About Dendrimers: Structure, Physical Properties, and Applications

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Contents

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Bert Meijer (right) was born in Groningen, The Netherlands, (1955) and received his Ph.D. degree (1982) in Organic Chemistry at the University of Groningen under the guidance of Prof. Hans Wynberg. From 1982 to 1989, he was research scientist at the Philips Research Laboratories in Eindhoven, and from 1989 to 1992 he was group leader at DSM Research in Geleen. In 1992 he was appointed full professor in Organic Chemistry at the Eindhoven University of Technology. Since 1995, he is also a part-time professor of macromolecular chemistry at the University of Nijmegen. His major current interests are in supramolecular chemistry, dendrimers, π-conjugated systems, and stereochemistry.

I. Introduction

Ideally, dendrimers are perfect monodisperse macromolecules with a regular and highly branched three-dimensional architecture. Dendrimers are produced in an iterative sequence of reaction steps, in which each additional iteration leads to a higher generation material. The first example of an iterative synthetic procedure toward well-defined branched structures has been reported by Vögtle,[1] who named this procedure a "cascade synthesis". A few years later, in the early 1980s, Denkewalter[2−4] patented the synthesis of L-lysine-based dendrimers. The patents describe structures up to high generations; however, except for size exclusion chromatography data,[5] no detailed characteristics of the materials are given.

The first dendritic structures that have been thoroughly investigated and that have received widespread attention are Tomalia's PAMAM dendrimers[6,7] and Newkome's "arborol" systems.[8] Both dendrimers are constructed divergently, implying that the synthesis is started with a multifunctional core molecule and is elaborated to the periphery. At a later date and on the basis of the original work of Vögtle,[1] divergently produced poly(propylene imine) dendrimers have been reported by Mülhaupt[9] and de Brabander.[10] In 1990, Fréchet introduced the convergent approach toward dendrimers.[11,12] In convergent procedures, the synthesis is started at the periphery and elaborated to the core. Fréchet's aromatic polyether dendrimers are easily accessible and have been studied frequently, not only by the Fréchet group but also by other researchers. Finally, Moore's convergently produced phenylacetylene dendrimers[13−16] are the last of the five classes of dendrimers, reported up to high generations, that are most studied and most known. Additionally, many other types of interesting, valuable, and esthetically pleasing dendritic systems have been developed,[17] and thus, a variety of dendritic scaffolds have become

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accessible with defined nanoscopic dimensions and discrete numbers of functional end groups.

Many of the intriguing properties of dendrimers as well as their syntheses and possible applications are discussed in excellent books and reviews that have been published by various experts in the field.[17−24] Here, we do not want to present a comprehensive or complete overview on reported dendrimers, but, instead, we have highlighted studies that contribute to a better understanding of the properties of dendrimers and studies that offer insight into the possibilities for and the limitations of the use of dendritic materials. Some of these studies relate to three somewhat controversial issues. First, one can question the perfection of higher generation dendrimers. In the divergent synthetic approach, for example, several hundred reaction steps have to be conducted on the same molecular fragment to obtain higher generation species. Thus, statistical defects in the final product are a reality. Second, the conformational behavior of dendrimers is an issue of debate, giving rise to the following questions: Are the end groups in dendrimers pointing outward or are they severely backfolded? Do dendrimers always have a globular shape or can this shape be highly distorted? Are cavities present inside the dendrimer? Is it possible to obtain site isolation in the core? How do the physical properties of dendrimers change at higher generations and how do these physical properties relate to those of linear analogues? Third, it seems adequate to separate facts from fantasies, when possible applications for dendrimers in functional materials are considered: applications in medicinal chemistry, host−guest chemistry, and catalysis will be surveyed.

This review addresses some of the controversial issues in dendrimer research and, independent of the outcome of current debates, we hope to show that dendrimers are a unique class of macromolecules with a bright future ahead.

II. The Purity of Dendrimers

Two conceptually different synthetic approaches for the construction of high-generation dendrimers exist: the divergent approach and the convergent approach. Both approaches consist of a repetition of reaction steps, each repetition accounting for the creation of an additional generation. The two methodologies have their own characteristics, and therefore, the perfection of the final dendritic product is related to this synthetic approach.

In the divergent synthesis, the dendrimer is grown in a stepwise manner from a central core, implying that numerous reactions have to be performed on a single molecule. Consequently, every reaction has to be very selective to ensure the integrity of the final product. For example, an average selectivity of 99.5% per reaction will, in the case of the synthesis of the fifth generation poly(propylene imine) dendrimer (64 amine end groups; 248 reactions, see Figure 1), only result in $0.995^{248} = 29\%$ of defect-free dendrimer. Since every new generation of divergently produced dendrimer can hardly be purified, the presence of a small number of statistical defects cannot be avoided. Bearing this in mind, the divergent synthesis can be seen as the macromolecular approach toward dendrimers: the purity of the dendrimers is governed by statistics. The reality of statistical defect structures is also recognized in the iterative synthesis of polypeptides or polynucleotides on a solid support (the Merrifield synthesis),[25] so the knowledge gathered in this field should be considered when the perfection of dendritic structures is discussed.

In the convergent approach, the difficulty of many reactions that have to be performed on one molecule has been overcome by starting the synthesis of these dendrimers from the periphery and ending it at the core. In this fashion, a constant and low number of reaction sites is warranted in every reaction step throughout the synthesis. As a consequence, only a small number of side products can be formed in each reaction, and therefore, every new generation can be purified (although the purification of higher generation materials becomes increasingly troublesome). Thus, convergently produced dendrimers, which can be seen as dendrimers prepared in an "organic-chemistry approach", can be defect-free.

The characterization of dendrimers is rather complex due to the size of and symmetry in these macromolecules. Various NMR techniques (^{1}H, ^{13}C, ^{15}N, ^{31}P), elemental analyses, and chromatography techniques (HPLC, SEC) are widely used, but these techniques cannot reveal small amounts of impurities in, especially, higher generation dendrimers.[26] Fortunately, recent progress in ESI (electrospray ionization) and MALDI (matrix-assisted laser desorption ionization) mass spectrometry allows for an in-depth analysis of dendrimers. ESI-MS has been used to identify the imperfections in both poly(propylene imine)[27] and poly amido amine (PAMAM) dendrimers.[28−31] Both of these dendrimer types are made via a divergent synthesis and are very suitable for electrospray ionization due to their polar and basic nature.

All generations of poly(propylene imine) dendrimers with either amine or nitrile end groups have been analyzed with ESI-MS to quantitatively determine the importance of various side reactions.[27] In the approach followed, all possible side reactions have been grouped in two different pathways that describe the formation of defect structures on going from one amine generation to the next (see Figure 1). One pathway accounts for incomplete cyanoethylations and retro-Michael reactions, the other pathway accounts for intramolecular amine formations (cyclizations).[32] With the ESI-MS spectra of all five generation poly(propylene imine) dendrimers in hand, the significance of both pathways has been calculated using an iterative computing process. Thus, every MS spectrum has been simulated. The results of the simulation are shown in Table 1 and in Figure 2. The simulation indicates a polydispersity (M_w/M_n) of 1.002 and a dendritic purity of ca. 23% for the fifth generation poly(propylene imine) dendrimer. Since the perfect structure is the dominant species in the final product, it seems more appropriate to discuss the mixture in terms of dendritic purity than in terms

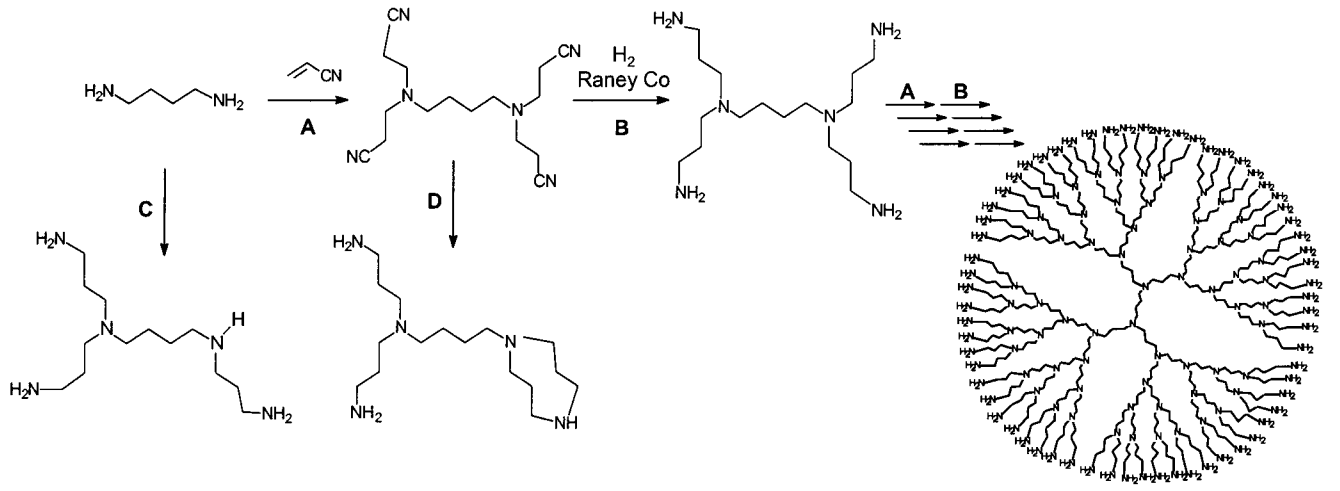

Figure 1. The synthesis of poly(propylene imine) dendrimers (reactions A and B) and alternative, unwanted reaction paths C and D. Path C illustrates "missed" Michael additions (either by an incomplete cyanoethylation or by a retro-Michael reaction). Path D illustrates unwanted cyclization reactions. Paths C and D describe defect reactions on going from one amine generation to the next.[27]

Table 1. Data of the DAB-dendr-$(NH_2)_x$ Series Calculated from the Simulated Spectrum of DAB-dendr-$(NH_2)_{64}$

product	percent per endgroup path C	percent per endgroup path D	dendritic purity % of total
DAB-*dendr*-$(NH_2)_4$	1.0	0.0	96
DAB-*dendr*-$(NH_2)_8$	1.0	0.55	86.7
DAB-*dendr*-$(NH_2)_{16}$	1.65	0.50	63.8
DAB-*dendr*-$(NH_2)_{32}$	0.97	0.77	41.3
DAB-*dendr*-$(NH_2)_{64}$	0.58	0.65	23.1

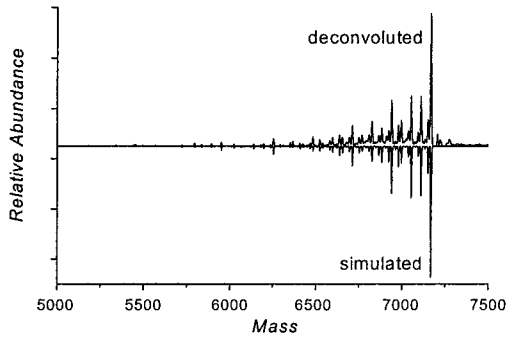

Figure 2. The measured and deconvoluted (upper graph) and simulated (lower graph) ESI-MS spectrum of DAB-dendr-$(NH_2)_{64}$.[27]

of polydispersity (the dendritic purity is defined as the percentage of dendritic material that is defect-free).

ESI-MS studies on PAMAM dendrimers indicate defect structures arising from retro-Michael additions and intramolecular lactam formations (see Figure 3).[28−31] For a fourth generation PAMAM dendrimer (48 end groups), a polydispersity of 1.0007 has been reported.[28] Interpretation of the published data reveals, however, a dendritic purity of at most 8%.

MALDI-MS studies on other divergently produced higher generation dendrimers (i.e., Newkome-type dendrimers[33−35] and carbosilanes[36−39]) have also shown the presence of small numbers of imperfect structures. Metallodendrimers that have been studied with L-SIMS,[40] MALDI-MS,[41] and ESI-MS[42] are of lower generations, and consequently, these materials

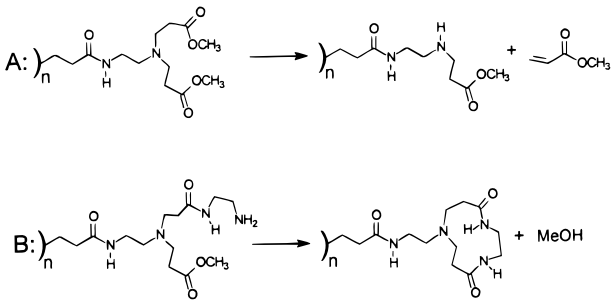

Figure 3. Unwanted reactions in the PAMAM-synthesis: retro-Michael reactions (A) and lactam formations (B).[28]

hardly contain defect structures, even though these materials have been produced in a divergent approach. Reinhoudt et al. have synthesized a third generation Pd(II) dendrimer with no observable defects in the mass spectrum.[43,44]

Dendrimers synthesized via the convergent approach can be produced nearly pure, as confirmed by MS data. MALDI mass spectra of Fréchet-type dendrimers display very limited amounts of impurities.[45,46] Moore's phenylacetylene dendrimers have also been investigated with MALDI mass spectrometry.[47] For a dendrimer with a mass of 39 969 D, almost no impurities have been found.[15] ESI-MS data on carboxylate-terminated phenylacetylene dendrimers subscribe the high degree of purity that can be attained for these dendrimers.[26]

The detailed mass studies that have been devoted to the characterization of dendrimers indicate the most important difference between both synthetic methodologies at hand. The "polymeric nature" of the divergent approach results in an accumulating number of statistical defect structures for every next generation. The defects are the result of the many reactions that have to be performed on the same molecular fragment. Furthermore, almost no possibilities exist for the purification of intermediate generations. The exponential growth in the number of reactions to be performed on higher generations, makes it virtually impossible to produce perfect dendrimers of generations beyond five or six. For

instance, using the average selectivity of 99.5% per reaction leads to a dendritic purity of 29% for a fifth generation poly(propylene imine) dendrimer and yields purities of $0.995^{504} = 8.0\%$ for the sixth generation and only $0.995^{1016} = 0.6\%$ for the seventh generation. Virtually no perfect structures will be present in even higher generation materials. The "organic nature" of the convergent approach results in defect-free dendrimers due to the limited number of reactions performed on the same molecule on going from one generation to the next. Additionally, it is possible to purify intermediate generations.

The—in the end—small differences in structural features of the divergently produced structures on one hand and the convergently synthesized structures on the other are not expressed in differences in overall properties of these two classes of dendrimers (for example, all investigated dendrimers show a maximum in the intrinsic viscosity as a function of their molecular weight). Therefore, dendrimers, regardless the way in which they have been prepared, can indeed be considered as the synthetic macromolecules with the most defined or most perfect primary structure known today.

III. The Physical Behavior of Dendritic Molecules

On paper, dendrimers are usually drawn in a highly symmetrical fashion. The molecular structure is displayed with all tiers—having the characteristic algorithmic growth pattern—pointing outward, the end groups are invariably located at the surface, and the overall picture suggests that the dendrimer is a spherical entity. Of course, the typical architecture of a dendrimer has consequences for its physical behavior and logically research in the past decade has sought to reveal the true nature of dendrimers, not only regarding their appearance but also regarding their physical characteristics.

The first part (part A) in this section deals with the studies on the localization of the end groups in dendritic systems. Such studies are of relevance since many of the proposed uses of dendrimers rely on the availability of the large amount of neighboring end groups (for modification, as active ligands, etc.). Related topics concern the density profiles in dendrimers and the limits of perfect dendrimer growth, and these subjects are also addressed. Further key issues in this section relate to the deviating properties of dendrimers as compared to their linear macromolecular counterparts (part B) and encompass the transition in physical properties when a sequence of dendrimer generations is considered (part C). Finally, numerous studies have dealt with amphiphilic dendrimers and with the behavior of dendrimers on solid or fluid surfaces (part D). These studies have revealed unexpected conformational features of dendritic molecules.

A. Localization of End Groups in Dendrimers

1. Theoretical Calculations

One of the first reports in which the position of end groups in dendrimers is considered has been published by de Gennes and Hervet.[48] The authors have used a self-consistent field model in which the monomers of each generation are assumed to be fully elongated and in which the end groups of the dendrimer are grouped in concentric circles around the core. The model indicates that dendrimers can freely grow up to a certain—predictable—limiting generation. It also shows that the core of the dendritic molecule has the lowest density.

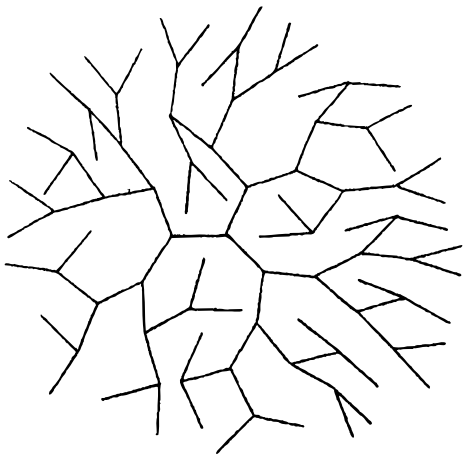

Figure 4. Schematic representation of a backfolded trifunctional fifth generation dendrimer according to Boris and Rubinstein.[52]

Numerical calculations using the kinetic growth model of Lescanec and Muthukumar predict a monotonic decrease in density on going from the center of the dendrimer to its periphery.[49] As a consequence, the ends of the branches are not positioned at the surface but are severely backfolded. Qualitatively similar results have been obtained from Monte Carlo simulations that have been performed by Mansfield and Klushin.[50] A molecular dynamics (MD) study of Murat and Grest shows that the importance of backfolding of the chains increases with generation (moreover, this study has shown a strong correlation between the solvent polarity and the mean radius of gyration).[51] Finally, Boris and Rubinstein have used a self-consistent mean field model (SCMF) to describe flexible dendrimers. The model predicts that the density is the highest in the core and shows that the end groups are distributed throughout the volume of the dendrimer (Figure 4).[52]

Studies on specific dendrimers have first been reported by Naylor et al., who have performed MD simulations on PAMAM dendrimers.[53] More detailed MD studies have been performed by Miklis et al.[54] and by Cavallo and Fraternali,[55] both on poly(propylene imine) dendrimers functionalized with *N*-*t*-BOC-L-phenylalanine. The investigation of Cavallo and Fraternali indicates that some backfolding of the terminal amino acids occurs, but not to such an extent that the dendrimer core is completely filled, resulting in a low-density region inside the higher generation dendrimers. In addition, the authors have found an increasing inter end group interaction on going from the first to the fifth generation. MD studies on poly(propylene imine) dendrimers with amine end groups have recently been performed with two different force fields representing a good and a bad solvent.[56] Both force fields produce a certain degree of backfolding, being more pronounced for the

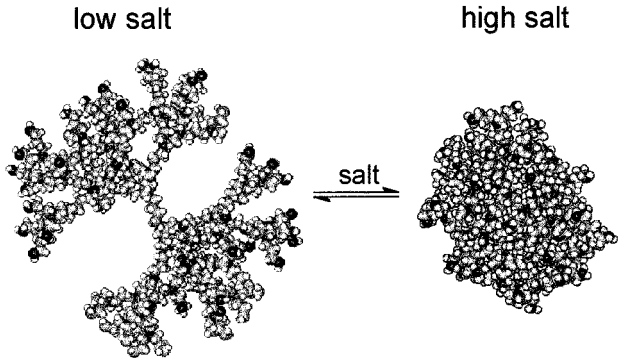

Figure 5. The occurrence of a dense shell (left) or a dense core conformation (right) of poly(propylene imine)dendrimers is dependent on the ionic strength of the solution (picture kindly provided by B. Coussens, DSM, The Netherlands).

force field representing a bad solvent. Monte Carlo simulations on dendritic polyelectrolytes by Welch and Muthukumar show a dramatic change in dendrimer conformation depending on the ionic strength of the solvent.[57] The investigated polyelectrolytes are topological analogues of poly(propylene imine) dendrimers. At high ionic strength, backfolding of the end groups takes place and a "dense core" dendritic structure is formed. At low ionic strength, the multiple charges in the dendrimer force the molecule to stretch out resulting in a "dense shell" structure (Figure 5).

Almost all aforementioned computational investigations predict backfolded branches in dendritic structures (the only exceptions being the study by de Gennes and Hervet and, to some extent, the work of Cavallo and Fraternali). Backfolding is an important process in most models, because the conformation of the tiers is mainly determined by repulsive monomer−monomer excluded volume interactions and by the entropic energy penalty for the swelling of the dendrimer. In the next paragraph, experimental data will show that the importance of backfolding is dependent on the actual dendritic structure. Attractive secondary interactions between the end groups, for example, can effect the conformations of branches significantly, thereby notably reducing backfolding.

2. Experimental Studies

The polyether dendrimers synthesized by Fréchet et al. (Figure 6) have been investigated in detail to establish the possibilities for backfolding in these molecules. One of the first studies by Mourey et al. uses an experimental setup in which size exclusion chromatography (SEC) is coupled to differential viscometry.[58] The hydrodynamic radii, calculated from the measured intrinsic viscosity, increase approximately linearly with the dendrimer generation. Additionally, a maximum in the intrinsic viscosity as a function of molecular weight is found. Both of these trends are in qualitative agreement with the model of Lescanec and Muthukumar,[49] implying that the end groups can be found throughout the dendrimer volume.

Rotational-echo double-resonance (REDOR) NMR studies on Fréchet-type dendrimers by Wooley et al.

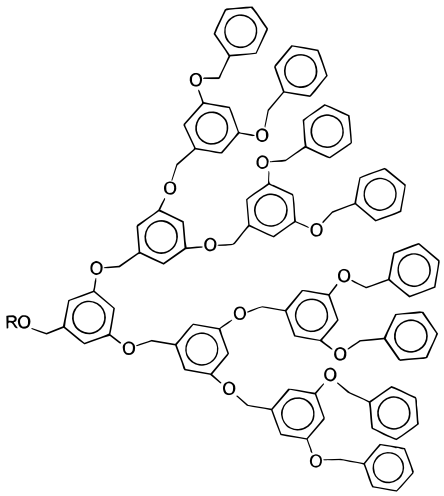

Figure 6. Structure of a Fréchet-type polyaryl ether dendritic wedge.

have shown that backfolding also takes place in the solid state.[59] The authors have found that the radial density for a fifth generation polyether dendrimer decreases monotonically with increasing distance from the center of mass. In addition, Gorman et al. have measured the spin lattice relaxation (T_1) in polyaryl ether dendrimers with a paramagnetic core.[60] The data reveal that the end groups are close to the core of the molecule. Recently, the hydrodynamic volumes of Fréchet-type dendrimers with rubicene cores have been determined by fluorescence depolarization measurements.[61] Qualitatively, this study has given the same results as those obtained by Mourey et al. (i.e., the end groups are backfolded).[58] In addition, the study has indicated that the hydrodynamic volume of the investigated dendrimers appears to be temperature independent, whereas this volume is strongly influenced by the solvent. The dendrimers are collapsed in poor solvents, while in a θ-solvent a more open dendritic structure exists.[61]

The previous examples of polyaryl ether dendrimers are built up from flexible noninteracting units. Percec et al. have produced polyaryl ether dendrimers with pendant perfluorinated[62] or perhydrogenated[63] aliphatic chains. The dendrimers assemble in the solid state in such a way that segregation between the dendritic wedge and the end groups takes place. The segregation is apparent from X-ray diffraction data and transmission electron microscopy (TEM) measurements.[64] Recently, Stühn et al. have observed similar phase separation phenomena in carbosilane dendrimers with perfluorohexyl groups on the periphery.[65] In contrast to the dendrimers with the noninteracting units discussed before, all these segregated systems do not exhibit backfolding.

The conformational behavior of PAMAM dendrimers has been studied with several techniques. SEC in combination with intrinsic viscosity measurements has been used to obtain the hydrodynamic radii of the PAMAM dendrimers.[18,66,67] The authors conclude that the acquired data are in agreement with the de Gennes model, i.e., the PAMAM dendrimers have a hollow core and a densely packed outer layer. ^{13}C NMR relaxation studies on PAMAM dendrimers by

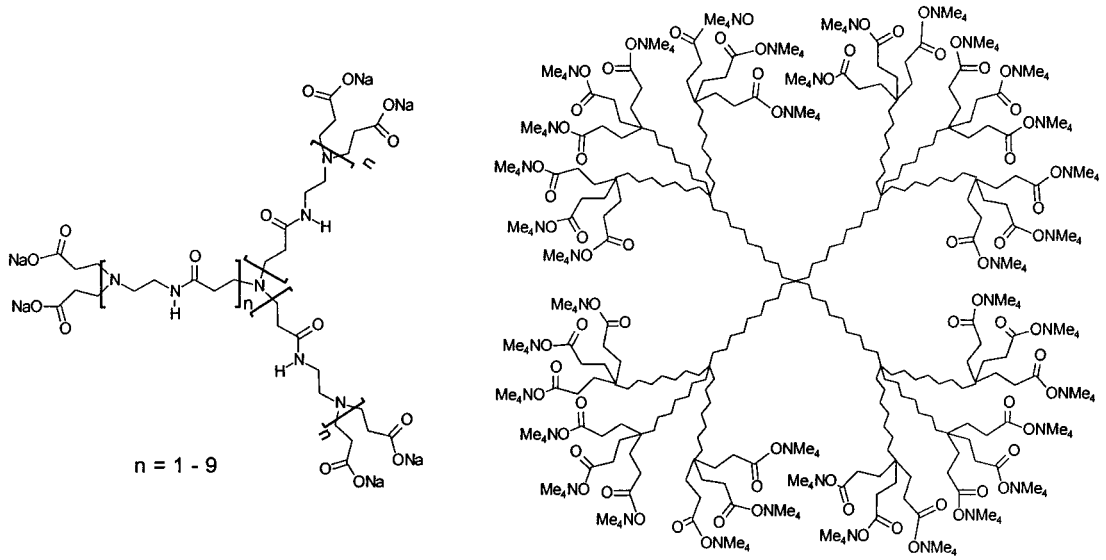

Figure 7. Examples of unimolecular anionic micelles reported by Tomalia[75] (A) and Newkome[81] (B), *n* denotes the generation number.

Meltzer et al. have indicated no dramatic change in chain dynamics up to the tenth generation.[68] The measurements show that chain motion is most rapid near the termini of the molecule and is slower in the interior. It has been concluded that the branches are backfolded to some extent to relieve the steric crowding on the dendritic surface. These conclusions have been confirmed in a subsequent ^{2}H NMR study by the same authors on various generation PAMAMs labeled with deuterium.[69] Small-angle X-ray scattering (SAXS) measurements on PAMAM dendrimers have not given clear-cut results.[70] For the higher generations (M_w > 50 000), the overall density appears to be independent of the generation. These data do not exclude any postulate: the terminal groups can reside on the dendrimer surface, but backfolded arrangements are also possible. Additional results from a small-angle neutron-scattering (SANS) study on a deuterium-labeled seventh generation PAMAM dendrimer indicate that the end groups are preferably positioned at the exterior of the molecule.[71]

End group modification of PAMAMs with naphthalenediimide anion radicals affords molecules that show strong $\pi-\pi$ stacking interactions between the modified end groups.[72,73] The stacking is apparent from near-infrared spectroscopy measurements. Comparable results have recently been obtained with amido-ether dendrimers functionalized with oligothiophenes on the periphery.[74] In the case of these dendrimers, backfolding is presumably prohibited by inter end group interactions.

Various studies have been devoted to the hydrolyzed "half-generation" PAMAM dendrimers. These molecules have a poly(amido amine) dendritic core that is surrounded by a shell of carboxylate end groups (Figure 7A). The picture of a unimolecular anionic micelle is supported by various photophysical measurements (data on pyrene fluorescence,[75] steady-state $Ru(bpy)_3^{2+}$ quenching,[76] and dynamic $Ru(phen)_3^{2+}$ quenching[77] have been disclosed) and by ESR measurements (Cu(II),[78] nitroxides[79] and Mn(II)[80] have been used as probe molecules). Unimolecular micellar systems based on dendrimers have also been reported by Newkome et al. Alkane[81] or polyamide[82,83] cores and carboxylate or amine end groups have been employed (Figure 7B). Both SEC and two-dimensional diffusion-ordered NMR-spectroscopy (DOSY) have shown that the hydrodynamic radii of the polyamide dendrimers strongly depend on the pH of the solvent.

Scherrenberg et al. have recently investigated poly(propylene imine) dendrimers with both nitrile and amine end groups using viscosimetry and SANS measurements.[56] Independent of the nature of the end group or the solvent used, the authors have found a linear relationship between the radius of the dendrimer and its generation number. This linear dependency correlates with the results of the molecular dynamics study by Murat and Grest.[51] Hence, poly(propylene imine) dendrimers are flexible molecules with a relatively homogeneous density distribution, implying that the end groups must be backfolded to some degree. Another SANS study on amine terminated poly(propylene imine) dendrimers has shown that the molecules tend to stretch when the amines are protonated.[84] These data reflect and confirm the flexible character of poly(propylene imine) dendrimers.

Various studies have been performed on poly(propylene imine) dendrimers that have been amidated (these materials are abbreviated by the formula[85] DAB-*dendr*-(NH−R)$_n$, see Figure 8). The fifth generation poly(propylene imine) dendrimer modified with *N*-*t*-BOC protected phenylalanine, the so-called "dendritic box" (DAB-*dendr*-(NH-*t*-BOC-L-Phe)$_{64}$), has been shown to have a rigid shell consisting of *t*-BOC-protected amino acids.[86] The soft-interior hard-exterior configuration is confirmed by spin lattice (T_1) and spin−spin (T_2) carbon relaxation measurements[86] and by the absence of optical rotation in this system.[87,88] The rigidity of the shell is thought to originate from the many possibilities for intra-

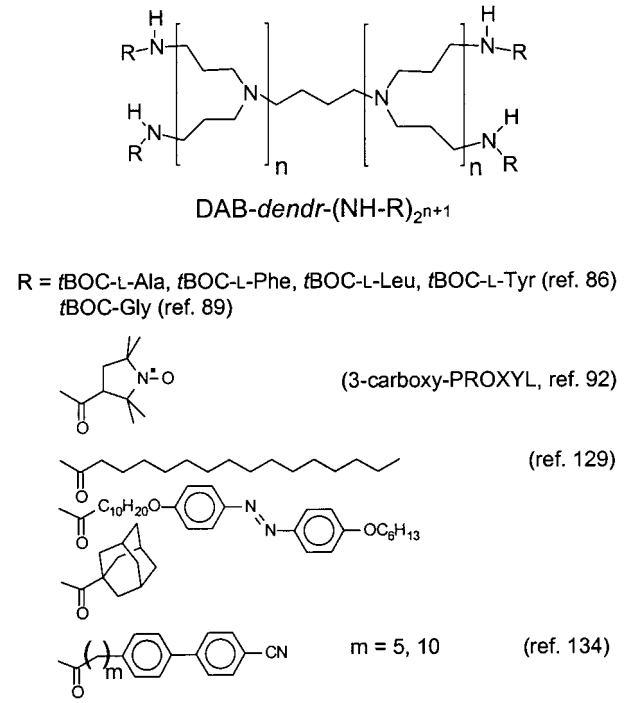

Figure 8. Poly(propylene imine) dendrimers functionalized to several polyamide structures.

molecular hydrogen bonding between the amides or the carbamates in the end groups. The first generation *N*-*t*-BOC-glycine-functionalized dendrimer also displays intramolecular H-bonding as confirmed by its X-ray structure (Figure 9).[89] The crystal structure clearly shows that secondary interactions between the end groups force the dendritic termini to associate. In solution, the importance of intramolecular H-bonding in amide-functionalized poly(propylene imine) dendrimers gradually grows with generation, as proven by NMR[89−91] and IR studies.[89,92] The interactions between end groups can also be derived from the ESR spectra of poly(propylene imine) dendrimers that have been functionalized with PROXYL radicals.[86]

Reviewing the cited reports, the localization of the end groups of dendrimers depends critically on the structure of the dendrimer in question. The flexible nature of most known dendrimers usually implies that the end groups are found throughout the dendrimer volume. Thus, the voids inside the dendrimer are filled up to a certain extent. However, when the end groups can communicate with each other via secondary interactions such as $\pi-\pi$ interactions, electrostatic repulsions, hydrogen-bonding interactions or hydrophobic effects, the dendritic terminal units will assemble at the periphery, thereby precluding backfolding.

B. Dendrimers versus Linear Macromolecules

When dendrimers in solution are considered, the occupied volume of a single molecule increases cubically with generation, whereas its mass increases exponentially. This typical "growth" pattern of dendritic molecules determines their solution properties and makes these properties deviate from those of linear molecules, especially at higher molecular

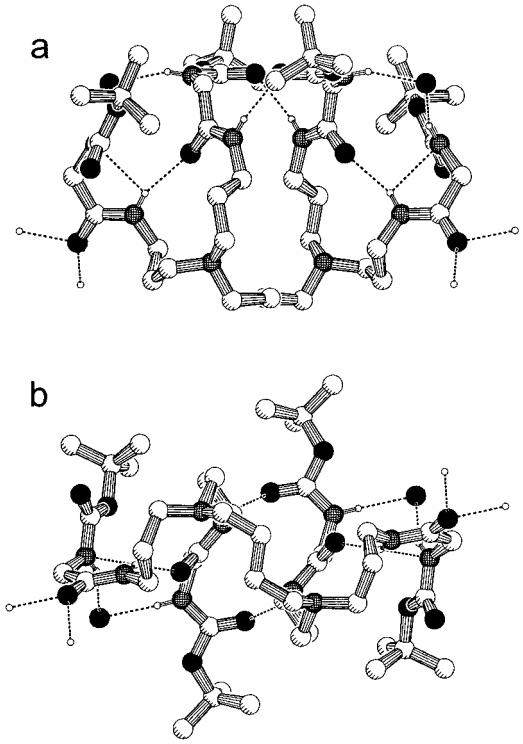

Figure 9. PLUTON representation of the crystal structure of the first generation *N*-*t*-BOC-glycine-functionalized dendrimer. Hydrogen bonds are shown by dotted lines; only protons involved in hydrogen bonding are shown for clarity. The acceptor oxygen atom as well as the donating hydrogen atoms of other neighboring molecules have been included to provide a complete scheme of all hydrogen bonding interactions: (a) side view; (b) top view.[89]

weights. The intrinsic viscosity is a physical parameter for which such a deviation has been measured. In contrast to linear polymers (that obey the Mark−Houwink−Sakurada equation), the intrinsic viscosity of dendrimers is not increasing with molecular mass but reaches a maximum at a certain dendrimer generation (for polyaryl ether,[58] poly(propylene imine),[10] and PAMAM dendrimers,[18] these maxima have been reported).[93] Also in the solid state, the growth pattern of dendrimers determines their physical characteristics. In general, it is believed that a gradual transition in overall shape, from a more extended arrangement for lower generation dendrimers to a compact and approximate globular shape for higher generation dendrimers, causes the deviation in physical behavior of dendrimers from those of linear macromolecules.

In the next paragraphs, various studies are surveyed in which the behavior of dendritic molecules is compared to the behavior of linear polymers or oligomers that are compositionally related. Until now, one study has dealt with the comparison of dendrimers with their linear isomers, having exactly the same number of repeat units and end group functionalities.[94] This study by Hawker et al. is the only investigation in which the influence of molecular architecture on physical properties is addressed absolutely. The reason for the absence of more of such studies can be found in the synthetic inaccessibility of the linear isomers (usually, the dendritic isomers can be produced far more easily).

Fréchet et al. have studied several physical properties of polyether and polyester dendrimers.[95] The increase in glass transition temperature (T_g) of the dendrimers levels off at higher molecular weights, a phenomenon that is also observed for the linear analogues. For linear polymers in general, a leveling off of the T_g increase has been known for a long time, and this effect is explained by the declining influence of the end groups and the role of the entanglement molecular weight. Dendrimers have more end groups at higher masses, but, as opposed to linear macromolecules, dendrimers are not significantly entangled. The absence of entanglements in the higher generation materials is subscribed in a study on the melt viscosities of polyether dendrimers.[96] In another study by the same authors, it appears that the melt viscosity is a physical parameter that is very dependent on the type of end group in the dendrimer.[97]

Miller et al. have compared the solubilities of 1,3,5-phenylene-based dendrimers with those of oligo-*p*-phenylenes.[98] Although *m*-phenylenes would have been more appropriate linear analogues, the study shows that the dendrimers have an enhanced solubility. Similar results have been obtained by Fréchet et al. who have compared dendritic polyesters with their linear counterparts.[99] In contrast to the linear polyesters, the dendrimers are soluble in a vast range of organic solvents. The authors also note a marked difference in reactivity: the debenzylation of the polyesters via catalytic hydrogenation on Pd/C is only possible for the dendritic structures. Differences in solubility and reactivity have also been found between poly(propylene imine) dendrimers with nitrile end groups and poly(acrylonitrile). The nitrile dendrimers are soluble in various organic solvents, whereas their linear analogues are crystalline and only soluble in very polar solutes such as dimethylformamide and concentrated sulfuric acid. Due to this limited solubility, the catalytic hydrogenation of poly(acrylonitrile) is not possible, while dendritic polynitriles are easily hydrogenated.[10,100] For all these cases, the observed differences in solubility and reactivity have been attributed to the globular architecture of the dendrimers and the accessibility of the end groups of the dendrimer.

The uniqueness of dendritic architectures has been shown in an elegant study by Hawker et al. in which polyether dendrimers are compared with their linear isomers (Figure 10).[94] Especially the fifth and sixth generation dendrimers display differing features when compared to their structural isomers. The hydrodynamic volume of the fifth generation polyether dendrimer is approximately 30% smaller than that of its linear analogue. The difference is ascribed to a more compact—backfolded—globular structure of the dendrimer. In addition, the fifth generation dendrimer is completely amorphous (a T_g of 42 °C is recorded) and is soluble in a variety of organic solvents, whereas the linear analogue is highly crystalline and poorly soluble in THF, acetone, and chloroform. The Hawker investigation solidly confirms that the physical behavior of dendrimers is different from that of linear polymers, and equally important, it shows that dendrimers need to have a certain size to display significantly different physical behavior. The next section concentrates on additional studies in which dendrimers of various generations have been compared.

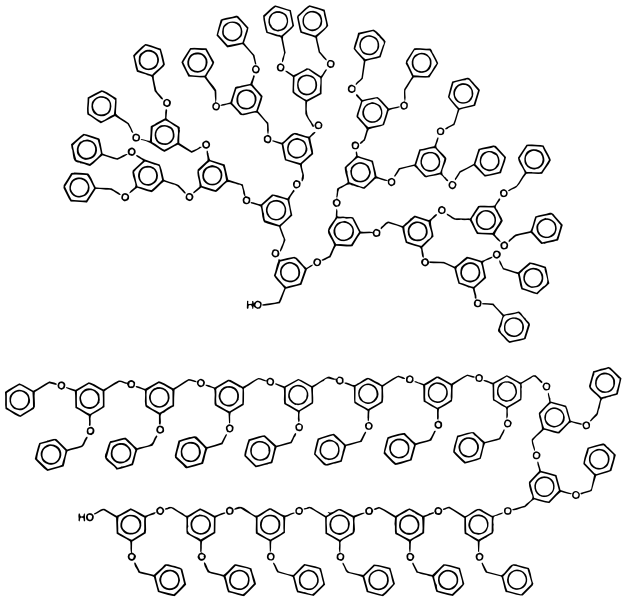

Figure 10. The fourth generation polyaryl ether dendrimer and its linear isomer.[94]

C. Lower versus Higher Generation Dendrimers

The differences in physical behavior between low and high generation materials within a homologous sequence of dendrimers have been investigated in numerous studies. Usually, photoactive probes have been used in these studies. Consequences of generation dependent characteristics for possible applications are reviewed in paragraph IV.B.1.

Fréchet et al. have attached the solvatochromic probe 4-(*N*,*N*-dimethyl)-1-nitrobenzene to the focal point of various generations of polyether wedges.[101] On the basis of measured chromophoric shifts in low-polarity solvents, a distinct transition in the polarity of the dendritic interior is observed on going from the third to the fourth generation. For the higher generations, the micro-environment of the chromophore is highly polar (comparable to the polarity of DMF as determined with the π^* scale[102]). The study indicates that the higher generation Fréchet dendrimers must have a closed and compact structure in order to severely limit the influence of the solvent on the probe (i.e., the core environment). In contrast with the study by Fréchet, Zimmerman et al. have concluded that the polarity of the interior of a polyether dendrimer is either apolar or controlled by the solvent.[103] The authors have based this conclusion on hydrogen-bonding studies using a naphthyridine core. The discrepancy between both studies can be explained by the different physical parameters that have been considered (solvent polarizability versus H-bonding), by the different immediate surroundings of the probes and by the fact that Zimmermann et al. have investigated four generations, whereas Fréchet has considered two additional bulkier generations.

Phenylacetylene dendrimers with a *p*-dimethoxybenzene moiety at the focal point have been made by Moore et al.[104] The maximum in fluorescence of a charge-transfer state in the dendrimer shows an anomalous shift for the fifth and sixth generation. Remarkably, a substantial shift in the fluorescence maximum can also be induced when pentane instead of hexane is used. Apparently, not only the solvent polarity but also the size and shape of solvent molecules are important factors in these kind of probe studies.

PAMAMs and poly(propylene imine) dendrimers also display transitions in their physical behavior when a sequence of generations is considered. Investigations on saponificated half-generation PAMAM dendrimers using various photophysical probes indicate a transition in dendrimer appearance on going from generation 3.5 to 4.5.[75,76] Spin relaxation data (T_1 and T_2 measurements) on a series of *N*-*t*-BOC-L-Phe-terminated poly(propylene imine) dendrimers[86] and hyper-Raleigh scattering (HRS) measurements on such dendrimers with 4-(dimethylamino)phenyl carboxamide end groups[91,105] show, in both cases, a transition in physical behavior around the fourth generation.

Spin relaxation data (T_1) of Fréchet-type dendrimers with porphyrin[106,107] or azobenzene cores[108] show a distinct transition between generation three and four, resulting in unique photophysical behavior for the higher generation materials. In the azobenzene systems, photoisomerization can be affected by using low energy photons (i.e., infrared irradiation), whereas in the porphyrin system a very efficient energy transfer from the dendron subunits to the porphyrin core takes place.

Poly(propylene imine) dendrimers of various generations have been grown from amine terminated polystyrene chains (PS$-NH_2$) with narrow molecular weight distributions.[109,110] Aggregation of these PS-*dendr*-$(NH_2)_x$ amphiphiles in water has been studied by various characterization techniques (monolayer experiments, pyrene probe fluorescence experiments, dynamic light scattering (DLS), conductivity and TEM measurements), showing that the morphology of the aggregates is determined by the size (generation) of the dendritic headgroup. As the headgroup becomes more bulky, the aggregates change their shape from inverted micelles, to vesicles and rodlike structures, and finally to spherical micelles. These observations are in line with Israelachvili's theory on the assembly of surfactant molecules.[111] The next section focuses on other amphiphilic dendrimers that have been investigated. Additionally, the behavior of dendrimers on surfaces will be discussed.

D. The Behavior of Dendrimers on Surfaces and in Amphiphilic Materials

Transmission electron microscopy (TEM) studies have been performed on unimolecular carboxylate-terminated micelles with either PAMAM[18,66] or alkane frameworks[81] (Figure 7). The PAMAMs of Tomalia have been studied with cryo-TEM using the sodium cations as contrast agents. For a 4.5 generation PAMAM dendrimer, spherical structures are visible with diameters varying from 80 to 100 Å. The structures have been assigned to individual molecules. Newkome et al. have visualized alkane dendrimers with 36 carboxylate end groups. When tetramethylammonium counterions are used, spherical monomolecular structures are visible with sizes of around 30 Å. When the carboxylic acids are used as end group, aggregated structures are observed that probably are caused by intermolecular H-bonding. Using TEM, Newkome et al. have also observed aggregates formed by second generation polyols.[112] Recently, amine-terminated PAMAMs (of generations five to ten) stained with sodium phosphotunstate have been investigated with TEM.[113] The dendrimers are spherical with radii that are consistent with SAXS-data (from 4 nm for generation five up to 15 nm for generation ten). The tenth generation dendrimer has also been investigated with cryo-TEM in vitrified water, revealing a polyhedral shape for these molecules. Noninterpenetrating ordered aggregates have been observed, the formation of which can be suppressed to some extent by adding HCl. This is probably due to protonation of the termini resulting in electrostatic repulsions between separate molecules. Accordingly, close-packed aggregates can be obtained in dilute NaCl solutions in which charges are shielded efficiently.

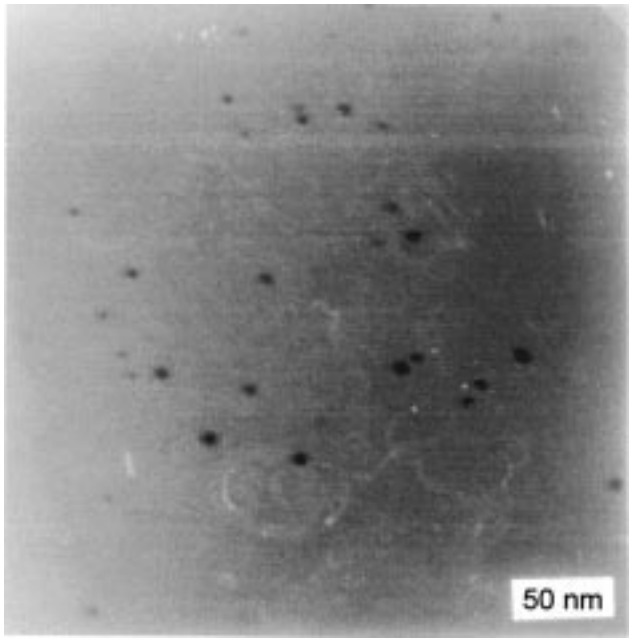

Figure 11. TEM micrograph of [Cu_{32}DAB-*dendr*-$(NH_2)_{64}$]-Cl_{64} as developed from an 10^{-4} M aqueous solution.[115]

Various types of metallodendrimers form monomolecular spherical structures on solid surfaces. Majoral et al. have used high-resolution TEM to visualize different generations of gold-containing polyphosphine dendrimers.[114] Dendrimers of generation three, four, five, and ten (theoretical number of Au sites: 24, 48, 96, and 3072, respectively) give isolated spheres with diameters of 60 ± 5, 75 ± 5, 90 ± 5, and 150 ± 5 Å, respectively. Single isolated molecules of the fifth generation poly(propylene imine) dendrimer loaded with 32 Cu(II) ions are also visible with TEM (Figure 11).[115] The diameters of the spherical structures are ca. 60 Å, a result that is in

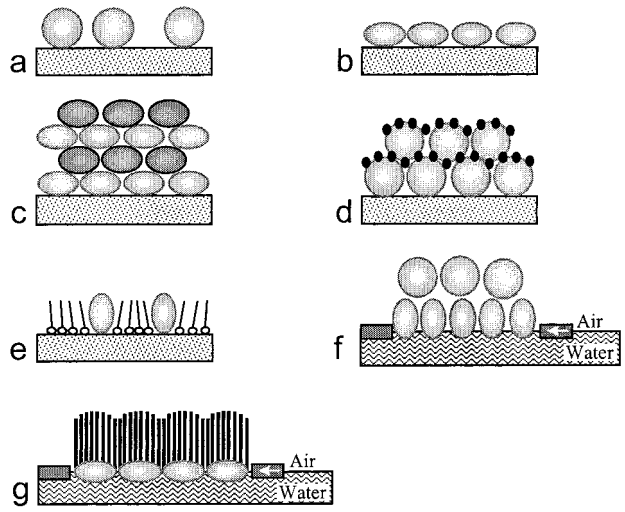

Figure 12. Schematic representation of the different modes of adsorption of dendrimers on surfaces: (a) adsorbed noninteracting dendrimers;[36] (b) adsorbed dendrimers with surface-interacting end groups;[117−121] (c) interacting multilayer dendrimer films;[118] (d) multilayer dendrimer films with ionic shielding;[122] (e) mixed monolayer;[124,125] (f) compressed dendrimer Langmuir bilayer;[127,128] (g) dendrimer Langmuir monolayer.[129]

line with SANS data on amine terminated poly(propylene imine) dendrimers.[56] Van Veggel et al. have reported on spherical aggregates of palladium-containing dendrimers that have been studied using AFM.[116] The second generation metallodendrimers have a radius of 15−20 nm and a height of 4.2 nm.

Carbosiloxane dendrimers with trimethylsilyl end groups have been visualized with scanning force microscopy (SFM).[36] On a glass substrate, single dendritic molecules are observed with globular shapes and diameters in the order of 3 nm (Figure 12a). The materials have a strong tendency to coagulate; therefore, in addition to monomolecular structures, clusters and even droplets are also visible. Complete wetting of a mica surface has been observed for carbosilane dendrimers modified with hydroxyl end groups.[117] The wetting is attributed to the preferential adsorption of the hydroxyl groups to the mica surface. Modification of the substrate with a semifluorinated coating results in dendrimer droplets on the surface.

The assembly of dendrimers in monolayers or multilayers on solid surfaces has been discussed in several studies. The previously mentioned hydroxyl-terminated carbosilanes organize in monolayers with thicknesses of approximately half the expected (theoretical) values.[117] Apparently, strong deformation of the surface-bound dendrimers takes place (Figure 12b). Tsukruk et al. have observed the deformation of PAMAMs in monolayers on silicon surfaces.[118,119] The PAMAMs are collapsed and highly compressed along the surface normal, resulting in flattened, disklike structures (Figure 12b). To explain the observed deformation, electrostatic interactions between the terminal cationic functional groups and the activated (negatively charged) substrate are assumed. Monolayers of carboxylated PAMAMs on positively charged surfaces also give flattened structures.[120,121] Compression of dendrimers is also observed in multilayer films of oppositely charged PAMAMs ($-NH_3^+$ and $-CO_2^-$ termini).[118] In this case, electrostatic interactions between the layers cause the compression (Figure 12c). Watanabe and Regen have illustrated that deformation resulting from electrostatic interactions can be prevented by using a low molecular weight shielding agent. The authors have used Pt(II) salts that are located between adjacent dendrimer layers, thereby shielding the electrostatic interactions (Figure 12d).[122]

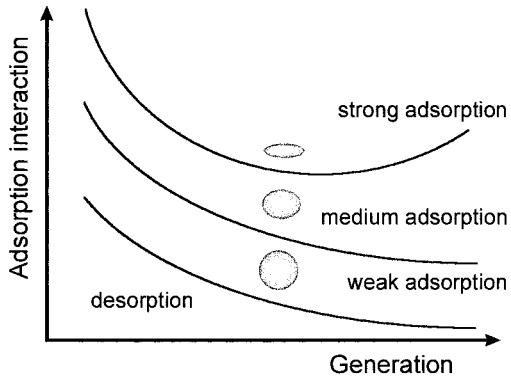

Figure 13. A "phase diagram" that shows how the shape of dendrimers in adsorbed monolayers depends on the strength of the adsorption interaction and the dendrimer generation. The data are based on calculations by Mansfield.[123]

Interestingly, the deformation of dendrimers on surfaces has been predicted by Mansfield in a Monte Carlo study.[123] The investigation considers the adsorption of dendrimers on a surface at different interaction strengths. The calculations show a flattening of the dendrimer shape with increasing adsorption strengths. As reflected in the "phase diagram" (Figure 13), the mode of adsorption of the dendrimers is dependent on adsorption strength and on the generation number (higher generation dendrimers have more interaction sites per molecule. and therefore, these dendrimers have a better chance to be adsorbed).

An interesting type of deformation has been found by Crooks et al.[124,125] Monolayers of PAMAMs adsorbed on a gold surface flatten due to multiple Au−amine interactions, but subsequent submission of alkanethiols to the surface results in a mixed monolayer in which the PAMAMs acquire a prolate configuration due to the shear exerted by the thiols (Figure 12e). The shear originates from the stronger thiol−Au interaction as compared to the amine-Au interaction. If the adsorption time of the dendrimer monolayer is rather short (45 s in stead of 20 h), exposure to hexadecanethiol results in piling up of the dendrimers to vacate the surface in favor of the thiols.[126] Eventually, this leads to complete desorption of the dendrimers from the surface.

The assembly of dendritic molecules on the air−water interface has been investigated by several authors. White et al. have investigated polyether wedges with a benzylic alcohol function at the core.[127,128] For generations one to four, the dendrimers behave as classical surfactant molecules in a Langmuir trough. The isotherms of generations five and six, however, indicate nonsurfactant behavior, once

more reflecting the deviating properties of higher generation dendrimers. Compression of the fourth generation polyether dendrimer results in the formation of a stable bilayer. In this bilayer, the dendrimers are compressed laterally with respect to the surface normal, producing an ellipsoid shape which is twice as high as broad (Figure 12f). Neutron reflectivity studies on analogues with perdeuterated end groups indicate that the terminal benzyl groups are located at the top of the lower layer.[128]

Poly(propylene imine) dendrimers functionalized with hydrophobic alkyl chains (palmitoyl chains or alkyloxyazobenzene chains) assemble in stable monolayers at the air−water interface.[129] In the assemblies, the dendrimers adopt a cylindrical, amphoteric shape, in which the ellipsoid dendritic moiety acts as a polar headgroup and the alkyl chains arrange in a parallel fashion to form an apolar tail (Figure 12g). This representation is based on the observation that the molecular area of a dendritic molecule increases linearly with the number of end groups in this molecule. Additionally, the observed molecular area corresponds to the area occupied by one hydrophobic chain, in an all-trans arrangement, times the number of hydrophobic chains in one molecule. UV/vis measurements on the azo-chromophore-containing dendrimers indicate H-type aggregates. When poly(propylene imine) dendrimers with pendant adamantyl or *N*-*t*-BOC-L-Phe end groups are spread on the air−water interface, a nonlinear dependency of the molecular area with generation is found and stable monolayers are not formed.

Amphiphilic PAMAM dendrimers comparable in design to those reported for the poly(propylene imine) dendrimers[129] have been studied on the air−water surface by Tomalia et al.[130] The PAMAMs with aliphatic end groups of varying lengths (6, 8, 10, and 12 carbon atoms) also display the linear behavior between the molecular area at the compressed state and the number of end groups per molecule. Tomalia et al. explain their findings in a model in which the lower generations are asymmetric like the poly(propylene imine) dendrimers, while the higher generations act as hydrophobic spheroids floating on the air−water interface. Since no indication for the latter behavior is found, it is proposed here that also the amphiphilic PAMAM dendrimers of high generations, when disposed on air−water interfaces, are highly distorted with all aliphatic end groups pointing upward.

In addition to the Langmuir−Blodgett (LB) studies, the aggregation in water of the palmitoyl and alkoxyazobenzene-functionalized poly(propylene imine) dendrimers has been studied.[129] At a pH of 1, vesicle-type structures are observed as evidenced by (cryo) TEM micrographs (Figure 14), dynamic light scattering (DLS) data, X-ray diffraction results and osmometry measurements. In the aggregates, the dendrimers are thought to have similar conformations as those observed at the air−water surface. The hydrophilic protonated dendritic component faces the water, while the aliphatic chains are packed in a parallel fashion to form an apolar bilayer. Within this assumption, the axial ratio is calculated at 8:1 for the highest dendrimer generation (the axial ratio is defined as the ratio between both characteristic distances in an ellipse). Thus, the dendritic headgroup has a flattened, far from globular, ellipsoid shape.

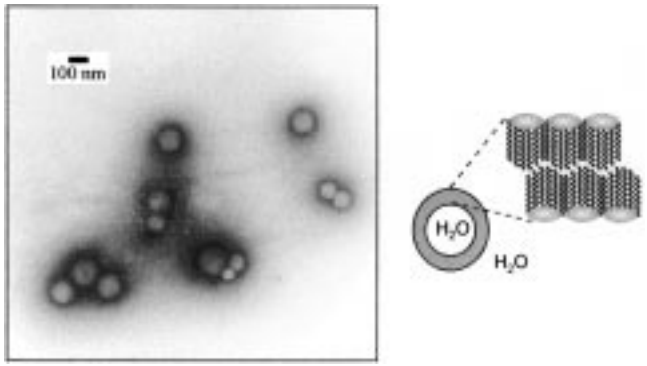

Figure 14. TEM micrograph of the fifth generation palmitoyl functionalized poly(propylene imine) dendrimer. An aqueous 10^{-4} M dispersion has been used and contrast is achieved by using uranyl acetate staining. On the right a schematic presentation of the bilayer is drawn.[129]

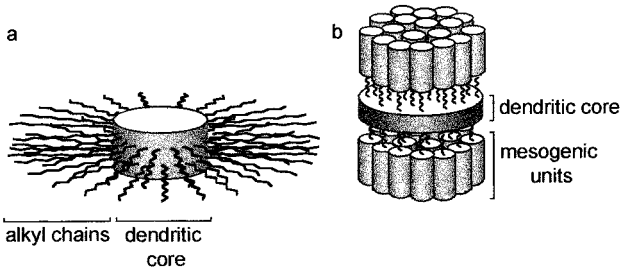

Figure 15. Proposed models for the conformation of poly(propylene imine) dendrimers bearing mesogenic groups in (a) hexagonal columnar phases[133] and (b) smectic-layered phases.[134]

Dendrimers containing mesogenic functionalities can behave as liquid crystalline (LC) materials. Percec et al. have constructed dendrimers with mesogenic units in the branches.[131] The dendrimers can adopt sheetlike conformations and are able to form nematic or smectic LC phases due to their flexibility. A second generation carbosilane dendrimer has been modified with cyanobiphenyl units on the periphery by Frey et al.[132] The material forms a smectic A (S_A) phase, and therefore, the rodlike mesogenic units are thought to deform the dendrimer to allow the formation of the layered LC structure. Latterman et al. have modified poly(propylene imine) dendrimers with mesogenic end groups (i.e., 3,4-bis-(decyloxy)benzoyl groups).[133] The resulting molecules form a hexagonal columnar mesophase, that is built up from cylindrical dendritic cores that are surrounded by apolar shells of alkyl chains (Figure 15a). The highest−fifth−generation dendrimer does not display mesomorphism, which has been attributed to the lack of conformational flexibility in this particular dendritic structure. In contrast, a study by Baars et al. shows that−regardless of the generation−poly(propylene imine) dendrimers modified with alkoxy-cyanobiphenyl moieties form S_A phases.[134] Since the calculated S_A layer spacings are independent of generation, a completely distorted dendrimer conformation is proposed (Figure 15b). Thus, Meijer

et al. have observed severely flattened, ellipsoid shapes for modified poly(propylene imine) dendrimers in LB layers,[129] in vesicle-type structures[129] and in LC materials.[131] Flattened dendrimers have also been observed for the first and second generation carbosilane dendrimers bearing perfluorinated end groups.[65] The distortion is the result of microphase separation. The third generation dendrimer produces a columnar superstructure, one that is comparable to those observed by Latterman.

The phenylacetylene dendrimers prepared by Moore et al. are distinguished from other dendrimers by their rigidity. The authors describe them as "shape persistent" and "dimension persistent".[16] The shape persistency has been confirmed by electron microscopy and diffraction measurements on the first and second generation phenylacetylene dendrimers.[135] However, even these rigid dendrimers can be deformed to "pancake"-shaped structures, when LC behavior is induced by modifying the outer functionalities with oligoethylene glycol chains.[136] Columnar discotic liquid crystalline phases are observed for these materials. Similar molecular organizations have been found for stilbenoid dendrimers.[137] Another type of shape persistency is found in polyphenylene dendrimers made by Müllen et al.[138−140] In these dendrimers, shape persistency originates from the very dense packing of benzene rings, as has been confirmed by molecular dynamics simulations.

In reality, dendrimers do not necessarily behave as might be expected from a simple representation on paper. Most dendrimers possess flexible branches that can adopt different conformations, implying that the end groups can fold back into the interior of the molecule. More surprisingly, the flexibility in dendritic molecules—even in bulky higher generation dendrimers—allows that these molecules can adopt shapes that are far from globular. Such shapes are only observed when dendrimers are exposed to "external stimuli", i.e., secondary interactions that force the dendrimers into specific supramolecular arrays. Flattened dendritic structures have for example been found in monolayers and in LC materials.

It has firmly been established that specific properties can only be expected from higher generation dendrimers. In this respect, the drop in intrinsic viscosity for higher molecular weight dendrimers has frequently been mentioned, although other properties also change for higher generation dendrimers (see for example the simple and elegant study by Hawker et al.[94]). This reality does not imply that lower generation dendrimers cannot be useful for certain functions, as some of the examples in the next section illustrate.

IV. Functional Dendrimers

Since the Tomalia and Newkome reports on dendrimers,[6,8] research on these branched molecules has mainly focused on the preparation and molecular characterization of a wide variety of dendritic macromolecules. Gradually, the interest in this field of chemistry has shifted to research in which specific functions of and particular applications for dendrimers are addressed. From the beginning, applications

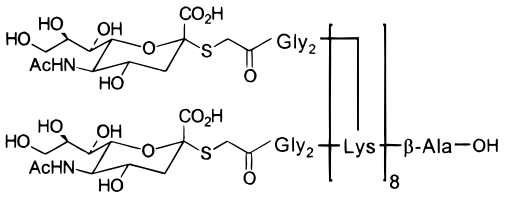

Figure 16. A glycodendrimer consisting of an L-lysine core and 16 sialic acid residues, as synthesized by Roy et al.[152]

in the fields of medicinal chemistry (e.g., in drug delivery systems), host−guest chemistry, and catalysis have been foreseen. The next section reviews the progress in these specific areas of interest. The reader is also referred to other review articles dealing with these subjects.[141−148]

A. Medicinal Applications

The combination of discrete numbers of functionalities in one molecule and high local densities of active groups, typical for dendritic molecules, has attracted a lot of attention from those active in medicinal chemistry. Dendrimers with multiple identical ligands are very attractive for pharmacochemists, since these structures can exhibit amplified substrate binding.[149] Enhanced substrate binding originates from either statistical effects or from cooperativity effects. An example of the latter can be found in carbohydrate−protein interactions (this specific cooperativity effect is known as the glycoside cluster effect).[150] Many research groups have been inspired to prepare carbohydrate containing dendrimers (glycodendrimers[151]),[152−172] although only a few of the newly prepared glycoconjugates have been investigated by in vitro techniques. The next few paragraphs summarize the results on the actually tested glycodendrimers.

Roy et al. have investigated glycodendrimers with an L-lysine core and with various carbohydrates substituted at the exterior.[152−155] Compared to a monofunctional residue, L-lysine dendrimers with 8 or 16 terminal sialic acid units (see Figure 16) show enhanced binding properties in a direct enzyme-linked lectin assay (ELLA) using horseradish peroxidase labeled wheat germ agglutinin (WGA).[152,153] The binding affinities are comparable to those found for a homologous sialylated polymer. The prepared sialylated dendrimers can efficiently be used to suppress the heamagglutination of erythrocytes, as evidenced by a test using the influenza A virus. L-Lysine dendrimers with *N*-acetylglucosamine (GlcNAc) or *N*-acetyllactosamine (LacNAc) terminal residues show enhanced inhibition of lectin binding to porcine stomach mucin.[154] The inhibition of binding of yeast mannan to concanavalin A (Con A) and to pea lectins by mannosylated L-lysine dendrimers displays maxima for the tetra- and octameric dendrimers, respectively.[155] The maxima have been attributed both to the limited number of binding sites in the lectins and to the possibly restricted accessibility of the dendritic mannose end groups. Optima in the inhibition potencies have also been found for other glycodendrimer systems (see Roy et al.[156] and Stoddart et al.[166] who have reported on α-thiosialo

PAMAM dendrimers and on α-D-mannopyranoside-containing polyamide dendrimers, respectively).

Okada et al. have functionalized PAMAM dendrimers with both a maltose and a lactose periphery.[168] These "sugar balls" interact with Con A and with peanut agglutinin (PNA), as demonstrated by quantitative precipitations. Only when a 1200-fold molar excess of D-glucose is added to the aggregate of maltose dendrimer and Con A, this aggregate dissociates.

The idea of using a dendritic multifunctional platform for the amplification of substrate binding has also been employed to generate antibodies. Already in 1988 Tam et al. have used dendritic peptides (peptides coupled to a dendritic lysine core) as multiple antigen peptides (MAPs).[173,174] When injected in mice or rabbits, these MAPs give high antibody responses. The enhanced immunoresponse of these particular MAPs is attributed to their high antigen content (82 mass percent); conventional peptide carrier conjugates have a low density of peptide antigens that are randomly distributed in the large protein carrier. An additional advantage of dendritic MAPs is connected to the use of lysine cores. The lysine carrier is nonimmunogenic,[174] whereas traditionally used carrier proteins may cause undesired immunological responses. Several other peptide-containing dendrimers have been prepared by Tam et al.[175−178] and others,[179] but the bioactivities of these compounds have not been reported yet.

Other medicinal applications for dendrimers lie in the field of imaging. Dendritic gadolinium polychelates have been used as magnetic resonance imaging (MRI) contrast agents. One set of employed dendrimers are PAMAMs that have been modified on the periphery with a diethylenetriaminepentaacetate (DTPA) derivative that serves as a Gd(III) chelator.[180] The sixth generation gadolinium dendrimer displays an enhanced performance when compared to a monomeric chelate or to linear polychelates. The higher molecular relaxivity is ascribed to the large number of metal ions attached to one molecule and to a higher ion relaxivity.[180,181] The increased ion relaxivity is thought to be related to a diminished flexibility in higher generation PAMAM dendrimers, as probed by an increased rotational correlation time for these species. In vivo experiments have shown that the Gd(III) dendrimers have much higher enhancement lifetimes in rats than monofunctional analogues (up to 10 times as high for generation six).[180] Qualitatively similar results concerning relaxivity have been found for PAMAMs modified with a macrocyclic tetraazatriacetate (DO3A) chelator.[182] A contradicting study has shown that no significant differences exist between PAMAM and linear polylysine based multigadolinium complexes, when these components are used as MRI contrast agents for the blood pool.[183] Finally, Bourne et al. have demonstrated the efficiency of Gd(III) dendrimers as intravasculair contrast media for 3D time-of-flight magnetic resonance angiography (3D-TOF MRA).[184]

A recent methodology in cancer treatment is the boron neutron capture therapy (BNCT).[185] In this therapy, the generation of cytotoxic and energetic products from nuclear fission reactions of low-energy neutrons and ^{10}B nuclei is used to destroy malignant cells. An efficient agent for the therapy is water soluble and has a high local density of boron clusters, requirements that are met for several synthesized boron-containing and water soluble dendrimers.[186−189] Qualmann et al. have, in addition, introduced antigen selectivity by coupling a lysine-based boronated dendrimer to antibody fragments (Fab′).[189,190] In these agents, the attachment of a poly(ethylene glycol) (PEG) moiety is necessary to keep the conjugates water soluble (Figure 17). The covalent nature of the boronated Fab′ fragments leads to a better stability of these conjugates as compared to, for example, borate coated polystyrene beads. The targeting efficiency of the dendrimer−Fab′ conjugates has been investigated with electron spectroscopic imaging (ESI).[190] The combination of the small size of the conjugates and their high local ^{10}B density makes these components superior for ESI applications when compared to the conventionally used "immunogold" technique, in which a larger colloidal component is used that has poorer penetration properties and that imposes higher steric hindrances. Studies on boronated PAMAMs attached to a monoclonal antibody have been reported by Barth et al.[191]

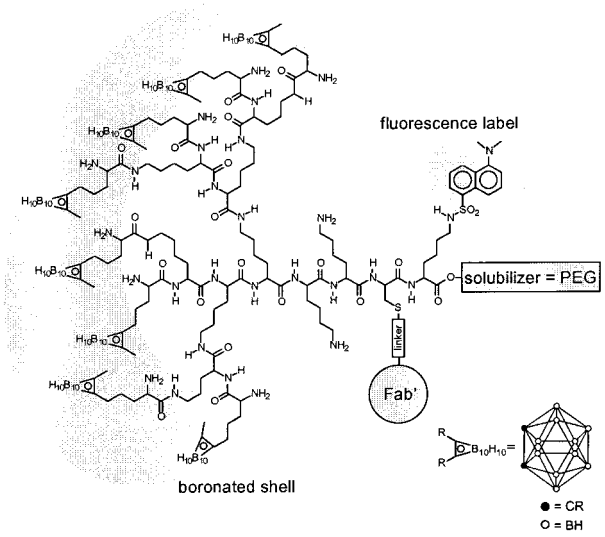

Figure 17. A boronated lysine-based dendrimer as used by Qualmann et al. The antibody is coupled to the thiol function of a cysteine residue by a bismaleimidohexane linker.[189]

PAMAM dendrimers have been investigated on their ability to transfer biomolecules into several mammalian cell lines.[192,193] PAMAMs are particularly suited for such a purpose, since these dendrimers are positively charged at physiological pH and can thus interact with biologically relevant anions such as nucleic acids. In vitro experiments indicate high-efficiency transfection in a variety of cell lines,[193] although transfection is strongly dependent on dendrimer generation, cell line and the presence of other reagents such as the DEAE dextran agent (which in itself is a transfection agent as well). In other in vitro studies, PAMAM dendrimers have been utilized as delivery vehicles for oligonucleotides to the cell,[194] as carriers for antisense oligonucleotides,[195] as probes for oligonucleotide arrays,[196] and as primers in poly-

merase chain reactions (PCR).[196] PAMAMs have also been coupled to antibodies to obtain an immunoassay that combines the advantages of hetero- and homogeneous immunoassays.[197] Recently, efficient gene transfer with PAMAMs has been accomplished in vivo.[198]

The biocompatibility and pharmacokinetics of dendrimers are important factors when in vivo applications are considered. Still, only a very limited amount of papers dealing with these subjects have appeared. The biological behavior of PAMAMs of the third, fifth, and seventh generations has been investigated by Roberts et al.[199] In vivo toxicity has only been observed for the seventh generation, while the in vitro toxicity of PAMAMs is concentration and generation dependent, with the seventh generation being more toxic than the third or the fifth. None of the investigated generations displays immunogenicity. Methylated PAMAMs are characterized by a high pancreas uptake, and in the case of the seventh generation, an unexplained high urinary output is observed. The authors hold the polycationic nature of the dendrimers responsible for the observed toxicity, a hypothesis that is subscribed by a study of Duncan et al., in which haemolysis and cytotoxicity have been observed for amine terminated PAMAMs, but not for their carboxylate terminated counterparts.[200]

B. Host–Guest Chemistry[143]

1. Site Isolation

The dendritic core is—at least to some extent—shielded from the medium, implying a typical micro-environment inside the dendrimer. This knowledge has inspired several research groups to prepare dendrimers with specific functionalities at the core. Thus, molecular systems are created in which a certain functionality is surrounded by a particular, sterically congested structure: the functionality is isolated at a specific site. Especially porphyrin based dendrimers have attracted a lot of attention in this research field. Porphyrins are found in many natural systems, where they play an essential role as photoactive, redox, guest-binding, and catalytic entities.

In different quenching studies, Aida et al. have demonstrated the site isolation of zinc porphyrins that are surrounded by Fréchet-type polyether dendrimers.[106,201,202] The authors have found that quenching of the porphyrin fluorescence is significantly more difficult for the higher generation dendrimers. Quenching also depends on the size[106] and charge[202] of the quencher.

Diederich et al. have extrapolated the concept of a site-isolated functionality by preparing mimics for cytochrome *c*, an electron-transferring protein.[33,34,203] The first reported model compounds consist of a zinc porphyrin core surrounded by Newkome-type dendrimers.[33] The redox couple characteristics of these dendrimers are strongly generation dependent, since the reduction in dichloromethane occurs at more negative potentials when the porphyrin has an electron-rich dendritic environment (shifts up to −300 mV are recorded). Diederich et al. have acquired water-soluble dendritic iron porphyrins by using peripheral triethyleneglycolmonomethyl ether (PEG-like) moieties (Figure 18).[34,203] Compared to the first generation, the second generation iron porphyrin has a 420 mV more positive reduction potential in aqueous solution. This result has been assigned to a reduced interaction between the porphyrin and the solvent in the second generation dendrimer. Thus, the dendritic micro-environment destabilizes the more charged Fe(III) state relative to the Fe(II) state. A comparable redox shift to more positive potentials has been found in cytochrome *c*, a result that has been ascribed to the hydrophobic protein shell surrounding the porphyrin moiety.[204]

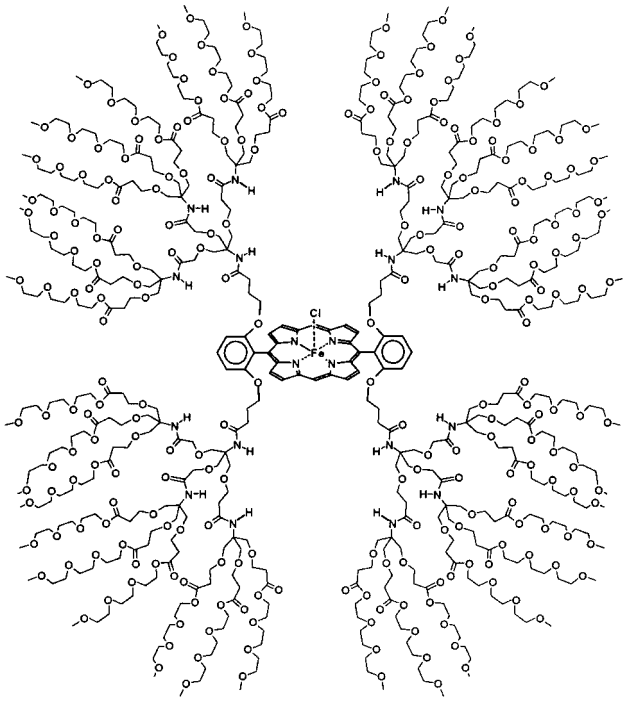

Figure 18. A dendritic water-soluble heme analogue that has been reported by Diederich et al.[34]

A zinc porphyrin surrounded by four polyether wedges has been studied by Fréchet et al.[205] In contrast to Diederich et al., there is no shift in redox potential of the dendritic core, only irreversibility has been observed for the third and fourth generation dendrimer. However, the core remains accessible to small molecules, as quenching studies with viologen have revealed.

Dendrimers with phthalocyanine (Pc) cores also display characteristics that are indicative for site isolation. Zinc phthalocyanine (ZnPc) with four pendant first generation amido ether wedges aggregates in water, whereas its second generation counterpart does not associate (as concluded from UV/vis and fluorescence measurements).[206] Interestingly, a phthalocyanine similarly substituted with four Fréchet wedges does not show any site isolation in chloroform, even when third generation wedges are used.[207] In another report, a silicon phthalocyanine (SiPc) core is sterically isolated by axial Fréchet-type dendritic ligands.[208] The isolation is directly visible in the X-ray structure of the SiPc with two second generation wedges as axial ligands (Figure 19).

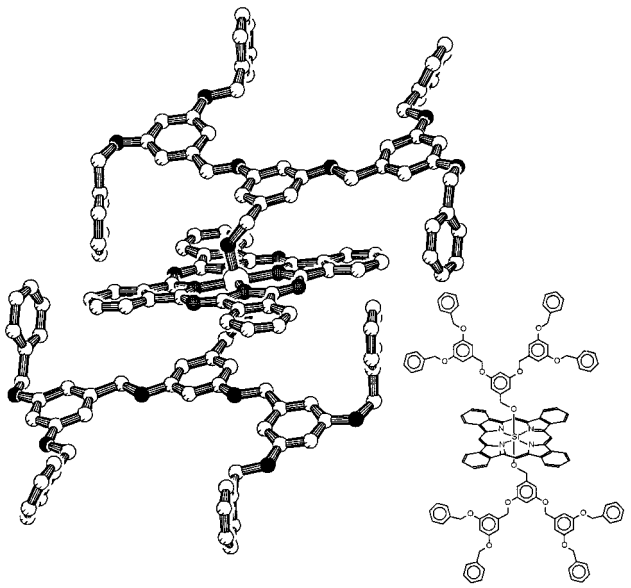

Figure 19. PLUTON representation of the crystal structure of a silicon phthalocyanine (SiPc) with dendritic axial ligands. The chemical structure in question is depicted on the right.[208]

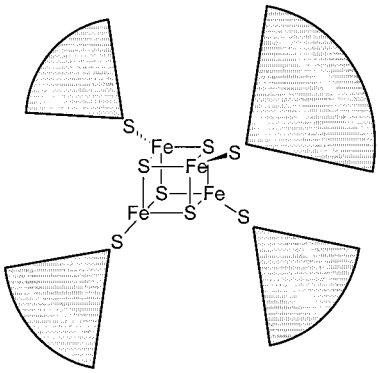

Figure 20. A schematic representation of a dendrimer-encapsulated electroactive site as reported by Gorman et al. The pie-shaped wedges represent aromatic ether dendritic units.[209]

Another example of a redox-active core with dendritic ligands consists of an iron−sulfur cluster surrounded by poly(aromatic ether) wedges (Figure 20).[60,209] Bulkier wedges result in a more negative reduction potential of the Fe_4S_4 cluster in DMF. Furthermore, the peak splitting in the cyclic voltammogram increases with generation. These effects indicate that the dendrimer hampers—both kinetically and thermodynamically—the reduction of the iron−sulfur cluster. The encapsulated electroactive molecules are thought to be applicable in molecular switches.[210]

Fréchet et al. have used polyether wedges to create a dendritic shell around various lanthanide cations (Er^{3+}, Tb^{3+}, and Eu^{3+}).[211] Three wedges with single carboxylate functions at the focal point form a salt with one Ln^{3+} cation. The acquired Ln^{3+} species display unique luminescence characteristics for the higher generation dendrimers due to hampered self quenching on one hand and the occurrence of an antenna effect on the other (the dendritic framework can transfer harvested light energy to the lanthanide center). The beneficial characteristics are not only displayed in solution, but also in the solid state and, thereby, these structures can potentially be used as fluorescers in devices for signal amplification (optical fibers).

2. Complexation of Guest Molecules in Dendrimers

Since their introduction, dendrimers have always been regarded as interesting candidates for applications in host−guest chemistry.[18,20] Speculations on the ultimate use of dendritic host−guest systems in complex drug delivery agents have often been made, although such or similar systems have not often been described (see also section IV.A). This section describes several host−guest systems, in which dendritic host have been used.

Tomalia et al. have shown that PAMAMs can bind guests such as 2,4-dichlorophenoxyacetic acid and acetylsalicylic acid in chloroform.[53] The presence of guest−dendrimer interactions are reflected in the ^{13}C spin−lattice relaxation times (T_1) of the guest molecules. The T_1 values decrease with increasing dendrimer generation and eventually reach a plateau. The plateau coincides with the region where molecular simulations predict a globular structure.

Unimolecular micelles have frequently been employed as host systems for guest molecules. Newkome et al. have used an alkane dendrimer with 36 terminal carboxylates to bind several lipophilic probes such as phenol blue, 7-chlorotetracycline and diphenylhexatriene.[81] The dendrimer-guest interactions are apparent from UV/vis and fluorescence spectroscopy. Fréchet et al. have constructed an unimolecular micelle from a polyaromatic ether dendrimer with 32 carboxylate end groups and a 4,4′-dihydroxybiphenyl core.[212] The amphiphilic dendrimer greatly enhances the solubility of pyrene in water. Various other aromatic compounds are also captured by the micelle, such as for example 2,3,6,7-tetranitrofluorenone. This electron-deficient guest is solubilized to a much greater extent than pyrene, indicating that $\pi-\pi$ interactions between aromatic guests and the dendrimer play an important role in the encapsulation process. The unimolecular micelle can be used in a recyclable extraction system: precipitation of a pyrene-loaded dendrimer in water by adding acetic acid, followed by resolvation in THF and subsequent removal of the dendrimer by washing with basic water, results in a complete transfer of the pyrene from the water layer to the THF phase.

Topological trapping of guests by core−shell molecules has been shown by Jansen et al.[86,213] (topological trapping, a term that has been introduced by Maciejewski as early as 1982,[214] refers to the binding of guest molecules in internal and confined cavities of a host system). Modification of the outer amine functionalities of a fifth generation poly(propylene imine) dendrimer (DAB-*dendr*-$(NH_2)_{64}$) with bulky substituents—typically, *N*-*t*-BOC-protected L-phenylalanine (*t*-BOC-L-Phe) substituents are used—results in the formation of a structure with a solid shell and a flexible core (see also section III.A.2). The soft-core, hard-shell framework of modified DAB dendrimers has also been named the "dendritic box" structure, since it can trap small molecules in its interior

cavities.[86] The encapsulation of molecules is performed by reaction of DAB-*dendr*-$(NH_2)_{64}$ with an activated ester of *N*-*t*-BOC-L-Phe in the presence of guest molecules with some affinity for the tertiary amine functions in the interior of the dendrimer. Excess guest molecules and molecules adhered to the surface of the box can conveniently be removed by a dialysis procedure. Liberation of guests in the dendritic box is only possible after destruction, i.e., hydrolysis, of the shell.[215] Lower generation poly(propylene imine) dendrimers cannot be used as boxes, since the shells in these systems are not dense enough to trap guest molecules: aqueous workup will release all adhered molecules. The encapsulation of dye molecules in general, and of Rose Bengal in particular, has been studied in detail.[216] The features of the guest molecules can change upon capturing, obviously as a result of the changed micro-environment. For example, Rose Bengal@DAB-*dendr*-(NH-*t*-BOC-L-Phe)$_{64}$[217] displays strong fluorescence at λ_{max} = 600 nm, whereas the fluorescence of free Rose Bengal is quenched in this wavelength region. Induced chirality upon encapsulation has also been found for Rose Bengal. When one molecule of Rose Bengal—an achiral compound—is trapped, a CD spectrum similar to the UV spectrum is found.[218] When four molecules are trapped, an exciton-coupled Cotton effect is observed, indicating the close proximity of chromophores with a certain fixed orientation. The CD experiments suggest that the cavities in the dendritic box must have retained some chiral features, although the shells of the box do not display any optical activity. The close proximity of trapped guest molecules has been confirmed in ESR spectroscopy measurements on dendritic boxes containing 3-carboxy-PROXYL radical guests. Ferromagnetic interactions are observed between the radical species present in one dendritic host molecule (Figure 21).[219]

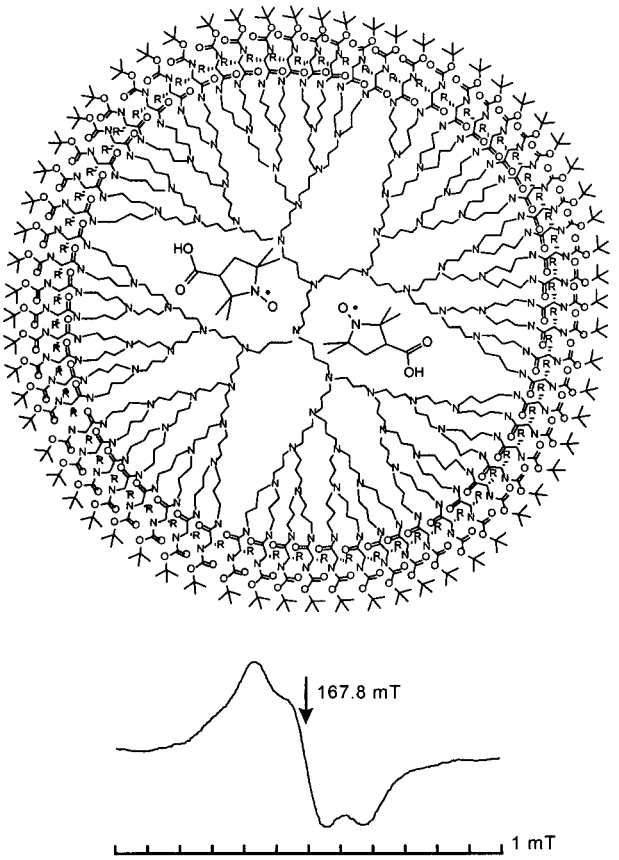

Figure 21. A two-dimensional representation of the dendritic box containing two 3-carboxy-PROXYL radicals, together with the half-field ESR spectrum of a solid sample at 4.2 K.[219]

Other hosts based on poly(propylene imine) dendrimers have been prepared by functionalizing the hydrophilic dendrimer with hydrophobic palmitoyl chains on the periphery.[90] The resulting structure behaves as an inverted unimolecular micelle in organic solvents (Figure 22). The dendrimers can extract several anionic xanthene dyes[220] from the water layer to the organic phase.[90,221] The amount of guests per dendrimer is directly related to the number of tertiary amines in the interior. For the fifth generation palmitoyl functionalized dendrimer, the load can be as high as 50 molecules. The efficiency of the extraction is related to the pK_a and the hydrophobicity of the guest, and the pH of the water layer. In contrast to classical extractants, such as for example tri-*n*-octylamine, the extraction efficiency of the dendritic micelles shows almost no solvent dependency for the organic phase. Apparently, the interior of the dendrimer is shielded from the solvent by the apolar palmitoyl barrier. As opposed to simple extractants, the dendritic extractants show a unique guest selectivity as a function of pH.

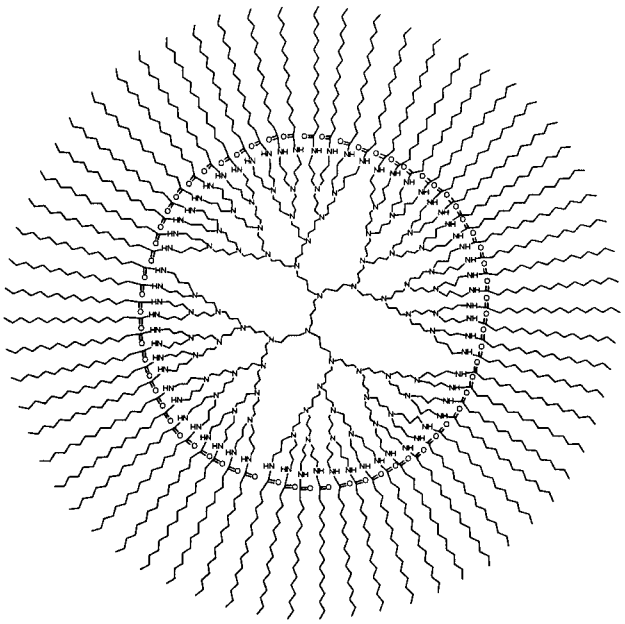

Figure 22. The inverted unimolecular micelle used by Baars et al. for the extraction of xanthene dyes.[221]

DeSimone et al. and Tomalia et al. have also reported on inverted unimolecular micelles. DeSimone et al. have prepared poly(propylene imine) dendrimers with hexafluoropropylene oxide chains to obtain dendritic surfactants that are soluble in supercritical CO_2.[222] Indeed, the CO_2-philic amphiphiles are able to extract methyl orange, a CO_2-insoluble guest, from water to supercritical CO_2. Tomalia et al. have reported on hydrophobically modified PAMAMs that are used as container molecules for copper-

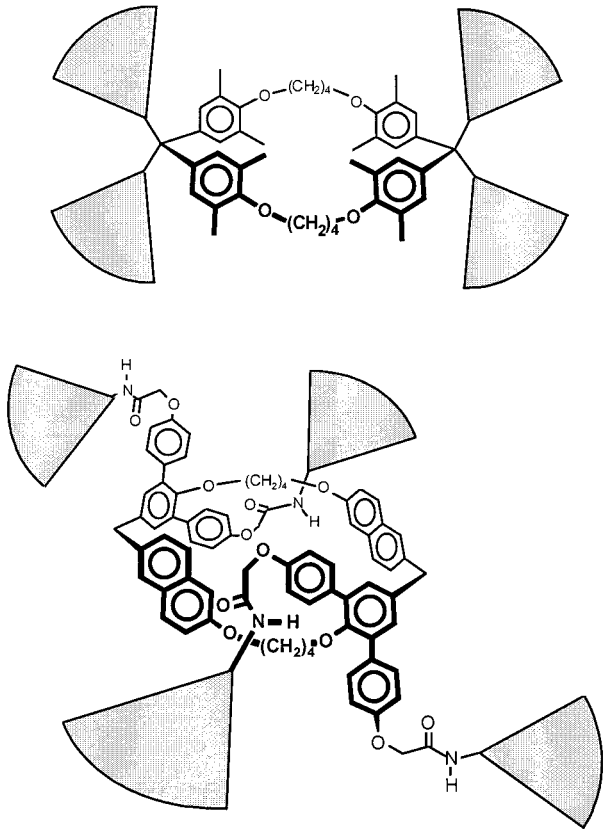

Figure 23. Cyclophane cores for dendrimers as used by Diederich et al. The structure at the top is a receptor for arenes, whereas the structure on the bottom is a receptor for steroids.[225] Pie-shaped wedges represent polyamide dendrons.

(II) sulfate in organic solvents such as toluene and chloroform.[130]

Dendrimers with specific receptors in the interior have been reported by Diederich et al. The authors have coined these molecules "dendrophanes", since the structures are composed of a cyclophane core modified with pendant poly(ether amide) dendrimers.[35,223−225] The structures can serve as models for globular proteins that have apolar binding sites. The employed cyclophane cores bind flat aromatic substrates or steroids (Figure 23). ^{1}H NMR and fluorescence studies in water and aqueous methanol mixtures show that the guests are exclusively bound in the receptor, and that the presence of the dendritic branches has little effect on the selectivity of binding. The only differences with nondendritic cyclophanes are the somewhat reduced exchange rate and the reduced polarity around the binding cavity, especially in the case of higher generation dendrimers.

Dendritic iron porphyrins have been employed as myoglobin models by both Aida[226,227] and by Collman and Diederich.[228] The studies show a reversible dioxygen binding and a diminished affinity for carbon monoxide in toluene due to the steric protection of the active site. In the system reported by Aida, the hydrophobic Fréchet-type dendrimers prevent the receptor from autoxidation. The polar poly(ether amide) dendrimer in the Diederich-system (Figure 18) causes the O_2-affinity to be very high. The elevated affinity is assigned to favorable hydrogen

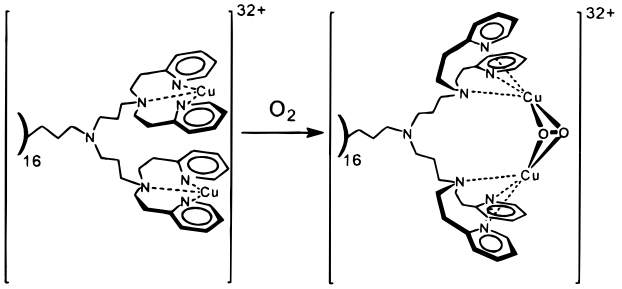

Figure 24. Proposed O_2 binding in a fourth generation poly(propylene imine) dendrimer with PY2 ligands.[229]

bonding between the terminal O-atom of the bound O_2 molecule and amide functions in the dendritic surroundings.

Klein Gebbink et al. have modified poly(propylene imine) dendrimers with bis[2-(2-pyridyl)ethyl]amine ligands (also named PY2 ligands) for Cu(I) complexation.[229] A fourth generation PY2 dendrimer has been loaded with $[Cu^I(CH_3CN)_4]ClO_4$, resulting in a dendrimer with 32 Cu(I) sites. The multi Cu(I) system is related to the natural copper protein hemocyanin (Hc), a protein that is capable of efficiently binding O_2 (Hc molecules are known to assemble into large aggregates to form a multimetal complex, which binds many molecules of O_2[230]). The presented dendritic Cu(I) complex can bind dioxygen in dichloromethane at low temperatures (−85 °C). UV/vis spectroscopy in the presence of dioxygen shows that ca. 60−70% of the copper centers are involved in binding, corresponding to 10−11 bound molecules of dioxygen per dendritic molecule (Figure 24). At room temperature, green Cu(II) complexes are formed. Therefore, it is concluded that the dendritic dioxygen complex is not stabilized in any way and that the complex may be regarded as a "hot" species, containing a large number of activated O_2 molecules.

Shinkai et al. have synthesized dendrimers with multiple aza crown ethers in the dendritic branches (Figure 25).[231,232] The crowned dendrimers can efficiently transfer alkali metal cations from water to dichloromethane phases. However, no interaction between the different aza crowns takes place, since adequate extraction of Cs^+ cations—that preferably require a sandwich complex—does not occur. Solubilization of myoglobin in DMF through interactions of multiple aza crown ethers with ammonium or carboxylate functions on the peptide is only possible when the lowest generation dendritic crown is used. Apparently, many dendrimers are required to solubilize one myoglobin molecule, and presumably, the higher generations are closed structures that do not allow adequate interactions with the protein.

Dendritic hosts with hydrogen bonding receptors have been made by Newkome et al.[233] The poly(amido ether) dendrimers contain (2,6-diacylamino)pyridine moieties that serve as donor−acceptor−donor (DAD) H-bonding units. Barbituric acid, a guest that contains two ADA arrays, is bound to the dendrimer, as evidenced by ^{1}H NMR measurements. For the higher generation dendrimers, intramolecular self-association competes with guest binding.

Cooperativity in guest binding has been reported for several modified dendrimers. A second generation

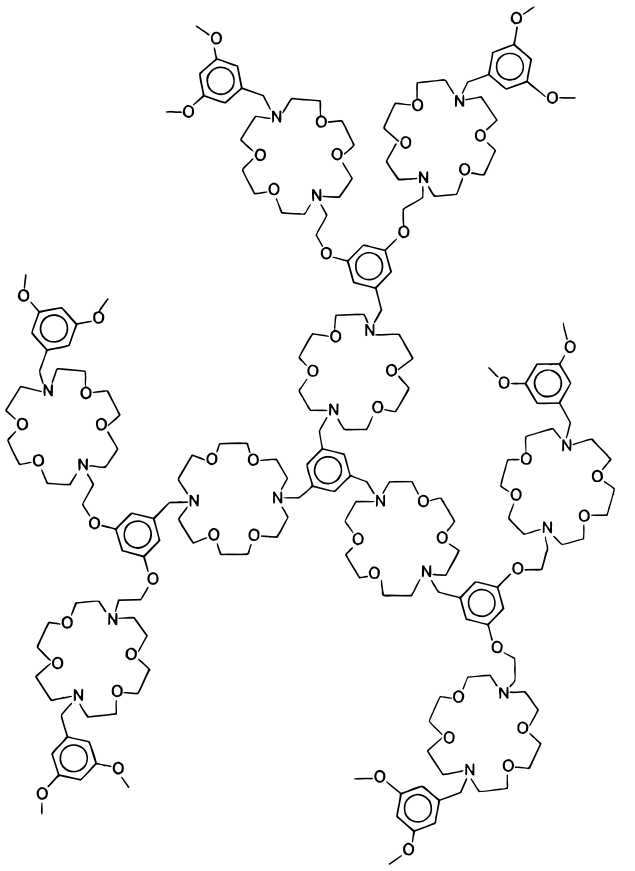

Figure 25. A dendritic azacrown ether produced by Shinkai et al.[232]

PAMAM dendrimer functionalized with boronic acid receptors and anthracene units acts as a fluorescent sensor for saccharides.[234] Saccharide complexes with a dendrimer host are more stable than those with a monofunctional host. The binding of saccharide involves two boronic acid moieties, and therefore, the observed effect can be assigned to a higher local concentration of acceptor sites in the dendrimer. Cooperativity has also been found in anion sensors using ferrocene functionalized dendritic hosts.[235]

C. Dendritic Catalysts

Catalysis seems to be a research area in which promising applications for dendrimers may be developed. Dendrimers have nanoscopic dimensions and can be molecularly dissolved. This combination of features makes dendrimers suited to close the gap between homo- and heterogeneous catalysis, or, in other words, dendrimers will combine the advantages of homo- and heterogeneous catalysts, if soluble dendrimers with defined catalytical sites are developed that can be removed from homogeneous reaction mixtures by simple separation techniques (i.e., ultrafiltration or dialysis).[236]

The previously mentioned concept of site isolation can be used to prepare catalysts with improved characteristics. The placement of the catalytic active site at a particular, isolated position—frequently, the core is used—can result in beneficial interactions between the substrate and the catalyst. The first part of this section deals with catalytic dendrimer systems

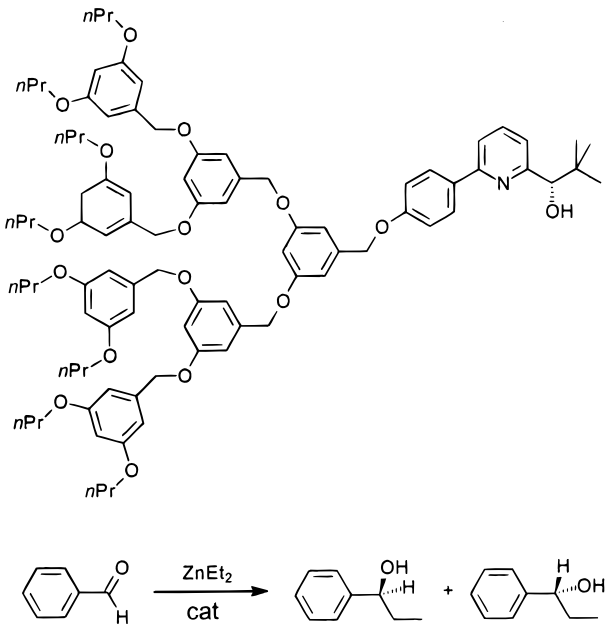

Figure 26. A third generation chiral catalyst (top) as used by Bolm et al. in the diethylzinc addition to benzaldehyde (bottom).[240]

in which the active center is located at the core. The exterior functionalities of dendrimers can be used to accommodate many catalytic sites on one molecule, possibly resulting in anomalous and favorable catalytic behavior. The second part of this section reviews dendrimers with catalytic functions positioned at the periphery.

1. Dendrimers with Catalytic Core Functionalities

Brunner has been one of the first authors to report on branched molecules containing internal catalytic sites. The resemblance of the produced structures to prosthetic groups in enzymes has prompted Brunner to introduce the word "dendrizymes" for the presented molecules.[237] The synthesized structures include a pyridine-containing Schiff-base as a Cu(I)-binding core, that is surrounded by (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol, (1*R*,2*S*)-ephedrine, or L-aspartic acid units.[238] The reported first generation dendrizymes are formed in situ by adding copper(I) triflate to the chiral compounds. For the investigated reaction, the cyclopropanation of styrene with ethyl diazoacetate, almost no asymmetric induction takes place (maximum recorded ee; 10% for the L-Asp-surrounded system). Another structure published by Brunner et al. is built up from a diphosphine core that is functionalized with menthyl-containing dendritic branches.[237] The molecules serve as chiral rhodium ligands. Unfortunately, the application of the Rh(I) catalysts in the hydrogenation of acetamidocinnamic acid does not lead to considerable enantioselectivities.[239]

Fréchet-type wedges with a chiral pyridyl alcohol at the focal point have been used by Bolm et al.[240] as catalysts in the enantioselective diethylzinc addition to benzaldehyde (Figure 26). All three generations investigated induce similar enantiomeric excesses (~85%) and yields. Evidently, the dendritic substituents have a negligible effect on the catalytic site in this example.

Suslick et al. have functionalized porphyrinatomanganese(III) chloride with first and second generation aromatic polyesters.[241] The dendritic wedges provide a certain confined environment around the metal center and, therefore, the catalyst may induce regio and shape selectivity. Indeed, the epoxidation of alkenes with iodosylbenzene displays both intramolecular and intermolecular regioselectivity. However, the selectivity of a classical picket-fence porphyrin, i.e. 5,10,15,20-tetrakis(2′,4′,6′-triphenylphenylporphyrin)), is much greater than that of the dendrimers investigated.

A dendrimer consisting of Fréchet wedges attached to triethanolamine has been used to catalyze the nitroaldol reaction (or Henry reaction).[242] In this reaction, an aldehyde is coupled to a primary nitroalkane to afford a nitro alcohol. The reaction is conducted in the presence of a base, typically a tertiary amine. The ethanolamine-based dendrimers are basic enough to catalyze the Henry reaction, although the activity of the catalyst decreases as the wedges become bulkier. Furthermore, the dendritic framework does not impose a stereoselective reaction course.

Chow et al. have synthesized a dendritic bis(oxazoline)copper(II) catalyst for the Diels−Alder reaction between cyclopentadiene and cronotyl imides.[243,244] The reaction consists of two consecutive steps. The reversible binding of the dienophile to the copper complex is followed by the rate-determining reaction between the dienophile−copper complex and the diene. The formation constant of the catalyst−dienophile complex decreases gradually with dendrimer generation. The rate of the Diels−Alder reaction, however, remains virtually constant for the first and the second generation, and displays a sudden drop for the third generation. The drop is explained by assuming backfolding of the aromatic ether containing dendritic branches, resulting in a more sterically hindered catalytic site.

Heterogeneous polymeric catalysts can elegantly be prepared by using dendritic cross-linkers. This approach combines the superior performance of open-structured low-generation dendrimers with the comfort of easily separable polymer beads. Seebach et al. have made dendrimers with TADDOL cores (TADDOL stands for α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) bearing Fréchet-type branches that have styryl end groups (Figure 27).[245] The C_2-symmetric TADDOL core is a ligand for Ti(IV) and can therefore be used for the catalysis of enantioselective nucleophilic additions to aldehydes.[246] Even after the copolymerization with styrene, high enantioselectivities for the diethylzinc addition to benzaldehyde are found. Furthermore, the Ti(IV)−TADDOL site in the dendritic polymer has a much higher turnover rate than a similar site in a linear polystyrene analogue.

The introduction of regio- or stereocontrol in a chemical reaction by using dendrimers with an interior isolated catalytic site is far from straightforward. Apparently, dendrimers are too flexible to impose consequential spatial constraints on the course of the reaction. Additionally, most published reports indicate that the use of bulky dendritic branches around a catalytic site lowers its turnover rate significantly. Progress in this field seems to require specific combinations of dendrimers and encapsulated catalytic sites, such that favorable interactions between these components and the reactants can be expected. In this fashion, more defined catalytic sites are created.

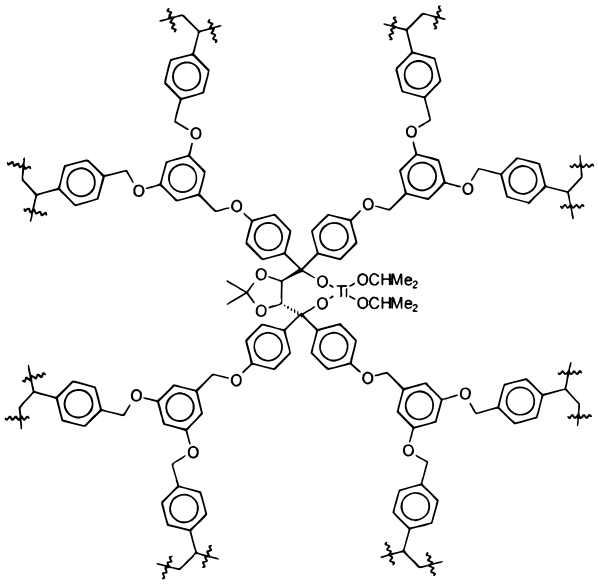

Figure 27. Catalytically active diisopropoxy-Ti-TADDOL-dendrimer embedded in cross-linked polystyrene.[245]

2. Dendrimers with Peripheral Catalytic Sites

The first dendritic catalyst with multiple catalytic sites at the periphery has been reported by Ford et al.[247] A polyether dendrimer with 36 pendant quaternary ammonium ions accelerates both the decarboxylation of 6-nitrobenzoisoxazole-3-carboxylate and the hydrolysis of *p*-nitrophenyl diphenyl phosphate in water (the latter reaction is catalyzed by *o*-iodosobenzoate). The third generation polycationic dendrimer displays an increase in catalytic activity as compared to a lower generation dendrimer with 12 pendant ammonium cations. The rate enhancement is attributed to high local concentrations of reactants that are bound to the dendritic micelles by hydrogen bonding interactions and hydrophobic interactions. Similar catalytic activities have previously been reported for other micellar catalysts[248] and for lattices[249] that have multiple quaternary ammonium sites. In relation to the lattices, the catalytic activity of the polycationic dendrimer is lower, probably due to the more hydrophobic nature of the lattices and their lower degree of hydration.

Van Koten et al. have synthesized a first generation silane dendrimer with pendant arylnickel(II) complexes.[250] Inspired by the idea of anchoring catalytic sites to soluble polymer supports, the authors have used the Ni(II)-containing dendrimer as catalyst for the Kharasch addition of tetrachloromethane to methyl methacrylate. These first organometallic modified dendritic catalysts have turnover frequencies (as observed for the first generation dendritic species), that are 30% lower than those observed for monomeric or polymer bound ana-

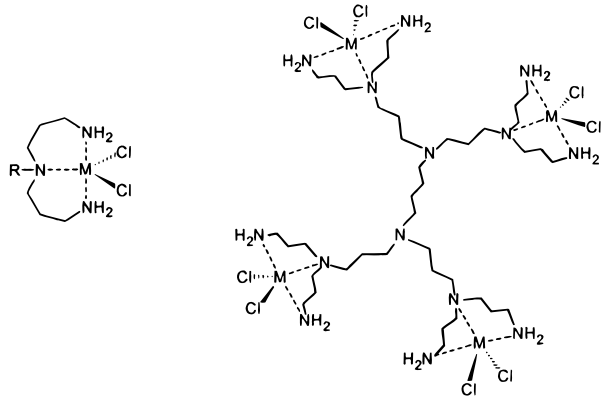

Figure 28. Tridentate complexation of the bis(3-aminopropyl)amine moiety with transition-metal chlorides. As an example, a metal complex with DAB-dendr-$(NH_2)_8$ is shown.[115]

logues.[251] However, challenging possibilities for ultrafiltration have been foreseen.

In a preliminary study on organophosphine dendrimers, dendritic wedges are described that contain five square planar Pd(II) sites, each site bearing a triphosphine ligand and an acetonitrile ligand.[252] The presented compounds catalyze the electrochemical reduction of CO_2 to CO.

Poly(propylene imine) dendrimers contain bis(3-aminopropyl)amine tridentate coordination sites that have a strong affinity for various transition metals, such as Cu(II), Zn(II), Co(II), and Ni(II), see Figure 28.[115] Indeed, UV/vis titration data show that DAB-*dendr*-$(NH_2)_x$ dendrimers bind to exactly $x/2$ units of $CuCl_2$ or $ZnCl_2$ in methanol. TEM data reveal spherical structures with the anticipated dimensions, indicating that unimolecular nanoscopic structures are formed (see Figure 11). Ford et al. have used the Cu(II)-, Co(II)-, and Zn(II)-loaded dendrimers as catalysts for the hydrolysis of *p*-nitrophenyl diphenyl phosphate in water.[253] The hydrolysis rates are highest for the copper-containing dendrimers, and for these catalysts, lower generations give higher activities at all investigated pH values. Only the fifth generation dendrimer—that contains 32 Cu(II) centers—gives a somewhat lower activity than the $Cu(II)Cl_2$ reference salt.

Following van Koten's initial approach, Reetz et al. have produced third generation poly(propylene imine) dendrimers with peripheral biphenylphosphine ligands.[254] The materials form catalysts with complexated $Pd(CH_3)_2$ or $Rh(cod)BF_4$.[255] The Pd(II)-containing dendrimer catalyzes the Heck reaction (Figure 29). A 4-fold increase in turnover number has been observed for the Pd(II)-dendrimer as compared to a mono-palladium analogue. The result has been ascribed to the higher thermal stability of the dendritic catalyst. Hydroformylation of 1-octene (Figure 29) is possible with the Rh(I) dendrimer, although a monomeric analogue shows a comparable turnover frequency. The introduced systems are promising, since the poly(propylene imine) dendrimers, the parent compounds in Reetz's syntheses, are commercially available up to the fifth generation. The bulkier nanosized catalysts derived from the higher generation poly(propylene imine) dendrimers should

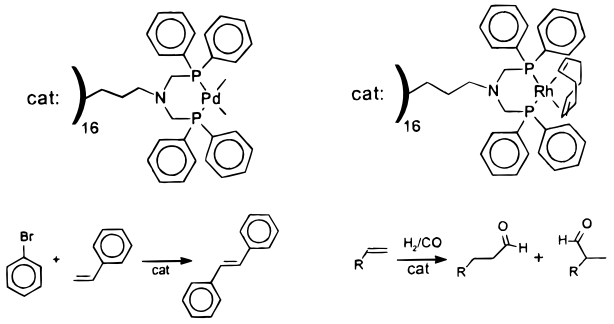

Figure 29. Catalytic dendritic diphosphane metal complexes used by Reetz et al. in the shown reactions.[254]

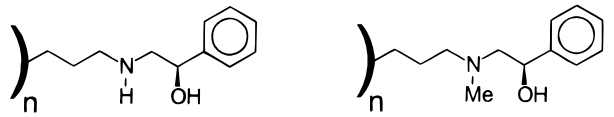

Figure 30. (*R*)-Phenyloxirane-modified poly(propylene imine) dendrimers.[88]

be large enough to be separable via membrane separation techniques.[92,213]

Marquardt and Lüning have prepared a second generation aromatic ether dendrimer with six pendant concave pyridine moieties that are able to catalyze the acylation of alcohols with diphenylketene.[256] In contrast to analogues coupled to a linear polymer or to a Merrifield resin, the dendritic systems do not show a decrease in selectivity toward primary, secondary, or tertiairy alcohols. Recovery of the catalyst by nanofiltration is possible in fair yields (70−90%).

Up to date, enantioselective catalysis using dendrimers functionalized at the exterior with catalytic sites has only received limited attention. The first and second generation PAMAM dendrimers have been modified with (1*R*,2*S*)-ephedrine moieties, thus creating a dendritic catalyst for the addition of diethylzinc to *N*-diphenylphosphinylimines.[257] The use of a bifunctional ephedrine ligand results in an addition with a high enantiomeric excess (ee = 92%), whereas the use of dendritic ligands induces substantially lower stereoselectivities (ee = 43% and 39% for the first and the second generation, respectively).

The addition of diethylzinc to benzaldehyde has been investigated with poly(propylene imine) dendrimers modified with (*R*)-phenyloxirane and their corresponding *N*-methylated derivatives (Figure 30).[88,258] When higher dendrimer generations are used, the chemical yields and the enantiomeric excesses decrease (e.g., the ee drops from 36% for the nonmethylated monofunctional compound to 7% for the nonmethylated fifth generation dendrimer). In both these examples of asymmetric catalysis, the bulkier dendrimers perform weaker. Possibly, the packed end groups at the periphery of higher generation dendrimers do not allow proper three-point interactions.

Recently Togni et al. have synthesized dendrimers containing up to eight ferrocenyl diphosphine ligands (see Figure 31).[259] The corresponding Rh complexes catalyze the hydrogenation of dimethyl itaconate in methanol in only a slightly lower enantiomeric excess than the mononuclear analogue, i.e., ee values of 98.0

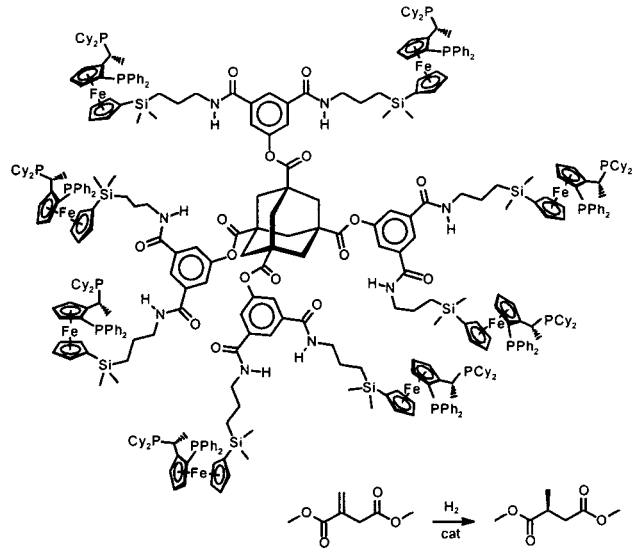

Figure 31. Dendrimer containing chiral ferrocenyl diphosphine ligands prepared by Togni et al. for the asymmetric hydrogenation of dimethyl itaconate (reaction shown in the lower right corner).[259]

and 99.0% are recorded for the octamer and the analogue (the Josiphos catalyst), respectively. The investigated dendrimers are all of low generation but can be separated from the reaction mixtures by applying a nanofiltration membrane.

Studies on catalytic dendritic systems, with the (chiral) catalytic sites positioned either in the interior or at the exterior, seem to indicate that most higher generation catalysts are less active and less enantioselective than their lower generation analogues. Beneficial properties of bulkier systems that have many peripheral catalytic sites may be found in those unique cases in which multiple interactions favor the reaction under investigation. In these cases, cooperativity effects are possible.

This field of research can be regarded as a revisitation of the research on polymer-supported catalysts, and the results found for dendrimers should therefore be compared to those found for modified linear macromolecules (in some of the studies surveyed above this is actually done). Ultimately, we expect that a more tailored design of dendritic catalysts can have a great future, especially since the scope and limitations in this field of research are sketched.

V. Conclusions

More than 10 years after the initial reports on the syntheses of dendritic macromolecules, many characteristics of these macromolecules have been revealed. The development of advanced mass spectrometry techniques (ESI-MS, MALDI-TOF MS) has enabled researchers to exactly determine the purity of dendrimers. Thus, it has been confirmed that dendrimers are synthetic macromolecules that are almost monodisperse (previously unattainable polydispersities well below 1.01 are common for dendrimers). Theoretical and experimental data have clearly shown that dendrimers are highly flexible molecules. The conformational flexibility brings about many initially unexpected properties, e.g., the end groups can be severely backfolded, the interior of a dendrimer is able to expose itself to the environment and huge distortions of the overall dendritic shape are possible under specific experimental circumstances. Finally, it has been established that higher generation dendrimers show deviating properties, not only in relation to their lower generation analogues but also when compared to linear and compositionally similar oligomers or polymers.

Today, research on dendrimers is not only focused on disclosing aberrant or special features of dendrimers but considerable effort is also invested in the development of applications for dendrimers. Dendritic molecules have been tested in supramolecular polymer chemistry, in medicinal chemistry, and in catalysis. Some studies in these fields have definitely shown that dendrimers have beneficial or even superior characteristics, although it should be noted that frequently more simple monomeric or polymeric systems are equally effective with respect to the investigated application. Nevertheless, soon dendrimers might be used in new devices, since it can be expected that highly defined molecules with precise submicron dimensions will be of relevance for those active in the emerging fields of bio- and nanotechnology. Additionally, research on dendritic materials is facilitated by the circumstance that, nowadays, a few types of thoroughly studied dendrimers are either commercially available or easily accessible. Thus, it has become possible to broaden the potential of these materials even further.

VI. Acknowledgments

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