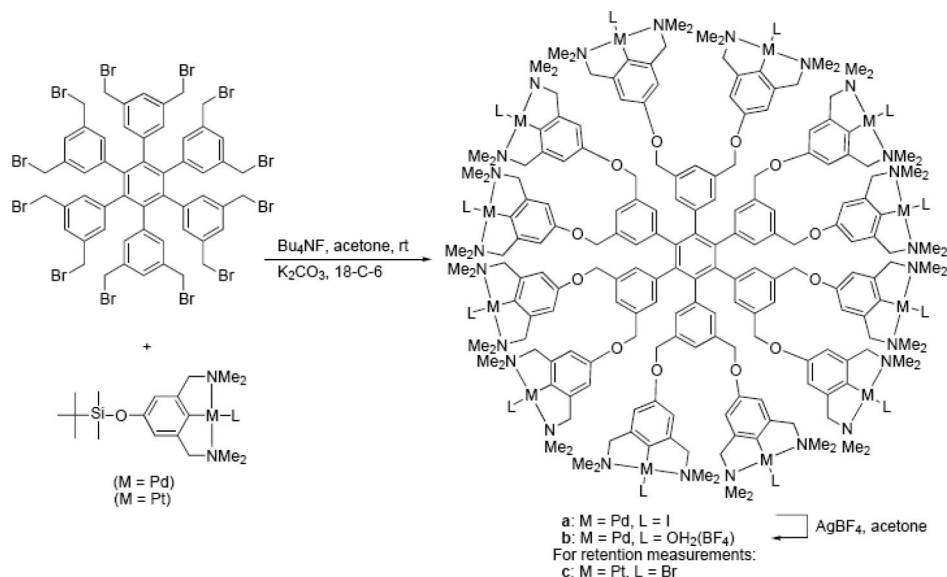


Figure 49. Modular approach for the synthesis of multi(pincer–metal) complexes. Reprinted with permission from ref 915 (van Koten's group). Copyright 2003 American Chemical Society.

catalysts immobilized on silica or polystyrene supports (cf. section 5.2.2), the area was developed in the 1990s by Cole-Hamilton et al.⁹²⁰ using silsesquioxane-cored dendrimers terminated by phosphine groups and by van Leeuwen et al.^{798,801} and has been reviewed.^{539,798,799,801} For instance, the phosphine-terminated silsesquioxane-cored G_1 dendrimer loaded with $[\text{Rh}(\text{acac})(\text{CO})_2]$ or $[\text{Rh}(\text{OAc})_4]$ catalyzed the hydroformylation of propen-1-ol followed by reduction of the aldehyde to butane-1,4-diol and 2-methylpropan-1-ol, and the mechanism was proposed to proceed via a rhodium-hydroxycarbene intermediate.⁹²⁰ G_1 – G_5 PPI dendrimers terminated with alkoxy-cyclopentadienyl rhodium complexes were shown to be active olefin hydroformylation catalysts.⁹²¹ Wilkinson's catalyst supported on dendrimer-SBA shows minimized leaching.⁹²²

Some rhodium(I)-phosphine dendrimers were also used for simple olefin hydrogenation reactions, with results comparable to those of monorhodium catalysts and slight turnover decrease for large dendrimers.^{923–925} Asymmetric hydrogenation of 2-acetylacetamidocinnamate using bicarbazole diol chiral phosphoramidite-rhodium dendrimers gave an excellent enantioselectivity (93% ee at full conversion), confirming that phosphoramidites are superb ligands for asymmetric olefin hydrogenation.^{926,927} G_1 – G_4 pyrphos-Rh^I-terminated dendrimers (pyrphos = 3,4-bis(diphenylphosphino)pyrrolidine) catalyzed asymmetric hydrogenation of α -acetamidocinnamic acid with dendritic effects assigned to dendrimer shape change from G_3 to G_4 .⁹²⁸ Monodentate phosphoramidite-Rh^I-terminated Fréchet-type dendrons catalyzed the asymmetric hydrogenation of α -dehydroamino acid esters and itaconate with up to 97.9% ee and high catalytic activities, although G_3 showed a slightly decreased activity. The positive dendritic effect in these reactions disclosed from the monomer to the low-generation dendrimers was assigned to the catalyst shielding by the dendrons against hydrolysis of the complex.⁹²⁹ Rhodium catalysts with imidazolium salts attached to Fréchet-type dendrons catalyze the hydrosilylation of acetophenone with dendritic effects and yield a decrease with time being observed for G_1 but not for G_2 – G_4 .⁹³⁰

5.3.3. Ruthenium Complexes

5.3.3.1. Olefin Metathesis Catalysts. Early work of ruthenium-branched compounds concerned metathesis catalysts. Hoveyda's group synthesized two tetrabranch Ru-based complexes in which the branches were $-(\text{CH}_2)_3\text{-SiMe}_2(\text{CH}_2)_3\text{OC(O)(CH}_2)_2-$ units that were connected to the styrenyl ether ligand. This complex catalyzed ring-closing, ring-opening, and cross metathesis. The yield of ring-closing metathesis of $\text{TsN}(\text{CH}_2\text{CH}=\text{CH}_2)_2$ using 5% mol Ru of the dendritic catalyst was 99%. The catalyst was recovered with 13% vacant styrenyl ligand (i.e., 13% Ru loss). It was suggested that the catalytically active Ru species was released from the dendrimer into the reaction mixture and could be trapped again by a styrenyl ether ligand arm of the dendrimer.⁹³¹ Another analogous 4-branch metallodendritic catalyst containing the *N*-heterocyclic carbene promoted the formation of trisubstituted allylic alcohol and was recovered with only 8% Ru loss. It also catalyzed tandem ROM/RCM and was easily separable from reaction mixtures because of its polarity and high molecular weight. RCM reactions of diethyl diallylmalonate to the favored 5-membered cyclopentene ring using chelating dendritic ligands coordinated to Ru were also reported by the van Koten group.⁹³² Thus, dendrimers containing 4 or 12 branches, i.e.,

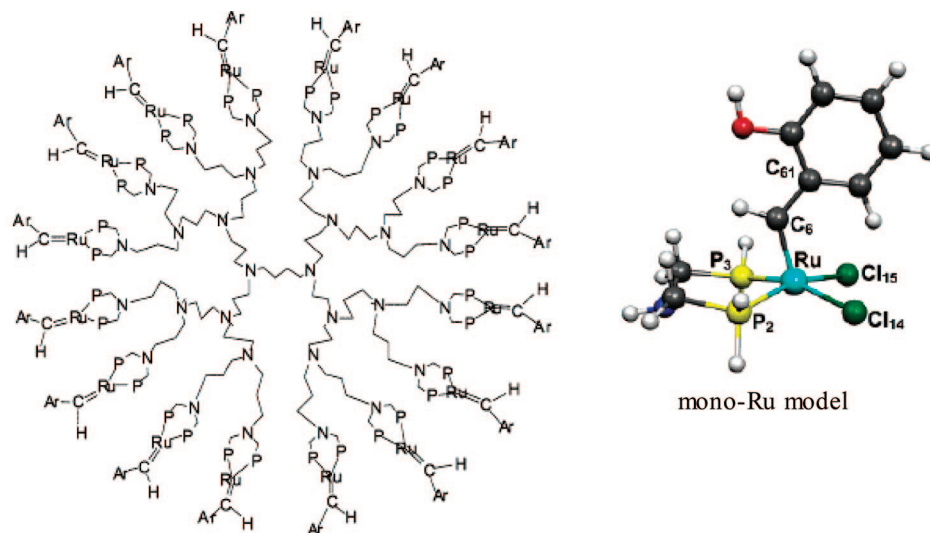
$\text{Si}[(\text{CH}_2)_3\text{SiMe}_2\text{pC}_6\text{H}_4\text{CHOH}(\text{CH}_3)\text{py}]_4$ and $\text{Si}\{[(\text{CH}_2)_3\text{Si}[(\text{CH}_2)_3\text{SiMe}_2\text{pC}_6\text{H}_4\text{CHOH}(\text{CH}_3)\text{py}]_3\}_4$ reacted with $[\text{Ru}(\text{=CHPh})\text{Cl}_2(\text{PR}_3)_2]$ ($\text{R} = i\text{-Pr}$ or *c*-Hex) to give 5-coordinate dendritic Ru complexes in which the O,N-chelating ligands were attached to Ru with the alkoxy ligand in equatorial position and the pyridyl ligand in axial position. The RCM reactions were quantitative after 30 min at 80 °C with 1 mol % (based on ruthenium) of either catalyst, as with the monometallic catalyst. In CFMR, conversion did not increase above 20%. Extensive decomposition occurred as a black precipitate formed in the vessel containing the catalyst, presumably because the catalyst was deactivated by the membrane surface.

The Ru-benzylidene dichloro complexes of G_1 – G_3 PPI dendrimers terminated by chelating amino-di(phosphino-ethyl) ligands were metathesis catalysts for the ROMP of norbornene under ambient conditions, forming metallodendritic stars in which each branch has incorporated, for instance, 100 norbornene units.⁸²⁴ The G_1 metallodendrimer containing 4 ruthenium centers was more active than the monoruthenium catalyst, which was taken into account by more tether-flexibility induced facile phosphine decoordination (rate-limiting step providing the active 14-electron catalytically active Ru centers) in this dendrimer than in the monomeric model catalyst. The metathesis polymerization rate decreased with increasing dendrimer generation, however, due to increasing steric congestion at the dendrimer periphery inhibiting the olefin approach to the Ru centers (Figure 50).^{933–935} Norbornene polymerization was also catalyzed by G_1 - and G_2 -nickel catalyst-terminated PPI dendrimers using methylaluminumoxane as the cocatalyst, whereby the catalytic activity was influenced by the dendrimer generation.⁹³⁵

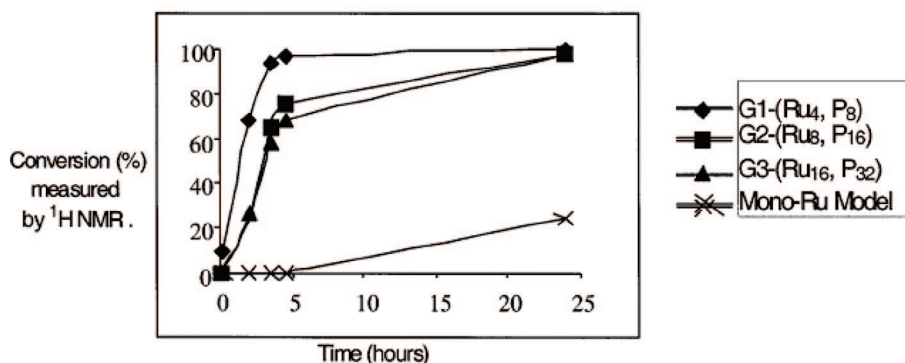
5.3.3.2. Hydrogenation Catalysts. The asymmetric hydrogenation of β -ketoesters was catalyzed by dendritic chiral phosphine ruthenium complexes with good activity and remarkable dendritic effects on the ee, with the stereoselectivity being strongly influenced by the dihedral angle of the diphosphine that is related on the generation-dependent dendritic wedge.⁹³⁶ A tetrabranch phosphoranyl-terminated carbosilane derivative coordinated to four $[\text{Ru}(p\text{-cymene})\text{Cl}(\text{bipyRu}(p\text{-cymene})\text{Cl}_2)]$ units catalyzed hydrogen-transfer hydrogenation of cyclohexanone, with the stoichiometric hydrogen donor being cyclohexadiene or formic acid. This G_1 dendrimer was very active but less so than the mononuclear species, and the dendritic effect was also negative up to G_3 , which was less active than G_1 .⁹³⁷

5.3.3.3. Other Types of Catalysis. Electron-transfer-chain catalysis was carried out with G_3 and G_4 Reetz' dendritic phosphines (PPI terminated with $\text{N}(\text{CH}_2\text{PPh}_2)_2$) loaded with the cluster $[\text{Ru}_3(\text{CO})_{11}]$ on each of the 32 or 64 phosphines. Fe^I-catalyzed substitution of one CO ligand of $[\text{Ru}_3(\text{CO})_{12}]$ by a phosphine branch.^{938,939} The reaction was very clean, as shown by ³¹P NMR, upon electron-transfer-chain catalysis under ambient conditions with 1% of the standard electron-reservoir complex $[\text{Fe}^{\text{I}}(\eta^5\text{-C}_5\text{H}_5)(\eta^6\text{-C}_6\text{Me}_6)]$.^{940–942}

The Knoevenagel condensation of malononitrile and cyclohexanone was catalyzed by a G_3 dendrimer terminated by 24 Ru-diphosphine species. The catalytic activity was often higher than that of the monomeric complex, and the dendritic catalyst was recycled without significant loss of activity.⁹⁴³ A hexabranch compound terminated with $[\text{Ru}(\eta^5\text{-C}_5\text{H}_5)(\text{CO})_2(\text{alkyl})]$ termini was supported on silica. This material was compared to Ru/SiO₂ in the CO hydrogenation



KINETICS OF THE ROMP AT 25°C :



G1 (94 %) > G2 (65 %) > G3 (59 %) > Mono-Ru Model (traces) after 3h

Figure 50. Comparison of norbornene ROMP rates for the mono-Ru model and the dendrimers. Reprinted with permission from ref 934 (Astruc's group). Copyright 2004 American Chemical Society.

catalysis but did not produce Fischer–Tropsch products, indicating that a single Ru site was insufficient for Fischer–Tropsch catalysis.⁹⁴⁴

5.3.4. Other Transition-Metal Catalysts

G_2 and G_3 alkoxy-silyl-terminated Ti-containing carbosilane dendrimers catalyzed the epoxidation of cyclohexene with better yields and initial rates than the Shell catalyst based on the reaction of silica with $\text{Ti}(\text{O}-i\text{-Pr})_4$. These catalysts were generated by acid-catalyzed hydrolysis of the carbosilane dendrimers in benzene giving monolithic gels followed by reaction with $\text{Ti}(\text{O}-i\text{-Pr})_4$. A positive dendritic effect was disclosed on the gel surface area.⁹⁴⁵ Fréchet-type dendrons having styrenyl end groups and bearing $\text{Ti}(\text{OCHMe}_2)_2$ species coordinated by TADDOL ($\alpha, \alpha, \alpha', \alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanol) were cross-linked into a polystyrene support, and this material catalyzed asymmetric addition of diethylzinc to benzaldehyde with 98% ee in 20 sequential applications. Nondendritic supported catalysts had slightly lower ee's. The catalyst efficiency decreased with increasing the spacer length between TADDOL and the polymer backbone.⁹⁴⁶ Rigid dendrimers based on 4,4',6,6'-tetrabromo-1,1'-bi-2-naphthol coordinated to $\text{Ti}(\text{O}-i\text{-Pr})_4$ catalyzed the addition of diethylzinc to 1-naphthaldehyde with 90% ee and 100% conversion and were easily separated by precipitation using methanol.⁹⁴⁷ Ti and Zr cyclopentadienyl (β -diketimi-

nato) complexes surrounded by dendritic wedges catalyzed ethylene polymerization with higher activity than $[\text{Ti}(\eta^5\text{-C}_5\text{H}_5)\text{Cl}_3]$, $[\text{Zr}(\eta^5\text{-C}_5\text{H}_5)\text{Cl}_3]$, and the monometallic β -diketiminato complexes.^{948–950} The zirconocene-type α -olefin polymerization precatalyst ($[\text{Zr}(\text{Ind})_2\text{Me}_2]$) showed enhanced activity even in aliphatic solvents when the perfluorophenylborane Lewis acid was covalently attached to the periphery of a carbosilane dendrimer (4, 12, or 36 tethers, but no effect of tether number was found).⁹⁵¹ Steric crowding of the anion resulting from the dendrimer frame can be compared to that in methylaluminoxane (MAO). Bis(imino)pyridyl iron(II) catalyst precursors of ethylene polymerization attached to similar G_1 and G_2 dendrimers provided positive dendritic effects (compared to the parent iron catalyst) on the activity, molecular weight, and melting temperature only at relatively low MAO/Fe ratio (<1000).⁹⁵² With Ni(II) pyridylimine catalyst decorating the periphery of G_0 – G_3 carbosilane dendrimers, strong generation dependence was found concerning the molecular weight and topology of polyethylene products, with increasing generations leading to preferred oligomerization (chain transfer) over polymerization (Figure 51).⁹⁵³

Dendritic G_1 - and G_2 -DAB–salicyldiimine–Ni complexes catalyzed ethylene oligomerization in the presence of EtAlCl_2 as an activator, with the octabranched G_2 dendrimer showing higher activity than the tetrabranched G_1 catalyst.⁹⁵⁴ A few

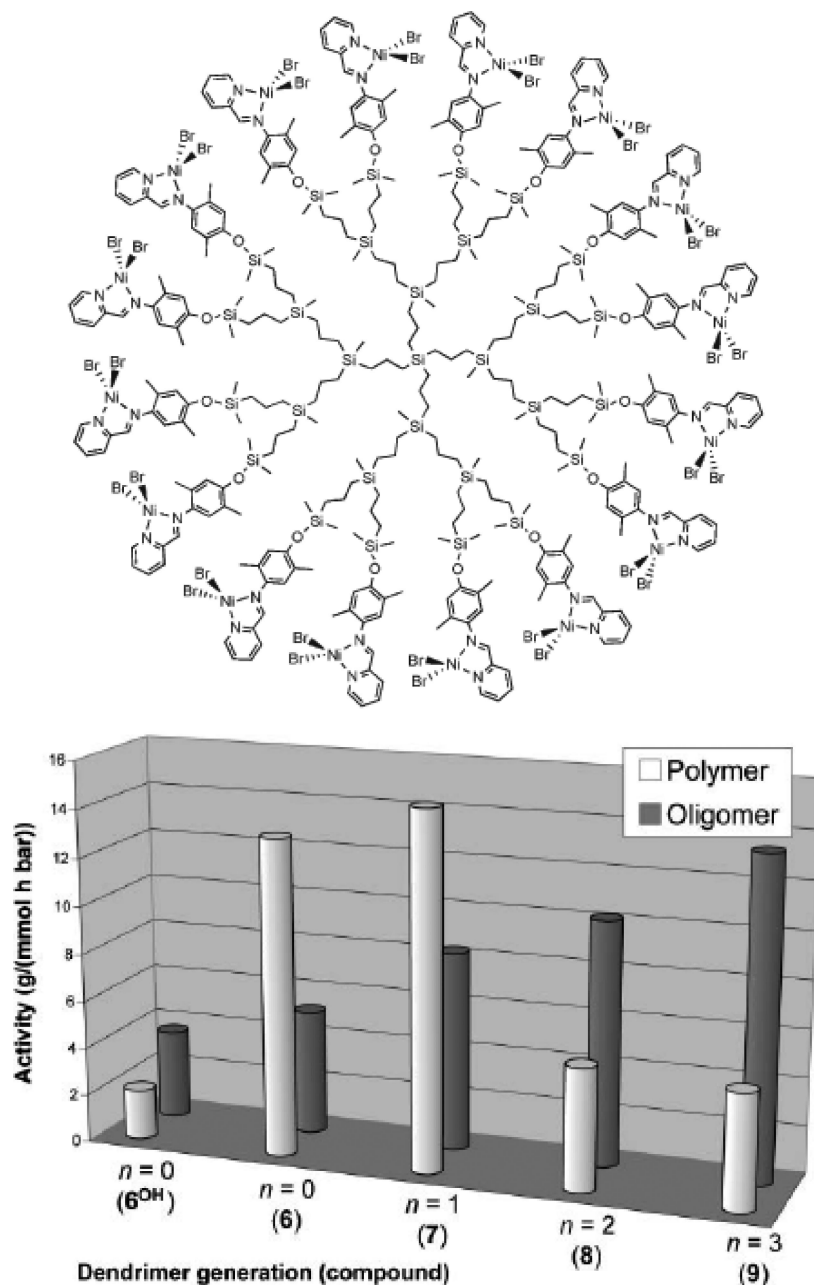


Figure 51. Metallo-dendrimer G_3 -[(ONNMe₂)NiBr₂]₁₆. Activities by precursors 6OH and G_n -[(ONNMe₂)NiBr₂]_m. Reprinted with permission from ref 953 (Flores' group). Copyright 2005 Royal Society of Chemistry.

copper and cobalt catalysts were reported in the 1990s.⁵³⁹ More recently, dendronized supports linked to 2- and 4-(diphenylphosphino)benzoic acid groups that were coordinated to cobalt by reaction with [Co₂(CO)₈] catalyzed the Pauson-Khand [2 + 2 + 1]-cycloadditions⁸⁸⁶ with increased activity and selectivity compared to nondendronized supports.⁹⁵⁵

After Suslick's seminal reports on dendritic Mn-porphyrin-catalyzed epoxidation,⁷⁹⁴ Mn^{II} salen complexes immobilized on ultrafine silica in PAMAM-catalyzed olefin epoxidation with an activity that improved with generation increase.⁹⁵⁶

The catalytic properties of PPI-bound carbo-BINAP ligands in Cu-catalyzed hydrosilylation of acetophenone displayed a strong dependence of the enantioselectivity and activity on the dendrimer generation, and immobilized BINAL ligands were recycled several times without loss of enantioselectivity.⁹⁵⁷

The dendritic polyoxometallate oxidation catalysts and various other transition-metal-based dendritic catalysts are discussed in section 5.2. Although selenium is not a transition metal, it behaves as such in catalysis upon accepting an oxo ligand from hydrogen peroxide as cytochrome P450 as its models do, despite mechanistic variations. Thus, positive dendritic effects were found in the dendritic organoselenide-catalyzed bromination of cyclohexene using hydrogen peroxide and sodium bromide and attributed to autocatalytic formation of Br⁺ at the selenide dendrimer surface (Figure 52).⁹⁵⁷⁻⁹⁵⁹

5.4. Organocatalysis

Organic reactions in dendrimers can be either accelerated or slowed down by the dendritic framework, i.e., the dendritic effect can be positive or negative. As an example of precise study of negative dendritic effect, a dendrimer-

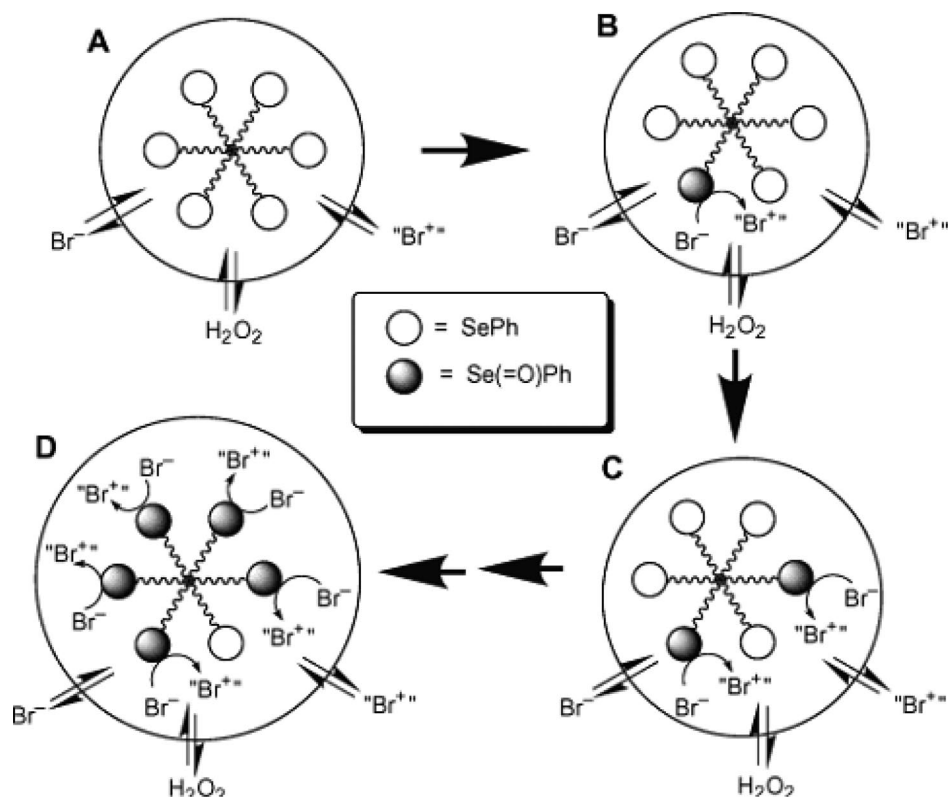


Figure 52. Illustration of the autocatalytic oxidation of dendrimeric polyorganoselenides. The large circles enclosing the dendrimers represent the local environment around the dendrimer (the “dendrimer sphere”) as opposed to the bulk solution. (A) Br^- diffuses into the dendrimer sphere or is generated via reaction of H_2O_2 and Br^- that have diffused into the dendrimer sphere. (B) Oxidation of the first selenide generates a selenoxide group that begins the catalyzed reaction of H_2O_2 and Br^- within the dendrimer sphere. The oxidation of the second selenide is accelerated by the higher local concentration of Br^{+*} , even though it is diffusing into the bulk solution. (C) The process is repeated with an accelerated rate for the next oxidation. (D) Oxidation of the final selenide group will have the fastest rate due to the much higher local concentration of Br^{+*} , even though it is diffusing into the bulk solution. Reprinted with permission from ref 959 (Detty’s group). Copyright 2003 American Chemical Society.

encapsulated tertiary amine catalyzed the nitroaldol (Henry) reaction between benzaldehyde and 2-nitroethanol with pseudofirst-order rate constants that decreased with increasing dendrimer generation (12.11, 1.89, and $1.03 \times 10^{-4} s^{-1}$ for generation 1, 2, and 3, respectively).⁹⁶⁰ The authors provided a quantitative treatment of the dendritic crowding by molecular dynamics simulations involving the “reagent accessible surface” of the dendrimer. Indeed, such negative dendritic effect due to increased crowding upon generation increase has been frequently observed experimentally.^{656,813,816,831,832,933–936,961–966}

On the other hand, examples of dendrimer-encapsulated metal complexes have been reported for which dendritic pyridine,⁹⁶⁷ phosphine,⁹⁶⁸ *N*-heterocyclic carbene,⁹⁶⁹ or P,O (*o*-phenylphosphinophenol)⁹⁷⁰ ligands increase the stability of the complex or protect it against deactivation when the generation increases. Sometimes, the environment of dendritic interior pockets provides optimized binding and reactivity as in enzymes (Figure 53),⁹⁷¹ and such a situation indeed led to positive dendritic effects in glutathione peroxidase activity for hydrogen peroxide reduction by benzenethiol in diselenide-cored Fréchet-type dendrimers.⁹⁷²

Another example of dendritic nanoenvironment is that using the dielectric effect⁹⁷³ inducing a radial polarity gradient. For this purpose, dendrimers were designed with long alkyl tethers at the periphery and polar ester or alcohol functionalities in the interior for the catalysis of reactions that develop a positive charge in the transition state. The unimolecular dehydrohalogenation of 2-iodo-2-methylhep-

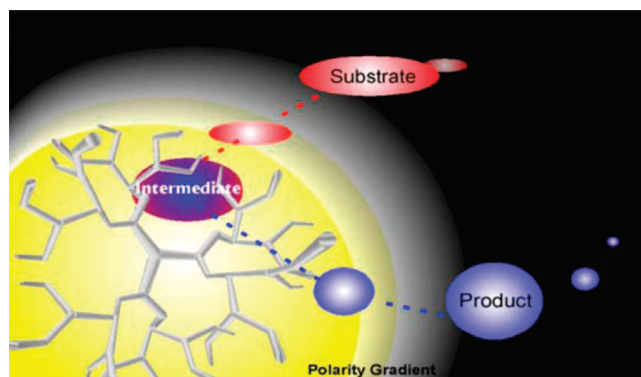


Figure 53. Illustration of substrate migration into the dendrimer interior. The nanoenvironment is greatly influenced by the branching units and creates a gradient of polarity with respect to the distinct interior and exterior solvent. These favorable conditions encourage substrate concentration and transition-state stabilization. The resulting product is released from the nanoreactor into the solvent. Reprinted with permission from ref 971 (Fréchet’s group). Copyright 2005 Elsevier.

tane proceeding with E_1 elimination mechanism matches these criteria, and it was achieved with a positive dendritic effect, i.e., improved with G_4 . In the higher-generation G_4 , the interior cavities were larger, thereby allowing a higher substrate concentration around polar alcohol groups, whereas the nonpolar olefin product escaped toward the nonpolar periphery to favor turnover and the so-called free-energy

driven catalytic pump⁹⁷⁴ The Fréchet group extended this concept to the ¹O₂-sensitizing benzophenone dendritic core incorporated in amphiphilic dendrimers with hydrophobic peripheries. Oxidation of hydrophobic cyclopentadiene with O₂ herewith was favored in the hydrophobic dendrimer core, and the *endo*-peroxide cycloadduct was reduced in situ with thiourea to hydrophilic *cis*-cyclopentene-1,4-diol in order to favor rapid conversion even with only 0.1 mol % of catalyst (despite some photobleaching). The dendritic effect was again positive, i.e., increasing the dendrimer generation from G₁ to G₃ gave the diol in 15%, 35%, and 50% yield, respectively, in contrast with the 10% yield obtained with a nondendritic model compound.⁹⁷⁵

The reverse polarity (hydrophilic dendritic polyammonium interior and hydrophobic periphery) was designed by Kaneda's group to use iodide anion for Lewis-base catalysis of the Mukayama aldol reaction of 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene with aldehydes, whereby these dendritic polyiodide polyammonium-cored dendritic catalysts were more efficient than tetrahexylammonium iodide salts. The anionic reaction intermediate is better stabilized by the polar polyammonium environment as well as by a more polar solvent, with DMF providing better results than toluene.⁹⁷⁶ The nanoenvironment effect was also similarly shown in acylation reactions of tertiary alcohols yielding linalol pivalate catalyzed by various amphiphilic dendritic and dendronized polymeric 4-(dialkylamino)pyridines, and nondendritic model compounds such as DMAP were only marginally efficient. Related positive nanoenvironment dendritic effects were observed in Ford's seminal and subsequent decarboxylation studies^{782,640-645} (sections 4.9 and 5.1) and in metallodendritic catalyzed reactions (section 5.3).^{793-797,869,977,978}

Several generations (G₁–G₆) of PAMAM dendrimers containing pyridoxamine and pyridoxal at their cores were used by Breslow's group as biomimics of transaminases and amino acid racemases. Positive dendritic effects were disclosed in the transamination of pyruvic acid and phenylpyruvic acid in aqueous buffer by PAMAM–pyridoxamine dendrimers, as indicated by Michaelis–Menten kinetics and higher efficiency than simple pyridoxamine. Thus, the more globular G₆ generation was shown to exhibit enzyme-like conformation with the highest reaction rates resulting from acid–base catalysis due to the large number of tertiary amines at the dendrimer periphery.⁹⁷⁹

Combinatorial libraries of diaminoacid units for dendritic branching with catalysts at the dendrimer periphery were constructed with the aim to mimic lipases.⁹⁸⁰⁻⁹⁸³ Knoevenagel condensations have been heterogeneously catalyzed with 100% selectivity by polystyrene-G₁ to G₃-PAMAM dendrimers, and these catalysts could be recycled 10 times.⁹⁸⁴ The esterolytic activity therein was selective and higher than that of the model catalyst 4-methylimidazole.⁹⁸¹ Along this line, a series of G₁–G₄ dendrimers with His-Ser dipeptide repeat units as catalysts were shown to undergo a positive dendritic effect attributed to enhanced substrate binding and more important contribution of the proximal His residue to the catalysis rate in G₄.⁹⁸² Dendritic chiral phosphine Lewis bases catalyzed asymmetric aza-Morita–Baylis–Hillman reactions of *N*-sulfonated imines with activated olefins in excellent yields with up to 97% ee and could be recovered and reused.⁹⁸³⁻⁹⁸⁵

5.5. Catalysis with Dendrimer-Encapsulated and Dendrimer-Stabilized Nanoparticles

5.5.1. Single-Metal Based Nanoparticles in Homogeneous Catalysis

In section 4.8, the stabilization of various metal- or metal oxide NPs by dendrimers has been reviewed. Such mono- and heterobimetallic NPs have been efficiently used in catalysis. The advantages of dendrimer-encapsulated NP (DEN) catalysis disclosed by Crooks' seminal work (see section 5.1) are (i) the control over the chemical composition of the catalyst and the solubility, (ii) the lack of passivation of the NP surface in the absence of anionic ligands such as thiolates that usually stabilize transition-metal NPs, and (iii) the possibility to heterogenize the catalyst by fixation on a solid support.^{652-657,696,790,860}

5.5.1.1. Selective Hydrogenation. From Crooks' concept of dendritic nanofilter using PAMAM dendrimers, size selectivity resulted in catalytic hydrogenation reactions carried out using Pd DENs in various media such as water,^{652,986} fluoruous phase,^{652,655} biphasic media,^{652,655} and supercritical CO₂.^{654,987} Similarly, selectivity was also observed with Pd DENs prepared using PPI dendrimers; for instance, the rate of hydrogenation decreased with increasing size of the cyclic dienes.⁹⁸⁸ The influence of bulk at the periphery of dendrimers on the catalytic efficiency of resulting DENs was studied to confirm the validity of the nanofilter concept. Using α -amino alcohol-terminated G₄-PAMAM dendrimers as templates for the preparation of Pd₄₀ NPs, it was shown that DENs functionalized with bulkier peripheral groups were poorer catalysts than those with less steric bulk on their surface.^{654,989} The effect of generation and peripheral groups on PdNP size and selective hydrogenation activity of cyclic dienes and internal alkynes to monoenes was determined (Figure 54).⁹⁹⁰

Poly(amidoamine) hyperbranched polymer-stabilized Pt-NPs (1.8 nm) were also shown to be effective and robust hydrogenation catalysts in water.⁹⁹¹

5.5.1.2. Nitroarene Reduction. 3,5-Dihydroxybenzyl-terminated dendrimer-stabilized AgNPs were found to be highly active catalysts for the selective reduction of chloronitrobenzenes to chloroanilines.⁹⁹² Nitrophenol reduction by NaBH₄ catalyzed by PAMAM Pd DENs was shown to depend on the nature of the terminal dendrimer group with rate constants in the following order: amine > carboxylate > sugar > methyl ester.⁹⁹³ Heterobimetallic Au–Pt, Au–Pd, and Pt–Pd DENs as alloys were also prepared for this reaction in water, based on G₃, G_{3.5}, and G_{5.5} PAMAM dendrimers. The Au–Pd and Pt–Pd DENs exhibited higher activities than monometallic DENs, but the Au–Pt DENs showed activity that was comparable to that of monometallic Pt DENs, and the rate decreased compared to that found with Au DENs, because Pt poisoned catalysis. The catalytic activity was also dependent on the nature of the terminal group of the PAMAM dendrimer.⁹⁹⁴

G₄-Phenylazomethine dendrimers and G₄-OH–PAMAM dendrimers were loaded with RhCl₃, and 1.2-nm Rh DENs formed upon reduction by NaBH₄ and containing 64 Rh atoms (assuming face-centered cubic, fcc, closed-packed structure) were active catalysts for the hydrogenation of various olefins and nitroarenes in methanol under 1 atm H₂ at room temperature.⁹⁹⁵

G₄-Phenylazomethine- and G₄-PAMAM–OH Rh DENs catalyzed olefin and nitroarene hydrogenation very ef-

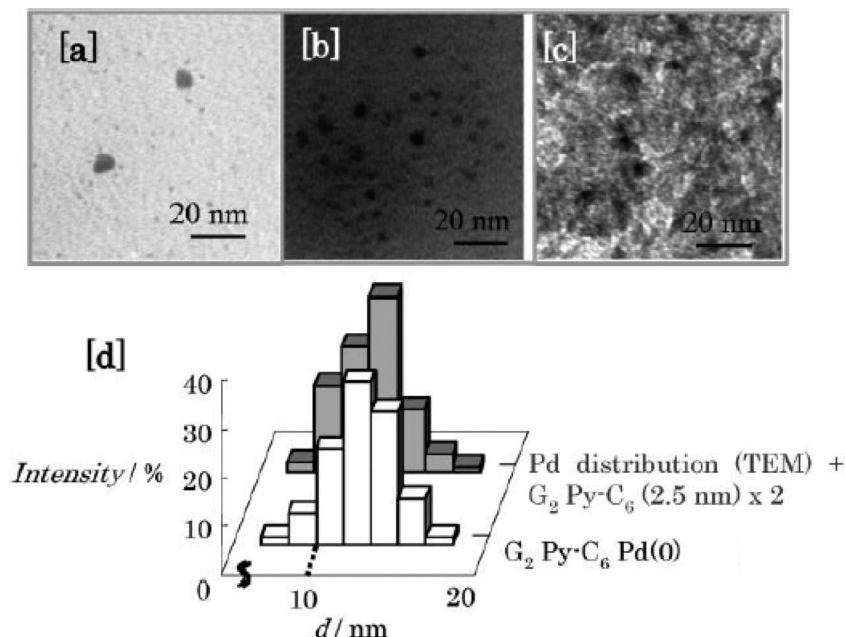


Figure 54. TEM images of Pd nanoparticles encapsulated within the G_2 dendrons; (a) G_2 Py-CO₂Me Pd(0), (b) G_2 Py-C₆ Pd(0), (c) G_2 Py-C₁₂ Pd(0), and (d) the size distributions of G_2 Py-C₆ Pd(0). Reprinted with permission from ref 990 (Kaneda's group). Copyright 2008 Royal Society of Chemistry.

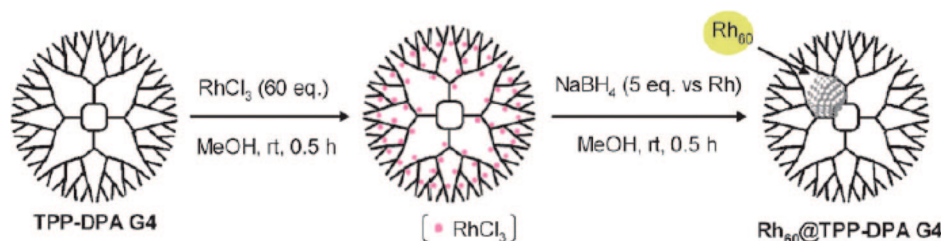


Figure 55. Synthetic procedure of Rh₆₀@TPP-DPA G₄. Reprinted with permission from ref 996 (Nishihara and Yamamoto's groups). Copyright 2008 Royal Society of Chemistry.

fectively, affording high TOFs (up to 17 520 h⁻¹). It was shown that the substrates could pass through the branches of the dendrimers without releasing the RhNPs (Figure 55).⁹⁹⁶

The Crooks group reported the synthesis and catalytic evaluation of Cu DENs as an undergraduate experiment to explore catalytic nanomaterials. The model reaction was the NaBH₄ reduction of *p*-nitrophenol to *p*-aminophenol. The rate constant for the catalytic activity was estimated by measuring the pseudofirst-order reaction kinetics obtained by monitoring the absorbance variations of *p*-nitrophenol reduction by UV-vis spectroscopy.⁹⁹⁷

5.5.1.3. Pd-Catalyzed Heterocoupling. DENs also show enhanced efficiency and selectivity of heterocoupling such as Heck reactions.^{655,987-992,998-1000} For instance, the coupling of *n*-butyl acrylate with aryl halides in biphasic organic solvents catalyzed by PPI Pd DENs was shown to proceed at 90 °C instead of temperatures higher than 120 °C used for other PdNPs. The reaction was also 100% selective for the *trans*-isomer of *n*-butyl formylcinnamate.⁶⁵⁵ The comparison of the catalytic efficiency of PdNPs stabilized by polymers such as poly(vinylpyrrolidone) (PVP) and dendrimers (DENs) for the Suzuki-Miyaura reaction by El Sayed's group showed that the dendrimers provide higher stability but lower activity than PVP. The lowest activity was disclosed for the highest dendrimer generations as a result of highest resistance to mass transfer and/or passivation

of catalyst surface by functional groups.^{998,999} Pd NP catalysis of the Suzuki-Miyaura reaction by DENs has been studied by several research groups.^{865,988,998,999}

The well-known "click" reaction has been used by the Astruc group to stabilize transition-metal ions including Pd^{II} by the 1,2,3-triazole ligand⁶⁵⁸⁻⁶⁶¹ and to form "click"-dendrimer-protected Pd nanoparticles by reduction of the Pd^{II} species to PdNP either as DENs or dendrimer-stabilized PdNPs (DSNs) when the dendrimers are too small (G_0). Such PdNPs are very active catalysts for selective hydrogenation^{536,1001} and Suzuki-Miyaura cross-coupling reactions.¹⁰⁰² This latter reaction was efficient under ambient conditions for the coupling of phenyl iodide with down to 1 ppm catalysts, and the TON of this catalyst went higher as the catalyst amount was decreased. This "homeopathic" behavior was taken into account by a leaching mechanism of extremely reactive ligandless Pd atoms from the PdNPs subsequent to oxidative addition of phenyl iodide and less efficient quenching of these Pd atoms by PdNPs as the catalyst concentration is decreased. Such a mechanism was proposed for the high-temperature Heck reaction with catalysts such as Pd(OAc)₂ that decompose to PdNPs,⁷⁸⁵ but in the present case, it is proposed to be operating at room temperature with PdNPs that are not bound to ligands (Figures 56 and 57).¹⁰⁰²

Moreover, the "click"-dendrimer-stabilized PdNPs can be solubilized in water by using propargyl sulfonate for the

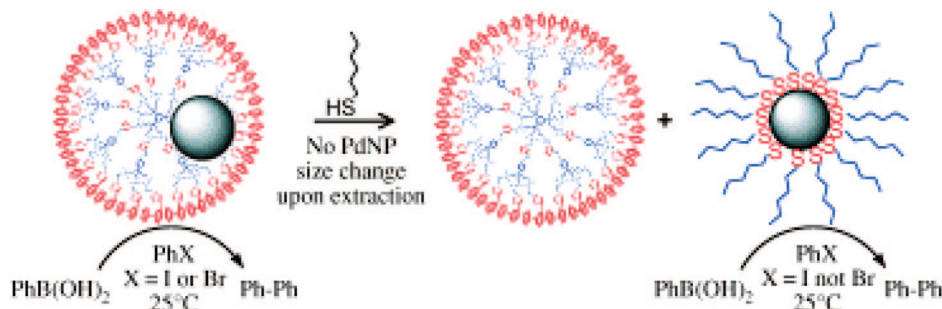


Figure 56. Extraction of PdNPs from DSNs or DENs with hexanethiol without any change in the size of the PdNPs to produce air- and water-stable, catalytically active hexanethiolate PdNPs. Reprinted with permission from ref 1002 (Astruc's group). Copyright 2007 Wiley-VCH.

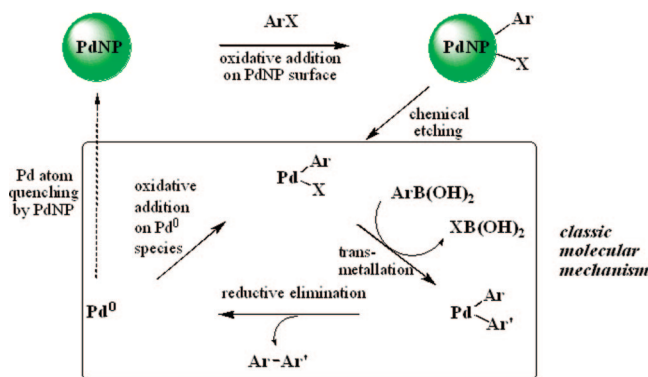


Figure 57. Proposed mechanism for the Suzuki reaction at RT by dendrimer-encapsulated Pd nanoparticles resembling that suggested by de Vries for the Heck reaction at 130 °C. Reprinted with permission from ref 1002 (Astruc's group). Copyright 2007 Wiley-VCH.

“click” reaction, leading to sulfonate-terminated “click” dendrimers. The PdNPs were then formed by NaBH_4 reduction of the Pd^{II} -sulfonate-triazole dendritic complexes and were equally efficient catalysts at room temperature for styrene hydrogenation and Suzuki–Miyaura cross-coupling reaction of phenyl iodide in an aqueous medium.^{1003,1004} Air-stable dendritic phosphine oxide-stabilized PdNPs were demonstrated to be efficient catalysts for Suzuki and Stille coupling reactions and for hydrogenation.¹⁰⁰⁵

5.5.2. Heterobimetallic Nanoparticles in Homogeneous Catalysis

5.5.2.1. Characterization of Heterobimetallic Nanoparticles.

Heterobimetallic nanoparticles can be alloys, obtained by coreduction of two metal salts, or of “core-shell” structure, obtained by successive reduction of each metal salt. A variety of techniques are being used for their analysis:¹⁰⁰⁶ TEM, including HRTEM, allows for examination of their size and morphology;^{986,1007–1009} AFM provides a vertical height measurement complementing the lateral dimensional TEM measurement;^{1006,1012} UV–vis explores the results of various synthetic routes but cannot quantitatively analyze the composition;^{1006,1008,1010} infrared spectroscopy analyzes the metallic surface composition for the distinction of different structures and approximately evaluates the surface composition;^{1006,1013} single-particle energy-dispersed X-ray spectroscopy (EDS) examines the variations in composition, but with large standard deviation when the NPs are smaller than 1.5 nm (Figure 58);^{986,1006–1016} XPS provides information about the surface electronic state and elemental composition; EXAFS estimates the possible structure via calculation of the number of surrounding atoms of each absorbing metal element (although

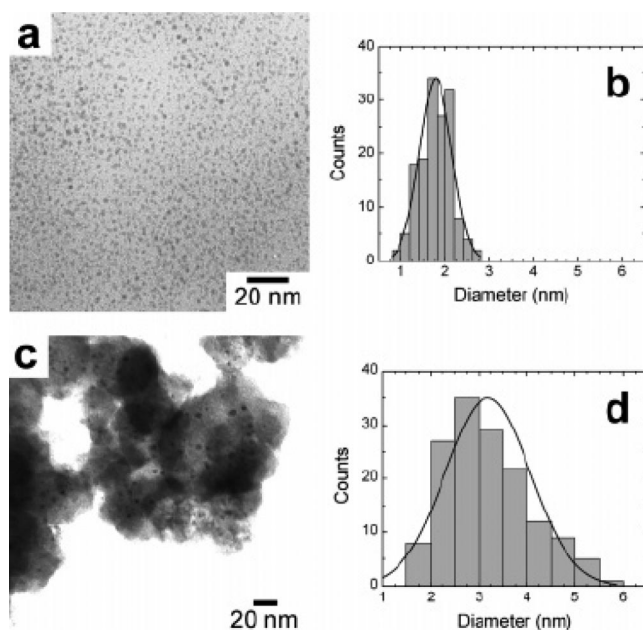


Figure 58. Bright-field TEM images and particle-size distributions for $G_4\text{-NH}_2(\text{Pd}_{27.5}\text{Au}_{27.5})$ DENs prepared by cocomplexation of the corresponding metal salts followed by reduction: (a), (b) as synthesized; (c), (d) after incorporation into the titania matrix and subsequent calcination at 500 °C under O_2 and H_2 . Reprinted with permission from ref 1011 (Crooks' group). Copyright 2005 American Chemical Society.

it may be difficult to get a precise set of absolute values of coordination numbers);¹⁰¹⁷ and chemical extraction allows for the analysis of the chemical composition.¹⁰¹⁰

5.5.2.2. Selective Hydrogenation. **5.5.2.2.1. Alloys.** Heterobimetallic nanoparticle catalysts find their origin in the late 1980s¹⁰¹⁸ and were developed in Toshima's group for 1–3-nm AuPdNPs stabilized using poly(*N*-vinyl-2-pyrrolidone). These NPs exhibited enhanced efficiency for the partial hydrogenation of 1,3-cyclooctadiene compared to mixtures of single-metal NPs.^{1017,1019,1020} More recently, Crooks pioneered the use of heterobimetallic DENs in selective catalysis including under “green” conditions.^{652–654} Heterobimetallic water-soluble alloy DENs were prepared by cocomplexation of $G_4\text{-PAMAM-OH}$ dendrimers with mixtures of K_2PdCl_4 and K_2PtCl_4 followed by NaBH_4 reduction. The resulting metal ratio in the DENs is controlled by the initial loading and verified by single-particle EDS. These PdPtNPs gave significantly higher TONs for the hydrogenation of allylic alcohol than for single-metal analogues.⁹⁸⁶ Related enhancements were also observed for the partial hydrogenation of cyclohexene¹⁰²¹ and 1,3-cyclo-octadiene.¹⁰¹⁵ Toshima had, in the early 1990s, taken such enhancements by 1–2-nm

PdPtNPs (alloy) stabilized by polymers into account by synergistic electronic effects involving the ligands.^{1019,1020}

5.5.2.2.2. Core–Shell. Core–shell heterobimetallic NPs were first synthesized by Schmid's group, with the core–shell structure being demonstrated by HRTEM and EDS microanalyses.¹⁰²² Crooks' group showed that some core–shell heterobimetallic NPs such as [Au]PdNPs ([Au] indicates the AuNP core) are also superior catalysts to PdNPs. For instance, selective reduction of PdCl_4^{2-} onto $G_6\text{-Q}_{116}(\text{Au}_{55})$ seeds using H_2 yielded [Au]PdNPs with shells of 95 and 455 Pd atoms and sizes of 1.8 and 2.3 nm, respectively, that had significantly enhanced catalytic activity for the hydrogenation of allylic alcohol in water.¹⁰⁰⁹ Peng et al found that dendrimer-derived PtXNPs and PtPdNPs showed kinetics trends indicating enhanced catalytic behavior for selective 3,4-epoxy-1-butene hydrogenation compared to traditional catalysts prepared by wet impregnation of metal salts.¹⁰⁰⁶ These authors also reported that $G_5\text{-Q}(\text{Ru}_5\text{Rh}_5)$ DENs catalyze the regioselective reaction of poly(methylhydro)siloxane with 1-hexene to poly(methylhexyl)siloxane with high efficiency.^{1006,1023}

5.5.3. Dendrimer-Encapsulated Nanoparticles in Heterogeneous Catalysis

In heterogeneous catalysis, nanoparticles stabilized by encapsulation in PAMAM dendrimers (PAMAM DENs) are immobilized on solid supports such as gold, silica, alumina, titania, or a polymer matrix, most frequently using the terminal- NH_2 and $-\text{OH}$ groups of the dendrimers. The advantage of using dendrimers is that the NP size, composition, and dispersity are well-defined and controlled. Although such systems are catalytically active when a solvent is present,⁶⁵⁵ this is no longer the case, however, in the absence of solvent. For instance, the gas-phase reactant CO cannot bind the DEN surface, because the dendrimer collapses around the NP and poisons the NP surface, rendering it inactive.⁸⁵⁹ The difficulty then resides in the removal of the dendrimer without transforming or perturbing the NP.^{853,854,863} Indeed, dendrimer removal may lead to increase in both particle size and distribution. This is illustrated by FT-infrared studies of PAMAM dendrimer removal leading to the formation of surface carboxylates and the need to use high temperature for decomposition.¹⁰²⁴

5.5.3.1. Methods of DEN Immobilization and Dendrimer Removal. DENs terminated with amine and partially quaternized amines covalently linked to mercaptoundecanoic acid formed self-assembled monolayers (SAMs) bound to the Au surface via their thiol groups.^{1025–1027} DENs terminated by alcohols were linked to glassy carbon electrodes by cycling the potentials three times between 0 and 1 V vs Ag/AgCl, 3 M NaCl.¹⁰²⁹ Thiophene-terminated PAMAM Pt DENs were coelectropolymerized with poly(3-methylthiophene).^{654,1028} Dendrimers have also been calcinated on support when they were loaded with unreduced metal ions.^{1029–1031} Pd DENs supported on mica or highly oriented pyrolytic graphite (HOPG) were calcinated at 630 °C, forming large aggregates from the PdNPs.⁶⁹⁶ Chandler reported the first successful dendrimer removal upon calcination using $G_5\text{-PAMAM-OH Pt}_{50}$ DENs and $G_5\text{-PAMAM-OH Pt}_{100}$ DENs at 300 °C in a O_2/He flow, which resulted in PtNPs that largely retained their original size (for instance, from 1.9 to 2.2 nm).¹⁰²⁴ Dendrimer removal was indeed accelerated by PdNP catalysis. Calcination using these conditions of Pd DENs and Au DENs required around 500

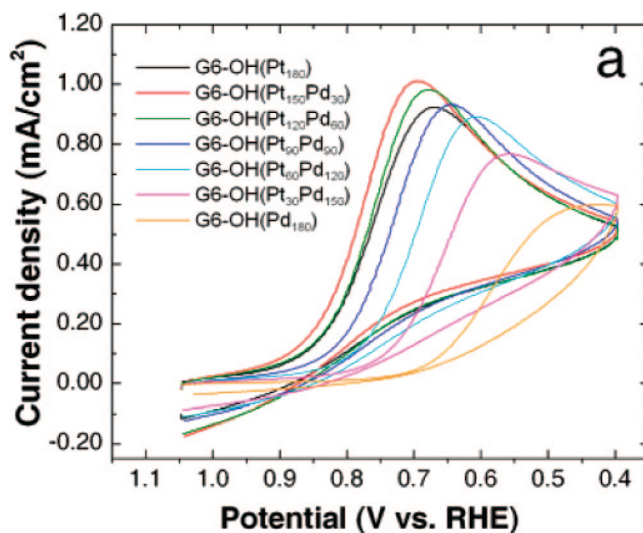


Figure 59. Cyclic voltammograms of $G_6\text{-OH}(\text{Pt}_n\text{Pd}_{180-n})$ ($n = 180, 150, 120, 90, 60, 30,$ and 0). Reprinted with permission from ref 1036 (Crooks' group). Copyright 2007 American Chemical Society.

°C to remove the PAMAM dendrimers accompanied by considerable NP size increase, for instance, from 1.7 to 7.2 nm for $G_4\text{-Q}_{32}\text{Au}_{55}$,⁶⁵⁴ although lower temperatures yielded better results.¹⁰³² Incorporation of Pd DENs and Au DENs into sol–gel matrixes minimize NP growth due to isolation within the sol–gel framework, for instance, from 2.0 to 2.7 nm for Au_{55} DENs upon calcination at 500 °C.^{1033,1034} Extension of this procedure to the heterobimetallic nanoparticles PdAu DENs for $G_4\text{-NH}_2(\text{Pd}_{27.5}\text{Au}_{27.5})$ increased the NP size from 1.8 to 3.2 nm upon calcination.¹⁰¹¹

5.5.3.2. Electrocatalytic O_2 Reduction. Electrocatalytic O_2 reduction using Pt DENs was initially shown subsequent to immobilization of OH-terminated PAMAM dendrimers onto Au surfaces, but these DENs were easily displaced from the electrode.¹⁰¹¹ Subsequently, $G_4\text{-PAMAM-OH Pt}_{40}$ DENs electrodeposited on glassy carbon electrodes as stable films upon anodic oxidation (vide supra) yielded electrocatalytic O_2 reduction at 0.22 V, with a gain of 0.6 V compared to the noncatalytic reduction.^{1033–1035} $G_6\text{-PAMAM-OH PtPd}$ DENs electrodeposited onto such electrodes in an aqueous 0.1 M LiClO_4 electrolyte solution catalyzed the 4-electron O_2 electroreduction as characterized by cyclic and rotating voltammetry with relative mass activity enhancement of a factor up to 2.4 compared to monometallic Pt DENs (Figure 59).^{1036,1037}

$G_4\text{-PAMAM-NH}_2$ AuPt DENs electrodeposition in a 0.5 M H_2SO_4 supporting electrolyte solution onto an indium tin oxide (ITO) surface yielded nanoflowers of bimetallic NPs that also exhibited a good electrocatalytic activity for O_2 reduction.¹⁰³⁸

5.5.3.3. CO Oxidation. The seminal work by Haruta on CO oxidation demonstrated the need of small (<5 nm) AuNPs deposited on oxides for facile CO oxidation by O_2 as well as many other AuNP–oxide catalyzed oxidation and reduction reactions.^{1039–1041} These very important systems still require improved mechanistic understanding, however, concerning the AuNP–oxide interaction for the precise substrate activation mode(s).^{1041–1045} CO oxidation by Pt DENs on TiO_2 has also been probed.¹⁰⁴² The dendrimer encapsulation of AuNPs and heterobimetallic NPs, which provides a unique way to control the exact definition in terms of size and

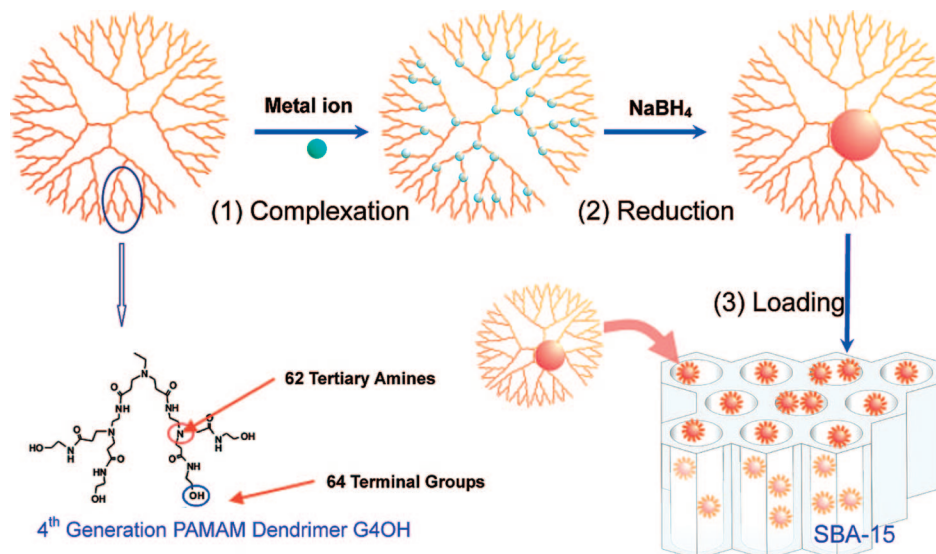


Figure 60. Synthesis of dendrimer-encapsulated metal nanoparticles and the subsequent immobilization of the nanoparticle on mesoporous SBA-15 support. Reprinted with permission from ref 1043 (Somorjai's group). Copyright 2008 American Chemical Society.

composition, should thus introduce enlightening data. Thus, Chandler's group reported the catalytic CO oxidation with SiO₂-supported PtAuNPs prepared from G₅-PAMAM-OH Pt₁₆Au₁₆. At 30–80 °C, Pt₃₂ NPs disclosed little activity, but the rate (2.0–2.6 mol CO/mol pt/min) for Pt₁₆Au₁₆ NPs catalysis was substantial. At 100 °C, Pt₁₆Au₁₆ NPs catalyzed the reaction at a rate 8.5 times higher than that of a mixture of Pt₁₆ NPs and Au₁₆ NPs. At 120 °C, the rates of Pt₃₂ NPs and Pt₁₆Au₁₆ were similar and Au₃₂ showed an activity of only 0.5 (mol of CO)/(mol of Au)/min. It appeared that Pt atoms, which are less active in PtNPs alone, play a favorable synergistic role in AuPtNPs, possibly by relocating O₂ activation at Au-atom sites of the AuPt NPs.⁸⁶¹ The catalytic activity for CO oxidation of TiO₂-supported G₄-PAMAM-NH₂ Pd_{27.25}Au_{27.25} NPs was compared to those of monometallic Pd₅₅NPs and Au₅₅NPs. At 150 °C, the PdAuNPs started to react with 1% CO conversion whereas the PdNPs and AuNPs were unreactive, and complete CO conversion was obtained at 250 °C for the PdAuNPs and only at 285 °C for PdNPs, in agreement with the above results.^{853–856,859–863,1011}

5.5.3.4. Ethylene Hydrogenation. G₄-PAMAM dendrimer-templated small RhNPs and PtNPs supported on a high-surface-area SBA-15 mesoporous support catalyzed ethylene hydrogenation under mild conditions with or without removing the dendrimer capping. The activity was highest after hydrogenation at 423 K. Pyrrole was also hydrogenated using this catalyst (Figure 60).^{1043,1044}

5.5.3.5. Nitrile Hydrogenation. Dendrimer-derived supported IrNP catalysts were active in benzonitrile hydrogenation and showed an increase in TOF with increasing dispersion, and selectivity toward dibenzylamine was affected by the catalyst preparation method, with the oxidation–reduction treatment resulting in lower selectivity.¹⁰⁴⁵

5.5.3.6. Ethane Hydrogenolysis. Heterogeneous RhNP/ZrO₂ catalysts have been prepared for ethane hydrogenation. [RhCl₃(H₂O)₃] was loaded in aqueous solution into G₄-PAMAM-OH dendrimers and reduced by NaBH₄, and the Rh₂₀-G₄-PAMAM-OH samples formed were impregnated with ZrO₂, followed by oxidation under O₂ at 400 °C for 1 h, and then reduction with H₂ at 200 °C for 1 h. The diameters of the resulting RhNPs were estimated by TEM to be 0.7 and 0.8 nm corresponding to Rh₁₀NP and Rh₂₀NPs,

respectively. In contrast, conventional preparation by wetness impregnation and identical treatment exhibited a 1.6-nm size corresponding to approximately 150 Rh atoms. Ethane hydrogenolysis at 200 °C is a classic structure-sensitive probe utilized to examine the catalytic properties of various Rh/ZrO₂ catalysts, and this study showed that the optimum RhNP size is 1.6 nm. The increase of activity when the RhNP size decreases from 6 to 1.6 nm is well-known and corresponds to an increase in the ratio of highly energetic low-coordination sites (corners and edges) required for C–C cleavage adjacent to high planar coordination sites required for hydrogen adsorption. Interestingly, this study showed a drastic decrease of activity when the RhNP size decreased from 1.6 to 0.7 nm, which was attributed to the absence of large planes on the surface of subnanometer RhNPs that restricted the ethane dehydrogenation step.^{1046–1048}

5.5.3.7. Photocatalysis with TiO₂ NPs. Subnanometer size control of both anatase and rutile forms of TiO₂ particles with phenylazomethine dendrimers led to samples with very narrow size distributions. Quantum-size effects were observed in the NPs, and the energy gap between the conduction and valence bands exhibited a crystal-form-dependent blue shift with decreasing NP size (Figure 61).³⁵⁰

5.5.3.8. Hydrodechlorination of 1,2-Dichloroethane. Dendrimer–metal nanocomposites were used as precursors to prepare SiO₂-supported monometallic Pt, Cu, and bimetallic Pt–Cu catalysts with PtCu at 1:1 and 1:3 ratio for heterogeneous hydrodechlorination of 1,2-dichloroethane. These MNPs on SiO₂ support were smaller and had narrower size distribution than those in conventional catalysts prepared using metal salts via the wet-impregnation method. The overall activity decreased with increasing CuNP loading in the catalyst. The process allowed for effective treatment of chlorinated hydrocarbon waste streams with recovery of useful chemical feedstocks.¹⁰⁴⁹

6. Biomedical Applications

6.1. Introduction

The biomedical future of dendrimers was apparent since their discovery with Denkewalter's polylysine dendrimers,⁶ Tomalia's multigeneration PAMAM dendrimers,⁷ and Newko-

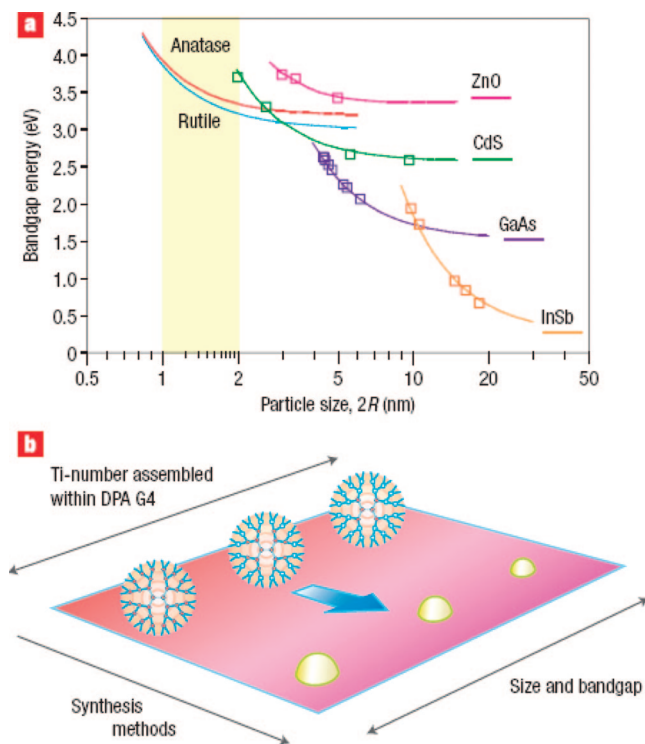


Figure 61. Subnanometer size control and synthetic strategy for Q-size TiO₂ using the DPA G₄ template. (a) Calculated size dependence of the TiO₂ bandgap energy. Unlike previously reported Q-size effects for other semiconductors (experimental data shown by squares), the estimated bandgap energy for TiO₂ dramatically increases as particle size decreases from 2 to 1 nm. In other words, in this range, a subnanometer difference in size critically affects the bandgap energy of TiO₂. (b) Scheme for size-controlled TiO₂ particle formation using the DPA G₄ template. The number of metal ions assembled within the DPA G₄ can be controlled, offering the means to construct size-controlled particles of ~1 nm in dimension. Different methods of synthesis are well-known to produce different crystal forms, that is, the anatase or rutile forms, under certain conditions. Reprinted with permission from ref 350 (Yamamoto's group). Copyright 2008 Nature Publishing Group.

me micellar arborols⁸ in the early 1980s. This aspect was delineated through comparison with biological systems and encapsulation properties, for instance in Tomalia's seminal review in 1990.⁹ The connection and analogy of dendrimers with biomolecules appeared from their sizes and globular shapes that match those of bioassemblies such as DNA duplexes (2.4 nm), insulin (4 nm), hemoglobin (5.5 nm), and lipid bilayer membranes (5.5 nm).^{800,801} Meijer's molecular box was a striking example along this line.¹⁰ In another review, Fréchet referred to dendrimers as artificial proteins in which the dendritic encapsulation of function applies the Nature site-isolation principle.²⁸ Dendrimers self-assemble by supramolecular interactions (see section 4) as do molecular-level organized biological structures. They are site-selective catalysts as shown with metalloporphyrin-cored systems mimicking hemoglobin;²⁴⁵ they are also enzyme mimics as shown by Fréchet upon designing dendritic nanoreactors with polarity gradient that stabilize polar transition states.^{816,817} Rigid dendrimers could mimic bacteriophilic units that are light-harvesting antennae¹⁸⁹ (section 3.1) and natural proteins including redox-active enzymes with iron–sulfur cores.⁵⁰⁷

Medicinal engineering using dendrimers started in the early 1990s by mimicking antibodies for immunological applications and sensor functionalities to selectively recognize DNA

branches and to detect and quantify AIDS virus, and this was reviewed in the mid-1990s.³⁹ Since then, biomedical applications became more and more promising, and reviews are available.^{1050–1076} Thus, we will focus here on the major concepts and most recent developments.

Dendrimers belong to a group of nanocarriers designed to improve the water solubility, pharmacodynamics, pharmacokinetics (circulation time, organ uptake, and tumor accumulation), and bioavailability of drugs in vivo.^{1077–1082} These nanocarriers started with liposomes.¹⁰⁸³ They more recently developed with macromolecules including polymeric micro- and nanoparticles,^{1084,1085} dendrimers, polymeric micelles (nanostructures formed by self-assembly of amphiphiles in water),¹⁰⁸⁶ and polymersomes (polymeric vesicles made of amphiphilic block copolymers that self-assemble in aqueous medium; Figure 62).^{1087,1088}

The leading principles for the use of dendrimers as delivery vehicles involve (i) the charge of the terminal groups that must be neutral or negative in order to avoid or minimize toxicity (or largely masked if cationic), (ii) the design of the molecular architecture to optimize the pharmacokinetics, (iii) the PEGylation for water solubility and biodistribution, (iv) the choice between dendritic encapsulation and covalent attachment to the branches, and (v) the use of targeting groups (folic acid, peptides, monoclonal antibodies, and glycosides) that bind specifically to the receptor targets overexpressed on cancer cells.

Dendrimers are also used as nonviral gene carriers. The dendrimers probed for this purpose are terminated by cationic groups to form electrostatic complexes with negatively charged DNA for gene transfection. Toxicity and efficiency issues are important in this field, however, and need to be discussed (see section 6.2.7).

Among biologically relevant dendrimers, peptide dendrimers are an important class that consists of assemblies of amino acids linked by amide bonds and contain both α -peptides and ϵ -peptides. The majority of peptide dendrimers currently in use are based on the multiple antigen peptide system and have been reviewed by Tam's group,¹⁰⁸⁹ who pioneered the field, and by Crespo et al.¹⁰⁹⁰ Their multiple applications are in immunoassays and serodiagnosis, as inhibitors, mimetics, and artificial proteins, and in intracellular delivery and medical diagnosis (MRI, magnetic resonance angiography, fluorogenic imaging, and serodiagnosis). They play key roles as anticancer, antimicrobial, and antiviral agents,¹⁰⁹¹ in the central nervous system, analgesia, asthma, allergy, and calcium metabolism, and some peptide dendrimers are useful in antiangiogenic therapy (cf. section 6.2.6).^{1089–1091} Glycopeptide dendrimers are a broad class of peptide dendrimers involved in targeting with antigen–antibody interactions (cf. section 6.2.5). In turn, classic dendrimers interact with peptides and proteins in a specific way, with the interactions being of electrostatic and hydrophobic nature. A dramatic example was the remarkable discovery by Prusiner (2004 Nobel Laureate in medicine) and his group in 1999 that 14 cationic PAMAM, PEI, and PPI dendrimers were effective in removing prion molecules in the infectious state (Pr^{PSc}) from both ScN2a cells (Pr^{PSc}-infected neuroblastoma cells) and from Pr^{PSc}-containing brain homogenates.^{1092,1093} This field of protein–dendrimer interactions is promising^{1094–1098} and has recently been reviewed.¹⁰⁹⁴

In addition to their function of drug and gene delivery nanovectors, dendrimers are used for their intrinsic drug

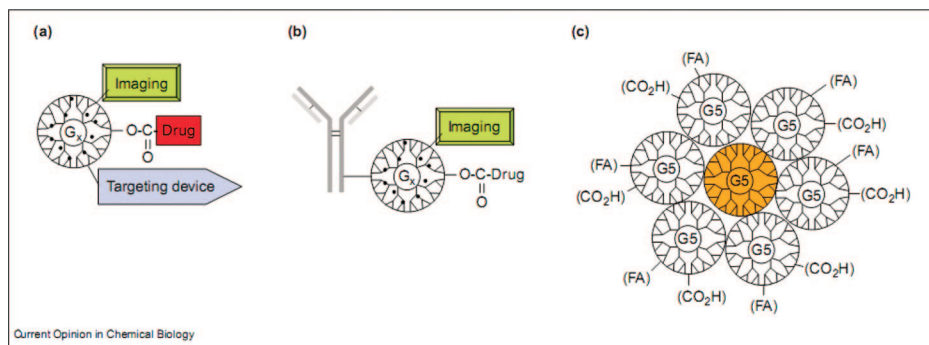


Figure 62. Dendritic nanodevices for therapeutic applications: (a) surface-modified PAMAM dendrimer for targeting, imaging, and drug delivery; (b) antibody–dendrimer conjugate; (c) tecto(dendrimer). FA = folate. Reprinted with permission from ref 1088 (Baker Jr.'s group). Copyright 2002 Elsevier.

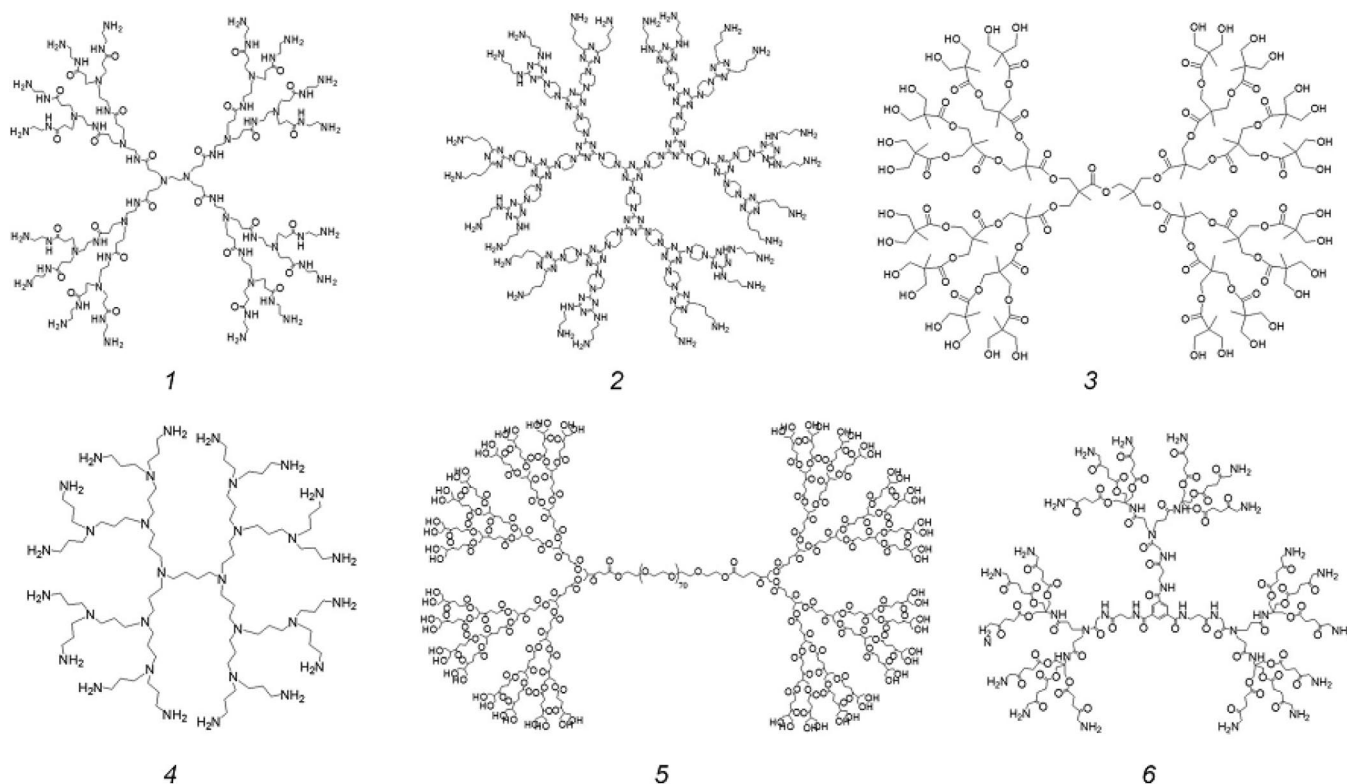


Figure 63. Structures of dendrimers used for delivery of cancer therapies: (1) PAMAM, (2) melamine-based dendrimer, (3) dendrimer based on 2,2-bis(hydroxymethyl) propionic acid, (4) PPI, (5) dendrimer based on glycerol and succinic acid with a PEG core, and (6) dendrimer based on 5-aminolevulinic acid. Reprinted with permission from ref 1070 (Grinstaff's group). Copyright 2008 Elsevier.

properties (for instance to remove prions), as scaffolds for tissue repair, photodynamic therapy based on photosensitizing agents, photothermal therapy based on gold and iron oxide nanoparticles, boron neutron capture therapy based on lethal $^{10}\text{B}(n,\alpha)$ capture reactions, antimicrobial therapy, antiviral therapy, immunogens, and vaccines. Besides therapy, dendrimers are used in diagnostics as sensors (molecular probes) and for imaging techniques (cf. section 6.8) based on magnetic resonance (MRI) with gadolinium paramagnetic contrast agents and computed tomography (X-ray contrast agents) especially with iodinated contrast agents (Figures 63–65).^{1069–1071}

6.2. Drug Delivery

Drug delivery using nanomaterials has revolutionized medicine by largely improving the efficiency and reducing the side effects of drugs, creating a new branch, nanomedicine.

Although polymers have been used for several decades for this purpose, better defined macromolecules such as dendrimers, dendronized polymers, and hyperbranched polymers are becoming more attractive because of their low dispersity, specific morphology, branching tethers, multivalency, high density of functional groups, globular or other well-defined shapes, and controlled molecular weights. In addition, high penetration abilities through the cell membrane result in increased levels of cellular drug uptake. Such enhanced penetration and retention (EPR) can be designed by the functionalization of dendrimers with polyethylene glycol (PEG) tethers, folate, etc. (Figures 66 and 67).

Very often, the lack of immunogenicity makes dendrimers safer than synthesized peptides and natural proteins. Finally, the pharmacodynamic (PD) and pharmacokinetic (PK) behaviors of dendrimer–drug assemblies can be monitored in a reproducible manner and thus optimized upon dendrimer

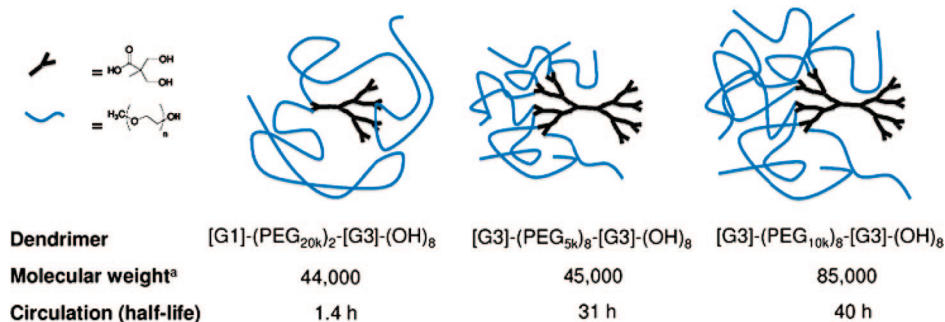


Figure 64. Poly(ethylene oxide) bow-tie hybrids. Pharmacokinetics of dendrons based on 2,2-bis(hydroxymethyl)propionic acid can be tuned by varying generation size (G_1 , G_2 , and G_3) and PEG chain molecular weight (5 000, 10 000, and 20 000). ^aMALDI-TOF MS. Reprinted with permission from ref 1070 (Grinstaff's group). Copyright 2008 Elsevier.

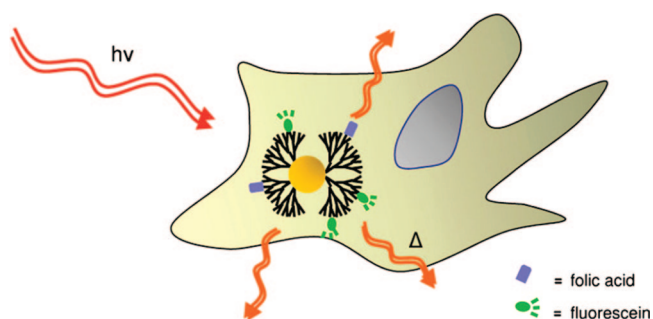


Figure 65. Photothermal therapy. Conceptual representation of photothermal therapy using dendrimer-entrapped gold nanoparticles. The nanoparticles would be targeted to tumor cells via folic acid receptors, and upon exposure to near-infrared light, the gold particles would emit heat and kill the host cell. Reprinted with permission from ref 1070 (Grinstaff's group). Copyright 2008 Elsevier.

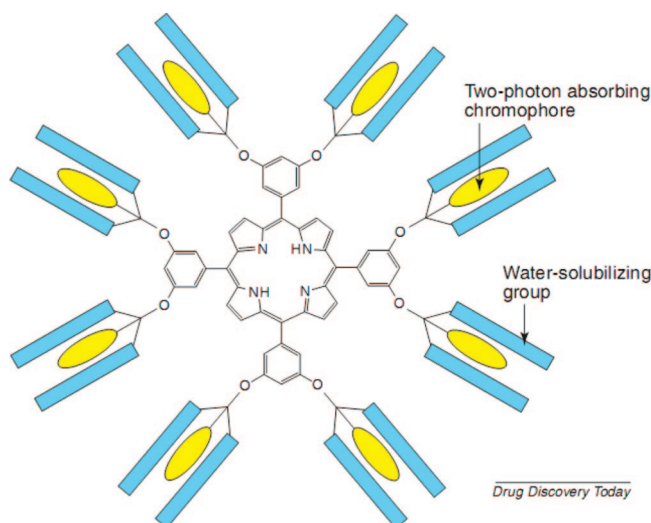


Figure 67. Water-soluble dendritic porphyrin incorporating two-photon-absorbing chromophores for photodynamic therapy. Reprinted with permission from ref 1169 (Fréchet's group). Copyright 2006 Elsevier.

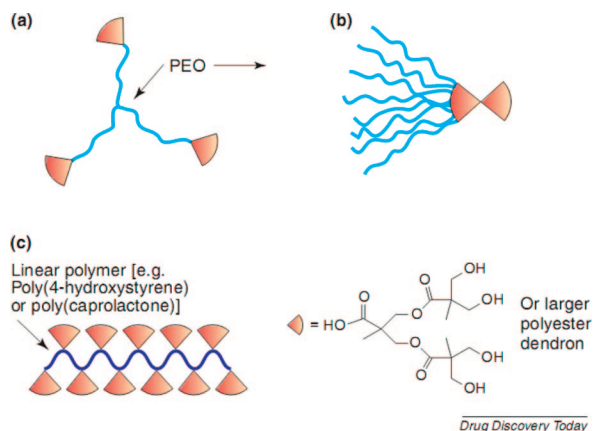


Figure 66. Polyester dendrimer-linear polymer hybrids: (a) hybrid of polyester dendrons and a poly(ethylene oxide) (PEO) star in which the multivalent dendron can carry several copies of drug and the linear PEO provides solubility; (b) "bow-tie" hybrid of polyester dendrimers and PEO; (c) polyester dendronized linear polymer. Reprinted with permission from ref 1169 (Fréchet's group). Copyright 2006 Elsevier.

design. The targeted properties of improvements brought by dendrimers or their derivatives are the water solubility, biodistribution, circulation time in blood, and therapeutic efficiency of formulations involving these nanocarriers. The drugs that are involved are mainly (i) potent anticancer drugs, (ii) nonsteroidal anti-inflammatory drugs, and (iii) antimicrobial and antiviral drugs, but many other drugs have been probed with dendrimers. Two distinct strategies are being used: (i) drug "complexation" to dendrimers by encapsulation inside dendrimers or electrostatic binding by ionic groups at the dendrimer periphery and (ii) drug "conjugation" by

covalent attachment to the dendritic tethers (Figures 68–70).^{1056–1062,1069–1073,1099–1116} These principles also apply to the design of antibacterial agents.¹¹¹⁷

6.2.1. Drug Solubilization by Encapsulation: Drug-Dendrimer "Complexes"

The major problem of most drugs is their lack of water solubility. The solubility of dendrimers is essentially dictated by the solubility of their terminal groups. Thus, dendrimers have been designed with water-soluble termini and hydrophobic interiors in such a way that they are able to encapsulate hydrophobic drugs.^{1056,1057,1062,1107–1127} Alternatively, positively or negatively charged dendrimer termini can electrostatically bind drugs bearing opposite charges.^{1106,1109,1128,1129} With the term "complex", the community of dendrimer scientists means drugs that are bound to the dendrimers by noncovalent bonds, i.e., supramolecular bonds: ionic, hydrogen bonding, van der Waals interactions, π bonding, hydrophobic solvation. Small drug molecules are encapsulated most of the time in the dendrimer interior, whereas large molecules preferably adsorb near the surface (Figure 69, even if some back-folding can still occur⁵³⁶).

A classic example is the anti-inflammatory drug ibuprofen for which 78 molecules were found to complex G_4 -PAMAM dendrimer at the amine dendrimer groups through electrostatic interactions with the carboxy groups of the drug. In vitro release was shown to be slow compared to the free

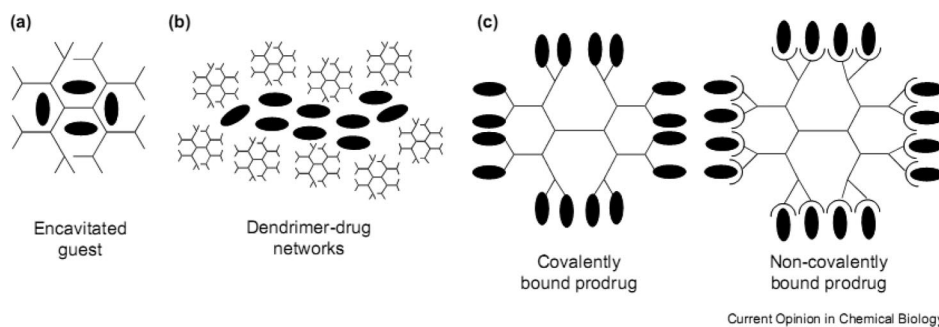


Figure 68. Schematic representations of dendrimer drug-delivery systems. The darkened oval represents an active substance. Reprinted with permission from ref 1105 (Cloninger's group). Copyright 2005 Elsevier.

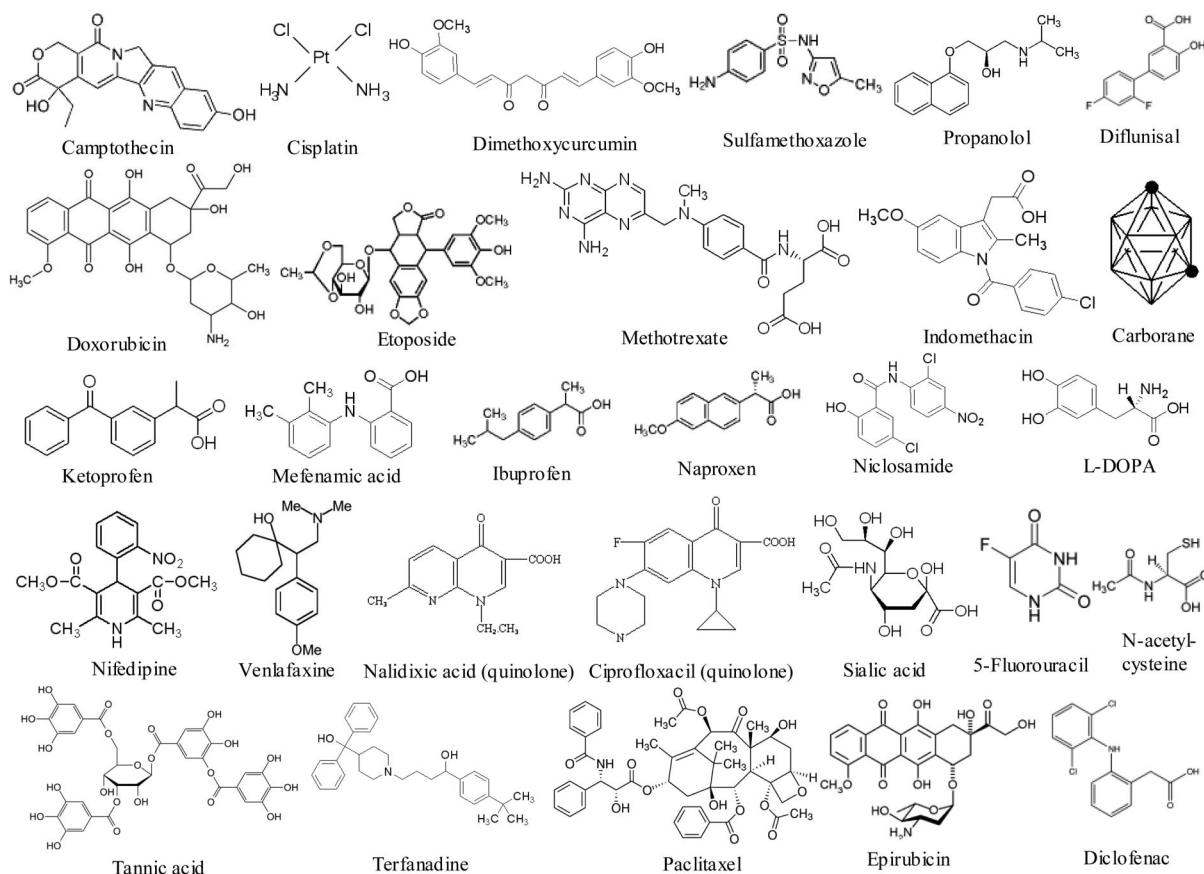


Figure 69. Molecular structures of drugs encapsulated or stabilized by dendrimers.

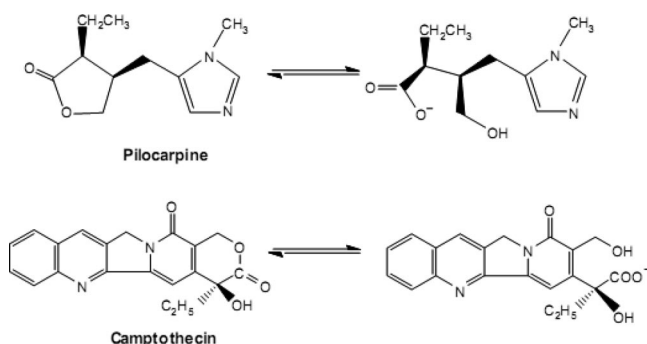


Figure 70. Hydrolysis of camptothecin and pilocarpine from lactone forms to carboxylate forms. Reprinted with permission from ref 1107 (Xu's group). Copyright 2008 Elsevier.

drug. The drug–dendrimer complex was found to enter A549 cells much more rapidly than free ibuprofen, suggesting efficient drug carrying inside the cell.^{1130,1131}

The water-insoluble anticancer drugs camptothecins were encapsulated in $G_{4.5}$ carboxylate-terminated polyester dendrimer.^{1125,1126,1132} Poly(glycerol succinic acid) dendrimers (PGLSA dendrimers) were also investigated for their capacity to encapsulate camptothecins. G_4 -PGLSA- CO_2Na (unlike G_4 -PGLSA- OH) was successfully used in the case of 10-hydroxycamptothecin, and exposure to MCF-7 human breast cancer cells led to significant toxicity increase with less than 5% of viable cells at a concentration of $20 \mu\text{M}$.¹¹³³ Solubilization of the dendrimer–drug complex depends on the dendrimer generation. For instance, the solubilization of the hydrophobic drug nifedipine, a calcium channel-blocking agent, was improved upon increasing the PAMAM dendrimer generation.^{1134,1135} PAMAM dendritic drug solubilization increased the flux of indomethacin in transdermal delivery in vitro and in vivo.¹¹³⁶ PAMAM–dendrimer encapsulation of pilocarpine nitrate and tropicamide resulted in significantly enhanced miotic and mydriatic activities on rabbit eyes

compared to that of free drug. Greatly enhanced penetration of the drugs through the cornea and drug release are favored by the bioadhesive properties of the dendrimers.¹¹³⁷

All these examples indicate that drug complexation in water-soluble dendrimers enhanced drug activities, but it has been pointed out that this rule is not universal. For instance, G_4 – G_6 amine-terminated dendrimer–camptothecin complexes showed lower anticancer activities than the free drug despite significantly enhanced drug solubilization using these dendrimers. This was taken into account by accelerated hydrolysis of camptothecins from an active lactone form to an inactive carboxylate form upon dendrimer complexation (Figure 70).¹¹⁰⁶

Thus, the pH of the medium plays an important role. In another such example, a 3 400 molecular-weight PEG core was introduced into G_4 -PGLSA providing (G_4 -PGLSA-OH)₂-PEG₃₄₀₀, and this complex with 10-hydroxycamptothecin showed 20-fold water solubility increase but only similar cytotoxicity to the free drug toward HT-29 human colon cancer cells.¹¹³²

Biodistribution of the PAMAM dendrimers has been considered to be a problem, because they mostly accumulate in the liver and, for instance, only 1% of intravenously injected dendrimer was still in the blood after one hour.¹¹³⁸ PEGylated dendrimers, however, exhibit a considerably longer circulation time in the blood (vide infra).¹¹³⁹

The nonsteroidal anti-inflammatory drugs (NSAIDs) are intensively studied as amino-terminated dendrimer complexes (PAMAM or PPI), especially because most of them contain a carboxyl group that can electrostatically bind these dendrimers, yielding ammonium carboxylate complexes. Thus, successful results were obtained with aspirin, indomethacin, flurbiprofen, ketoprofen, ibuprofen, naproxen, diflunisal, diclofenac, aceclofenac, and proicam.^{559,1106–1119,1140,1141} Inflammatory inhibition, mean residence time in blood, and bioavailability are generally superior with these dendrimer–drug complexes compared to the corresponding free drug. Thus, the pharmacodynamic (PD) and pharmacokinetics (PK) are usually improved with these complexes, and when this is not the case, the problem can be resolved by local administration of the complex or using targeting groups such as PEG, folate or galactose in dendrimer conjugates (vide infra).^{1106–1118,1136,1142–1146}

A drawback of drug–dendrimer complexes is the possible primary removal of the drug from the complex before it reaches the cancer cells. Indeed dendrimer–drug complexes have been shown to be unstable in plasma and buffers (Figure 71).^{1130,1131,1147,1148}

Therefore, the drug–dendrimer conjugate strategy has also been used (vide infra). The advantage of noncovalent drug–dendrimer interactions, however, is a higher solubility of otherwise water-insoluble drugs than with conjugates. On the other hand, conjugation allows a higher drug payload.^{1149–1154}

6.2.2. Covalent Drug Binding to Dendrimer Termini: Drug–Dendrimer “Conjugates”

Dendrimer–drug conjugates turn out to be superior to drug–dendrimer complexes, because on the latter the drugs can be released before reaching the targeted cell. They are superior to the free drugs, because the drug can be specifically targeted to the cancer cell, and then the multiple drug molecules are released from a single dendrimer–drug conjugate by pH change at the cancer cell. They decrease nonspecific toxicity, optimize biodistribution, and increase

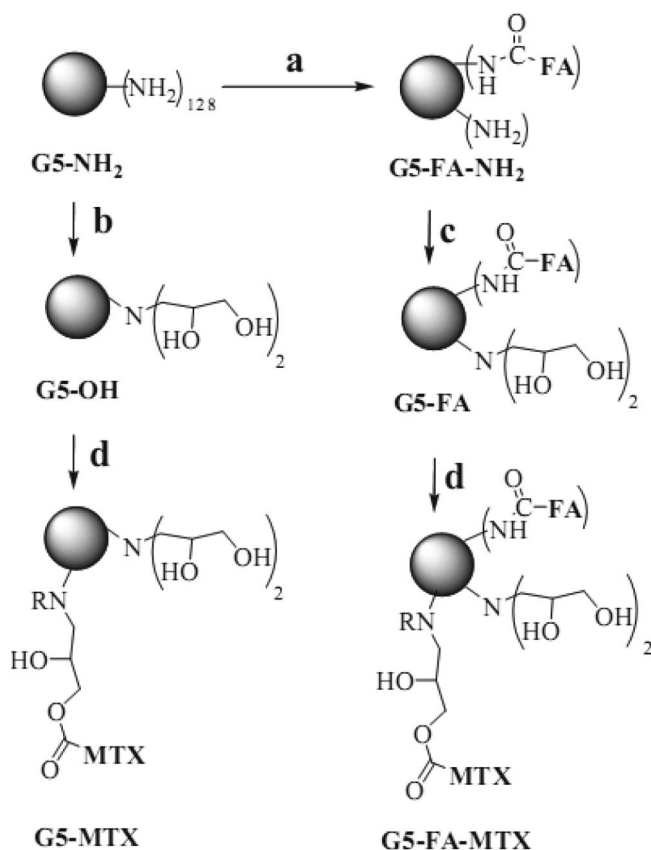


Figure 71. Synthesis of dendrimer conjugates: (a) folic acid, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, dimethyl sulfoxide (DMSO); (b) glycidol, DMSO; (c) glycidol, DMSO/phosphate-buffered saline (PBS); (d) methotrexate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMSO. Reprinted with permission from ref 1147 (Baker’s group). Copyright 2005 Elsevier.

circulation time in blood. Plasma half-life is increased as well as drug resistance.¹⁰⁷³ Dendrimer–drug conjugates rapidly penetrate into the cells and cytoplasm.^{1155–1159} For instance, when PAMAM dendrimers were conjugated with ibuprofen via an ester linkage, hydrolysis in the cells produced prostaglandin expression in 30 min instead of 1 h for the free ibuprofen.¹¹⁵⁸

In another example, methotrexate delivery to CCRF-CEM human acute lymphoblastoid leukemia and CHO Chinese hamster ovary cell lines was achieved by PAMAM–methotrexate conjugates. It was more efficient when the $G_{2.5}$ -PAMAM dendrimer was functionalized with CO₂H termini (3- and 8-fold more potent than free methotrexate) than with amine G_3 -PAMAM, with the latter showing no sensitivity increase compared to the free drug. The decrease of lysosomal residence time of the cationic PAMAM subsequent to drug cleavage was taken to be responsible for reduced drug release.¹¹⁶²

When paclitaxel was conjugated to PAMAM dendrimers via a succinic acid linker, the release profile and cell penetration were as good as those of PEG–paclitaxel conjugates, but the dendrimer–paclitaxel conjugate exhibited much higher anticancer activity than free paclitaxel (10-fold) and than the PEG–paclitaxel conjugate (250-fold).¹¹⁶³ 5-Fluorouracil (5-FU), an anticancer drug with very toxic side effects, was conjugated with dendritic polymers centered on 1,4,7,10-tetraazacyclododecane, and these water-soluble conjugates release free 5-FU at a slow rate with concomitant

Table 1. Alphabetical List of Drugs Solubilized in Dendrimer–Drug “Complexes”¹⁰⁵²

drug	disease	dendrimer	reference
Artemer	malaria	poly(L-lysine)–PEG	1218
Camptothecin	cancer	polyester, polyether	1052, 1125–1127
Cisplatin	cancer	PAMAM	1165
Diclofenac	inflammation	citric acid–PEG ₆₀₀	521
Diflunisal	inflammation	G ₂ –G ₄ -PAMAM	1128, 1146
Dimethoxycurcumin	cancer	G _{3,5} –G ₄ -PAMAM	1149
Doxorubicin	cancer	G ₃ –G ₄ -PAMAM–PEG ₂₀₀₀	1059, 1050, 1192–1195
Etoposide	cancer	G ₂ -PAMAM–OH–PEG ₅₀₀₀	1151
5-Fluorouracil	cancer	G ₄ -PAMAM–PEG	1216, 1217
Ibuprofen	inflammation	G ₄ -PAMAM	1128, 1130, 1131
Indomethacin	inflammation	G _{3,5} -PAMAM–CO ₂ [–] , PEG	1100, 1143, 1469
Ketoprofen	inflammation	G ₂ –G ₅ -PAMAM	1109, 1110, 1144
Mefenamic acid	inflammation	citric acid–PEG ₆₀₀	521
Methotrexate	cancer	G ₃ –G ₄ -PAMAM–PEG ₂₀₀₀	1147, 1148, 1150, 1152, 1206–1208
Naproxen	inflammation	G ₄ -PAMAM	1128
Niclosamide	tapeworm infection	PAMAM	1135
Nifedipine	inflammation	G ₀ –G ₃ -PAMAM	1134
Paclitaxel	cancer	polyglycerol	1202, 1203
Quinolones	infections	G ₃ –G ₅ -MAMAM	1107, 1108
Sialic acid	Alzheimer	PAMAM	1209
Silver salts	gram-positive bacteria	G ₄ -PAMAM	664
Sulfamethoxazole	infections	G ₂ –G ₄ -PAMAM	1111, 1112

reduction of toxicity upon incubation with phosphate-buffered saline.¹¹⁶⁴ In an early study, it was shown that G_{3,5}-PAMAM–*cis*-platin conjugates were active against intraperitoneal B16F10 melanoma, whereas *cis*-platin alone was not; 50-fold increase toxicity was found against solid tumor tissues, and toxicity was 3- to 15-fold smaller than that of the free drug.¹¹⁶⁵ PPI dendrimer–*cis*-platin conjugates were obtained by reactions of the free amine dendrimers with potassium tetrachloroplatinate.¹¹⁶⁶ The anticancer drug doxorubicin conjugated to a dendritic polyester was used to deliver the drug using a pH-sensitive linkage. Whereas this linkage is stable at the physiological pH of 7.4, it is cleaved at the lower pH value of the cancer cell,¹¹⁶⁷ which then allows liberation of doxorubicin.^{1168–1170}

The linkage is the acid-labile hydrazone group, allowing the drug to be released and successfully taken up by several cancer lines (Figure 72).^{1139,1168–1170} G₄-PAMAM was conjugated to 12 molecules of a glutaric acid derivative of methylprednisolone, a model construct in A549 human lung epithelial carcinoma cells and further to fluorescein isothiocyanate. Evaluation of the dynamics of cellular entry on A549 human lung epithelial carcinoma

cells by fluorescence and confocal microscopy showed localization in the cytosol, and the pharmacological activity was comparable to that of free methylprednisolone.¹¹⁷¹

N-acetyl cysteine, an anti-inflammatory agent with significant potential for clinical use in the treatment of neuroinflammation, stroke, and cerebral palsy, was conjugated to PAMAM dendrimers via a disulfide linkage for intracellular delivery of this drug to enhance its efficacy, reduce its dosage, and prevent it from binding plasma proteins. Evaluation of the conjugates for their release kinetics in the presence of glutathione, cysteine, and bovine serum albumin at both physiological and lysosomal pH indicated that the conjugate could deliver 60% of its *N*-acetyl cysteine payload within 1 h at intracellular GSH concentrations at physiological pH.¹¹⁷²

Streptokinase, a 47 kDa single-chain protein used as intravenous thrombolytic agent especially in myocardial ischemia and stroke since the 1980s, was conjugated to G_{3,5}-PAMAM dendrimers using the active ester method under mild aqueous conditions, and the conjugates exhibited high

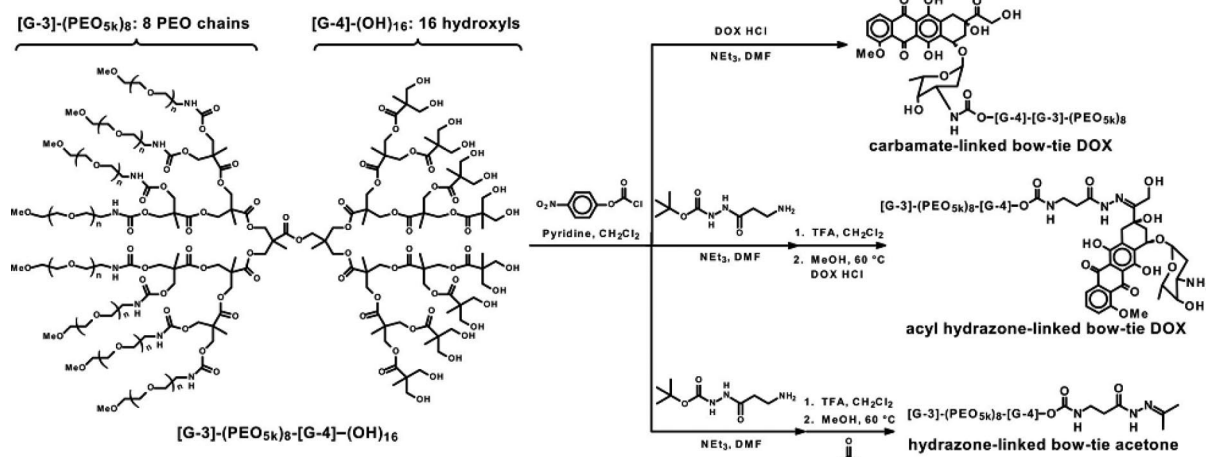


Figure 72. Functionalization of the [G₃]-[PEO₅₀₀₀]₈-[G₄]-[OH] dendrimers for therapeutic studies. Doxorubicin (DOX) is linked to the bow tie by means of a carbamate (top) or acyl hydrazone (middle) linkage. In the bottom route, hydrazone groups of the bow tie are blocked upon reaction with acetone. The top and bottom bow ties represent control treatments. Reprinted with permission from ref 1169 (Szoka's and Fréchet's groups). Copyright 2006 National Academy of Sciences of the U.S.A.

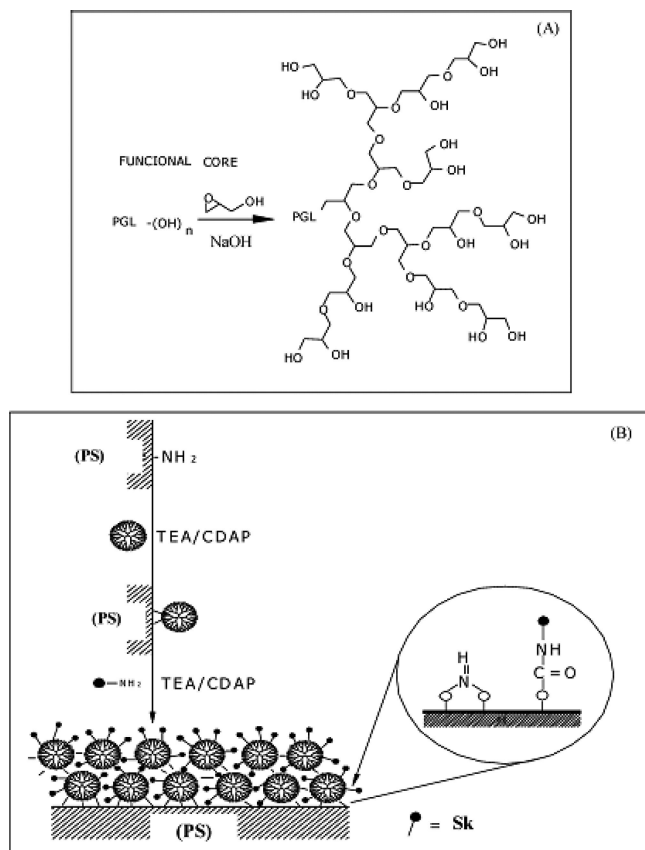


Figure 73. (A) Schematic diagram of the polyglycerol-dendrimer (PGLD) synthesis and (B) immobilization of the bioconjugate PGLD-streptokinase (Sk) onto wells of ELISA (PS) plates. The epifluorescence microscopy results indicate that PGLD-Sk coating showed an improved antithrombogenic character relative to the uncoated ELISA plates. Reprinted with permission from ref 1212 (Roman's group). Copyright 2006 Springer Science.

enzymatic activity retention (up to 80%) and quick in vitro clot lysis (comparable to that of free streptokinase).¹¹⁷³

In conclusion, noncovalent and covalent drug-dendrimer assemblies usually increase drug efficiency compared to the free drug, and several drug-dendrimer complexes or conjugates are in early clinical trials.¹¹⁷⁴ Remaining problems include hemolytic toxicity of NH_2 -terminated dendrimers;^{1073,1175–1178} therefore, biocompatible dendrimers containing PEG tethers, i.e., PEGylated dendrimers, have

been more recently actively investigated as drug-delivery nanocarriers.

6.2.3. PEGylated Dendrimers As Biocompatible Drug Nanocarriers

The advantages of drug biostability in polymeric nanocarriers have been initially illustrated by Ringsdorf in 1975.^{1179,1180} Subsequently, many water-soluble polymers were tested for drug delivery. Among a variety of water-solubilizing groups,¹¹⁸⁰ PEG has appeared as one of the most promising components of polymers^{1180,1182–1186} and dendrimers^{1175,1176,1187,1188} or so-called dendrimeric micelles (Figure 75)¹¹⁸⁹ in drug-delivery systems, in particular because of its biocompatibility.¹¹⁹⁰

The advantages of attaching PEG tethers to the dendrimer termini are (i) solubilization of the dendrimers in water, (ii) solubilization of the hydrophobic drugs in water by encapsulating the drug inside the water-soluble dendrimer, (iii) increased drug loading inside the dendrimer compared to the non-PEGylated dendrimers, (iv) eliminated hemolytic toxicity, (v) considerably increased circulation time in blood of the drug-dendrimer assemblies, (vi) decreased dendrimer uptake by the organs, (vii) considerably increased bioavailability of the drug, (viii) improved dendrimer kinetic stability, (ix) decreased undesired toxicity, (x) reduced immunogenicity and antigenicity by shielding the dendrimers against destructive mechanisms in the body, and (xi) improved targeting to the active site by EPR effect.

Fréchet's group, who pioneered the design and use of PEGylated dendrimers,^{1175,1176} also combined PEGylation with biodegradable polyester dendrimers for therapeutic applications of drug delivery in cancer treatment with studies of accumulation in solid tumors. These "bow-tie"-shaped dendrimers consisted of two covalently attached polyester dendrons, where one dendron provided multiple functional handles for the attachment of therapeutically active moieties, while the other was used for attachment of PEG tethers. Drug loading could be controlled by varying the generation of the dendrons and the mass of the PEG tethers.¹¹⁹¹ Since PAMAM dendrimers are by far the most frequently probed dendrimers toward biomedical applications, early studies involved the decoration of G_3 - and G_4 -PAMAM generations with PEG tethers, and the water-insoluble anticancer drugs MTX and adriamycin were encapsulated into these PAMAM-PEG dendrimers. The encapsulation ability increased with increas-

Table 2. Examples of Drug-Dendrimer "Conjugates" (Figures 73 and 74)

drug	dendrimer	linker	reference
Methotrexate (cancer)	G_3 -PAMAM	amide	1162
Propranolol (cardiac)	G_3 -PAMAM	amide	1156, 1159
Terfenadine (allergy)	G_1 -PAMAM	succinic acid	1156
		succinyl-diethylene glycol	1156
L-DOPA (Parkinson)	L-DOPA	diester	1178
Doxorubicin (cancer)	polyester	carbamate	1169, 1170
Epirubicin (cancer)	adipic- or β -glutamic acid	PEG	1132
Methotrexate (cancer)	G_5 -PAMAM	ester	1249–1254, 1158
Naproxen (inflammation)	G_0 -PAMAM	amide	1155
<i>N</i> -acetylcysteine (neuroinflammation)	PAMAM- CO_2H	amide	1214
		ester (L-lactic acid, DET)	1152, 1157
Paclitaxel (cancer)	G_4 - G_5 -PAMAM-OH	ester (succinic acid)	1163, 1250
Carborane (NCBT, cancer)	G_5 -PAMAM	ester	1154, 1242–1244
Sialic acid (Alzheimer)	G_4 -PAMAM	amide or ether (anomeric)	1210
Hydroxypyridinone (hemochromatosis)		polyamide dendrimers	1211
Streptokinase (thrombosis)	polyglycerol	ether	1212
Venlafaxine (depression)	$G_{2,5}$ -PAMAM-PEG	ester	1213
Tannic acid (aneurysm)	tannic acid mimicking dendrimers		1215

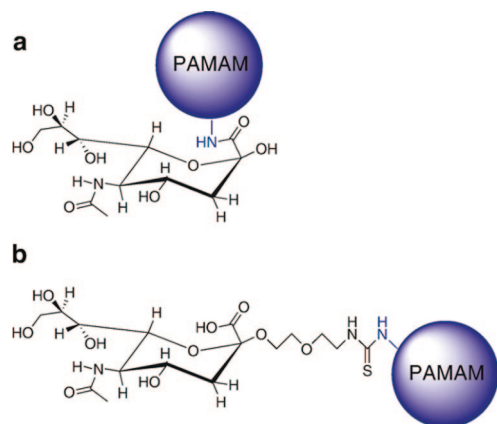


Figure 74. Two different attachments of the sialic acid moiety on the dendrimers: (a) nonphysiological attachment of sialic acid to dendrimeric termini via carboxylic acid and (b) physiological attachment of sialic acid to dendrimeric termini via anomeric hydroxyl group. Sialic acid functionalized dendrimeric polymers can act as mimics of cell-surface sialic acid clusters and attenuate the neurotoxicity of β -Amyloid ($A\beta$), the primary protein component of senile plaques in Alzheimer's disease. Reprinted with permission from ref 1209 (Good's group). Copyright 2006 Elsevier.

ing PAMAM generation and length of the PEG chains, with the highest results being obtained with G_4 -PAMAM-PEG₂₀₀₀, which could retain 26 MTX molecules or 6.6 adriamycin molecules per dendrimer.^{1192–1195}

Melanine dendrimers are an interesting family of dendrimers synthesized by Simanek's group, and functionalization of these dendrimers using various water-solubilizing surface groups (amine, guanidine, carboxylate, sulfonate, phosphonate, and PEG) was followed by evaluation for hemolytic potential and cytotoxicity in vivo in mice. In particular, PEGylated dendrimers showed no toxicity, lethality, or abnormalities in blood.^{1196–1198}

G_3 , G_4 , and G_5 polyglycerol dendrimers increased the water solubility of the anticancer drug paclitaxel by 270-, 370-, and 434-fold, respectively. With a similar molecular weight of 2000, the water solubility of paclitaxel was 11-fold increased with G_3 dendrimer compared to nondendritic PEG₂₀₀₀. The paclitaxel solubility in water is commonly increased using PEG₄₀₀ as a cosolvent or hydrotropic agent, but the solubility increase using these dendrimers is considerably higher.^{1201–1203}

PEGylation of PAMAM dendrimers with higher-generation (G_4) and longer PEG strand (2000 Da) gave better drug encapsulation.^{1192–1200} The solubility of guest molecules is not always enhanced by increasing the length of the PEG tethers, however. For instance, G_3 -PAMAM-PEG₂₀₀₀ solubilized more pyrene in water than either G_3 -PAMAM-PEG₇₅₀ or G_2 -PAMAM-PEG₂₀₀₀, which was explained by interpenetration from adjacent dendrimers.^{1204,1205} Heterofunctionalization of PEG for instance with di-*tert*-butylpyrocarbonate can be used to covalently link the drug to the PAMAM dendrimer.^{1160,1161,1202,1203} A study of the influence of the degree of PEG substitution on the methotrexate encapsulation efficiency and release profile of PEGylated G_3 -PAMAM dendrimer indicated only a small effect. This was taken as an indication that the drug was enclosed in the dendrimer interior and not on the surrounding chains of the PEG. Effect of PEG chain substitution on the release profile was not significant (Figure 74).^{1206–1215} PEGylation of G_4 -PAMAM dendrimer with PEG₅₀₀₀ increased 12-fold

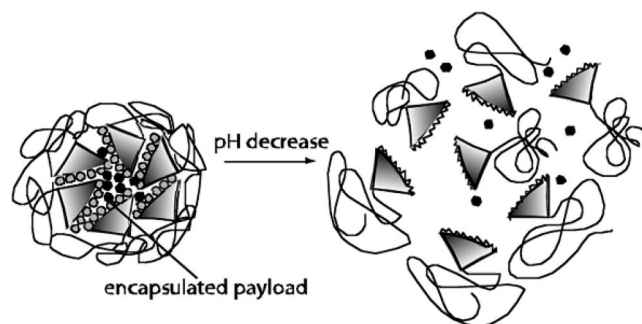


Figure 75. Schematic representation of release of guest molecules from a pH-sensitive micelle of linear-dendritic copolymer. Reprinted with permission from ref 1189 (Thayumanavan's group). Copyright 2005 National Institutes of Health.

the entrapment of 5-fluorouracil, which was taken into account by sealing of the dendritic structure at the dendrimer periphery by PEG coating that prevented drug release. This PEGylated dendrimer showed a drug-release profile rate that was one-sixth that of the non-PEGylated dendrimer, and release of 5-fluorouracil was observed for up to 6 days across the dialysis membrane. PEGylation of the dendrimers also resulted in decreased hemolysis of red blood cells to less than 5% of the level recorded with the non-PEGylated dendrimers, and similar results were obtained in related studies with other drugs and PEGylated dendrimers.^{1216,1217} Although the toxicity of PAMAM dendrimers is controversial and seems to be concentration- and dose-dependent, an interesting observation is that PEGylation or lauroylation resulted in a significant decrease in the toxicity of cationic PAMAM dendrimers, due to a shielding of the positive charges.^{1218,1219} For instance, the IC_{50} values of PEGylated PAMAM dendrimers were 12–105-fold higher than those of parent PAMAM dendrimers. PEGylation of PAMAM dendrimers indeed reduced PAMAM-induced cell apoptosis by attenuating the reactive oxygen species production and inhibiting PAMAM-induced mitochondrial membrane potential collapse. PAMAM dendrimers with low molecular-weight PEG or with little PEG did not significantly change the endocytic properties, and PAMAM dendrimers with high molecular weight were much less cytotoxic.¹²²⁰ Similarly, other chemical groups are also efficient in toxicity reduction.^{1221–1225} PEGylation of G_6 -lysine dendrimers resulted in blood retention, lower accumulation in organs depending on the degree of PEGylation, and effective accumulation in mice tumor due to the EPR effect.^{1226,1227}

For dendrimer conjugates, the introduction of the PEG chain can be carried out either in a bow-tie dendrimer without PEG functionalization¹¹⁹¹ or by linking the dendrimer core to the drug via a PEG tether. In the latter case, a functionalization of the PEG is necessary. For instance, the functionalization of PEG with a bicarboxylic amino acid was achieved.^{1228,1229} In complement, the pH-driven hydrolysis of the drug-dendrimer linker at the lower pH value of the cancer cells is an elegant solution pioneered by the Fréchet group (acetal,¹²³⁰ hydrazone^{1139,1168–1170}).

The Paleos group achieved mono- and polyfunctionalization of G_5 -PPI dendrimer using PEGylation with methoxy PEG isocyanate (MW = 5 kDa), leading to 4 or 8 PEG chains out of the 64 amino termini. The water-insoluble betamethanosone valerate and betamethanosone diprononate were solubilized in water, with the loading being 13 and 7 wt %, respectively, for G_5 -PPI-8PEG and

6 and 4 wt %, respectively, for G_5 -PPI-4PEG.¹²³¹ Further functionalization of the latter dendrimer was achieved with guanidinium moieties for targeting by interaction with carboxylate and phosphate receptors toward gene therapy (vide infra section 6.2.6). The introduction of eight guanidine moieties almost doubled the water solubility of betamethasone valerate.¹²³² Hyperbranched polyglycerol exhibiting low toxicity and biocompatibility was also functionalized by PEGylation and folate-PEGylation, providing a multifunctional drug-delivery system.¹²³³ PEGylation was also carried out with PAMAM dendrimers such as G_5 , which decreased toxicity and allowed gene transfection.¹²³⁴ Bifunctional PEG was linked to the dendrimer on one side and to brain-targeting transferrin or lactoferrin on the other side, and the DNA dendriplex was shown to cross the blood-brain barrier of mice subsequent to intravenous injection for transfection to the brain.^{1235,1236} PEGylated poly(L-lysine) dendrimers coated with chondroitin sulfate A (CSA) were used to encapsulate the drug by the dialysis method, which increased drug-loading capacity and controlled and sustained the release of a blood schizonticide, chloroquine phosphate.¹²³⁷ The proportion of branch PEGylation was optimized in the more biocompatible low-generation $G_{2.5}$ - G_4 -PAMAM dendrimers in order to efficiently utilize as many remaining branches as possible for drug loading, while maintaining the drug carrier cytocompatibility. 3PEG- G_3 and 10PEG- G_4 were considered initially optimized stealth dendrimers that would be further modified to deliver drugs of interest.¹²³⁸ A G_5 -PPI dendrimer was PEGylated using dicarboxylic acid PEG₂₀₀₀ and was loaded with famotidine. PEGylation improved the dendrimer drug-loading capacity, reduced hemolytic toxicity, and demonstrated suitability for prolonged drug delivery in vitro and in vivo level and tissue distribution in albino rats (Figure 76).¹²³⁹

6.2.4. Folate: A Major Tumor Recognition Group in Drug-Dendrimer Conjugates

Tumor cells overexpress folate, specific glycosides (vide infra, section 6.2.5), and some other receptors such as specific peptide sequences (vide infra, section 6.2.6) that can be used as targets when they are conjugated to dendrimers or other nanocarriers that are also conjugated to anticancer drugs.¹²⁴⁰⁻¹²⁴⁴ This strategy of vectorization considerably reduces the drug distribution to normal cells and reduces side effects in the same time as it improves the drug efficiency.

Cancer inhibition by folic acid has been known since 1944.¹²⁴⁵ The folate receptor is overexpressed by ovarian, lung, colon, kidney, choriocarcinoma, choroid plexus (brain) and childhood ependymomas tumors, and various diseased tissues.^{1073,1246} Therefore, folate has been conjugated to various delivery devices (polymers, polymeric micelles, liposomes, nanoparticles, proteins, protein toxins)^{1073,1247} and especially to dendrimers first by the groups of Fréchet¹²⁴⁸ and Tomalia.¹⁰⁵³ The former used polyether dendrimers conjugated to an average of 12.6 folate residues and to an average of 4.7 molecules of the antineoplastic drug MTX via hydrazide linkers, whereas the latter used G_5 -PAMAM-folate conjugate dendrimers with complexation to MTX. In a recent study, G_5 -PAMAM dendrimers, conjugated to folate, MTX, and fluorescein through thiourea, ester, and amide linkages, respectively, inhibited cell growth in KB cells more efficiently than nontargeted dendrimers. Slow hydrolysis of the dendrimer-MTX linkage, however, caused reduced antiproliferative activity compared to free

MTX. This was attributed to the function of the β -carboxyl group as a linker inhibiting physiological polyglutamation of MTX (Figure 77),¹²⁴⁹⁻¹²⁵⁴ which proceeded with this β -carboxyl group in free MTX.¹²⁵⁵

PAMAM dendrimers conjugated to folic acid and MTX or tritium were 10 times more efficient than the free drug in delaying human tumor growth in immunodeficient mice bearing KB tumors, and they could also extend the life of these mice. In addition, these dendrimers were also conjugated to fluorescein or 6-carboxytetramethyl rhodamine for detection. Folate conjugation provoked the concentration of the conjugate in the tumor tissue during 4 days, and confocal microscopy confirmed internalization into tumor cells.¹²⁵⁶ High-performance liquid chromatography (HPLC), size-exclusion chromatography, and capillary electrophoresis have been used to analyze the purity of G_5 -PAMAM-folate-MTX dendrimer conjugates.^{1257,1258}

Finally, G_5 -PAMAM dendrimer-folate conjugates that also contain oligonucleotides such as 5'-phosphate-modified 34-base long oligonucleotides were specifically bound to KB cells that express folate receptor, with internalization being shown by confocal microscopy.¹²⁵⁹ This approach also using cDNA is promising for imaging and gene transfection (vide infra).^{1260,1261}

The delivery of dendritic folate-bound MRI contrast agents and fluorescent probes to tumor cells that overexpress folate is a powerful diagnostic strategy.¹²⁶² For this purpose, 2-(4-isothiocyanatobenzyl)-6-methyldiethylene triaminepentaacetic acid (TU-DTPA), a chelating ligand of Gd for MRI, and fluorescein isothiocyanate for fluorescence were bound to G_4 -PAMAM-folate conjugates and disclosed largely enhanced signals monitoring rapid cell surface fixation followed by slow internalization.¹²⁶³ In the same way, ovarian tumor xenografts resulted in large MRI contrast enhancements,¹²⁶⁴⁻¹²⁶⁶ and biodistribution studies indicated a low level of agents in blood and a high level in kidneys.^{1266,1267} A water-soluble PAMAM-folate-poly(L-glutamic acid) dendrimer conjugated to the near-infrared dye indocyanine green was bound to tumor cells using human nasopharyngeal epidermal carcinoma cell line KB with similar results (Figure 78).^{1073,1268}

In addition to overexpression of folates, tumor cells also express some peptides (vide infra) and surface antigens. Thus, specific interactions between antigens and antibodies (150 kDalton glycopeptides) mediate targeting.

6.2.5. Glyco- and Glycopeptide Dendrimers: Antibacterial, Anticancer, and Antiviral Agents Using the "Cluster Effect" and Antigen-Antibody Interactions

Glycodendrimers (a term introduced by Roy)¹²⁶⁹⁻¹²⁷³ now feature a broad branch of dendrimer chemistry that is devoted to promising biomedical applications, at least for dendrimers terminated by the carbohydrate groups, due to their lack of immunogenicity.¹²⁷⁴⁻¹²⁸³ Glycodendrimers incorporate sugar moieties such as glucose, galactose, mannose, and disaccharides in their structures. Glycopeptide dendrimers are sometimes referred to as glycoclusters in which the multivalency resulting from the multiple carbohydrate groups at the dendrimer periphery allows useful affinities between these carbohydrate groups and their protein receptors. The so-called "cluster effect" (in this context) results in significant amplification of the biological activity by a factor that is several orders of magnitude higher than the sum of the individual contributions. Indeed, although isolated carbohydrate-protein interactions are very weak (with association

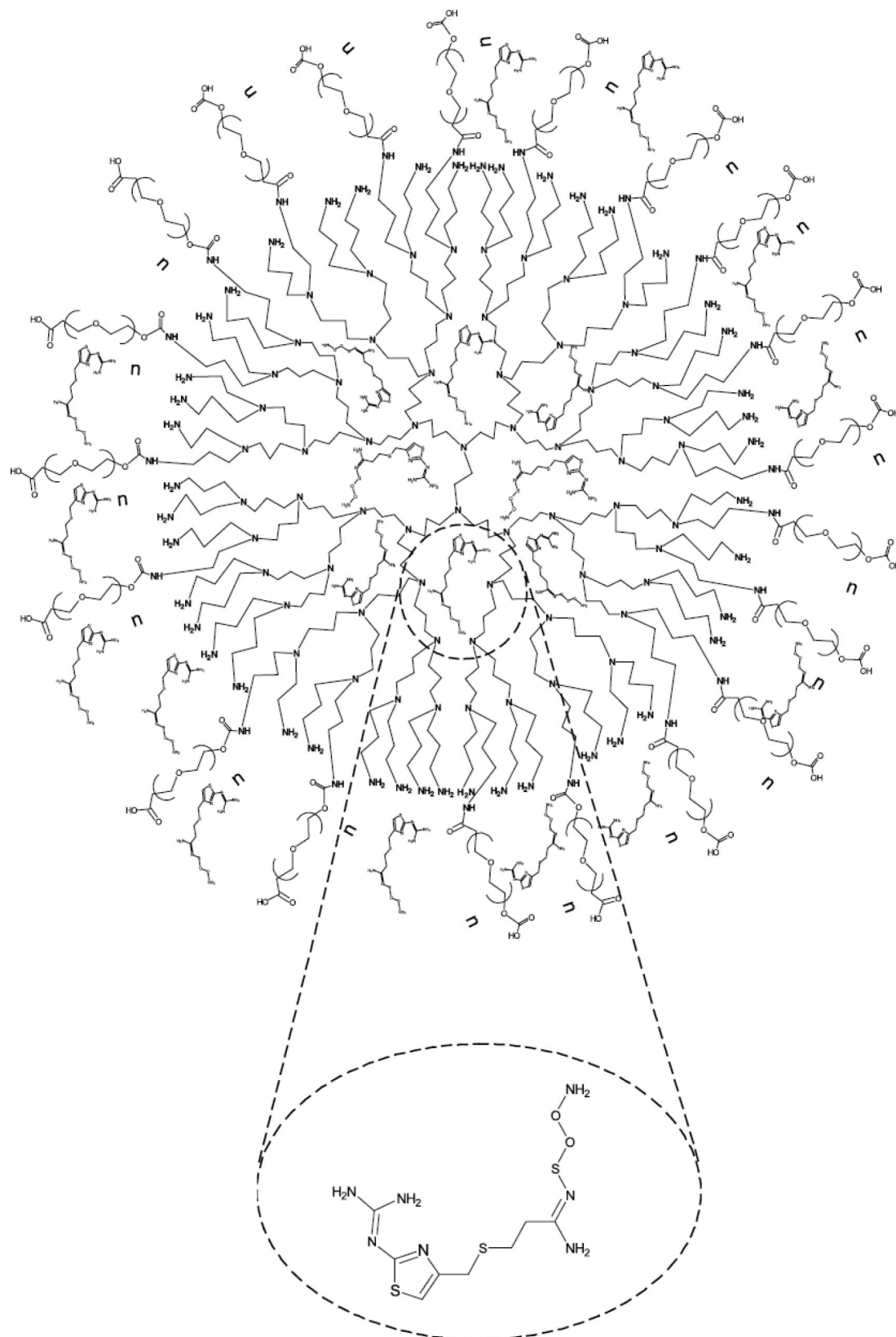


Figure 76. Famotidine loaded PEGylated PPI $G_{5.0}$ dendrimer ($n = 1/4\text{PEG}_{2000}$). Reprinted with permission from ref 1239 (Jain's group). Copyright 2009 Elsevier.

constants of the order of 10^{-6} to 10^{-3} M), cooperative binding by cluster (multivalent) effect results from supramolecular-type interactions,^{1284,1285} yielding affinities that increase exponentially with the glucoside number up to the optimal limit number of carbohydrate units, which is usually

small.^{1271–1273,1276,1280} Tetravalent glycoside often gives the best results, although cases with larger numbers are known.^{1271–1273,1276,1278–1280,1286–1291} This “cluster effect” is typically observed in the increase of lectin-binding affinity.^{1292–1301} As a typical example, a cysteine-cored dendrimer terminated

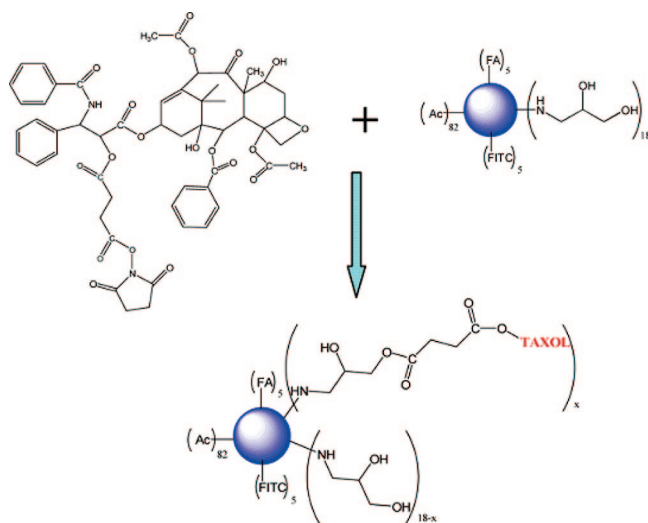


Figure 77. Conjugation of taxol to the carrier G_5 - Ac^3 -FITC-FA-OH, forming the trifunctional dendrimer conjugates G_5 - Ac^3 -FITC-FA-OH-Taxol. Reprinted with permission from ref 1250 (Baker's group). Copyright 2006 American Chemical Society.

by eight 2,3-diaminopropionic acid-branched glycoside groups was not as antiproliferative as the drug cholicine alone but was 20–100 times more effective at inhibiting proliferation of HeLa cells than nontransformed mouse embryonic fibroblasts (nonglycosylated dendrimers showed a selectivity of less than 10-fold for HeLa cells).¹²⁹⁶

The cores of glycodendrimers are mostly based on classic ones (most frequently PAMAM,^{1270–1273,1280,1281,1288,1302} but also PPI,^{1271–1273,1279,1280,1296–1300} polypropylamine,^{1271–1273,1280,1295} carbosilane,¹²⁹⁷ silsesquioxane,¹²⁹⁸ polyphenylene,¹²⁹⁹ etc.¹²⁸⁰), cyclic ones (carbohydrates,^{1279–1282,1296–1300} cyclodextrins,^{1303–1305} cycloveratrylene,¹³⁰⁶ calixarene,^{1291,1303–1310} calix(4)resorcarene (Figure 79),^{1311–1313} carbopeptides^{1276,1314,1315}), porphyrin,¹³¹⁶ fullerene,¹³¹⁷ transition metal (Cu^{2+}) bipyridyl,^{1318–1321} and cyclic decapeptide template.^{1319–1321}

Glycopeptide dendrimers contain polypeptides branches including inter alia lysine (in most cases)^{1281,1305,1322} and also ornithine,¹³²³ proline,¹³²⁴ and α,α -disubstituted β -alanine.¹³²⁵ Other less frequently found glycodendrimer types are also known (i.e., self-immolative).^{1269–1273,1280–1283} In particular, nonsymmetrical dendrimers such as dendronized oligopeptide polymers (for instance, based on “chitosan”,^{1282,1326} “brush”,^{1282,1327,1328} and “comb”¹³²⁹) have

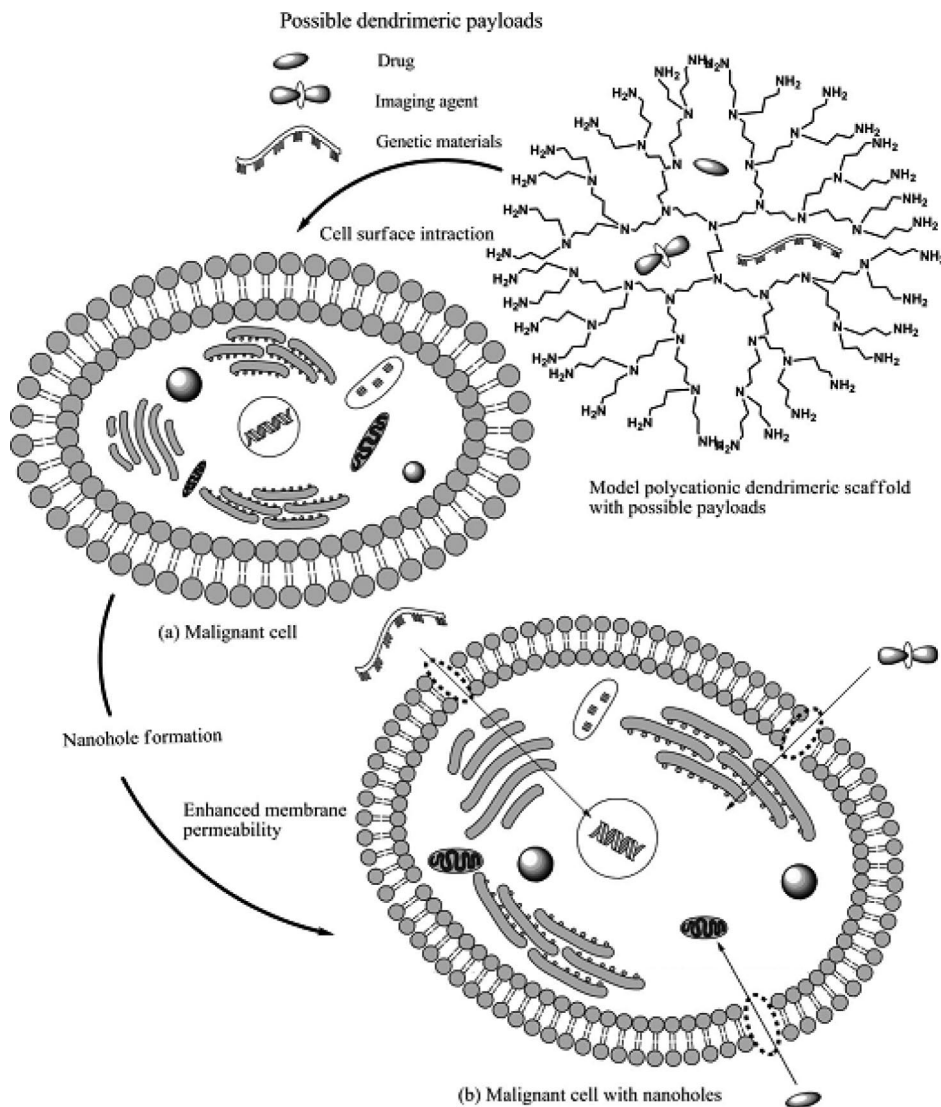


Figure 78. Schematic showing interaction of polycationic dendrimers with cells: nanoscale hole formation and enhanced membrane permeability. (a) Malignant cell in usual state; (b) malignant cell with nanoholes, which possibly mediate enhanced cellular uptake. Reprinted with permission from ref 1073 (Jain's group). Copyright 2009 American Chemical Society.

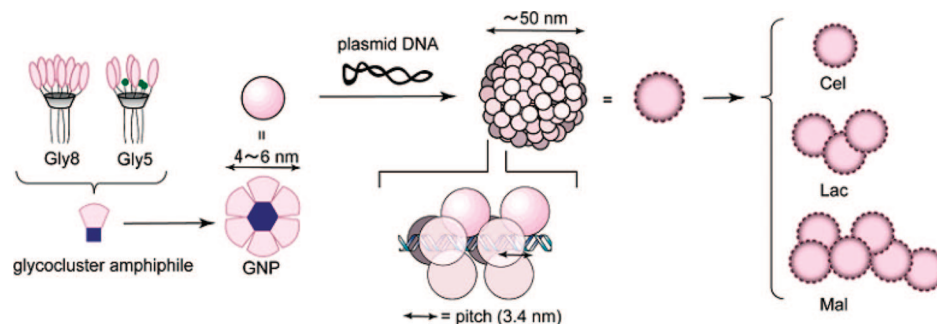


Figure 79. Multivalent hierarchical growth of glycocluster amphiphile Gly8(5) through GNP to glycovirus and its aggregates. Reprinted with permission from ref 1312 (Aoyama's group). Copyright 2003 American Chemical Society.

been designed. Linker groups are usually amide, thiourea, and thioether, and current coupling reactions are also glycosylation, photoaddition to allyl ethers, and reductive amination.¹²⁸¹

Multiple antigen glycopeptide (MAG) are now of common use for glycopeptide dendrimers, since this term (MAG) was first coined by Cantacuzene et al., when they prepared tetrabranched glycopeptides containing four T_N antigens bound to peptide T groups. Note that the word dendrimer is not necessary at this point, and is really overdue for tetrabranched compounds.¹³⁰¹ Glycopeptide dendrimers have biomedical applications as (i) antibacterial agents, (ii) anticancer agents (immunotherapy and antiangiogenic), and (iii) antiviral (including anti-HIV and anti-influenza) agents.^{1269–1283} Glycopeptide dendrimers that contain tumor-associated carbohydrate antigens (T_N, TF, sialyl-T_N, sialyl-TF, sialyl-Le^x, sialyl-Le^a, etc.) have been used in cancer diagnosis and therapy. These dendrimers with T-cell glucosides have been used as antitumor vaccines, especially with multiantigenic vaccines containing five or six different tumor-associated antigens.¹²⁸² Therefore, both the peptide and the carbohydrate groups of the glycoprotein contribute to change immunological behavior in comparison with healthy tissues. Thus, tumor-associated carbohydrate antigens play a key role in cancer diagnosis and synthesis of anticancer vaccines.^{1330–1337} For instance, a single dose of glycodendrimer could be a substitute for multiple injections of neoglycolipid-coated liposomes.¹³³⁸ Anticancer vaccines have to fulfill several criteria for success: (i) antigen highly expressed on tumor cells; (ii) high Ab reduction dependence on clustering of the antigen and adequate choice of carrier and adjuvant; (iii) specific high T-cell response against tumor antigens; and (iv) expression of the same antigen in normal epithelial tissues that is not a problem. There are important obstacles, however, and the mechanisms of carbohydrate antigen processing and presentation in the context of major histocompatibility complex class II molecules are not yet fully understood. Tumor-associated carbohydrate antigens that are overexpressed in clusters at the cancer cell surface represent targets for epithelial cancer immunotherapy, but their immunogenicity is a limiting factor for the design of efficient synthetic anticancer vaccines. A new generation of multiple antigen glycopeptides based on dendritic lysine scaffold is promising as nonimmunogenic carriers for B-cell antigens and T-cell helper peptides, however.^{1283,1330} Glycodendrimer antitumor reagents have been reviewed.^{1283,1330,1336–1345} For instance, Reymond's group showed that colchicine, located at the core of glycosylated peptide dendrimers, is cytotoxic to cancer cell lines such as HeLa and is more selective toward these cancer cells than noncancerous cells compared to colchicine itself (Figure 80).^{1296,1340,1341}

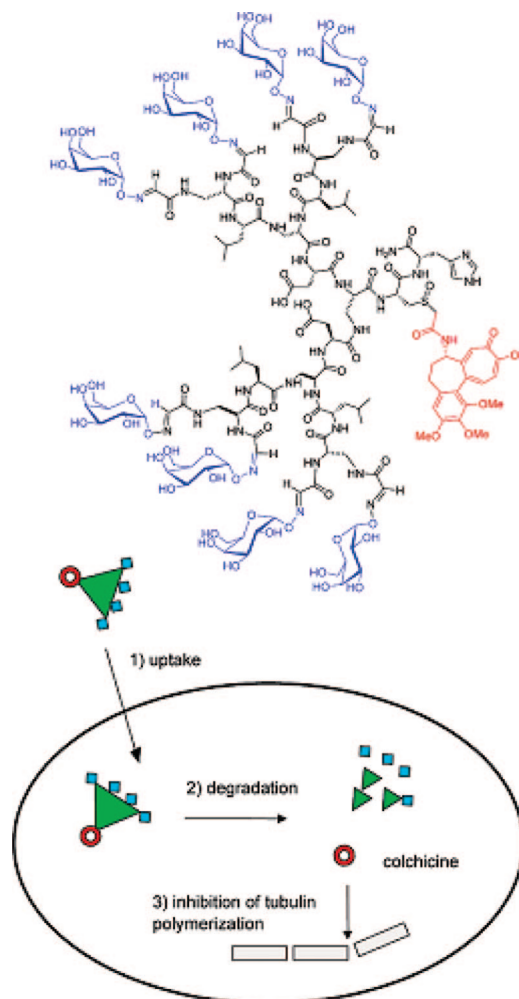


Figure 80. Glycopeptide dendrimer drug conjugates deliver colchicine selectively to cancer cells. Reprinted with permission from ref 1340 (Reymond's group). Copyright 2006 American Chemical Society.

Glycoprotein antibodies can fight against tumors in various ways: (i) they specifically combine with antigens on malignant cell surfaces and make them susceptible to destruction by immune host cells or direct them to self-destruction and (ii) they attack blood vessels or stroma that supports the tumor.^{1346–1350} Difficulties are involved in modifications of antibodies such as changes of biological activity and solubility, however. Thus, alternatives such as immunoliposomes and other immunoconjugates that can be loaded with cancer drugs are used (Figure 81).^{1073,1348} The number of conjugates on the dendrimer, not the dendrimer size, determines the immunoreactivity.¹³⁴⁹

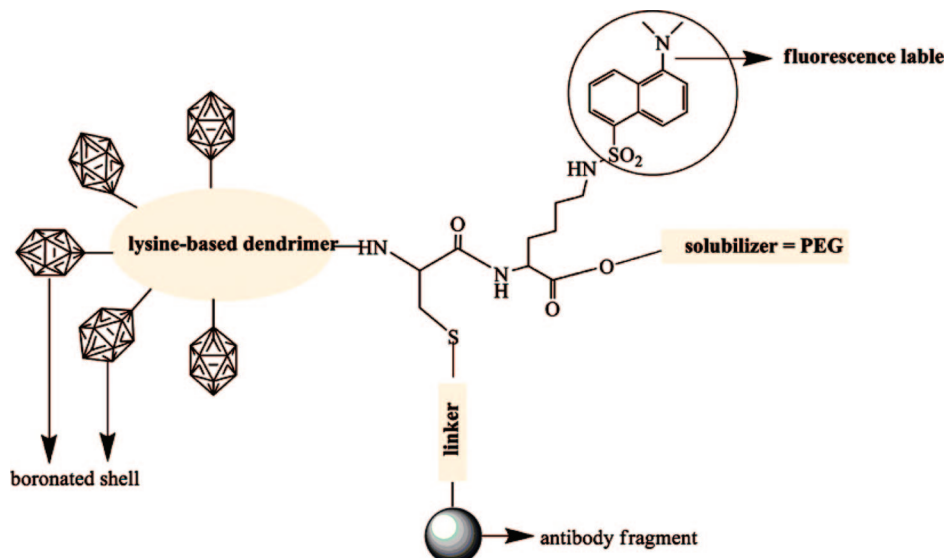


Figure 81. Example of PEG–antibody conjugated boronated lysine dendrimers. Reprinted with permission from ref 1073 (Moroder's group). Copyright 2009 American Chemical Society.

For instance, a prostate-specific membrane antigen (PSMA), J591, was conjugated to G_5 -PAMAM dendrimers, and it was found that PSMA is overexpressed in all prostate cancers, nonprostatic tumor neovasculature, and vascular endothelium in most solid sarcoma and carcinoma tumors.¹³⁵⁰

Dendrimer-based anti-HIV vaccines have to induce both humoral and cellular immunity. The identification of glycosides is the most difficult task in HIV vaccine design. Major HIV defense mechanisms are (i) frequent mutation of neutralizing glycosides, (ii) conformational masking of receptor binding sites, (iii) extensive glycosylation to evade immune recognition of the underlying protein domain, and (iv) formation of an envelope of glycoproteins to occlude conserved glycosides.^{1283,1346–1355} Sulfatation of oligosaccharides resulted in an increase of their antitumor and antiviral activities.¹³⁵⁶ Glycopeptide antigens as HIV vaccines have been reviewed.^{1283,1342,1344,1345}

Concerning influenza, the binding of HA, a viral carbohydrate-binding membrane protein to SA-containing oligosaccharides on the host cell surfaces, plays an important role in infectivity. Therefore, glycopeptide dendrimers with high affinity to HA are candidates for blocking this virus.^{1283,1357–1359}

Multiple Ag peptides (MAPs) containing eight proteolipid proteins arranged around a dendritic branched lysine core were used to influence the expression and development of relapsing allergic encephalomyelitis in SJL mice. The PLP 139–151 MAPs were very efficient agents in preventing the development of clinical disease when administrated after immunization with the PLP 139–151 monomeric encephalitogenic peptide. Glycopeptide dendrimer biofilm inhibitors were synthesized combinatorially and optimized for binding to the fucose-specific lectin LecB that has high fucose affinity. These dendrimers are potential antibacterial agents against *Pseudomonas aeruginosa*, an antibiotic-resistant human pathogen.^{1360,1361} A collagen model peptide-attached dendrimer was designed as a potential functional collagen material. The peptides that clustered at the dendrimer surface formed a thermally reversible functional collagen material. This dendrimer worked as a drug carrier with thermoresponsive capabilities and produced a hydrogel at low temperature (Figure 82).¹³⁶²

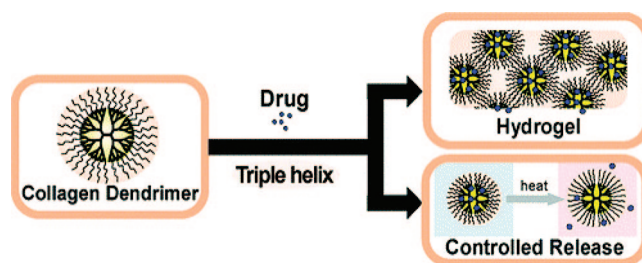


Figure 82. Mechanism of the collagen model peptide-attached dendrimer. Reprinted with permission from ref 1362 (Kono's group). Copyright 2009 American Chemical Society.

6.2.6. Peptide Dendrimers for Antiangiogenic Therapy

Angiogenesis consists of the formation of new blood vessels from existing ones. “Abnormal angiogenesis” plays a key role in the growth and spread of cancer, because cancer cells are fed with oxygen and nutrients by the new blood vessels. Angiogenic therapy involves the prevention of this neovascularization by inhibiting proliferation, migration, and differentiation of endothelial cells. Tumor-induced angiogenesis results from ligation of extracellular matrix proteins to the $\alpha_v\beta_3$ integrin, which is one of the most exclusive markers highly expressed on many tumor cells and found on the luminal surface of the endothelial cells only during angiogenesis.^{1346,1347} Peptides and peptidomimetics that contain the common amino acid sequence arginine-glycine-aspartic acid (RGD) are antagonists of the $\alpha_v\beta_3$ integrin, which is inhibited in order to block angiogenesis. Alexa Flu 488 fluorescent-labeled, partly acetylated G_5 -PAMAM dendrimer was conjugated to the multiple $\alpha_v\beta_3$ selective doubly cyclized RGD (RGD-4C) peptide sequence to target the tumor neovasculature. Binding studies were performed on several cell lines with varying levels of integrin receptor expression. The free RGD-4C bound much more rapidly than the RGD-4C–dendrimer conjugates, but the dendrimers dissociated approximately 500 times more slowly, which suggested a synergistic effect of multiple peptide conjugation on binding avidity.^{1363–1365} RGD-4C has also been bound to DOTA-conjugated mono-, bis-, and tetravalent alkyne-terminated dendrimers to target $\alpha_v\beta_3$ integrin. Biodistribution studies in vitro and in vivo in mice with human SK-RC-52

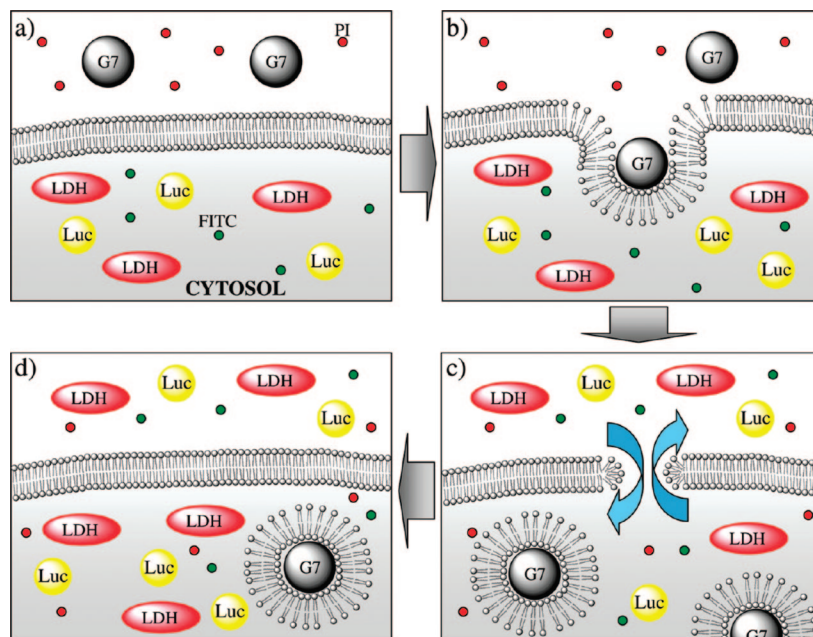


Figure 83. Schematic diagram of the proposed nanoscale hole formation mechanism induced by positively charged PAMAM dendrimers. Reprinted with permission from ref 1389 (Banaszak Holl's group). Copyright 2009 American Chemical Society.

tumors showed that the tetrameric RGD-4C–dendrimer showed the highest level of tumor targeting.¹³⁶⁶

6.2.7. Dendritic DNA Carriers for Gene Therapy

Gene therapy involves the transfer (transfection) of DNA into cells to correct genetic defects.^{1367–1369} The vector should be cell-specific, efficient, biodegradable, nontoxic, and non-immunogenic.¹³⁷⁰ Viruses,¹³⁷¹ cationic lipids and cationic peptides,¹³⁷² cationic polymers¹³⁷³ such as the successful polyethylene imine (PEI),¹³⁷⁴ and chitosan¹³⁷⁵ have been used. Viruses and chitosan have been discarded due to severe toxicity problems.^{1371,1375} Then, the difficulty is that some nonviral synthetic vectors are insufficiently efficient to transfer genes into the interior of the nucleus.^{1372,1376,1377} Also, the carrier must be released from the endosome following endocytosis.¹³⁷⁷ Dendrimers are much more stable than liposomes and present the advantage of precise design of the size, monodispersity, generation, and nature of termini. Early work on dendrimers as transfecting agents has been reviewed.^{1378–1380}

Electrostatic interactions between the anionic phosphate groups of the DNA backbone and the positively charged protonated (under physiological conditions) primary amine-terminated dendrimer result in the formation of a dendrimer–DNA association called dendriplex,¹³⁸¹ and this has been reviewed.¹³⁸² The dendriplex binds the cell membrane, again by electrostatic interaction between its positive charges and the phosphate and carboxylate membrane groups, and is internalized into the cytoplasm upon endosomal uptake. The mechanism of follow-up introduction into the nucleus is unclear.^{1383,1384}

The unmodified amino-terminated dendrimers PAMAM, by far the most frequent dendrimer family used for gene transfection, enhance the transfection of DNA into the cell nucleus. PAMAM dendrimers are now a well-established, commercial class of gene-transfer agents that has been reviewed.^{1056,1057,1380,1384} Partially degraded, nonspherical PAMAM dendrimers (commercialized as “Superfect”) are about 50 times more efficient for gene delivery than intact

ones, with fragmentation by hydrolytic amide bond cleavage enhancing transfection. Nonspherical PAMAM dendrimers, such as those obtained upon fragmentation, seem to be more flexible to form a more compact complex with DNA as desired for gene delivery through endocytosis.^{1056,1057,1385} A cholesterol-dependent mechanism has been proposed for transfection with “Superfect”.¹³⁸⁶ Polycationic dendrimers also induce nanoscale hole formation enhancing molecular exchange across cell membranes.¹³⁸⁷ Dynamic interaction between PAMAM dendrimers and cellular lipid membranes can indeed stimulate such membrane hole formation and expansion, as with some natural proteins (MSI-78 [pexiganan] and trans-activator of transcription protein) (Figure 83).^{1388,1389}

Low-generation PAMAM and PPI dendrimers are less cytotoxic, thus being more appropriate for effective gene transfection than high-generation dendrimers.¹³⁹⁶ Gene transfer has been carried out in vivo using these dendrimers to cure mice tumors.^{1390,1391} Phosphorus dendrimers^{1390,1391} and carbosilane dendrimers,¹³⁹² both series also terminated by various amino groups, were efficient transfecting agents, as well as various Janus-type dendrimers with long alkyl chains on one side and amine-terminated tethers on the other side.^{1393–1395}

PAMAM dendrimers terminated by OH groups (PAMAM–OH) appeared less toxic but also inefficient because of the lack of positive surface charge. Internally quaternized PAMAM–OH dendrimers with various quaternized proportions of the tertiary amino groups preserve both the lack of toxicity by rendering the dendrimer surface neutral and (partly) the transfection efficiency with positive charges to bind DNA electrostatically. The transfection efficiency of these dendrimers is 1 order of magnitude lower than with parent PAMAM dendrimers, however.¹³⁹⁷ PAMAM dendrons were used for gene delivery to mammalian cells, and functionalization at the focal point with PEG increased their efficiency while decreasing toxicity.¹³⁹⁸ Attachment of PAMAM dendron focal point to magnetic iron oxide nanoparticles allowed dendriplexes to enter into tumor cells and inhibit their growth. The magnetic nanoparticles

therein are useful for imaging and hyperthermal cancer treatment.^{1399,1400} A significant improvement to transfection efficiency appeared with arginine-rich peptides,^{1401–1403} because they are terminated by guanidinium moieties that form, with DNA phosphate groups as well as cell carboxylate and phosphate groups, hydrogen bonds coupled to electrostatic interactions.^{1404,1405} PAMAM-Arg, i.e., PAMAM dendrimers terminated by arginine groups, are easily prepared and effect more efficient gene delivery than parent PAMAM dendrimers. This efficiency is comparable to that of PEI for HepG2 and primary rat vascular smooth muscle and is higher than that of PEI and lipofectamine with Neuro 2A cells. Thus, it is remarkable, with relatively low cytotoxicity.¹⁴⁰⁵ G_4 -partially functionalized PPI dendrimers with guanidinium termini and containing residual amino termini were reacted with propylene oxide to give hydroxylated derivatives in order to avoid the toxicity of these residual amino groups. Study with HEK 293 and COS-7 cells and of the serum effect in HEK 293 cells showed that the transfection efficiency increased with increasing the number of guanidinium groups introduced with a maximum for the fully functionalized dendrimer (or supposed to be so), whereas the lowest toxicity was exhibited with 12 guanidinium groups. The introduction of terminal hydroxy groups was proposed to contribute to lowering cytotoxicity.¹⁴⁰⁶ Likewise, PAMAM-arginine dendrimers self-assembled electrostatically with plasmid DNA to form dendriplexes (dendrimer–DNA complexes) that were shown to be 200-nm large based on dynamic light-scattering measurements and increased gene delivery compared to parent PAMAM dendrimer and PAMAM-lysine dendrimers.^{1407,1408} L-Phenylalanine and leucine moieties have been introduced at the termini of a G_4 -PAMAM dendrimer, and its transfection efficiency for CV1 cells, an African green monkey kidney cell line, increased concomitantly with the increase of the number of phenylalanine termini up to 46 phenylalanine moieties but was not improved with leucine moieties (probably due to the lower hydrophobicity of this latter amino acid), compared to the parent G_4 -PAMAM dendrimer. With 64 phenylalanine termini, the dendrimer had poor water solubility and hardly formed a dendriplex with DNA at neutral pH, but in weakly acidic conditions, the dendriplex formed, achieving highly efficient transcription. These phenylalanine-terminated PAMAM dendrimers exhibited low toxicity and were efficient, promising gene carriers.¹⁴⁰⁹ A dendrimer–peptide conjugate based on G_5 -PAMAM platform and LH-releasing hormone peptide as a targeting moiety was found to be stable after 72 h of incubation in phosphate-buffered saline buffer (pH 7.4) and may find applications in gene delivery.^{1410,1411} Electrostatic shielding and steric blocking by histones participate in the control of the local rates of transcription of chromatin. How the degree of DNA condensation affects enzyme accessibility and gene expression has been determined with a simple model disclosing the G_5 -PAMAM dendrimer–DNA self-assembly.¹⁴¹² Charge–charge interactions are prevalent, and the shape of the polymer helps direct the packaging of the nucleic acid.¹⁴¹³ Interactions between positively charged G_4 -PAMAM and DNA of 2000 base pairs and 4331 base pairs have also been modeled (Figure 84).¹⁴¹⁴

The use of PPI dendrimers for delivering a triplex-forming oligonucleotide in breast, prostate, and ovarian cancer cell lines using ³²P-labeled antisense oligonucleotides enhanced oligonucleotide uptake by 14-fold in MDA-MB breast cancer cells, with G_4 -dendrimer having the maximum efficacy.¹⁴¹⁵

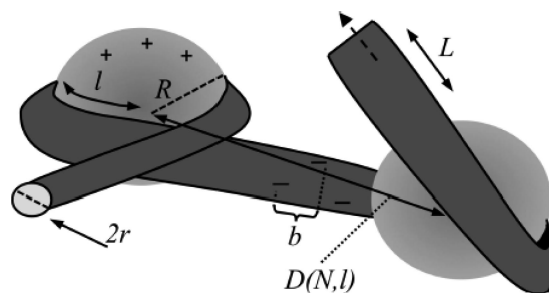


Figure 84. Proposed binding model between DNA of contour length L , radius r , and distance between negative charges b and G_4 PAMAM dendrimers modeled as hard spheres of radius R . The DNA is shown to wrap around the dendrimer with the length of the wrapping part equal to l , and a distance between the centers of two neighboring dendrimers, $D(N, l)$. Reprinted with permission from ref 1414 (Qamhieh's group). Copyright 2009 American Chemical Society.

G_2 - and G_3 -PPI dendrimers grafted via 1,6-hexanediol diacrylate with branched oligoethyleneimine (88 D) or G_2 -PPI dendrimers were able to efficiently compact DNA to nanosized polyplexes (100–200 nm) and exhibited an increased colloidal stability and in vitro much higher transfection levels as compared to unmodified counterparts. The incorporation of linear or branched polyethyleneimine was demonstrated to be the key factor to this boosted transfection efficiency. No polymer-induced erythrocyte aggregation resulted, and tumor gene expression levels in tumor-bearing mice significantly increased with the higher dendrimer core generation.¹⁴¹⁶

Protection of the peripheral amino groups was also combined with targeting properties using folate termini. This was achieved by the synthesis of a PEI–PEG–folate dendrimer, with the folate moiety being bound to the termini of PEG tethers. This nanocarrier (MW = 25 000) transfected plasmid DNA to the folate receptor-overexpressing GFP-KB cells that produce the exogenous green fluorescent protein, more efficiently than the comparable folate-free carrier. This confirms that the folate receptor-mediated endocytosis is a major pathway for cellular uptake.¹⁴¹⁷ Lipidic dendrimers were used for protein transduction into cultured cells and intracellular protein delivery, and these dendrimers could also be used for gene and drug delivery.^{1418–1420} PAMAM-coated multiwalled carbon nanotubes conjugated with antisense c-myc oligonucleotides have been designed and successfully tested for application in gene-delivery systems.¹⁴²¹ α -Cyclodextrin conjugates could enhance gene-transfer activity (Figure 85).^{1422–1424}

Dendrimer–DNA complexes were encapsulated in the functional water-soluble biodegradable polymer poly(α, α, β -[N-(2-hydroxyethyl)-(L)-aspartamide]) for substrate-mediated gene delivery.¹⁴²⁵ Even though all dendrimers are taken up by fluid-phase endocytosis upon transfection, significant differences in uptake mechanisms exist. Anionic dendrimers appear to be mainly taken up by caveole-mediated endocytosis in A549 lung epithelial cells, while cationic and neutral dendrimers appear to be taken in by a nonclathrin, noncaveolae mediated mechanism that may involve electrostatic interactions or other nonspecific fluid-phase endocytosis.¹⁴²⁶ DAB-8 dendrimer conjugated to β -cyclodextrin had low toxicity and high transfection efficiency in vitro.¹⁴²⁷ In conclusion, it is likely that the first synthetic gene-delivery agent that will complete the clinical development journey may be a cationic dendrimer with targeting ability.

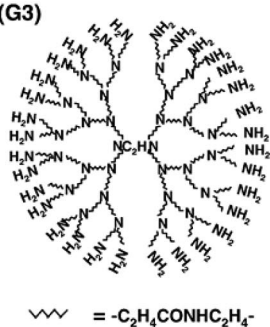
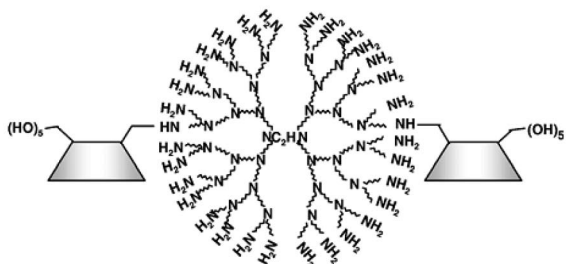
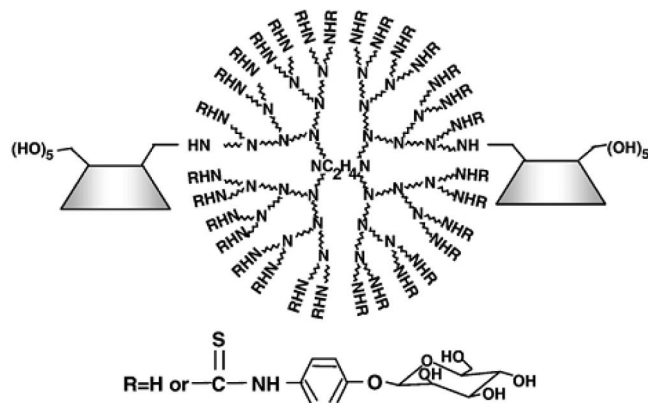
(A) Dendrimer (G₃)**(B) α -CDE conjugate (G₃)****(C) Man- α -CDE conjugate (G₃)**

Figure 85. Chemical structures of dendrimer (G₃) (A), α -CDE conjugate (G₃) (B), and Man- α -CDE conjugate (G₃) (C). Reprinted with permission from ref 1422 (Uekama's group). Copyright 2006 Elsevier.

Nontoxic phototriggered gene transfection by G₄-PAMAM-dendrimer conjugate was developed as an innovative strategy in cytosolic release providing the possibility of light-induced gene-delivery systems.^{1424–1434} Synergistic effects in gene delivery were disclosed on combining cholesterol units with spermine-functionalized dendrons. Enhanced transfection ability resulted from mixing aspects of both main classes of synthetic vectors, i.e., cationic polymers or dendrimers and lipids.¹⁴²⁹

Cell-penetrating peptides (CPPs) are promising delivery vectors for nucleic acids, and their potentials have been evaluated using a functional splicing redirection assay. CPP oligomerization greatly improves cellular delivery and increases transfection of plasmid DNA; CPP-peptide nucleic acids incorporating dendrimer-like tetrameric (p53t) forms of the p53 tetramerization domain containing peptides enhance the splice-redirecting activity of DNA conjugates in cells.¹⁴³⁰

Interactions and recognition between dendrimers and double-helical DNA have been modeled, allowing reproduction of the observed binding effects. These modeling studies indicate that ligand flexibility and framework rigidity are not

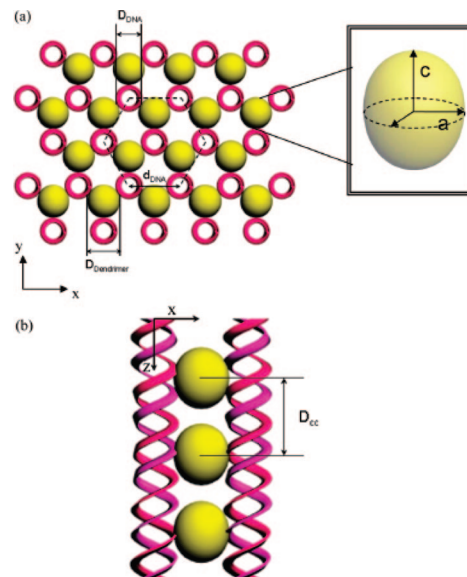


Figure 86. Schematic illustrations of the organization of dendrimer molecules in the 3-fold interstitial tunnels of the hexagonal lattice formed by DNA: (a) the top view and (b) the side view. D_{cc} represents the center-to-center distance between dendrimer molecules along the DNA long axis (i.e., z axis). Reprinted with permission from ref 1432 (Ivanov's group). Copyright 2009 American Chemical Society.

always beneficial for multivalent recognition; ligand sacrifice and binding site screening combine to enable high-affinity binding, which brings about a new paradigm in multivalency.¹⁴³¹ The supramolecular structures of DNA duplex- G_2 - and G_3 -PAMAM dendrimer complexes were characterized in pure water by small-angle X-ray scattering as a function of dendrimer charge (degree of amine protonation) and molar ratio dendrimer amine group/DNA phosphate group. The DNA chains were found to self-organize into two-dimensional hexagonal (G_2) or square lattice (G_3) (Figure 86).¹⁴³²

Using various generations of PAMAM dendrimers for transfection studies and a β -galactosidase reporter gene system, the Madeira group showed that even a low transfection level could be sufficient to induce in vitro differentiation of mesenchymal stem cells to the osteoblast phenotype.¹⁴³³ Phosphorus dendrimers with pyrrolidine, morpholine, methylpiperazine, or phenylpiperazine terminal groups disclosed low cytotoxicity toward cell strains, and electrophoresis study of DNA interaction indicated the formation of dendriplexes, with pyrrolidinium-terminated dendrimers yielding the best transfection results.¹⁴³⁴

Short, double-stranded RNAs, known as interfering RNA (siRNA), can be used to specifically downregulate expression of the targeted gene in the RNA interference (RNAi) process. One of the primary limitations of siRNA as a technique for gene regulation, however, is effective siRNA delivery into the target cells. PAMAM dendrimers self-assemble with siRNA into nanoscale particles that are efficient for siRNA delivery and induce potent endogenous gene silencing.^{1435,1436} Amino-terminated carbosilane dendrimers were used to protect and transport siRNA, and siRNA was found to be resistant to degradation by RNase. Cytotoxicity assays of these dendriplexes with peripheral blood mononuclear cells (PBMCs) and the lymphocytic cell line SupT1 revealed a maximum safe dendrimer concentration of 25 $\mu\text{g}/\text{mL}$, lymphocytes were successfully transfected by fluorochrome-labeled siRNA, and the dendriplexes silenced GADPH

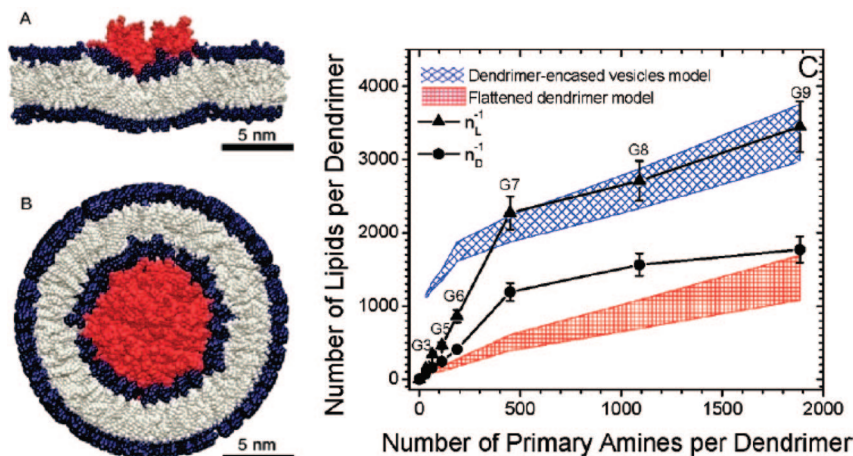


Figure 87. (A) Flattened dendrimer model and (B) dendrimer-encased vesicle model of dendrimer–lipid complexes. These models depict the interaction of a single dendrimer with a lipid bilayer and suggest a fundamental structure of local dendrimer–lipid interaction. Aggregation of the flattened dendrimers may induce sufficient curvature to create a separated vesicle, and separated vesicles may readily aggregate. (C) ITC-determined binding stoichiometries for the dendrimer–lipid complexes compared with the expected stoichiometry of these models. Small and medium dendrimers ($<G_6$) flatten over the membrane and induce slight membrane curvature and/or flocculation of vesicles. Larger dendrimers ($>G_6$) become encased by a lipid vesicle. (A) G_5 and (B) G_7 are colored red. The hydrophilic headgroups are colored blue, and the hydrophobic tails are colored gray. Reprinted with permission from ref 1443 (Banasak Holl's group). Copyright 2009 American Chemical Society.

expression and reduced HIV replication in SupT1 and PBMC.¹⁴³⁷ A bis(guanidinium)–tetrakis-(β -cyclodextrin) tetrapod formed molecular association with siRNA and DNA whose affinity was evaluated using capillary electrophoresis; an efficient transfection of siRNA into human embryonic lung fibroblasts was observed by fluorescence microscopy.¹⁴³⁸ Increased efficiency for siRNA delivery was disclosed with internally cationic PAMAM dendrimers, with modification of surface amine groups to amides also reducing cytotoxicity.^{1439,1440}

6.2.8. Dendrimer–Liposome Assemblies

Liposomes, artificial vesicles formed by concentric amphiphilic phospholipid bilayers containing aqueous compartments, are more and more used as intravenous drug nanovectors, because they can carry hydrophilic as well as hydrophobic drugs, protect them against enzymatic degradation or elimination by the immune system, limit side effects, and also allow carrying imaging agents. Their drawbacks, however, are their lack of cell specificity, the oxidation and instability of phospholipids, and drug leaking out of the liposome after dilution or application.¹⁴⁴¹ Liposome formulations of doxorubicin, amphotericin B, and cytarabine are on the market, however, and various others are in clinical phase. It has appeared that dendrimers can largely improve the efficacy of liposomes, and dendrimer–liposome associations (dendrisomes) are now actively studied as nanocarriers.

The Florence group examined the nature of the interactions between dendrimers and lipids, which paved the way for applications in drug delivery.^{619–631,1381,1442} The Baker group investigated the stoichiometry and structure of PAMAM dendrimer–lipid complexes as a function of generations. Large dendrimers demonstrated a decreased number of bonds and heat release per primary amine, possibly due to steric restriction of dendrimer deformation by the lipid layer. The G_7 -PAMAM dendrimer and larger ones bound to lipids with an average stoichiometry that was consistent with each dendrimer were wrapped by a bilayer of lipids, whereas smaller dendrimers were not (Figure 87).¹⁴⁴³

It was shown that dendrimers, having the size corresponding to that of the thickness of the aqueous space between two liposomal bilayers, could be encapsulated in this aqueous liposome phase to form a dendrisome stabilized by electrostatic interactions. This type of interaction also favors accumulation of positively charged dendrisomes on negatively charged cancer cell surfaces.^{1444,1445} Indeed, encapsulation of MTX molecules in liposomes increased in the presence of dendrimer (best generation, G_4). A liposome formulation incorporating a doxorubicin–PAMAM complex ensured controlled drug release, avoiding fast release of cytotoxic drug observed with conventional liposomes.¹⁴⁴⁶ G_4 -PAMAM dendrimer–poly(styrene sulfonate) microcapsule deposited using a layer-by-layer method around a removable melanine formaldehyde colloidal core provided an even better stability than the dendrisome.^{1447,1448} Altogether, this dendrisome transfection approach looks very promising.¹⁰⁷³

Liposomes are considered the closest analogues of cells. Thus, the interactions of guanidinium-terminated DAB dendrimers with multilamellar liposomes consisting of phosphatidylcholine, cholesterol, and guanidinium-complementary dihexadecylphosphate (19:9.5:1) dispersed in aqueous or phosphate buffer solutions were investigated, in order to model drug-delivery efficiency. Such DAB–guanidinium dendrimers were loaded with a corticosteroid drug betamethasone valerate or betamethasone dipropionate to investigate its transfer to liposomes. The liposomes are molecularly recognized by these dendrimers behaving as glues adhering liposomes together, which forms large aggregates at dendrimer/dihexadecyl phosphate molar ratios higher than 1:30, as observed by phase-contrast optical microscopy. The liposome membrane remains almost intact during this molecular recognition, a reversible process as shown by redispersion upon addition of concentrated phosphate buffer. The amount of drug in the precipitate increases from 25% in the absence of guanidinium termini to 80% with 12 guanidinium termini on the DAB dendrimer, showing that the functionalization with guanidinium results in an effective adhesion to the multilayer liposomes¹⁴⁴⁹ (see also

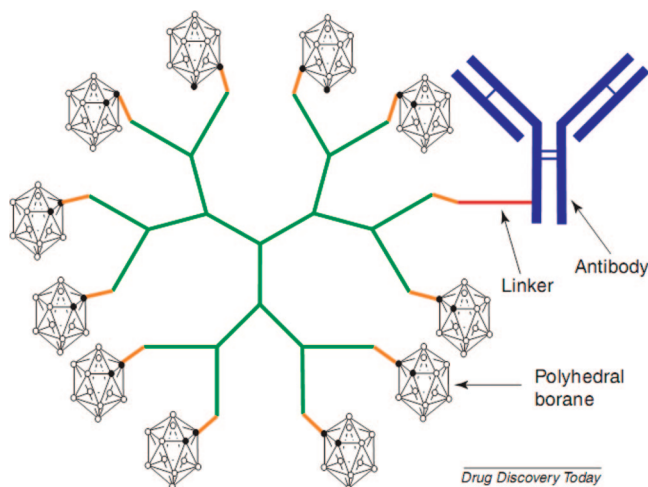


Figure 88. Antibody-targeted dendritic boron carrier for boron neutron capture therapy. Reprinted with permission from ref 1169 (Fréchet's group). Copyright 2006 Elsevier.

Paleos' excellent review¹³⁷⁷). PEG chains mediate the steric stabilization of complexes formed between negatively charged liposomes and folate-conjugated PAMAM dendrimers in water; thus, they play an important role in the dispersion stability of these supramolecular complexes, preventing them from aggregating.¹⁴⁵⁰

6.3. Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT) relies on lethal $^{10}\text{B}(n,\alpha)^7\text{Li}$ capture reaction occurring when a substrate containing ^{10}B atoms is irradiated with low-energy thermal neutrons that produce high-energy α -particles and ^7Li nuclei.^{1449,1450} ^{10}B atoms must be internalized in the targeted cells, because these α -particles have a path in tissues that is limited to less than $10\ \mu\text{m}$.¹⁴⁵¹ It is necessary to locate a minimum of $10\text{--}30\ \text{mg/g}$ to the tumor (10^9 atoms/cell) for effective therapy. Consequently, tumor targeting of the ^{10}B -containing substance is crucial, which has been a severe limit to this technique for some time. Therefore, conjugated boron-containing substances to receptor-targeting reagents are called for (Figure 88).^{1451–1454}

Dendrimers are adequate molecular tools, because they can contain many branches with boron-containing moieties at their periphery, and target-type engineering is well-advanced. The PAMAM dendrimers have been the most used dendrimers for this purpose and have been reviewed.^{1069–1071,1073,1452–1456}

A review of recent reports follows. Intratumoral injection of G_5 -PAMAM dendrimers conjugated with cetuximab, an EGF receptor-specific monoclonal antibody, and containing 1100 B atoms increased by 13.8 times the tumor B content compared to free boronated G_5 -PAMAM dendrimer.^{1457,1458} The same dendrimer–cetuximab conjugate delivered for the treatment of F98_{EGFR} glioma followed by BNCT on animals approximately doubled animal survival compared to dendrimer-free treatment, demonstrating the therapeutic value of this conjugate. This treatment was best delivered via convection-enhanced delivery, a positive-pressure method facilitating transport across the blood–brain barrier, which resulted in 50% more accumulation than using intratumoral treatment. In addition, survival time still increased by 30–50% when this treatment was carried out together with borophenylalanine or sodium borocaptate, two drugs cur-

rently used for BNCT.¹⁴⁵⁹ A similar study for the treatment of L8A4, a monoclonal antibody targeting a mutant isoform of EGFR, EGFRvIII, exclusively expressed in tumors (EGFR is also located in healthy liver and spleen) resulted in a mean survival time of 85.5 days with 20% long-term survival, compared to 30.3 days when the dendrimer was not used.¹⁴⁶⁰ Treatment by G_5 -PAMAM dendrimer conjugated with vascular endothelial growth factor (VEGF, overexpressed in tumor vasculature) and near-infrared Cy5 dye allowed confirmation by near-infrared imaging that VEGF–dendrimer–Cy5 accumulates in 4T1 mouse breast carcinoma with increased concentration at the tumor periphery where tumor neovascularization was most active.^{1461,1462} Gadolinium neutron capture therapy has been proposed but rarely used due to difficulty in achieving therapeutic doses intravenously. Simultaneous imaging (vide infra) and neutron therapy treatment to sentinel lymph node was optimized for G_6 -PAMAM dendrimers.¹⁴⁶³

6.4. Photodynamic and Photothermal Therapies

6.4.1. Photodynamic Therapy

Photodynamic therapy (PDT) was discovered by Friedrich Meyer-Betz with porphyrins in humans in 1913. It consists of irradiating with visible or infrared light a sensitizer, such as protoporphyrin IX that subsequently transfers its excited-state energy to dioxygen by intersystem crossing to form singlet oxygen (Figures 89 and 90).

The latter is a very aggressive species that then destroys the cell through apoptosis or necrosis.¹⁴⁶⁴

A precursor, 5-aminolevulinic acid (ALA), is a classic photosensitizer that produces protoporphyrin IX in cells via the heme-biosynthesis pathway,¹⁴⁶⁵ and various other sensitizers are authorized or under clinical evaluation.¹⁴⁶⁶ Skin cancer is the main focus of PDT. The porphyrin sensitizers are selective for tumor cells because of their leaky vasculature and collagen and lipid content. Dendrimers, however, can largely improve the selectivity and pharmacokinetics, leading to efficient killing of cells after illumination. A major limitation of ALA and some ALA-containing dendrimers is their hydrophilicity, which inhibits penetration through the skin and cell membranes. Indeed, dendrimers with improved in vitro and in vivo transdermal fluxes have been designed and probed by the Jain group¹⁰²⁰ and others.^{1069–1071,1073,1467,1468}

Compared with the lipophilic hexyl ester derivative of ALA that has been much investigated, tris-ALA dendrons led to higher porphyrin accumulation in vivo.¹⁴⁷⁰ The phototoxicity, in cell culture, of these dendrons containing amino, aminobenzoyloxycarbonyl, or nitro groups at the focal point was shown to be likely related to lipophilicity and esterase accessibility, with the nitro dendron being the most lipophilic with 10-times higher porphyrin accumulation than

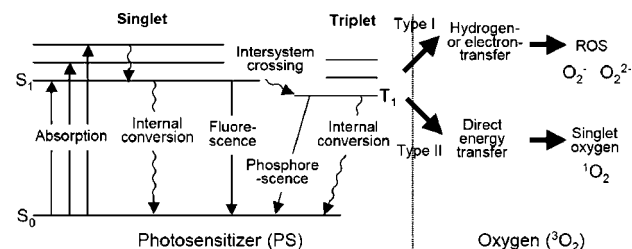


Figure 89. Jablonski diagram showing the energy transfer from photosensitizers (PS) to molecular oxygen. Reprinted with permission from ref 1487 (Kataoka's group). Copyright 2009 Elsevier.

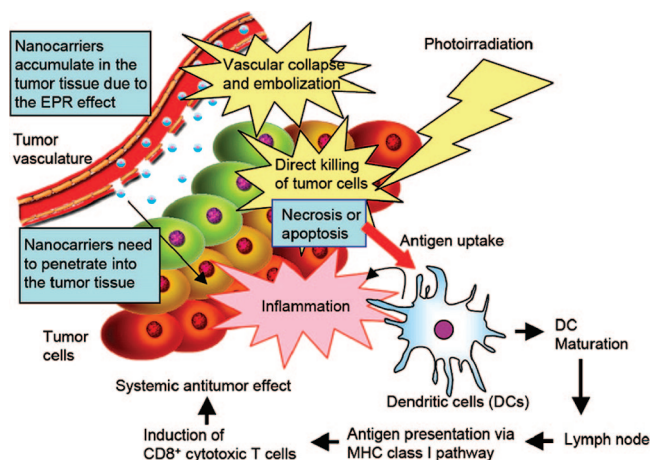


Figure 90. In vivo mechanisms of PDT (photodynamic therapy). The nanocarrier-encapsulated PSs accumulate in the tumor tissue by the enhanced permeability and retention (EPR) effect. Upon photoirradiation, reactive oxygen species (ROS) generated from PSs can directly kill tumor cells. PDT can also cause vascular collapse and embolization, leading to tumor destruction through a lack of oxygen and nutrients. Furthermore, PDT induces acute inflammation, attracting leukocytes such as dendritic cells (DCs). PDT might provide a tumor environment that facilitates antigen uptake by DCs and antigen presentation via the major histocompatibility complex (MHC) class I pathway. As a result, PDT can induce CD8⁺ cytotoxic T cells, thereby achieving a systemic antitumor effect. Reprinted with permission from ref 1487 (Kataoka's group). Copyright 2009 Elsevier.

free ALA. The aminobenzoyloxycarbonyl dendron was also able to generate high porphyrin fluorescence when applied to expanded rat skin and was especially most effective at high concentration at which the nitro dendron precipitates.¹⁴⁷¹ With larger tripodent aromatic-cored dendrimers terminated by 18 ALA moieties, polyamidoamine linkers to the core resulted in higher efficiency than acetamido linkers, because the former allowed greater esterase accessibility for the cleavage of the ALA groups. At lower concentrations, these large dendrimers were superior to free ALA for porphyrin production even after one day of incubation, which showed that cleavage of the polyamido bridges was gradual over time.¹⁴⁷²

G_3 -zinc-porphyrin-cored poly(benzylether) dendrimers terminated by carboxylate groups were found to be 280 times more phototoxic against Lewis lung cells in vitro when they were surrounded by positively charged PEG-lysine block copolymers than alone. This micellar dendritic assembly was found to target the neovascular regions due to the EPR effect. On the other hand, the dendrimer alone exhibited decreased uptake due to the negatively charged carboxylate termini, and lack of steric protection in the absence of micelle caused porphyrin aggregation, resulting in fluorescence quenching.^{1473,1474}

The pH value was found to play an important role in these¹⁴⁷⁴ and electrostatically connected PAMAM-porphyrin dendrimers, because of the aggregate structures that were involved.¹⁴⁷⁵ Iron chelators were also shown to improve the efficiency of ALA.¹⁴⁷⁶ Photobleaching rates were temperature¹⁴⁷⁷ and solvent-polarity dependent,¹⁴⁷⁸ and photofrin was shown to strongly activate PDT.¹⁴⁷⁹ Micellar-formulation optimization¹⁴⁸⁰ and immunoconjugates^{1481–1483} can improve circulation time and accumulation.¹⁴⁸⁰ PEGylated tetraarylporphyrins have been incorporated in vesicular carriers for improved efficacy.¹⁴⁸⁴ PEGylated PAMAM and PEGylated PPI dendrimers are also promising vehicles for PDT.¹⁴⁸⁵ Two-photon excitation with ultrafast pulses of near-infrared

light (see section 3.7) is a less tissue-damaging technique than the standard single-photon PDT that causes damages to healthy tissues, because the low-energy two-photon beam is localized in three dimensions, allowing treatment volumes of a few femtoliters.¹⁴⁸⁶ The Kataoka group revealed that dendrimer photosensitizer-loaded micelles showed a higher antitumor effect than clinically used photofrin without any sign of phototoxicity to the normal tissues even at high dose (Figures 91–93).^{1487–1490}

A photosensitizer formulation with dendrimer phthalocyanine-encapsulated polymeric micelle induced efficient rapid cell death and cell membrane blebbing upon irradiation. In addition, treated mice did not show skin phototoxicity, suggesting usefulness in clinical PDT.¹⁴⁹¹

6.4.2. Photothermal Therapy

Besides PDT, another recently emerging phototherapy technique is photothermal therapy. It is based on irradiation in the visible or infrared region of the plasmon band of silver and gold nanoparticles AgNPs and AuNPs, respectively (for review, see ref 1247), that are encapsulated in targeted dendrimers (see section 4.10).^{663,1492–1496} The principle consists of irradiating the AuNPs that convert absorbed light to thermal energy that is transferred to the nearby cells, resulting in hyperthermia treatment by cell destruction. Appropriate targeting is required to be specific for cancer cells. G_5 -PAMAM-folic acid-fluorescein dendrimers containing AuNPs were shown to be specifically delivered to KB cells in vitro and were internalized into lysosomes within 2 h.¹⁴⁹³ G_4 -PAMAM-PEG dendrimers,¹⁴⁹⁴ and “click” dendrimers⁶⁶³ incorporating AuNPs were also probed and found to be superior to PEG-free dendrimers in terms of thermal stability. Acetylation of amine terminated G_5 -PAMAM-encapsulated AuNPs and AgNPs decreases the surface charge toward neutral with an increasing degree of acetylation, transfers Ag DENs to dendrimer-stabilized AgNPs, and is expected to decrease the toxicity of DENs.¹⁴⁹⁵ These dendrimer-stabilized AuNPs can specifically target to cancer cells expressing high-affinity folic acid receptors in vitro.¹⁴⁹⁶

6.5. Drug Delivery to Specific Organs and for Specific Diseases

Colonic delivery of 5-aminosalicylic acid was efficiently carried out using PAMAM dendrimers, with the drug being bound to the dendrimers using two spacers containing azo bonds.¹⁴⁹⁷ PAMAM dendrimers demonstrated physicochemical characteristics (pH, osmolality, viscosity) that are compatible with ocular dosage formulations. In addition to size and molecular weight, charge and molecular geometry of bioadhesive dendrimers also influenced the residence time; $G_{1.5}$ and G_4 -PAMAM-OH and PAMAM-CO₂H showed the best bioavailability for drugs.¹⁴⁹⁸ Antiarrhythmic quinidine was covalently attached to anionic $G_{2.5}$ and cationic G_3 -PAMAM-PEG (stealth) dendrimers via a glycine spacer, and in vitro hydrolysis was carried out in pH 7.4 buffer at 37 °C to confirm the bioavailability of the conjugated quinidine.¹⁴⁹⁹ Ionic binding was shown between the amino groups of cationic PAMAM dendrimers and sulfate groups of enoxaparin, a low-molecular weight heparin, and the resulting drug-dendrimer complex was effective in preventing deep-vein thrombosis after pulmonary administration. Positively charged dendrimers increased enoxaparin bioavailability by 40%, whereas negatively charged dendrimers

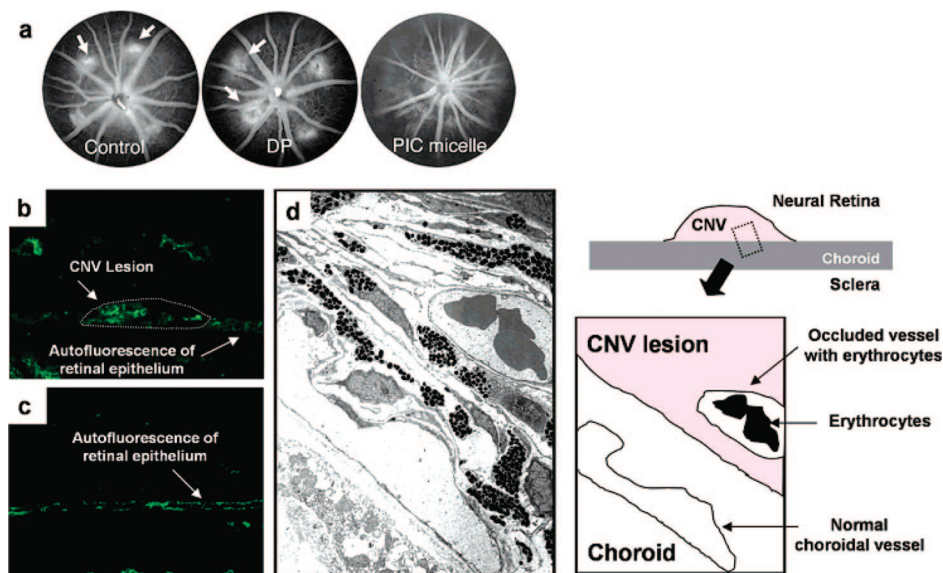


Figure 91. Efficacy of PDT laser after administration of the DP(dendrimer porphyrin)-loaded micelle. (a) Representative images of fluorescein angiograms in control, PDT-laser-irradiated eye after free DP was administered (DP), and PDT-laser-irradiated eye after the DP-loaded micelle was administered (PIC micelle). Note that the enhanced accumulation of DP-loaded micelles in CNV (choroidal neovascularization) lesions resulted in a significantly pronounced photodynamic effect, whereas almost all of the CNV lesions showed a strong hyperfluorescence (marked with arrows), and the CNV endothelial cells appeared normal when free DP was administered. (b) Immunostaining of the endothelial cells with factor VIII antibody. Strong fluorescence from the CNV lesion is observable. (c) Immunostaining of the endothelial cells with factor VIII antibody after PDT treatment with DP-loaded micelle. Note that CNV lesion is occluded, and only autofluorescence from retinal pigment epithelium is observable. (d) Transmission electron microscopy of the CNV lesion of the PDT-laser-irradiated eye after the DP-loaded micelle was administered. The neovascular blood vessel in CNV lesion is occluded by erythrocytes, whereas the normal choroidal vessel is not destroyed. Reprinted with permission from ref 1490 (Kataoka's group). Copyright 2005 American Chemical Society.

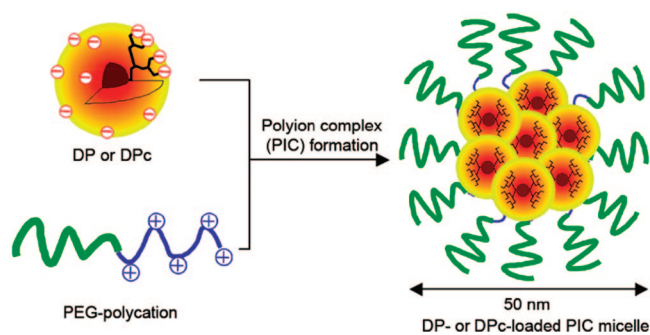


Figure 92. Formation of DP (dendrimer porphyrin)- or DPc-loaded polyion complex (PIC) micelles through the electrostatic interaction between anionic dendrimers and PEG-polycations. The DP or DPc-loaded micelle is assumed to induce an effective photochemical reaction because the dendritic wedges can sterically prevent or weaken aggregation of the center dye molecules in the micellar core. Reprinted with permission from ref 1487 (Kataoka's group). Copyright 2009 Elsevier.

had no effect.¹⁵⁰⁰ The binding between glitazones, PPAR γ agonistic insulin sensitizers clinically used for the treatment of type-2 diabetes, via free hydrogen bonds with dendrimers was shown using ab initio calculations and molecular electrostatic potentials.¹⁵⁰¹

Tissue integration between a tissue-engineered corneal equivalent and the host eye is of critical importance in ensuring long-term implant success. Therefore, collagen matrices were cross-linked with heparin-modified G_2 -PPI octaamine dendrimer for the delivery of basic fibroblast growth factor (FGF-2).¹⁵⁰² Mimicking key aspects of the multivalent architecture of the phage on an AB₅ dendritic wedge enhanced the affinity of a phage-display derived

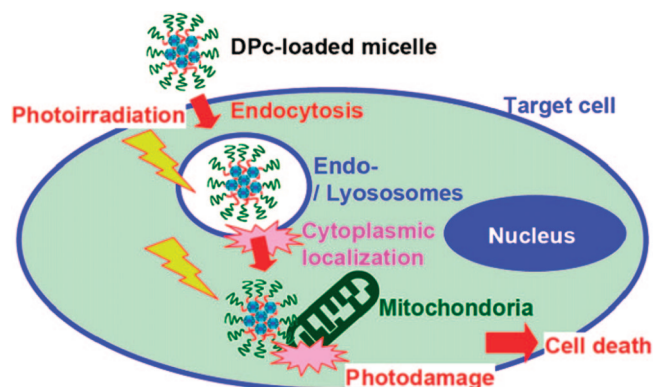


Figure 93. Hypothetical mechanisms of the light-induced cell death by the DP (dendrimer porphyrin) c-loaded micelle. The DPc-loaded micelle is internalized through endocytosis. Upon photo-irradiation, the DPc-loaded micelle might escape from the endo/lysosomes to the cytoplasm by photodamaging the endo/lysosomal membranes. Finally, the DPc-loaded micelle might induce photodamage to the mitochondria, leading to the oncosis-like cell death. Reprinted with permission from ref 1487 (Kataoka's group). Copyright 2009 Elsevier.

collagen-binding peptide 100-fold, which allows direct visualization of collagen architecture in native tissue (Figure 94).¹⁵⁰³

Dual drug delivery was explored as a treatment against leukemia under optimized pH conditions and dialysis time. One molecule of PAMAM dendrimer could entrap 27 molecules of methotrexate and 8 molecules of all-*trans* retinoic acid. The release kinetics was governed by the degree of dendrimer protonation, with more sustained and controlled behavior at pH 7.4.¹⁵⁰⁴ G_3 - to G_5 -PAMAM dendrimers were shown to be potential efficient agents against fibrillation of

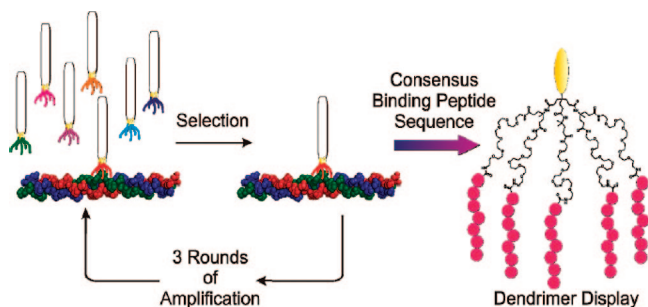


Figure 94. From phage display to dendrimer display: phage display to collagen reveals a consensus binding sequence that is translated into a high affinity, versatile synthetic collagen-specific probe by mimicking the original pentavalent phage architecture on a dendritic wedge. Reprinted with permission from ref 1503 (Meijer's group). Copyright 2009 American Chemical Society.

α -synuclein, a Parkinson's disease-related protein.¹⁵⁰⁵ The release kinetics of PAMAM dendrimers, conjugated with the anti-inflammatory drug *N*-acetyl cystein containing disulfide linkages, was determined in the presence of glutathione, cysteine, and bovine serum albumin, in activated microglial cells, using the reactive oxygen species. The conjugates showed an order of magnitude increase in antioxidant activity compared to the free drug.^{1506,1507}

6.6. Drug Biocompatibility and Toxicity

Toxicity has been defined as "a measure of nonspecific, unwanted harm that the drug may elicit towards cells, organs or the patient as a multi-organ system".^{1066,1067} The toxicity is assessed by

- In vitro testing (i) the cytotoxicity on a panel of cell lines, hematocompatibility (red blood cells, RBC), lysis (Hb release), and complement activation, (ii) ability to induce cytokine release and biodegradation of the dendrimer (cytotoxicity of the degradation products), (iii) intracellular fate (endocytic pathway and fate of the dendrimer, degradation), and (iv) pharmacological activity of the construct.

- In vivo testing (i) the body distribution (short-term fate, 1 h, and long-term fate, 1 month), (ii) definition of organ-specific toxicity (liver, kidney, etc.), immunogenicity (IgG and IgM induction and cytotoxine induction), and metabolic fate.

- Preclinical testing (teratogenicity, therapeutic index, single-dose and multiple-dose toxicity, metabolic fate).

- Testing on the patient (Figure 95).

Biocompatibility was defined as "the ability of a material to perform with an appropriate host response in a specific application".¹⁵⁰⁸ These definitions must be intended to a precise use.¹⁰⁶⁶ A dendritic carrier to be suitable for parental application should be nontoxic, nonimmunogenic, and preferably biodegradable. In vitro and in vivo tests were developed by Duncan and have been routinely used as a prescreen of polymers and dendrimers under consideration as potential drug-delivery systems.¹⁵⁰⁹ Overall, dendrimers show promising biocompatibility. The cytotoxicity of dendrimers with cationic amino surface groups is similar to that found for liposomes, which have found medical applications (e.g., Doxil, the liposomal formulation of doxorubicin).¹⁰⁵² The toxicity of a dendrimer is connected to the pharmacodynamics and biodistribution that depend on the dendrimer molecular weight, charge, and hydrophobicity and must be screened at the early stage as well as antigenicity (IgG and IgM induction) and cellular immunogenicity (cytokine and

chemokine induction). Cytotoxicity studies require appropriate incubation time and concentration to define the inhibitory concentration diminishing viability (IC₅₀ value). Toxicity to vital organs such as the lungs, liver, or kidneys may result if the dendrimer accumulates in these organs.

The toxicities of the main families of dendrimers, i.e., PAMAM and DAB, have been reviewed.^{1510–1513} For PAMAM dendrimers, cytotoxicity is generation-dependent. Cationic *G*₄-PAMAM and *G*₄-DAB dendrimers were found to be cytotoxic with IC₅₀ values of 50–300 μ g/mL, but cytotoxicity strongly depended on the nature and charge of the surface groups.^{1066,1067,1220,1225} Atomic force microscopy and fluorescence microscopy were used to visualize membrane damage. The addition of two PEG₂₀₀₀ chains had no effect on *G*₄-PAMAM dendrimers, but 4 PEG₂₀₀₀ chains resulted in a 6-fold decrease in toxicity, showing that sufficient shielding of the terminal amino group is necessary for toxicity reduction.^{1221,1222} PEG stars with polyester dendrons had IC₅₀ of 40 mg/mL toward B16F10 cells during a 2-day incubation, indicating real potential for further development in drug-delivery applications.^{1139,1509}

Hemolytic activity is defined by the measure of hemoglobin (RBC) release (hemolysis) and is a simple method to study dendrimer–membrane interactions. Cationic PAMAM and polyethyleneimine (PEI)-based DAB dendrimers show generation-dependent hemolysis above concentrations of 1 mg/mL, but PEG dendrimers were not hemolytic. Anionic *G*_{1.5–3.5}-PAMAM dendrimers showed no hemolysis up to 2 mg/mL after 1 h, but anionic *G*_{7.5–9.5}-PAMAM dendrimers were hemolytic at doses of 2 mg/mL and above, confirming that the previously observed general toxicity is likely to be due to the increase in molecular weight.^{1514,1515} PAMAM dendrimers and some other high-molecular-weight dendrimers were found to be complement activators. Toxicity studies have also been reported for dendrimers of the PEI, carbosilane, polyether, and melamine families.^{1066,1067,1510–1513} The intracellular responses such as the content of reactive oxygen species (ROS, superoxide radical anion and hydrogen peroxide), mitochondria membrane potential, cell size, and cell cycles profiles in U-937 human macrophages treated with PPI dendrimers (*G*₂-DAB and *G*₃-DAB) showed that ROS responses in macrophages were strongly influenced by the nature of the dendrimer surface and the generation.¹⁵¹⁶ Other recent studies on PPI dendrimers show decreased toxicity when the terminal amino groups are protected or masked.^{1517,1518} Intravenous injection of poly(lysine) dendrimers resulted in rapid removal from plasma, and highly charged cationic dendrimers rapidly bind to endothelial cell surfaces immediately after injection and are subsequently hydrolyzed to produce free lysine.¹⁵¹⁹

Dendrimers, like other macromolecules, are transported into and across cells by endocytosis, although the mechanisms are not well-known.^{1066,1067} On the other hand, the biodistribution of dendrimers has been widely studied especially with dendrimer-conjugated imaging agents and for their use in BNCT. A detailed hemocompatibility testing in vitro of high-molecular weight (*M*_n up to 700 000) polyglycerol dendrimers for effects on coagulation, prothrombotic time, activated partial thromboplastin time, plasma recalcification time, thrombelastography parameters, complement activation, platelet activation, RBC aggregation, and cytotoxicity showed that they are highly biocompatible and potential candidates for various applications in nanomedicine (Figure 96).^{1520–1522}

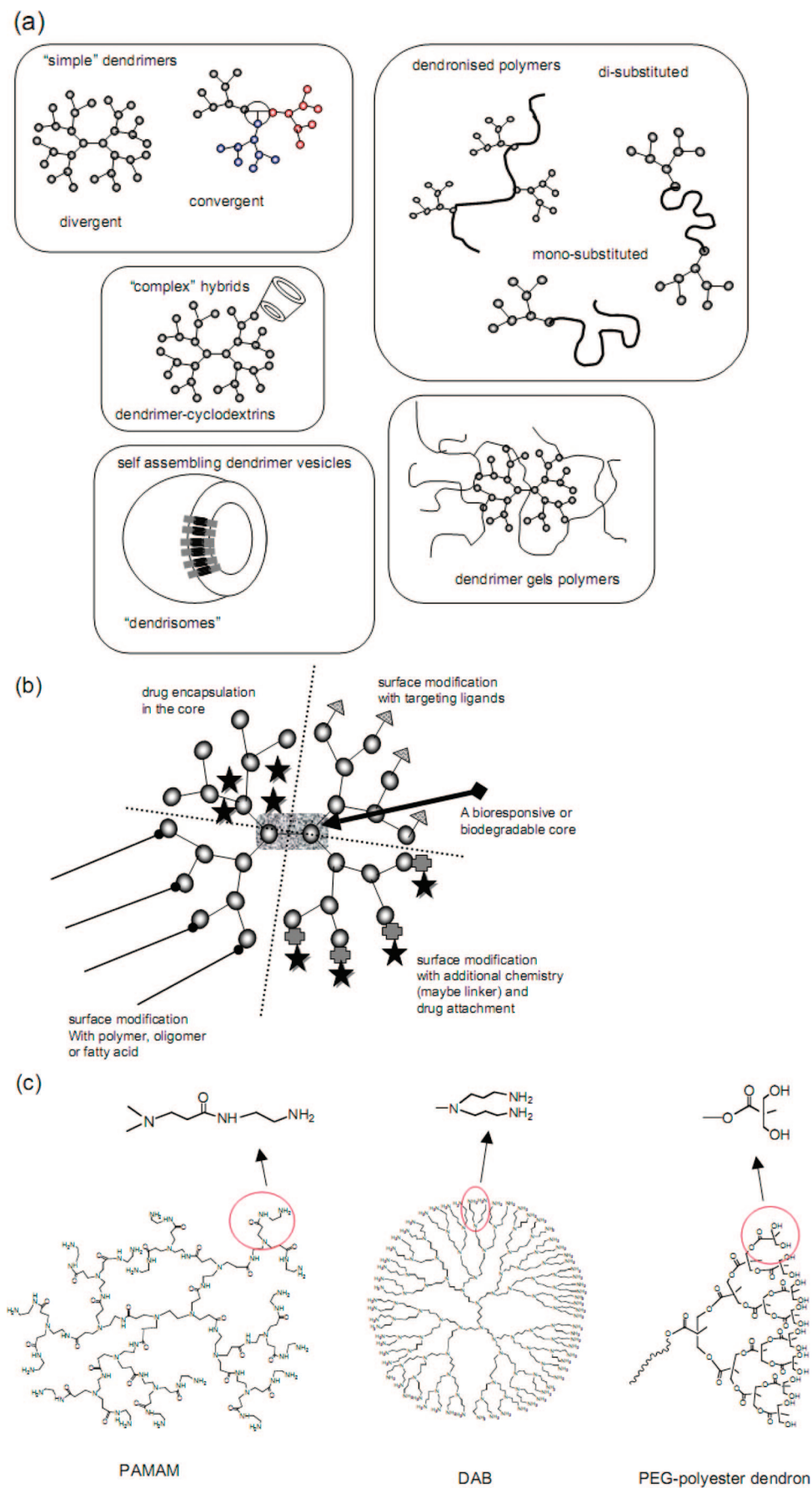


Figure 95. Diagram showing schematically (a) dendritic architectures under development for biomedical and (b) approaches for design of therapeutics and drug-delivery systems. Reprinted with permission from ref 1066 (Duncan's group). Copyright 2005 Elsevier.

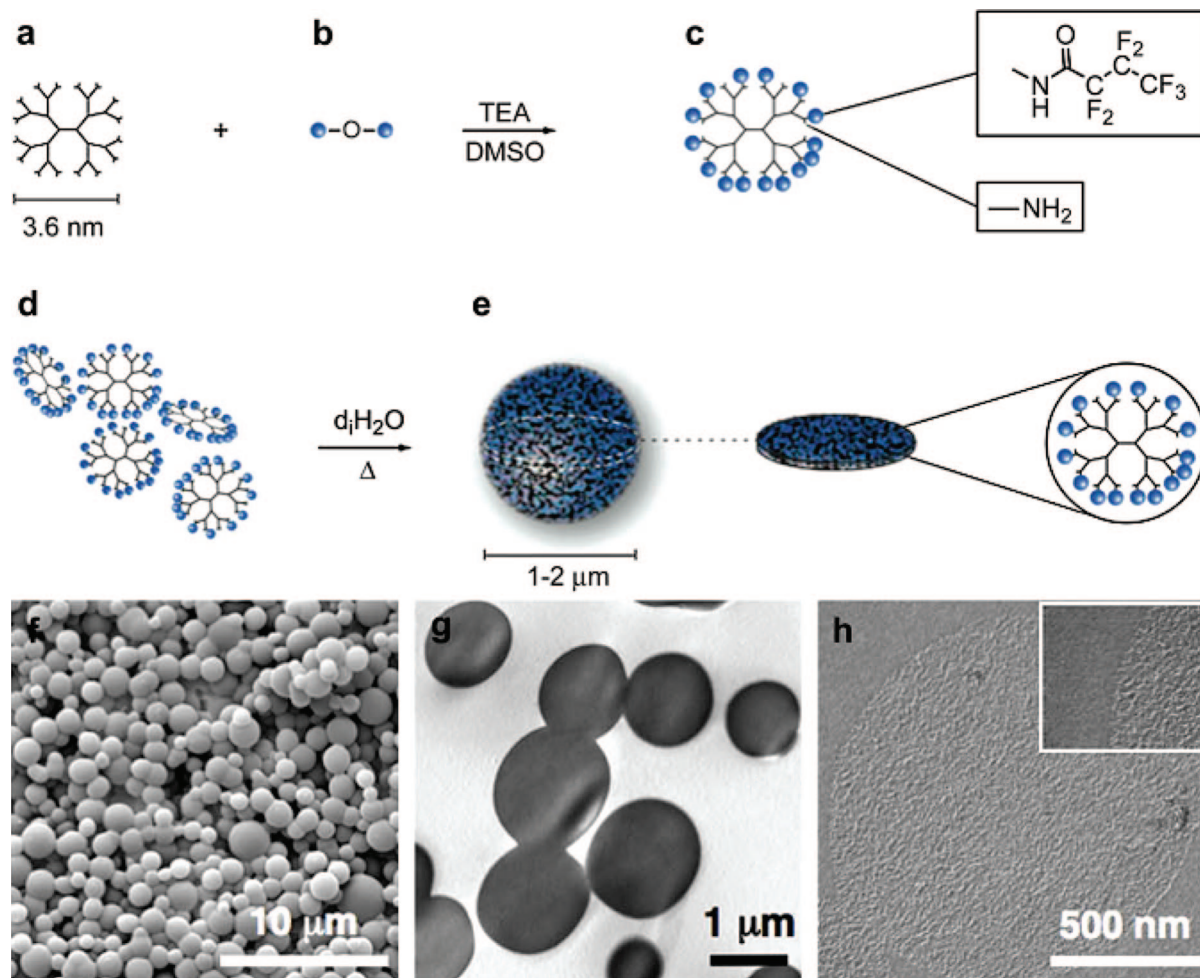


Figure 96. Self-assembly model of fluorinated, PAMAM(G_3) dendrimer-based particulates. Fifteen primary amines on the surface of (a) PAMAM(G_3) starburst dendrimers were functionalized through reaction with (b) HFAA (heptafluorobutyric acid anhydride) to yield (c) heptafluoroacylated PAMAM(G_3) terminal branches. The blue sphere and the branch terminus represent the heptafluoroacyl substituent and the terminal primary amine, respectively. The (d) randomized mixture of partially fluorinated dendrimers aggregated in aqueous environment and formed (e) self-assembled particulates with the addition of sufficient thermal energy (100 °C for 1 h). The cross-sectional diameter of the particulate in (e) illustrates the densely packed internal network of partially fluorinated dendrimers. (f) Scanning electron micrograph of the fluorinated PAMAM(G_3) dendrimer-based particulates formulated with 5 mg/mL initial concentration of PAMAM(G_3) dendrimers and 25 mol equiv of HFAA. Scale bar is 10 μm . (g) Transmission electron micrograph of 80-nm-thick cross section of the particulates in (f) treated with 1.0% OsO_4 , embedded in Embed-812 epoxy, and stained with uranyl acetate and lead citrate. Scale bar is 1 μm . (h) Transmission electron micrograph of a freeze fracture replica of the particulates in (f) depicting a dense matrix-like internal structure upon cross-fracture. Scale bar is 500 nm. Reprinted with permission from ref 1521 (Fahmy's group). Copyright 2009 Elsevier.

There are rather few studies *in vivo* concerning the general toxicity of dendrimers,^{1056,1057,1066,1067,1196–1198,1241} and, although little general toxicity is reported in these studies, no definitive conclusion can be formulated. Unwanted immunogenicity (antigenicity) of dendrimers could prohibit clinical development, but few reports of studies have appeared, and no evidence of immunogenicity has been found.^{1066,1067}

Interestingly, naked, unmodified G_4 - and $G_{4.5}$ -PAMAM dendrimers bearing simple surface groups ($-\text{NH}_2$, $-\text{OH}$, CO_2H) showed anti-inflammatory properties with three independently recognized *in vivo* anti-inflammatory assay methods. For instance, G_4 -PAMAM- NH_2 showed higher activity compared to naked indomethacin.¹⁵²³

D'Emanuele's Manchester group showed the influence of G_3 -PAMAM dendrimer surface modification on the mechanism of cellular internalization into HT-29 cells using confocal laser scanning microscopy and flow cytometry using dendrimers that were labeled with fluorescein isothiocyanate at an average molar ratio of 1:1 and modified with lauroyl

and propranolol chains. The subcellular colocalization data showed that all these G_3 -PAMAM dendrimers were internalized and trafficked to endosomes and lysosomes.¹⁵²⁴ G_5 -PAMAM dendrimer-biotin-fluorescein isothiocyanate conjugates were shown not to exhibit much higher cellular uptake into HeLa cancer cells than the conjugate without biotin; thus, the dendrimer-biotin conjugates might be a promising nanoplatform for cancer diagnosis and therapy.¹⁵²⁵

6.7. Oral Drug Delivery and Other Delivery Means

A major challenge for drugs is the possibility of oral delivery, but an obstacle is the limited drug transport across the intestinal epithelium due to their large size relative to the tight epithelial barrier of the gastrointestinal (GI) tract. Duncan's group showed that only macromolecules with diameters up to 3 nm could penetrate through the rat's intestinal membranes via the transcellular or paracellular pathway, which allows $G_{2.5}$ - $G_{3.5}$ -PAMAM dendrimers to

transport across the intestine.^{1515,1526} In addition, the acidic environment of the stomach and GI-tract enzymes can affect the drug and the nanocarrier. Nonspecific interactions with food proteins must also be reduced. D'Emanuele et al. also investigated the transport route of a G_3 -PAMAM–propranolol dendrimer conjugate across Caco-2 cell monolayers. They suggested that the route of propranolol transport was primarily transcellular, while the conjugate was able to bypass the P-gp efflux transporter, and they arrived at the same conclusion as above concerning the penetration pathway of the intestinal membrane.¹¹⁵⁹ The PAMAM–phospholipid dendrimer conjugate with the anticancer drug 5-FU was found by the Jain group to be significantly more effective upon oral delivery to albino rats than the free drug.¹⁵²⁷ The Cheng and Xu group, who recently reviewed the field,¹⁵²⁶ found that a PAMAM dendrimer complex of the anti-inflammatory drug ketoprofen sustained antinoinceptive activity (inhibit rate > 50%) until 8 h of oral administration to Kunming mice, whereas this activity was absent with the free drug after 3 h.¹¹¹⁰ G_4 -PAMAM complexation brings about a 10-fold increase in permeability and more than 100-fold increase in cellular uptake with respect to free 7-ethyl-10-hydroxycamptothecin, suggesting that this complex has the potential to improve the oral bioavailability of this drug.¹⁵²⁸ Permeability studies of 4-PAMAM–arginine and –ornithine conjugates across IPEC-J2 cell monolayers, a new intestinal cell line model for drug-absorption studies, suggested that these dendrimer–polyamine conjugates are potential carriers for antigen/drug delivery through the oral mucosa.¹⁵²⁹

Transdermal drug delivery (TDD) is a noninvasive, safe method of penetrating drugs through the skin that has revolutionized the pharmaceutical industry, because skin is the most easily accessible organ in the body and TDD provides a steady drug concentration in the blood, thus simplifying dosing and minimizing pain.^{1530,1531} Dendrimers can act as effective transdermal penetration enhancers that are required to overcome the barrier function of the skin involving closely packed dead cells that impose tortuosity on the diffusion path across the membrane. PAMAM dendrimers including cationic ones were found to be efficient, in particular to solubilize hydrophobic drugs.¹¹⁴⁶ This technique appears as an emerging choice for various skin diseases in clinical trials.¹⁵²⁶

In ocular drug delivery, the main challenge is to increase the drug bioavailability and prolong the residence time on the cornea, conjunctival and corneal epithelia. Dendrimers might dissolve hydrophobic drugs and accomplish retention and sustained, controlled drug release.¹¹³⁷ Various PAMAM– NH_2 , PAMAM–OH, and PAMAM– CO_2^- dendrimer complexes, and some PPI, PAMAM, and lipid–lysine dendrimer conjugates, significantly improved the bioavailability of drugs.^{1526,1532–1538} Recent studies indicated that some lipid–lysine dendrimers, for which in vivo studies showed lack of toxicity, might be used as biocompatible ocular gene carriers to prevent ocular neovascularization that can be a main cause of blindness, when it is not controlled.^{1537,1538} Dendrimers are being increasingly proposed in various other delivery routes including rectal, vaginal, and nasal routes due to their tissue-penetration abilities. For instance, the poly(L-lysine)–dendrimer based microbiocide Vivagel (Starpharma) has been clinically tested for topical administration in the vagina against HIV and other sexually transmitted infections such as herpes.^{1351,1539,1540} An advanced local,

noninvasive, and effective technique, iontophoresis, consists of inducing the penetration of ionic nanomaterials such as highly charged drug–dendrimer complexes or conjugates into tissues using a weak electric field; it is widely used in transdermal and ocular delivery.¹⁵³²

Transepithelial transport of PEGylated anionic $G_{3.5}$ - and $G_{4.5}$ -PAMAM– CO_2H dendrimers with 1, 2, and 4 PEG per dendrimer was examined concerning the cytotoxicity, uptake, and transport across Caco-2 cells in view of oral drug delivery. Dendrimer PEGylation reduced the opening tight junctions; modulation of the tight junctional complex correlated well with changes in PEGylated dendrimer transport and suggested that anionic PEGylated PAMAM dendrimers are transported primarily through the paracellular route and show promise in oral delivery.¹⁵⁴¹

6.8. Medical Diagnostics: Imaging

Pretargeting of receptors is a useful approach in molecular imaging and therapy to reduce background noise or toxicity and enhanced selectivity. Such an approach was carried out using a biotinylated antibody, avidin/streptavidin, and a biotinylated imaging with a G_4 -PAMAM-MRI T1 DTPA–Gd–biotin dendrimer.¹⁵³³

6.8.1. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is now currently used in medical diagnostics to visualize organs and blood vessels. It consists of improving the quality of visualization by enhancing the longitudinal (T_1) relaxation rate of protons of H_2O molecules by coordination to paramagnetic contrast agent that are Gd^{III} chelates complexes such as widely used [Gd^{III} (DTPA)] (DTPA = diethylenetriamine pentacetic acid) commercially known as Magnevist (Schering AG) and [Gd^{III} (DOTA)] (DOTA = tetracarboxymethyl-1,4,7,10-tetraazacyclododecane). In these complexes, the relaxativity (relaxation rates of H_2O protons per mmol of Gd^{III} ion as a function of the magnetic field strength) is high enough. The key properties required for Gd^{III} MRI contrast agents are the good biocompatibility (low toxicity), the use at a low dose, a good excretion from the system, and a high thermodynamic and kinetic stability (Figure 97).^{1542–1550} Gd^{III} -containing PAMAM dendrimers were loaded with paramagnetic probes, which allowed determining the relative locations and concentrations of Gd^{III} by ESR.¹⁵⁵⁰

Major problems of low-molecular-weight complexes are short circulation times within the body and lack of

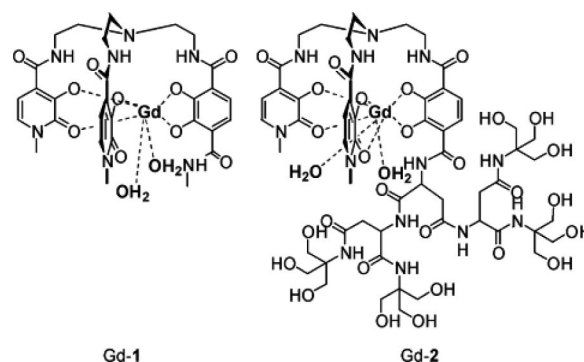


Figure 97. Gd-TREN-bisHOPO-TAM-Me(H_2O)₂ (Gd-1) and Gd-TREN-bisHOPO-TAM-Asp-Asp₂-12OH(H_2O)₂ (Gd-2). Reprinted with permission from ref 1547 (Reymond's group). Copyright 2005 American Chemical Society.

Delivery mechanism of nano-size particle

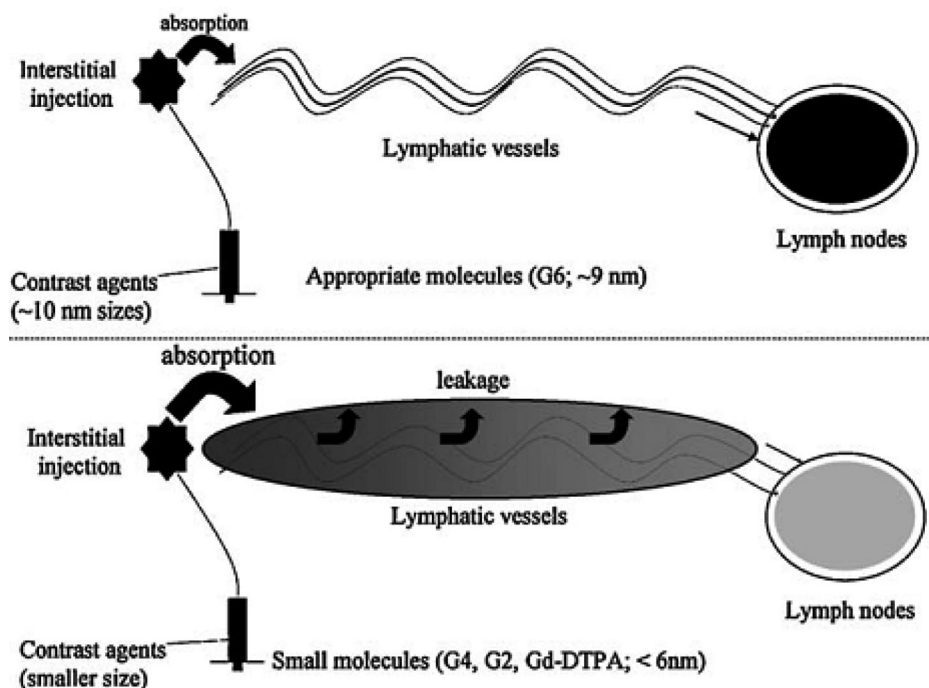


Figure 98. Mechanism of interstitial delivery of nanosize particles. Top: G6 dendrimers are taken up by lymphatics resulting in specific uptake by the lymphatics resulting in opacification of the lymph nodes (black). Lower-molecular-weight contrast agents (bottom) are absorbed by the lymphatics but leak out from them, resulting in lower lymph node concentrations (gray). Reprinted with permission from ref 1560 (Kobayashi's group). Copyright 2006 Elsevier.

discrimination between diseased and normal tissues. Subsequently, macromolecular derivatives were designed by combination with polylysine, PEG, polysaccharides, and proteins, but their slow secretion rate and resulting accumulation in the liver and toxicity risk related to Gd^{III} release during metabolism limited their clinical applications.^{1050–1052,1055}

The development and commercialization of PAMAM dendrimers was decisive in bringing a breakthrough in the MRI field when, in 1994, the groups of Lauterbur (2003 Nobel Prize in medicine) and Tomalia reported G₂- and G₆-PAMAM dendrimer-based Gd^{III} chelates conjugated to the chelate [Gd^{III}(dtpa)] {dtpa = 2-(4-isothiocyanatobenzyl)-6-methyldiethylenetriaminepentacetic acid} via a thiourea linkage. Excellent MRI images of blood vessels and long blood circulation times (>100 min) were obtained with G₆-PAMAM-[Gd^{III}(dtpa)] upon intravenous injection on rabbits.^{1551–1554} The relaxativity increasing linearly with the molecular weight, the best results were obtained later with G₉- and G₁₀-PAMAM dendrimers. The incorporation of PEG units was successful in considerably lowering liver retention after seven days (from 40% without PEG) to 1–8%, and conjugation to monoclonal antibodies or avidin provided tumor-specific MRI agents. Commercial applications of these concepts followed with Gadomer 17, a 24-Gd^{III}-DTPA dendrimer containing trimesic acid core connected to G₂-polylysine dendrons bearing 24 DTPA and 24 DOTA peripheral chelating-Gd^{III} groups, respectively.⁸⁰⁰ PPI-Gd^{III}(dtpa) dendrimers were used as well.^{1555,1556} Dendrimer-Gd^{III} complexes for MRI have been reviewed.^{1050–1052} More recently, a G₈-PAMAM-Gd dendrimer conjugate allowed visualization of changes in tumor permeability after a single dose of radiation.¹⁵⁵⁷ In vivo imaging in mice of a G₄-PAMAM-dendrimer-Gd^{III}-DTPA conjugate showed a

reasonably fast clearance ($t_{1/2} = 24$ min), suggesting that it is a viable agent for use in clinical applications.¹⁵⁵⁸ Micro-magnetic resonance lymphangiography, a new method relying on temporarily enhanced permeability of tumor vasculature to drugs, was probed in mice bearing hematomas to improve the contrast between intralymphatic and extralymphatic imaging (Figure 98).^{1559,1560}

Beside PAMAM and lysine dendrimers, PPI and DAB dendrimers conjugates have been used as macromolecular MRI agents.¹⁵⁶¹ With the same number of termini, DAB-based reagents cleared more rapidly from the body than PAMAM-based agents.¹⁵⁶² High generations such as G₅ showed more gradual diffusion than lower ones.¹⁵⁶³ Imaging of oncogene mRNA in tumor cells by hybridization of complementary oligonucleotides was achieved with polyamidopropionate-peptide nucleic acid-Gd^{III} conjugates.¹⁵⁶⁴ The groups of Fréchet and Prasad examined the generation of cytotoxic singlet oxygen for PDT to subcutaneous tumors by fluorescence resonance energy transfer (FRET) using porphyrin sensitizers as dendritic cores of dendrimers containing two-photon donor chromophores such as the complex polyaromatic AF-343 at the periphery (see section 3.7).^{267–269} ¹⁹F NMR has been used as an MRI technique utilizing pH-responsive fluorinated dendrimers.¹⁵⁶⁵ MRI lymphangiography using dendrimer-based contrast agents has been compared at 1.5T and 3T.¹⁵⁶⁶ A dual computer tomography (CT)-MRI dendrimer contrast agent was used as a surrogate marker for convection-enhanced delivery of intracerebral macromolecular therapeutic agents.¹⁵⁶⁵

Superparamagnetic iron oxide NPs are effective contrast agents for labeling cells to provide high sensitivity in MRI, but this sensitivity depends on the ability to label cells with sufficient quantities of SPIO, which is challenging for nonphagocytic cells such as cancer cells. Therefore, cell-

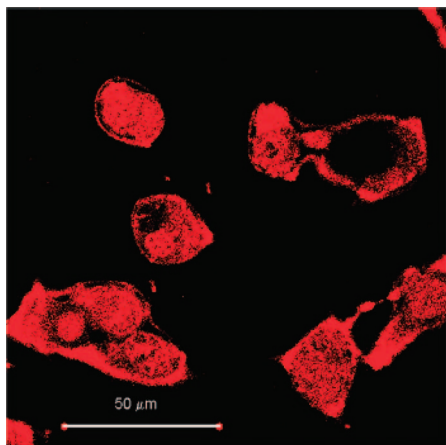


Figure 99. Confocal laser scanning microscopy image of GL261 cells following a 2 h incubation with the dendritic nanoparticle at a concentration of 25 μg of Fe/mL. Reprinted with permission from ref 1566 (Gillies' group). Copyright 2008 American Chemical Society.

penetrating polyester dendron with peripheral guanidines was conjugated to the SPIO surface. In GL261 mouse glioma cells, the dendritic guanidine exhibited similar cell-penetrating capabilities to the HIV-Tat47-57 peptide for the transport of fluorescein, and when conjugated to SPIO, it provided enhanced uptake in comparison with NPs having no dendron or dendrons with hydroxyl or amine peripheries. Greater toxicity than with hydroxylated or aminated dendrons was disclosed, however, although the NPs were relatively non-toxic at the concentrations required for labeling (Figure 99).¹⁵⁶⁶

Multicolor imaging of lymphatic function was advantageously carried out with two probes: dendrimer-based optical agents and quantum dot-labeled cancer cells, because the lymphatics, critical conduits of metastases, are difficult to study using only one method given their size and location.¹⁵⁶⁷

6.8.2. Computed Tomography, A Radiolabeling and Imaging Method

Computed tomography (CT) is a medical imaging method used to generate a three-dimensional image of the inside of

an object from a large series of two-dimensional X-ray images taken around a single axis of rotation. It is an important tool in medical imaging used in the diagnosis of various disease entities and has recently begun to also be used for preventive medicine or screening for disease. CT usually utilizes mostly iodinated agents and is regarded as a moderate-to-high radiation diagnostic technique. Targeted delivery is a key issue, as for other imaging methods; therefore, dendrimer conjugation is most useful. Iodinated contrast agents based on iobitridol- G_3 - G_5 poly(lysine) dendrimers containing PEG cores have been used for tumor microvasculature CT imaging and produced strong visualization of normal rat vasculature. The large molecular weight of the dendrimer conjugate was responsible for good retention, with the half-time in blood being 35 min, compared to the typical exhaustion time of 5 min recorded for small-molecule CT contrast agents.¹⁵⁶⁸

Metalation of G_5 - G_7 -dendrimers terminated with tridentate bis(pyridyl)amine by another radioactive element, $^{99\text{m}}\text{Tc}(\text{I})$, provided dendrimer radiolabeling, and distribution in healthy adult Copenhagen rat using dynamic small-animal single photon emission computed tomography indicated that the labeled dendrimers were rapidly eliminated from the bloodstream via the kidneys.¹⁵⁶⁹

Positron-emitting tomography (PET) allows a tridimensional view, and the Fréchet group designed a biodegradable dendritic radiohalogen-based (^{125}I and ^{76}Br) PET nanoprobe targeted at $\alpha_v\beta_3$ integrin, a biological marker for the modulation of angiogenesis (cf section 6.2.6). The radioactive halogens were located at the dendrimer core in order to prevent in vivo dehalogenation that is frequently encountered in imaging. Targeting peptides of arginine-glycine-aspartic acid (RGD) motifs were located at the termini of the PEG chains to favor their accessibility to the $\alpha_v\beta_3$ integrin receptors. This dendritic engineering enabled a 50-fold increase of the binding affinity to $\alpha_v\beta_3$ integrin receptors compared to the monovalent RGD alone. In vivo biodistribution studies of ^{76}Br -labeled dendritic nanoprobe showed excellent bioavailability. In vivo studies in a murine hindlimb ischemia model for angiogenesis showed high nanoprobe

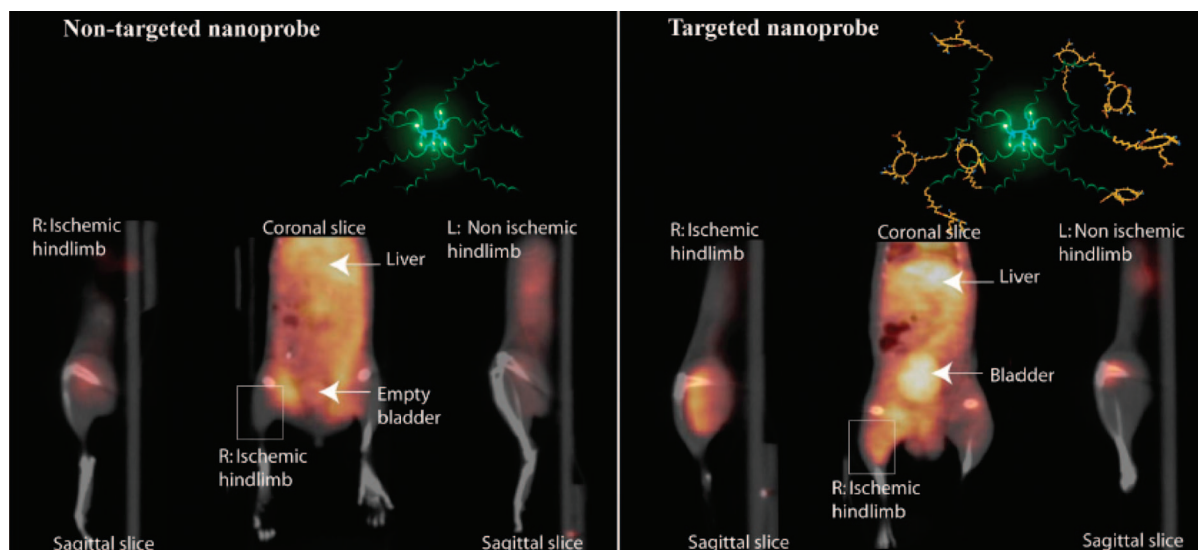


Figure 100. Noninvasive PET/CT images of angiogenesis induced by hindlimb ischemia in a murine model. (A) Nontargeted dendritic nanoprobe (shown bottom center). (B) Uptake of $\alpha_v\beta_3$ -targeted dendritic nanoprobe was higher in ischemic hindlimb (left side of image) as compared with control hindlimb (right side of image) Reprinted with permission from ref 1570 (Fréchet's group). Copyright 2009 National Academy of Sciences of the U.S.A.

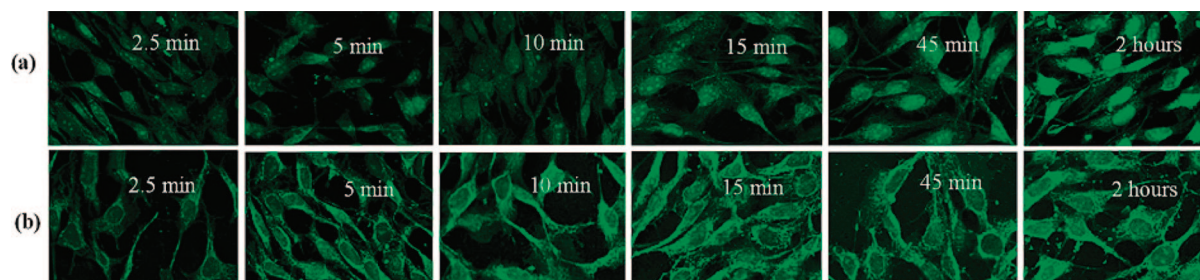


Figure 101. Time course of internalization of (a) FD-1 and (b) FD-2 into NIH-3T3 cells (fixed) at 37 °C. The conjugate concentration was 10 μ M. Reprinted with permission from ref 1578 (Harth's group). Copyright 2007 American Chemical Society.

accumulation targeted at $\alpha_V\beta_3$ integrins in angiogenic muscles, allowing highly selective imaging (Figure 100).¹⁵⁷⁰

6.8.3. Fluorescence

Fluorescence quantification in tissues using conventional techniques can be difficult due to the absorption and scattering of light in these tissues. One-photon (see also section 3)¹⁵⁷¹ and two-photon^{255,256} (see section 3.7) fluorescent tumor-sensing systems have been developed with the advantage for the latter of high spatial (μ M) resolution. Two-photon optical fluorescence fibers use a single-mode fiber to transport femtosecond laser pulses for excitation and to collect emitted tissue fluorescence.^{1572,1573} This technique has been used with a G_5 -PAMAM dendrimer conjugated to folic acid and the fluorescent probe 6-carboxytetramethylrhodamine succinic ester (6-TAMRA) to target xenograft tumors in mice; it showed accumulation in the tumor up to 673 ± 67 nM at 2 h, whereas the analogous conjugate without folic acid reached only 136 ± 28 nM in 2 h.^{1574–1576} The same fiber probe was used for labeling human squamous KB cell tumors grown *in vivo* in mice and detected a 3-fold increased tumor fluorescence in animals that were treated with the targeted dendrimer conjugate compared to the conjugate that did not contain folic acid, which demonstrated the utility of this technique.¹⁵⁷⁷ Newkome-type dendrimers were found to be ideal nanovectors of two nonpeptidic fluorescent markers that were internalized into mammalian cells with strong subcellular localization (Figure 101).¹⁵⁷⁸ Antibody–Au quantum dot–PAMAM dendrimer complexes were used as an immunoglobulin immunoassay based on linear fluorescence quenching over a micromolar to nanomolar concentration range.¹⁵⁷⁹ Dendrons containing fluorescent probes with two other usefully functionalized tethers (carboxylic acid and azido) have been designed for branching to biomedical devices.¹⁵⁸⁰

The interactions between $G_{4,5}$ -PAMAM dendrimers and bovine serum albumin were analyzed using fluorescence and equilibrium dialysis.^{1581–1585} Optical fluorescence has been coupled to MRI in a single hybrid probe in dendrimers to localize the sentinel lymph node and other targets.^{1586–1588} Dansyl fluorescence in dendrimers (cf. section 3.4) has been used for cellular uptake and intracellular localization by confocal fluorescence microscopy.¹⁵⁸⁹ Covalent encapsulation of near-IR fluorophores in a biodegradable dendrimer surrounded by a shell of polyethylene oxide conferred enhanced stability to the nanoprobe with additional resistance to enzymatic degradation, prolonged blood residence time, and enabled monitoring fluorescence lifetime changes *in vivo*.¹⁵⁹⁰ The extracellular cell matrix (ECM) surrounds cells and plays important roles in many aspects of cellular fate, including cell migration, stem cell differentiation, and cancer progression. Therefore, the Müllen group has reported a positively

charged fluorescent core–shell dendritic macromolecule containing multiple $-\text{NH}_2$ groups that bind to highly charged ECM components with advantageous optical properties and biological specificity.¹⁵⁹¹

6.9. Biosensors

6.9.1. Dendritic DNA Biosensors

Nucleic acids have been used as dendrimer constituents at the end of the 1990s and the beginning of this decade,^{1592,1593} and some of them are commercially available (3DNA).¹⁵⁹⁴ Physical properties of interest included AFM, dynamic light scattering,¹⁵⁹² flow cytometry,^{1593,1595} fluorescence,¹⁵⁹⁵ diffusion,¹⁵⁹⁶ and conductivity (Figure 102).^{1597–1599}

DNA microarrays and biosensors are a broad area, in which dendrimers are involved, and it has been the subject of two special volumes^{1600,1601} and a review article by Rosi and Mirkin¹⁶⁰² published in 2005. The principle consists of immobilizing nucleotides on glass slides by covalent grafting in order to analyze mixtures of fluorescent-labeled nucleic acids, with fluorescence serving for quantifying the hybridization. First, dendrons were grown on the slide,¹⁶⁰³ a technique that has been then largely improved.^{1604–1606} In 2001, the Niemeyer group pioneered the field with PAMAM dendrimers and obtained stable fluorescence intensity that was considerably increased compared to that for nondendritic linkers.^{1607,1608} PPI dendrimers have also been used.¹⁶⁰⁹ Subsequently, larger increases in intensities were obtained,^{1610–1614} in particular using high-generation aldehyde-terminated dendrimers and aminated slides that provided high sensitivities.^{1610–1613} A G_3 -PAMAM dendrimer conjugated to biotin was immobilized on glass slides using avidin complexation and examined using AFM and SEM for low-concentration DNA detection, increasing the sensitivity for fluorescence-labeled target DNA.¹⁶¹³ An elegant patterning method reported by Reinhoudt's group involved stamps for microprinting, providing microarray replication. The stamp, inked with the PPI dendrimer, was incubated with DNA labeled with fluorescein. The dendrimer was then washed out after printing on the slide, allowing fluorescence analysis of the patterned DNA microarray.^{1615,1616}

Other recently used techniques in this context involve dendrimer nanotubes,¹⁶¹⁷ ZnCdSe quantum dots,^{1618,1619} quartz-crystal microbalance, piezoelectric membranes, gold colloids,¹⁶²⁰ plasmon resonance,¹⁶²¹ and electrochemistry (Figure 103).^{1622–1625}

Electrostatic interactions between positively charged (mostly) PAMAM dendrimers and oligonucleotides involved studies that were essentially directed toward gene transfection (cf. section 6.2.7); they provided information on these interactions through various physical methods^{619,620,1599,1626–1631} and were reviewed in 2005 by Florence.^{619,620}

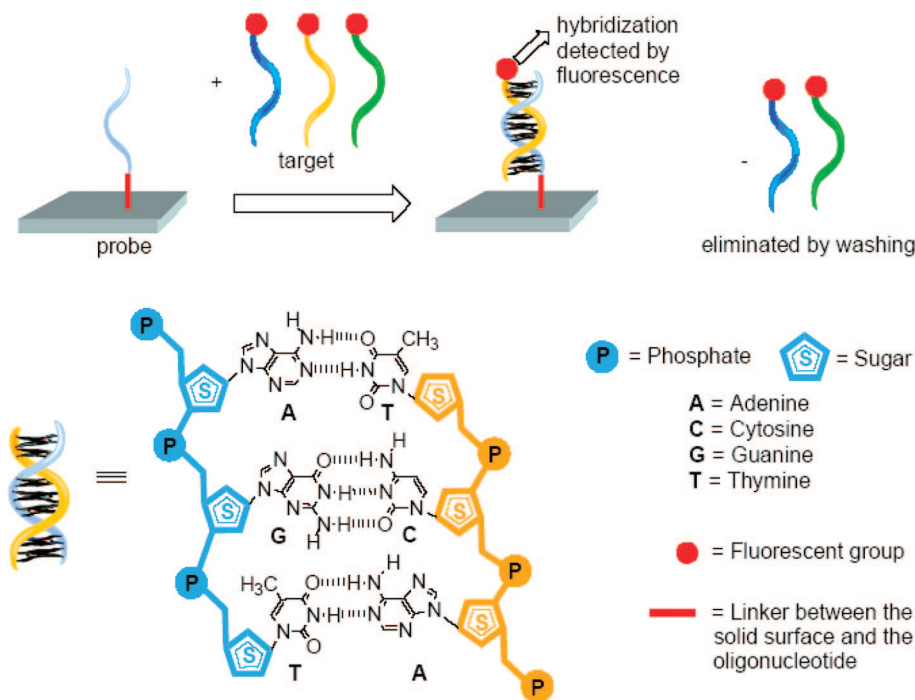


Figure 102. Principle of a DNA chip or DNA array. Only the oligonucleotide complementary to the one immobilized on the surface can hybridize. The hybridization occurs through supramolecular recognition of complementary bases (adenine with thymine and cytosine with guanine) linked to the sugar and phosphate backbones, as illustrated by one example. Reprinted with permission from ref 1598 (Majoral's group). Copyright 2006 Molecular Diversity Preservation International.

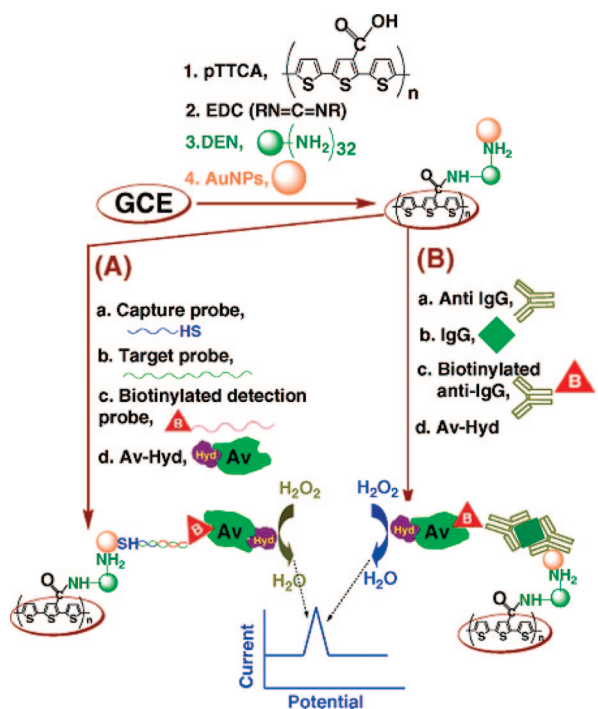


Figure 103. Schematic diagram of the pTTCA/DEN/AuNP/biomolecules-linked avidin-hydrazine assembly for (A) DNA and (B) protein sensors, which are based on the electrocatalytic activity of hydrazine. Reprinted with permission from ref 1625 (Shim's group). Copyright 2007 American Chemical Society.

6.9.2. Electrochemical Dendritic ATP Sensors

Adenosine triphosphate (ATP), a DNA fragment, is a cell energy source and cellular messenger. It can be recognized by electrostatic binding with a synthetic cationic sensor, for instance, electrochemically using the redox potential fluctuation of ferrocenyl⁴⁹⁰ or cobaltocenyl^{526,527} redox systems.

It is the cationic form of the redox system that forms an ion pair with the anionic groups of ATP. If this sensor is linear, however, this interaction is too weak to provoke a significant change of redox potential. On the other hand, ferrocenyl-terminated dendrimers show a positive dendritic effect, i.e., a new ferrocenyl redox wave at a less positive anodic potential is appearing in the cyclic voltammogram upon addition of ATP to a solution of the ferrocenyl-terminated dendrimer of low or high generation. Thus, ion pairing in the ferrocenyl dendrimers in which the ferrocenyl groups are simply linked to the core by alkyl chains involves dendritic encapsulation of ATP in the dendrimer interior, provoking a much stronger interaction than with linear alkylferrocenes. This also allows titration of the ATP solution (Figure 104).¹⁶³²

It is possible (although not indispensable) to introduce additional supramolecular interactions that can enhance the ionic interaction between the ATP phosphate groups and the ferricenium moiety. For instance, gold-nanoparticle-cored dendrimers containing silylferrocenyl termini show an increased interaction as indicated by a larger potential difference between the ferrocenyl dendrimer in the presence or absence of ATP.^{487,1633–1635} This is probably due to the hypervalency of the silicon atom in the silylferricenium form. Thus, although the silicon atom has no oxygen affinity in tetraalkyl silanes, such an interaction can be envisaged in silylferricenium because of the partial positive charge of silicon resulting from silicon hypervalency.^{487–490,1636–1638} Another kind of additional supramolecular interaction is provided in triazolylferrocenyl⁶⁵⁸ or triazolylmethylferrocenyl dendrimers⁴⁸⁷ formed by click reactions of azido-terminated dendrimer with ethynylferrocene or alkyne-terminated dendrimers with azidomethylferrocene, respectively, providing facile electrochemical recognition and titration of ATP. Supramolecular assistance of dihydrogenophosphate recognition by endoreceptors was pioneered by Beer,^{725,726}

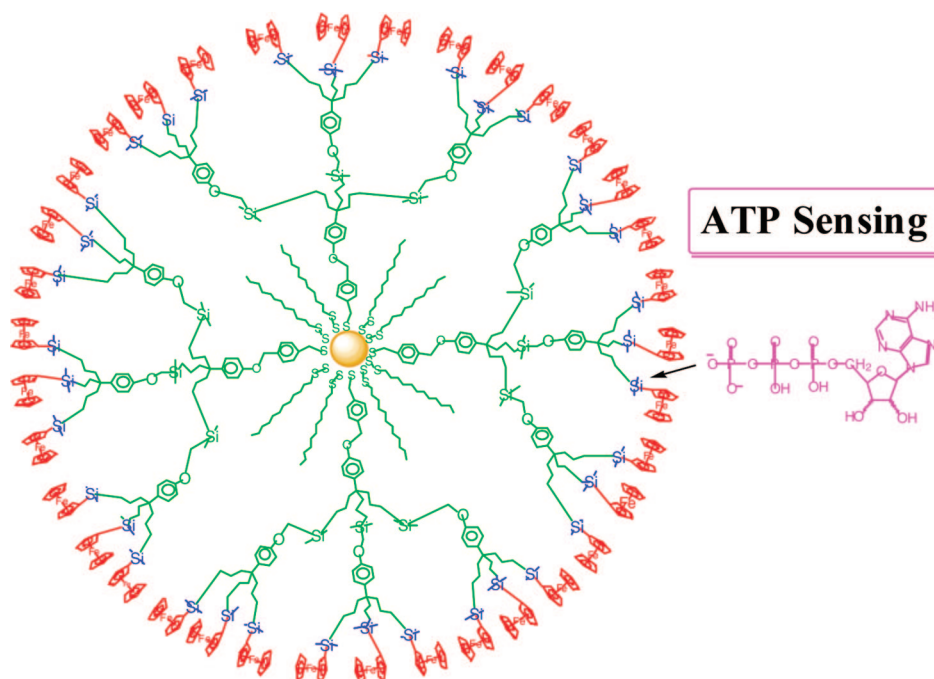


Figure 104. ATP²⁻ sensing and regeneration of the modified electrode for reuse. Reprinted with permission from ref 1632 (Astruc's group). Copyright 2009 American Chemical Society.

and the first example of dendritic endoreceptors capable of dihydrogenophosphate recognition was disclosed by our group in 1997.¹⁶³⁹ At this occasion, a dramatic positive dendritic effect was disclosed using amidoferrocenyl-terminated dendrimers, i.e., recognition was all the easier with a larger difference of redox potential as the dendrimer generation was higher. The amido group is ideal in provoking a large potential difference because of the synergy between the double hydrogen bonding with the dihydrogenophosphate.¹⁶³⁶ Ferrocenylurea termini have also been successfully used by Alonso et al. for hydrogenophosphate sensing,¹⁶³⁷ and inorganic molybdenum cluster-cored silylferrocenyl-terminated dendrimers were also used for ATP sensing.¹⁶³⁸

An additional advantage of large ferrocenyl dendrimers is that they adsorb on Pt electrodes all the more easily as they are larger, facilitating sensing by dendrimer-derivatized electrodes that allow subsequent ATP washing and reuse of the electrode sensor. This also is an advantage provided by AuNP-cored dendrimers that are very large.^{487–490} Dihydrogenophosphate anion is a good ATP model, but sensing is slightly easier with dihydrogenophosphate anion than with ATP using ferrocenyl-terminated dendrimers.^{490,1640} With larger [Fe₄Cp₄(CO)₄]-cluster termini instead of ferrocenyl termini, however, ATP recognition is easier and is observed with larger redox potential variations of the redox system [Fe₄Cp₄(CO)₄]⁺⁰ than with ferrocenyl (Fe^{III/II}) termini, because the cluster better matches the ATP size than the smaller ferrocenyl group.^{1641,1642}

6.9.3. Electrochemical Dendritic Glucose Sensors

Enzyme glucose biosensors for *in vitro* assays have been developed extensively to monitor the glycemia of diabetic patients, and therefore, glucose oxidase (GOx)-based electrodes are a major application of immobilized enzymes. The reaction involved is the GOx-catalyzed oxidation of β -D-glucose by O₂ to D-glucono-1,5-lactone and H₂O₂.¹⁶⁴³

Losada et al. used silylferrocenyl dendrimers as mediators in amperometric biosensors. It was shown that these sensors

respond rapidly to the addition of glucose by steady-state amperometric response of carbon paste electrodes containing these dendritic mediators and glucose oxidase as a function of the glucose concentration and applied potential.¹⁶⁴⁴ Subsequent to this seminal work, the Losada group also developed the electrochemical method with other dendrimers such as PPI-cored polymethylferrocenyl dendrimers deposited onto a platinum electrode, including studies of the influence of the layer thickness and concentrations, quantifying hydrogen peroxide produced by the oxidase catalysis during the enzymatic reaction in direct proportion to the available glucose (amperometric titration: H₂O₂ → O₂ + 2H⁺ + 2e⁻). Amperometric enzyme electrodes with horseradish peroxidase and lactate oxidase were also used.^{1645–1651} The electro-oxidation ability of glucose in alkaline solution was tested using a sensor based on dendritic CuNi alloy.¹⁶⁵²

Streptokinase, GOx, and phosphorylcholine were immobilized on polyglycerol dendrimers in order to obtain a blood-compatible bioconjugate possessing glucose-sensing properties. This bioconjugate was entrapped in polyaniline nanotubes through template electrochemical polymerization of aniline. This material was used as a glucose-oxidation mediator and appeared as a good candidate for oxidoreductase-based implantable biosensors.¹⁶⁵³ Other glucose-biosensor systems with GOx involve PtNPs on multiwalled carbon nanotubes^{1654–1656} or layer-by-layer dendrimer–AuNP membranes (Figure 105).¹⁶⁵⁷ Other dendritic hydrogen peroxide amperometric sensors are based on horseradish peroxidase.¹⁶⁵⁸

Nonelectrochemical methods for glucose sensing are based on luminescence. Affinity adsorption solid-substrate phosphorimetry allowed the determination of glucose traces, based on labeling *Triticum vulgaris* lectin on the surface of PAMAM dendrimers.¹⁶⁵⁹ A flow-through electrochemical immunosensor for monitoring IgG in human serum has been developed using core–shell SiO₂/Au nanocomposites and G₄-PAMAM dendrimer as matrixes. Ferrocenecarbaldehyde-labeled anti-IgG was initially chemisorbed onto the NP

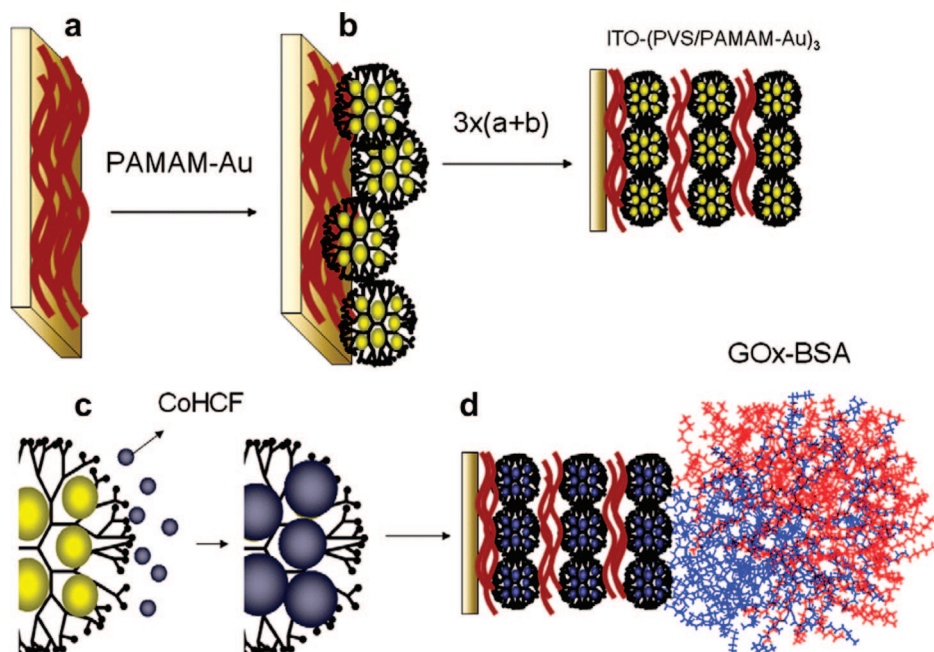


Figure 105. Schematic fabrication of LbL films comprising PVS and PAMAM–Au. The sequential deposition of LbL multilayers was carried out by immersing the substrates alternately into PVS (a) and PAMAM–Au (b) solutions for 5 min per step. After deposition of 3 bilayers, an ITO-(PVS/PAMAM–Au)₃@CoHCF electrode was prepared by potential cycling (c). The enzyme immobilization to produce ITO-(PVS/PAMAM–Au)₃@CoHCFGOx (d) was carried out in a solution containing bovine serum albumin (BSA), glutaraldehyde, and GOx. Reprinted with permission from ref 1657 (Brett’s group). Copyright 2006 Elsevier.

surface, and then GOx was backfilled onto the modified surface. The selectivity, reproducibility, and stability of the immunosensor were acceptable.¹⁶⁶⁰

6.9.4. Functionalized Antibody and Antigen Biosensors

The reversible affinity interactions of immunosensing surfaces are based on biospecific association and displacement reactions between functional antigen ligands and antibody molecules. A typical example of antigen/antibody couple is biotin/antibiotin system. Functionalized monolayers provided a platform for biospecific recognition with monoclonal antibiotin immunoglobulin G (IgG) using PAMAM dendrimers functionalized with ferrocenyl and biotiny groups, with the ferrocenyl termini serving as mediators for the electrochemical track method with GOx.¹⁶⁶¹ Glycoproteins, especially antibodies, were sensed amperometrically based on the content of galactosyl and *N*-acetylgalactosamidyl residues in glycoprotein carbohydrate chains. This method does not require antibody labeling or enzyme-tagged secondary antibodies, and total assay time was about 20 min.¹⁶⁶²

The antibody IgG were used as dendronic supramolecular structures connected to the antibody IgM that has a pentameric structure of IgG and ten antigen binding sites, which enables tight binding to antigens containing multiple identical epitopes. The antibody dendrimer has an advantage in its amplification of detection signals for antigens, with the characteristics of being composed of proteins with noncovalent bonds and strong specific antigen binding capacity.¹⁶⁶³

The use of immunoassays in clinical diagnostics has stimulated the development of sensitive and specific techniques to determine the presence of specific antigen in samples. For instance, noncompetitive fluoroimmunoassay allows the analysis of cortisol based on the blocking of unbound sites of the capture antibody by a PAMAM dendrimer–cortisol conjugate.¹⁶⁶⁴ Dendrimerized cellulose

was used as a scaffold for artificial antigens, which provides a tool for developing clinically testable materials to study adverse immunological responses to drugs in human (Figure 106).¹⁶⁶⁵

DNA dendrimers, conjugated with both antibiotin and up to 350 labeling entities, were adapted to protein microarray and ELISA cytokine detection resulting in up to 3-fold improvement of the detection limits with no significant increase in the inter- and intra-assay coefficient of variation compared to streptavidin horseradish peroxidase detection.¹⁶⁶⁶

Antigen mannosylation has been shown to be an effective approach to enhanced antigen uptake and presentation by APC. Mannose-based antigen delivery system with a PAMAM dendrimer has been used in order to overcome disadvantages associated with conventional methods involving the mannosylation of antigens. Mannosylated dendrimer overalbumin (MDO) was shown to be a potent immune inducer of OVA-specific T cell response *in vitro*. The immunogenicity of MDO was due to both enhanced antigen presentation and induction of DC maturation.¹⁶⁶⁷

Immunotherapeutic approaches are investigated for treatment of neurodegenerative Alzheimer disease. The identification of a β -amyloid-plaque specific epitope Ab(4–10) (4FRHDSGY10), recognized by therapeutically active antibodies from transgenic Alzheimer dementia could provide the basis for the development of vaccines. Therefore, the design and immuno-analytical properties of antigenic bioconjugates comprising a β -amyloid-plaque specific epitope were reported.¹⁶⁶⁸

6.9.5. Miscellaneous Dendritic Biosensors

Recognition according to the supramolecular lock-and-key principle that is the basis of sensor design is intrinsic to natural processes, specifically with enzymatic catalysis, and has been applied to many biomolecules as diagnostic tools. Seminal works by the groups of Lehn,³ Whitesides,¹⁶⁶⁹ and

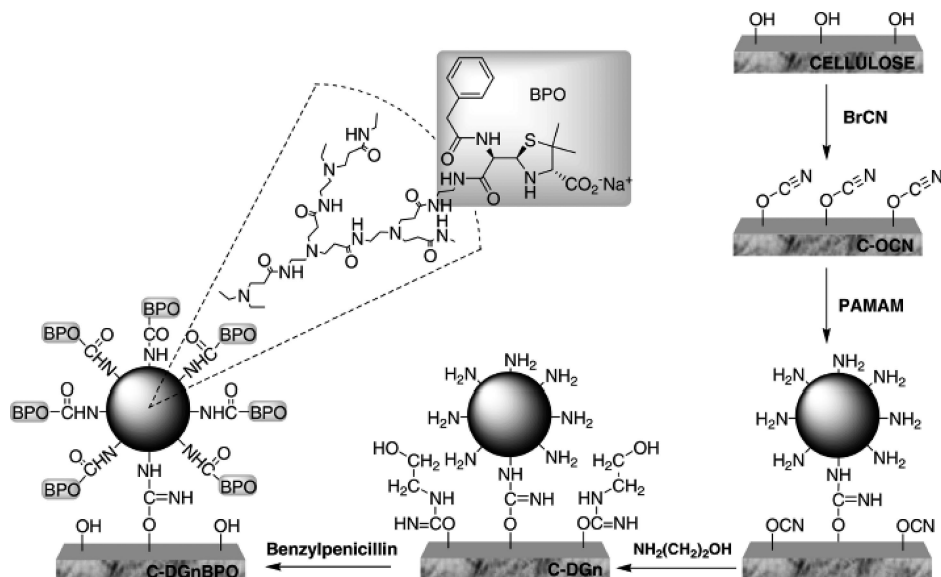


Figure 106. Modification of cellulose surfaces to generate dendritic-linked systems for the preparation of solid-surface supported GnPBO conjugates. Reprinted with permission from ref 1665 (Perez-Inestrosa's group). Copyright 2008 American Chemical Society.

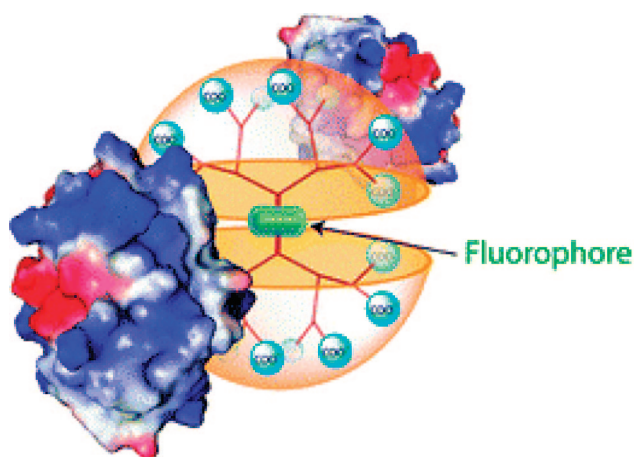


Figure 107. Fluorophore-cored dendrimers for patterns in metal-protein sensing. Reprinted with permission from ref 1676 (Thayumanavan's group). Copyright 2009 Royal Society of Chemistry.

Reinhoudt¹⁶⁷⁰ beautifully illustrate this concept. Thus, organizations of biocomposite-sensing materials based on supramolecular interactions were actively searched inter alia by Willner's group¹⁶⁷¹ and others.^{1672,1673} A single weak-binding event is multiplied into an efficient receptor site for protein surfaces because of the subsequent binding events that take advantage of the preorganization in biological processes, but also in biomimetic ones with dendritic artificial receptors.¹⁶⁷⁴ Sophisticated artificial receptors exhibiting nanoscale substrate recognition can be obtained by introducing unsymmetrical patched structures in dendrimers. This strategy has been developed with porphyrin dendrimers; for instance, oligopeptide-patched dendrimers are nanoscale receptors of cytochrome *c* proteins.¹⁶⁷⁵ Fluorophore-cored dendrimers interact with proteins that quench the fluorescence, a generation-dependent phenomenon that could provide selective protein sensors (Figures 107 and 108).¹⁶⁷⁶

Bile acid dendrons show a remarkable ability to act as normal and inverse micelles owing to the facially amphiphilic nature of the bile acid backbone. Exploiting Newkome's concept of dendritic unimolecular micelles,^{8,128} it has been possible to show the supramolecular function of

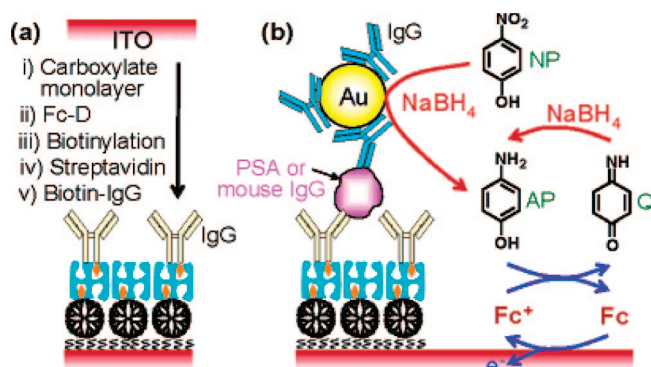


Figure 108. (a) Schematic representation of the preparation of an immunosensing layer. (b) Schematic view of electrochemical detection of mouse IgG or PSA. Reprinted with permission from ref 1676 (Yang's group). Copyright 2009 American Chemical Society.

these gelling bile acid dendrons in biomimetic molecular recognition.¹⁶⁷⁷ An ultrasensitive and simple DNA-free method for protein sensing by electrochemical signal amplification was reported with an IgG layer on an indium oxide electrode using ferrocenyl dendrimers and AuNPs as nanocatalysts. The IgG–AuNP conjugate and the immunosensing layer sandwiched the target protein, and the AuP label generates aminophenol from nitrophenol by catalytic reduction. The kinetics is fast, due to the easy access of the small nitrophenol molecules to the AuNP surface through pinholes of IgG–AuNP conjugate and to the large number of catalytic sites per nanocatalyst label.¹⁶⁷⁸

Glutamate, an important neurotransmitter in the mammalian central nervous system and neuronal pathway in the brain, is related to several neurological disorders such as schizophrenia, Parkinson's disease, epilepsy, and stroke. Amperometric glutamate have been developed with glutamate oxidase incorporated into modified electrodes using multiwall carbon nanotubes modified with PAMAM dendrimers loaded with PtNPs as an efficient redox mediator.^{1679,1680} Another neurotransmitter, dopamine, also plays an important role in the functioning of the central nervous system as well as in the cardiovascular, renal, and hormonal systems. The Unified Parkinson's Disease Rating Scale is currently used to assess

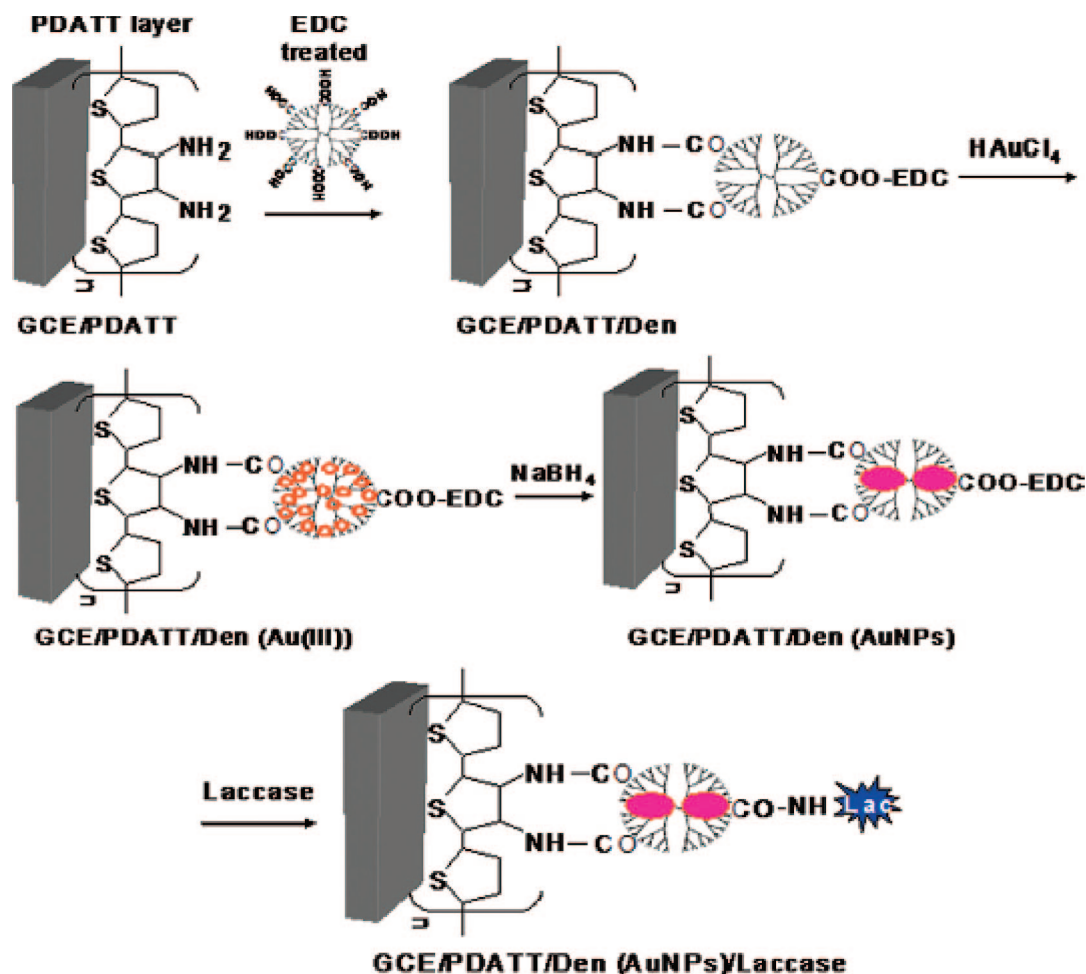


Figure 109. Schematic representation of the fabrication of PDATT/Den(AuNPs)/laccase-modified electrode. Reprinted with permission from ref 1688 (Shim's group). Copyright 2008 American Chemical Society.

Parkinson's disease, although it cannot quantify the extent of disease. Accordingly, the dopamine concentration, which is one of the key factors in determining this disease, needs to be quantified. Compared analytical performances indicated that the electrochemical detection was the method of choice for dopamine determination with PAMAM-OH-dendrimer loaded with RhNPs and immobilized on glassy carbon electrodes.¹⁶⁸¹ Forster resonance energy transfer involved in optical sensors has also been used for this purpose.¹⁶⁸² Sensing of the carbohydrate-binding proteins lectins, important in cell growth, inflammatory response, and viral infections, was achieved optically using a Ru^{II} -tris(bipyridine) cored-dendrimer (cf. section 3.2) terminated with carbohydrate groups (mannose) in order to increase avidity.¹⁶⁸³

The Niemeyer group has reported photomasks for surface patterning using the thiol-ene reaction. This allows the control of biotinylated enzyme immobilization on silica surface upon surface fixation by interaction with silica-PAMAM-dendrimer derivatized with streptavidin.¹⁶⁸⁴ Recognition by cell surface integrin receptors was provided by transglutaminase enzyme-cross-linked G_2 -PAMAM dendrimers that mimic collagen withstanding triple-helical conformation.¹⁶⁸⁵ In vitro targeting efficacy to integrin receptors expressing cells was shown with G_5 -PAMAM Au DENs functionalized with fluorescein isothiocyanate and Arg-Gly-sp (RGD) as template.¹⁶⁸⁶ Amperometric detection of 8-hydroxy-2'-deoxyguanosine was achieved with a low limit of 1.2×10^{-9} M using a Au electrode modified with $G_{3.5}$ - and $G_{4.5}$ -PAMAM- CO_2H dendrimers-based thin films.

This Au electrode was modified by SAMs using aliphatic aminothiols on which the PAMAM- CO_2H dendrimers were attached using peptidic bonds.¹⁶⁸⁷ The direct electrochemistry of laccase was promoted by 1.7 nm-sized Au DENs, and this was applied to catechin detection with a lower limit of $0.05 \pm 0.003 \mu\text{M}$. The quasi-reversible peak of the Cu redox center of laccase was observed at $-0.03/0.13$ V vs AgCl, and the electron-transfer rate constant was 1.28 s^{-1} (Figure 109).¹⁶⁸⁸

Poly(dimethylsiloxane) elastomers were surface-modified with both polyethylene oxide and G_3 -DAB dendrimers, and these dendrimers were used as linkers for surface grafting of cell-adhesion peptides including endothelial cells.¹⁶⁸⁹

Although redox cycling of enzymatically amplified electroactive species has been widely employed for signal amplification in electrochemical biosensors, Au electrodes are generally not suitable for redox cycling using a redox reagent because of the high background current due to the redox reaction of the reagent at highly electrocatalytic Au electrodes. Thus, Au electrodes were modified with a mixed-assembly monolayer of mercaptododecanoic acid and mercaptoundecanol and a partially ferrocenyl-tethered dendrimer layer. The SAM of long thiols significantly decreases the background current of the modified Au electrode, and the ferrocenyl modification facilitates easy oxidation of *p*-aminophenol and its redox cycling using NAD (NADH) that enables a low detection limit for mouse IgG (1 pg/mL).¹⁶⁹⁰

7. Conclusion and Prospects

Dendritic macromolecules, pioneered in the 1980s, have been developed in a variety of ways that involve molecular engineering in order to target precise functions and applications. Concerning dendrons and dendrimers, purity aspects must be continuously considered and carefully checked, because consequences on functions and applications can be crucial. The physical and photophysical studies of dendrimers have led to the disclosure of supramolecular properties that are the basis of functional use. These properties, reviewed in the first four sections, have shown the role of the generation number and peripheral groups. In particular, when the generation number increases, the dendrimer becomes globular, the periphery becomes bulkier despite backfolding of the terminal groups, and possibilities of encapsulation and dendrimer–substrate interactions (surface, medium, other dendrimer, etc.) also increase. The nature of the peripheral groups governs the solubility and related biological properties such as biocompatibility and, for instance with PEG, the enhanced penetration and retention (EPR) effect. Although properties of dendrimers may vary from one series to the next, these two properties appear to be more important than the nature of the core that is hidden within the dendritic structure. Most of the studies have been carried out using the PAMAM dendrimers, because they were commercialized very early after their discovery in the 1980s and can be functionalized in a variety of ways.¹⁶⁹¹ The PAMAM dendrimers are also useful for most applications in catalysis, molecular electronics, photonics, sensing, and nanomedicine. Several other dendrimer families are equally useful, however, such as the polylysine, PPI, polyether, polyamine, melanine, polyaryl, phenylazomethine, phosphorus, peptide, and glycopeptide dendrimer families depending on which property, function, or application is targeted. Biodegradable polyester dendrimers are of prime importance in future biomedical applications. Indeed, encapsulation properties depend on whether the dendrimer frame is rigid or flexible, and in the latter case on the medium (solvent), the nature of which governs tether contraction. Modeling studies are becoming more and more frequent to predict, define, and optimize the dendrimer features and properties.

The photophysical applications of dendrimers include light harvesting with the antenna effect to funnel energy from many photosensitive branch termini toward the focal group of the dendron, organic light-emitting diodes (OLEDs), organic field effect transistors (OFETs), and photovoltaic (PV) devices). A crucial point in these photophysical dendrimer devices is that quenching the photoactivity of the core is inhibited by the dendrimer tether framework, which provides a considerable advantage compared to regular polymers. Green phosphorescent dendrimers providing highly efficient OLEDs lead to important applications. The photophysical properties are a powerful source of sensors, as are the redox properties using, for instance, the ferrocenyl groups located at the dendrimer branch termini for anion and glucose sensing. Photochemical, redox, and pH switches are useful for such sensing, with the dendrimer behaving then as a molecular machine considerably changing structure upon application of one of these stimuli. Dendrimer effects, i.e., generation-depending properties, are spectacular in this area. The photophysical field is also intimately connected to the biomedical applications, because fluorescence is essential for diagnostics.

Catalysis is another important application of dendrimers, because the location of catalytic sites at the dendritic core or periphery offers unique topological aspects, allowing one to mimic the enzyme catalytic site when the catalytic center is buried and protected at the core by the dendrimer frame or to multiply the number of catalytic sites within a small place when the catalyst is located at the periphery. The macromolecular size of these dendritic catalysts also allows easy removal from the medium and recycling using a solid support, membrane nanofiltration, precipitation, or biphasic systems. Various dendritic effects were observed and are precious pieces of mechanistic information to understand and optimize the catalytic constraints. Here again, encapsulation plays a key role, because small catalytically active transition-metal nanoparticles can be embedded in the dendritic nanoreactor that dictates its specific properties. Another interesting effect is the positive dendritic effect brought about by the polarity gradient in the framework in dendritic organocatalysis. It should be noted that the catalysis by dendrimers is also important for the biomedical applications, because many biosensors involve redox catalysis with electrodes modified with redox-active dendrimers.

The role of dendrimer in biomedical applications, i.e., nanomedicine, is bursting. Again, the supramolecular properties of dendrimers govern the functions. They are involved in drug encapsulation and solubilization in so-called supramolecular “complexes” for vectorization, although “conjugates” resulting from covalent dendrimer–drug binding are often preferred for efficient delivery. They are also governing dendrimer–DNA interaction for gene transfection using ionic bonding between the ammonium groups of the dendrimer termini and the anionic phosphate DNA groups. They are essential in the crucial role of PEG chain termini of dendrimers for the biocompatibility, biodistribution, and EPR effect of these groups. They can also be found in the antibacterial “cluster effect” of glycopeptide dendrimers and in the overexpression of folate, glycosides, and specific peptide receptors by tumor cells. These supramolecular properties of dendrimers are thus involved in both great domains of dendrimers applications in nanomedicine: diagnostic (with fluorescence) and therapy (with vectorization), with targeting functions being needed in both area in which the benefits of dendrimers include the multiplication of active terminal groups in a minimal space. The precise molecular definition of dendrimers including the choice of generation number and terminal groups and the possibility to introduce two or more functional group types at the periphery are enormous advantages of dendrimers over polymers. This is the reason why dendrimers represent a true hope to largely improve diagnostic and therapeutic facilities for major human diseases. Toxicity remains a crucial issue, however, that needs to be examined. In this review, we have delineated the toxicity issues in many instances, but broad investigations are continuously required in order to bring dendrimers to human drugs. The advent on the market of Vivagel (Starpharma), a poly(L-lysine) dendrimer-based microbicide against HIV and herpes infections, represents a first success that will undoubtedly be followed by others.

Last but not least, the importance of synthesis in dendrimer chemistry should be emphasized, because molecular engineering requires more and more sophisticated design and synthetic skill. This aspect has not been treated here, but an invaluable comprehensive review covering it (as numerous

other earlier reviews mentioned in the Introduction) is being published by Newkome in *Chemical Reviews* in 2010.

To conclude, if in chemistry the XVIIIth century was that of atoms, the XIXth century was that of compounds, and the XXth century was that of reactions, the XXIth century already is and will be that of nanoscience engineering, and dendrimers are, therefore, a major family of tools in the tool box.

8. Acknowledgments

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9. List of Abbreviations

A	acceptor chromophore
AFM	atomic force microscopy
AIDS	acquired immune deficiency syndrome
ALA	5-aminolevulinic acid
AM	air mass
ANS	8-aniline-1-naphthalene sulfonate
APC	antigen-presenting cell
ATP	adenosine triphosphate
BARF	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINAL	binaphthol-modified lithium aluminum
BNCT	boron neutron capture therapy
Boc	<i>t</i> -butoxycarbonyl
CCRF-CEM	human T cell lymphoblast-like cell line
CD	cyclodextrin
CFMR	continuous-flow membranes reactor
CHO	Chinese hamster ovary
CID-MS	collision-induced dissociation mass spectroscopy
CPK	Corey, Pauling, and Koltun
CPP	cell-penetrating peptides
CSA	chondroitin sulfate A
CT	computed tomography
CV	cyclovoltammetry
D	donor chromophore
DAB	diamino butane
DC	dendritic cell
DEA	dielectric analysis
DEN	dendrimer-encapsulated nanoparticle
DFT	density functional theory
DLS	dynamic light scattering
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DNA	deoxyribonucleic acid
DOSY	diffusion-ordered spectroscopy
DOT	dendritic oligothiophene
DOTA	<i>N,N',N'',N'''</i> -tetracarboxymethyl-1,4,7,10-tetraazacyclododecane
DSC	differential scanning calorimetry
DSR	dielectric relaxation spectroscopy
ECM	extracellular cell matrix
EDS	energy-dispersed X-ray spectroscopy
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EO	electrooptic
EPR	enhanced penetration and retention
ESR	electron spin resonance
EXAFS	extended X-ray absorption fine structure
Fmoc	9-fluorenylmethyloxycarbonyl
FRET	fluorescence resonance energy transfer

FTIR	Fourier transform infrared
5-FU	fluorouracile
Gn	number of generations
GFP	green fluorescent protein
GI	gastrointestinal
GOx	glucose oxidase
GSH	glutathione
HA	hemagglutinin
HEK	human embryonic kidney
HepG2	human hepatocellular liver carcinoma cell line
HIV	human immunodeficiency virus
HOMO–LUMO	highest occupied molecular orbital–lowest unoccupied molecular orbital
HOPG	highly oriented pyrolytic graphite
HRTEM	high-resolution transmission electron microscopy
IC ₅₀	half-maximal inhibitory concentration
IgG	immunoglobulin G
IPEC-J2	intestinal pig epithelial cell jejunum
IR	infrared
ITO	indium tin oxide
L-DOPA	L-dihydroxyphenylalanine
LEDs	light-emitting diodes
LH	luteinizing hormone
MAG	multiple antigen glycopeptide
MAO	methylaluminoxane
MAP	multiple antigen peptide
MDO	mannosylated dendrimer overallbumin
MNP	metal nanoparticle
MRI	magnetic resonance imaging
MTX	methotrexate
MV ²⁺	methylviologen
NAD	nicotinamide adenine dinucleotide
NCAFM	noncontact atomic force microscopy
NLO	nonlinear optical
NMR	nuclear magnetic resonance
NP	nanoparticle
NSAID	nonsteroidal anti-inflammatory drug
OFET	organic field-effect transistors
OLED	organic light-emitting diode
OVA	ovalbumin
PAMAM	polyamido amine
PBMC	peripheral blood mononuclear cells
PCBM	[6,6]-phenyl C ₆₀ butyric acid methyl ester
PD	pharmacodynamic
pD	polydispersity
PDT	photodynamic therapy
PEG	polyethylene glycol
PEI	poly(ethyleneimine)
PET	positron emitting tomography
PFM-AFM	pulse force mode atomic force microscopy
PGLSA	poly(glycerol succinic acid)
PGSE	pulse gradient stimulated echo
PK	pharmacokinetics
PL	photoluminescence
PLP	proteolipid proteins
PMMA	dendrimer–poly(methyl methacrylate)
POM	polyoxo metallate
PPAR	peroxisome proliferator-activated receptor
PPI	poly(propylene imine)
PPP	poly- <i>p</i> -phenylene
PSMA	prostate-specific membrane antigen
PV	photovoltaic
PVP	poly(vinylpyrrolidone)
RBC	red blood cell
RCM	ring-closing metathesis
REDOR	rotational-echo-double-resonance NMR
R _G	gyration radius
RGD	arginine-glycine-aspartic acid
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
RNase	ribonuclease

ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerization
ROS	reactive oxygen species
SA	sialic acid
SANS	small-angle neutron scattering
SAM	self-assembled monolayers
SAXS	small-angle X-ray scattering
SBA	Santa Barbara amorphous silica
SEC	size-exclusion chromatography
SEM	scanning electron microscope
SiRNA	interfering ribonucleic acid
SPIO	superparamagnetic iron oxide
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanol
TAMRA	6,6-carboxytetramethylrhodamine succinic ester
TDD	transdermal drug delivery
TEM	transmission electron microscopy
Tg	glass-transition temperature
THG	third harmonic generation
TNT	2,4,6-trinitrotoluene
TOF	turnover frequency
TON	turnover number
TPA	two-photon absorption
TPI	two-photon ionization
TTF	tetrathiafulvalene
TU-DTPA	2-(4-isothiocyanatobenzyl)-6-methyldiethylene tri-aminepentaacetic acid
UV	ultraviolet
UV-vis	ultraviolet-visible
VEGF	vascular endothelial growth factor
WAXD	wide-angle X-ray diffraction
XNOR	exclusive-NOR
XOR	exclusive-OR
XPS	X-ray photoelectron spectroscopy

10. Supporting Information Available

List of the references including both the first and last page numbers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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