Dendrimers in Supramolecular Chemistry: From Molecular Recognition to Self-Assembly

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Contents

I. Introduction

Dendrimers, also known as arborols, or cascade, cauliflower, or starburst polymers are attracting increasing attention because of their unique structures and properties.[1−6] These aesthetically appealing synthetic macromolecules distinguish themselves from normal polymers in two critical ways. First, they are constructed from AB_n monomers (n usually 2 or 3) rather than the standard AB monomers which produce linear polymers. Thus, they contain hyperbranched structures. Secondly, they are synthesized in an iterative fashion. The combination of these two features leads to a nonlinear, stepwise synthetic growth wherein the number of monomer units incorporated in each successive iteration roughly doubles (AB_2) or triples (AB_3) that in the previous cycle. In one of the main synthetic approaches to dendrimers (*vide infra*), each repetition cycle leads to the addition of one more layer of branches—called a *generation*—to the dendrimer framework. Therefore, the generation number of the dendrimer is equal to the number of repetition cycles performed, and may be easily determined by counting the number of branch points as one proceeds from the core to the periphery.

An appropriately activated AB_n monomer may be polymerized in a single step, but the resulting polymer will have a higher polydispersity (PD) and a lower degree of branching than an analogous dendrimer.[5,7] Such macromolecules are called *hyperbranched polymers*. Of course, the iterative synthesis of linear polymers is well known, for example, the Merrifield solid-phase peptide synthesis method,[8] but these methods are normally limited in the number of subunits that can be linked in high yield and purity. The hallmark of dendrimer synthesis is ability to synthesize in a controlled manner very high molecular weight polymers with narrower molecular weight distributions. Indeed, smaller dendrimers (e.g., MW 10−50 kDa) are often produced from short syntheses and are available as single compounds (polydispersity, PD = 1.0) not mixtures which are characterized by a Gaussian distribution of polymer molecular weights. Equally impressive is the fact that considerably larger macromolecules can be synthesized with a few extra steps. Thus, dendrimers with molecular weights over a 10^3 kDa and molecular dimensions in the 1−100 nm range have been synthesized, although unlike the smaller dendrimers these are not very homogeneous compounds.

Since the initial report on this class of molecules by Vögtle in 1978, many different structural classes of dendritic macromolecules have been reported. Indeed, the structural diversity in the repeat units is impressive, ranging from pure hydrocarbons to peptides to coordination compounds. Less than a handful of these have been routinely synthesized in gram quantity in different laboratories. Arguably the two most commonly used dendrimers, the poly(amidoamine) (PAMAM) dendrimers **1** and poly(propylene imine) dendrimers **2**, have been produced industrially and both are commercially available.

Two main synthetic strategies for synthesizing dendrimers have emerged over the past decade: the divergent and convergent approaches. In the divergent strategy, which was pioneered by Newkome and Tomalia (*vide infra*), dendrimers are built from the central core out to the periphery. In each repeat cycle some number of reactive groups, n, on the dendrimer periphery react with n monomer units to add a new layer or generation to the dendrimer. In the next repeat cycle $2n$ or $3n$ reactive sites will be available

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Fanwen Zeng was born in Fujian, China, and received his B.S. degree from Nanjing University in 1987 and an M.S. from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, in 1990. He worked in the Fuzhou Institute of Chemical Industry before he came to the United States in 1992 to continue his graduate studies. He attended the University of Illinois at Urbana—Champaign where he received his Ph.D. in February of 1997 under the guidance of Professor Steven C. Zimmerman. After a temporary postdoctoral position in the same group, he will join Professor Peter G. Schultz's research group as a postdoctoral research associate. Dr. Fanwen Zeng's research interests range from bioorganic chemistry to supramolecular chemistry.

Steven C. Zimmerman was born in Chicago in 1957, the second son of the world-renowned organic chemist, Howard E. Zimmerman. He attended public schools in Madison and then the University of Wisconsin, where he received a B.S. degree in 1979 working for Hans Reich. In 1983 he received a Ph.D. at Columbia University in New York City where he worked with Ronald Breslow on pyridoxamine enzyme analogs. After an NSF-NATO Postdoctoral Fellowship at the University of Cambridge with Sir Alan R. Battersby, he joined the faculty at the University of Illinois (1985). He was promoted to Full Professor in 1994. Professor Zimmerman has been the recipient of an American Cancer Society Junior Faculty Award (1986–1989), NSF Presidential Young Investigator Award (1990), Camille and Henry Dreyfus Teacher–Scholar Award (1989–1992), Alfred P. Sloan Fellowship (1992–1993), Buck-Whitney Award from the Eastern New York Section of American Chemical Society (1995), and an Arthur C. Cope Scholar Award from the American Chemical Society (1997). He has also won teaching awards at the University of Illinois. His research interests are in the area of molecular recognition, self-assembly, and catalysis using both small molecules and dendrimers. He currently resides in a suburb of Champaign with his wife Sharon, and their two daughters, Arielle and Elena.

depending on whether the monomer unit's branch multiplicity is 2 or 3 (i.e., AB_2 vs AB_3 monomer). Thus, the number of coupling reactions increases with each successive generation. Early examples of divergent dendrimer synthesis come from the work of Denkewalter,[9] Vögtle,[10] Meijer,[11] Mülhaupt,[12] Tomalia,[13] and Newkome.[14]

Classical examples of the convergent approach to dendrimer synthesis can be found in the work of Fréchet,[15] Miller,[16] and Moore.[17,18] In contrast to the divergent strategy, this approach builds the dendrimer from the periphery toward the central core. Thus, the initial reaction sites ultimately reside on the periphery of dendrimer, while the reactions take place at the reactive core (called the *focal point*). Another key difference is that the number of coupling reactions needed to add each new generation—usually 2 or 3, depending on branch multiplicity—is constant throughout the synthesis making defective products easier to separate. For this reason, dendrimers prepared by the convergent strategy are generally considered to be more homogeneous (often monodisperse) than those prepared by divergent approach, because defects begin to accumulate at higher generation numbers when a large number of coupling or condensation reactions have to occur on a congested dendrimer surface. Throughout this review, dendrimers prepared by the divergent approach are drawn as monomolecular species, but it should be understood that they will contain a statistical array of defects. On the other hand, the convergent strategy is often limited to dendrimers of lower generation numbers. The problem is that the core becomes so congested that the reaction yields drop precipitously. The limits of both approaches have yet to be firmly established, but at this time one can generalize and say that the convergent approach produces dendrimers with less than eight generations, whereas divergent syntheses can make dendrimers with as many as 10 generations. Both the commercially available PAMAM and poly(propyleneimine) dendrimers are made by the divergent method.

The synthetic availability of dendrimers in a wide range of sizes (i.e., generations) combined with their unique structure, makes them versatile building blocks for a wide range of applications. This review focuses on the use of dendrimers in supramolecular chemistry; in particular, the use of dendrimers in (1) molecular recognition, and (2) self-assembling systems. Molecular recognition and self-assembly are two important areas in *supramolecular chemistry*, which Lehn has broadly defined as the chemistry beyond the molecule.[19−21] For a more detailed definition of the terms in this area, interested readers are referred to excellent review articles.[22,23] In the following discussion we use the terms molecular recognition and self-assembly rather loosely. Indeed at times the distinction between the two is rather arbitrary. In general, the molecular recognition sections will cover the selective binding of a guest molecule(s) by a dendritic host, while the latter concentrates more on the noncovalent self-assembly or self-organization of monomeric units into larger structures, including aggregates, phases, and mono- and multilayers.

II. Dendrimers in Molecular Recognition

Whereas linear polymers often adopt random-coil structures, the three dimensional structure of dendrimers is better defined in possessing a central core with branches that more or less radiate out to a peripheral surface. Dendrimers of lower generation number tend to exist in relatively open forms. However, as the successive layers are added, and often at the fifth generation, dendrimers adopt a spherical three-dimensional structure which very loosely re-

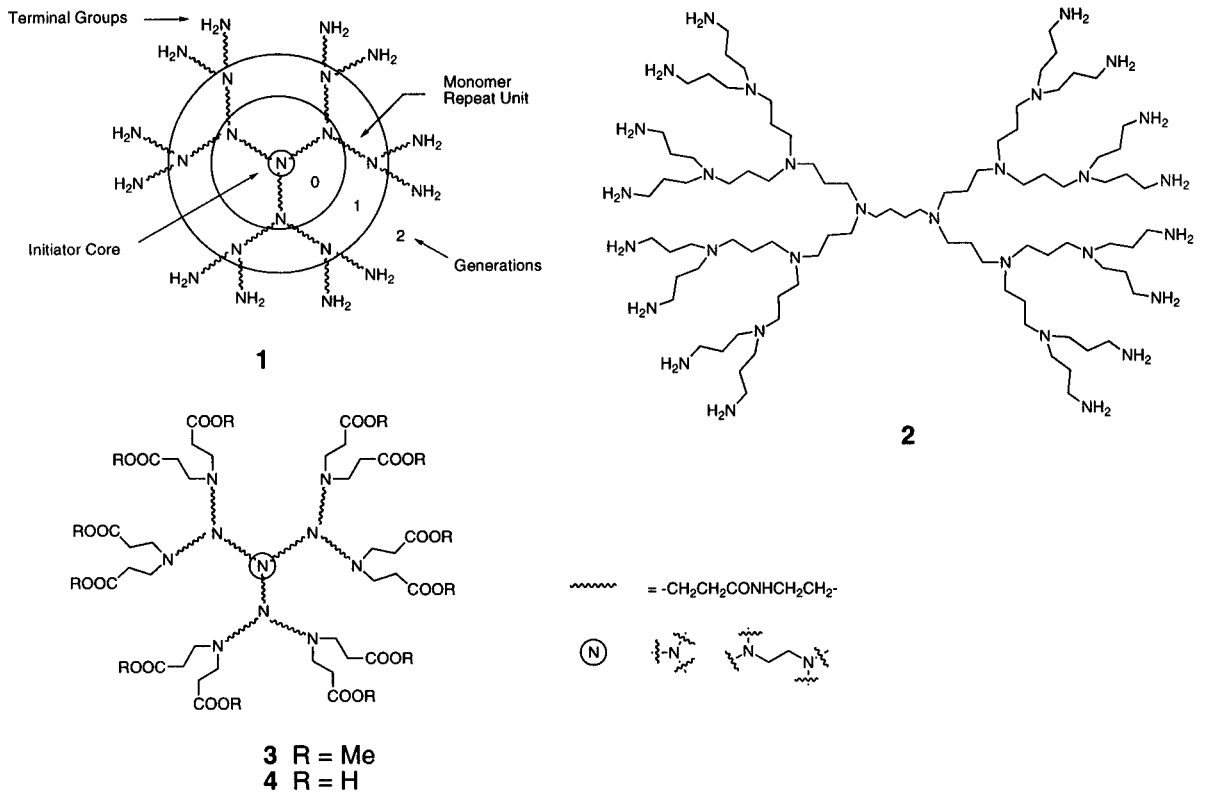

Figure 1. Commercially available PAMAM dendrimers and poly(propylene imine) dendrimers.

sembles that of a globular protein. This gross structural similarity suggests that dendrimers might function in many of the same ways as their natural counterparts. Indeed, host−guest chemistry can take place either in the interior or on the periphery of the dendrimer, just as the molecular recognition exhibited by proteins may occur deep within the biopolymer or at its surface. Binding groups on the interior of the dendrimer have been called *endo-receptors*, whereas peripheral, or end groups involved in complexation chemistry are called *exo-receptors*.[1]

A. Complexation in Dendrimer "Interiors"

As early as in 1982, Maciejewski[24] proposed the possibility of constructing a dendritic "core-shell molecule" to "topologically" entrap small molecules. Theoretical calculations on Tomalia's poly(amidoamine) (PAMAM) dendrimers (e.g., **1**, Figure 1) by de Gennes and Hervet[25] also predicted that the generation growth of a dendrimer will reach a limit in which the space on the surface becomes too highly congested to allow further growth. Computational studies on the PAMAM dendrimers by Goddard and Tomalia[26] indicated that above the fourth generation, dendrimers adopt a globular structure with large hollow cavities inside. There remains considerable uncertainty about detailed structure of dendrimers, in particular whether they are fully extended or folded back and whether the density is highest at the surface or the core.[27,28] Nonetheless these calculations suggested the possibility of binding or even entrapping small molecules in the interior of dendrimers and provided significant impetus for research in this area.

1. Hydrophobic Interior Binding

The ability of PAMAM dendrimers **3** (Figure 1) terminated with methyl ester groups to complex 2,4-dichlorophenoxyacetic acid and acetylsalicylic acid was investigated by Goddard and Tomalia[26] by measuring the guest C-13 spin−lattice relaxation times (T_1). The T_1 values of these guest molecules in chloroform-*d* changed in the presence of dendrimer, and these, in turn, were highly dependent on the generation number. As the generation number increased from 0.5 to 3.5 (the carboxy-terminated layer is considered a half-generation), the T_1 values decreased, but remained constant as the generation number was further increased. The transition to constant T_1 values occurred at the point where the molecular simulations suggested that the dendrimers become spherical with more compact surfaces and hollow cavities inside. Thus, the results were interpreted in terms of a more effective interior complexation by the larger dendrimers. The authors noted that the guest molecules need not be fully encapsulated, but rather might congregate at the dendrimer surface.

When the surface of an apolar dendrimer contains charged functional groups, its gross structure resembles that of a micelle.[14] Newkome and co-workers[29] prepared "unimolecular micelle" **5** (Figure 2) with a completely hydrophobic (alkane) interior. It was expected that these types of compounds would exhibit concentration-independent micellar properties, in contrast to normal micelles which possess a characteristic critical micelle concentration (cmc) below which the micelle dissociates and ceases to function. Dynamic light scattering studies indicated that micellanoate **5** was monomeric in aqueous solution over a broad concentration range. Its micelle-like behavior was established with several hydrophobic probes (e.g., diphenylhexatriene and phenol blue) and a variety of techniques including fluorimetry, fluorescence microscopy, and UV−visible spectroscopy.

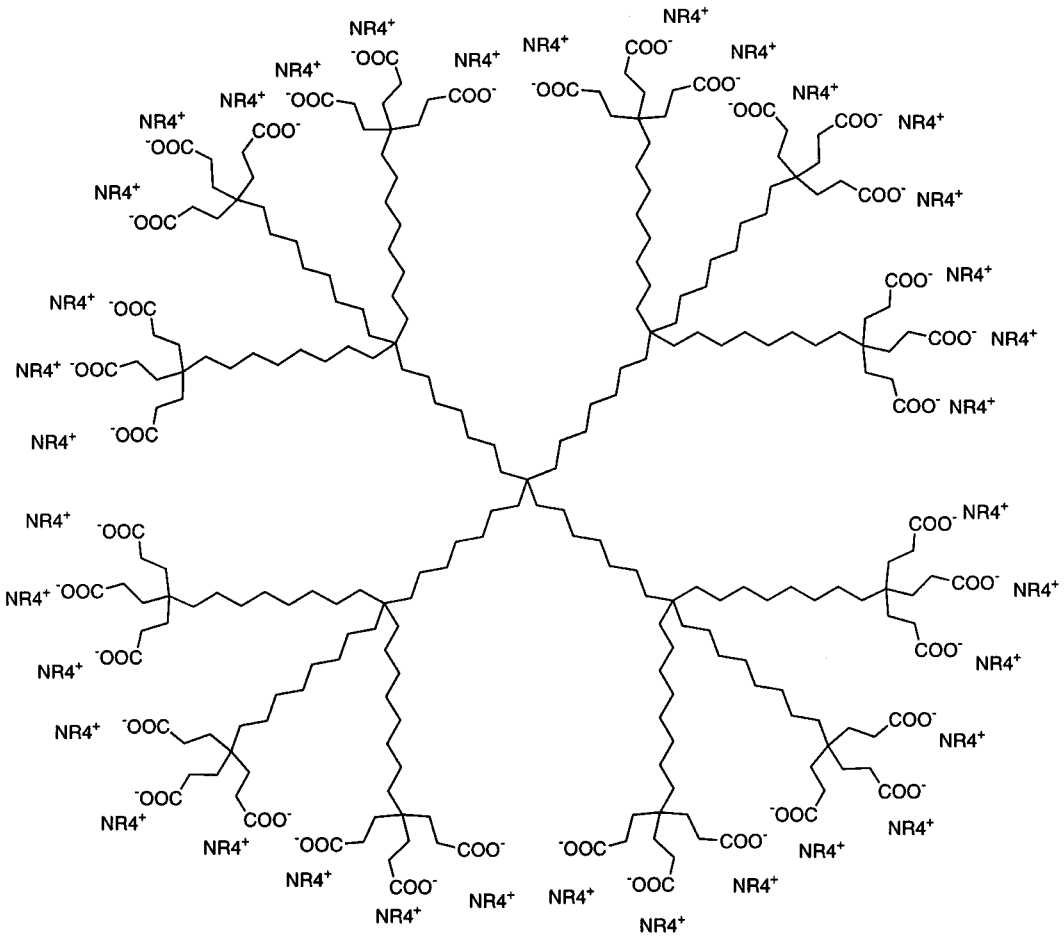

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Figure 2. A unimolecular micelle prepared by Newkome and co-workers.

Fréchet[30] reported a unimolecular micelle based on his polyaryl ether dendrimers. The 32 carboxylate groups on the surface of dendrimer **6** make it highly soluble in basic aqueous solution (Figure 3). The solubilization of apolar organic molecules by this dendrimer was investigated by mixing the guest and dendritic host in water at elevated temperature and with sonication. A linear relationship between the amount of solubilized pyrene and the dendrimer concentration was observed. The solubilization efficiency of **6** was found to be comparable to that of micelles formed from sodium dodecyl sulfate (SDS), although the former retained its ability to solubilize guest molecules at concentrations as low as 5×10^{-7} mol dm^{-3}, whereas SDS worked only above its cmc (8.1×10^{-3} mol dm^{-3}). On average about 0.45 molecules of pyrene were dissolved by each dendrimer. This value was increased to 1.9 pyrene molecules per dendrimer by the addition of sodium chloride, which may cause the elimination of some water from the interior of dendrimer.

A possible $\pi-\pi$ contribution to the complexation was suggested by a study using other aromatic guests. Almost twice as much of the highly electron-deficient 2,3,6,7-tetranitrofluorenone was solubilized by the dendrimer as pyrene, while the solubility of 1,4-diaminoanthraquinone was only half that of pyrene. Finally the use of dendrimers as recyclable solubilization agents was demonstrated by precipitating the pyrene−dendrimer complex with acetic acid, dissolving the precipitate in tetrahydrofuran (THF), and extracting the resultant solution with an aqueous solution of base to separate host from guest.

The use of hyperbranched polymers as unimolecular micelles by Kim and Webster actually predates the dendrimer studies.[31] The hyperbranched polymer used was obtained by polymerization of (3,5-dibromophenyl)boronic acid under the Suzuki coupling conditions, and subsequent treatment with *n*-butyllithium followed by quenching with carbon dioxide (~70% conversion of bromide to acid). This poly(phenylenecarboxylic acid) was converted to its lithium salt, which was used for the complexation studies. The ability of the polymer to bind *p*-toluidine in basic aqueous solution was evaluated by ^{1}H NMR titration methods. The upfield chemical shift of all *p*-toluidine protons indicated penetration of the guest into the aromatic "walls" of the dendritic polymer, presumably through $\pi-\pi$ interactions. Assuming formation of a 1:1 complex and a limiting shift for the guest, an association constant of 590 M^{-1} was calculated for the complex.

Meijer and co-workers[32] reported the synthesis of a series of inverted unimolecular dendritic micelles by reacting the amino end groups of poly(propylene imine) dendrimers **2** with aliphatic acid chlorides. The resultant dendritic macromolecules have a hydrophobic shell and a hydrophilic interior. ^{1}H NMR and dynamic light scattering studies suggested that at higher generation numbers ($n \geq 4$), these unimo-

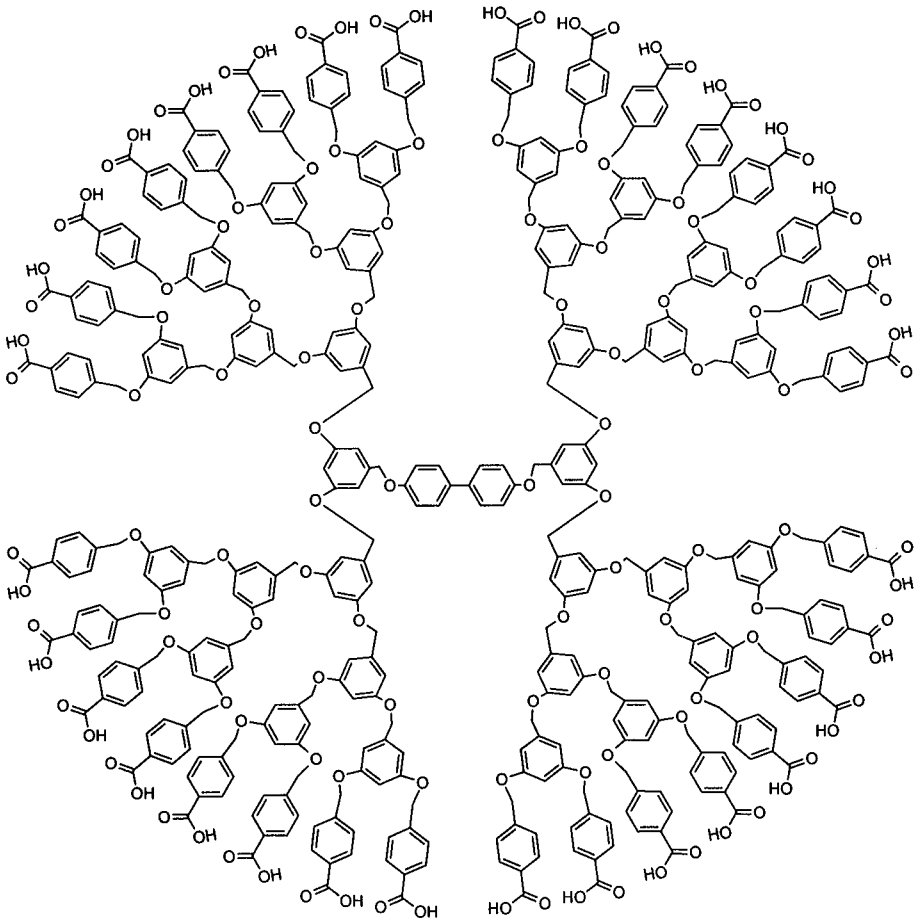

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Figure 3. A water-soluble polyaryl ether dendrimer reported by Fréchet.

lecular micelles have a compact surface and do not aggregate. The binding of hydrophilic molecules such as Bengal Rose in the dendritic interior occurred in hexane solution, whereas the dye was released by adding toluene, but not water. In contrast to normal micelles, these inverted unimolecular micelles make it possible to solubilize polar molecules in apolar solvents through the shell separation created by the dendritic framework.

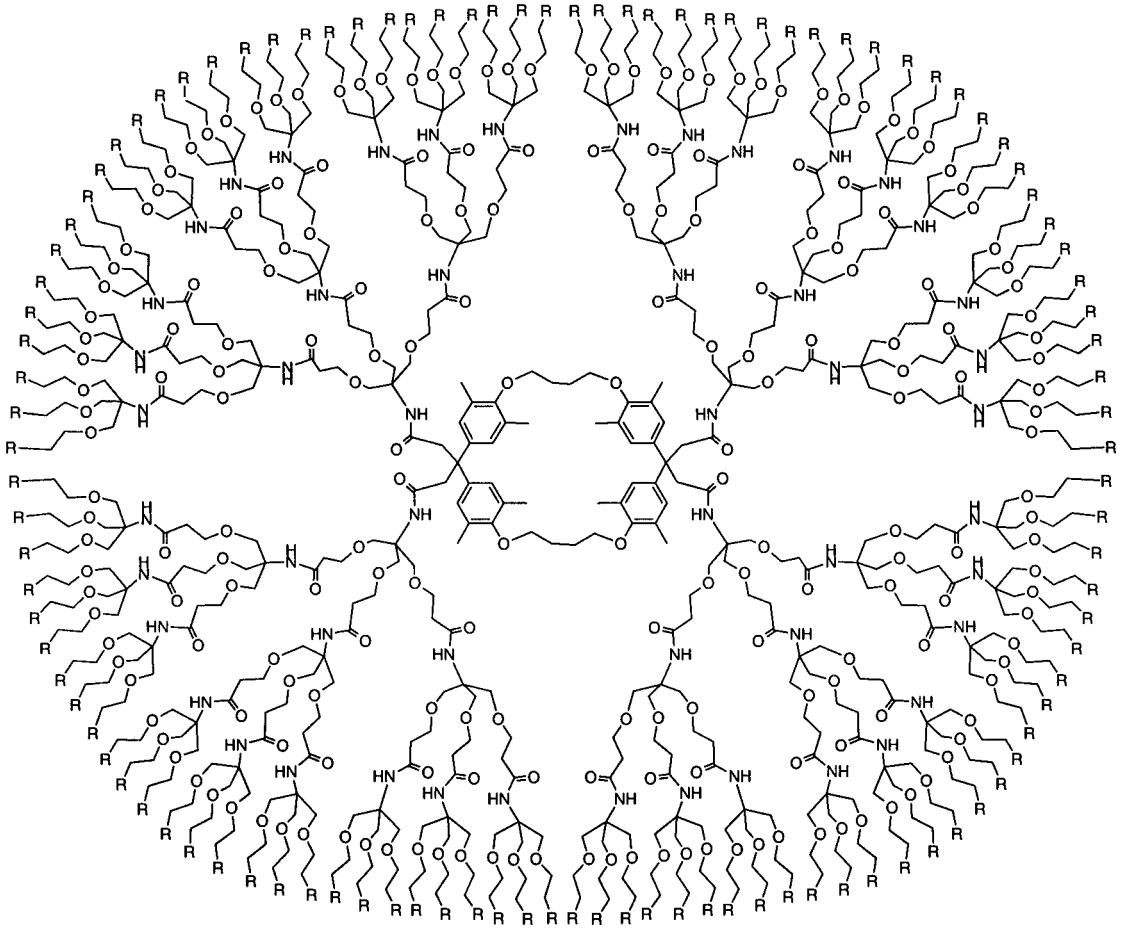
The examples thus far involve a nonspecific apolar binding of guest molecules inside the dendrimer. The location of the guest is not controlled nor is it known. The design of dendrimers with well-defined and localized cavities or binding sites can be realized by the specific incorporation of a hydrophobic core, hydrogen-bonding moiety, or a metal ion coordination site.

Diederich and co-workers[33] recently described a new class of dendritic host molecules which they call dendrophanes. Dendrophanes (e.g., **7**) contain a diphenylmethane-based cyclophane of the type extensively studied by Diederich, linked to four water-soluble dendrons previously reported by Newkome[34] (Figure 4). These dendrophanes were designed as models of globular proteins. Their complexation chemistry in aqueous solution was evaluated by spectrofluorimetric or ^{1}H NMR titrations using various aromatic compounds. The upfield shifts of proton signals on both the cyclophane moiety and the aromatic guest molecules upon complexation suggested binding inside the cavity of the cyclophane, rather than a nonspecific apolar interaction with the dendritic substituents.

The decreasing values of the emission λ_{max} of fluorescent probes further suggested a reduced polar environment in the binding cavity as the generation number of the dendritic substituents increased. However, the binding constants did not change significantly with generation number. This result suggests a relatively open structure for the dendritic host even at the third generation (i.e., **7**). A similar conclusion was reached in studies of a different dendrophane which contained a larger cyclophanic core capable of binding steroids.[35] One possible explanation is that the surface of the higher generation host may be compact but highly disordered, allowing the diffusion of guests into the dendrimer cavity, although at a somewhat reduced rate.

2. Interior Hydrogen Bonding

Hydrogen-bonding interactions are ubiquitous in the biological systems, and the past decade has seen a significant interest in synthetic hosts that complex guests by hydrogen bonding. As intermolecular interactions go, hydrogen bonding is both a directional and strong binding force, at least in apolar media. Because of these advantages, and the considerable body of data available from published host−guest studies, hydrogen-bonding sites have been incorporated into dendrimer interiors. Key questions to be answered are how the dendrimer affects the strength and kinetics of the complexation. Con-



7a R = COOH
7b R = COOMe

Figure 4. Dendrophanes reported by Diederich and co-workers.

versely, the binding ability of the external guest might be useful as a probe of the nanoenvironment within dendrimers. For example, it is well known that the strength of hydrogen-bonding interactions is highly sensitive to the polarity of solvent.

Newkome and co-workers[36] described a series of dendritic hosts (e.g., **8**, Figure 5) containing (diacylamino)pyridine hydrogen-bonding units. These hydrogen-bonding units contain a donor−acceptor−donor (DAD) hydrogen-bonding motif that has been widely used to bind complementary guests such as imides or barbituric acids. In **8** two such units may cooperate to bind the two ADA sites on barbituric acid. The host−guest interactions were evaluated by ^{1}H NMR titration. For higher generation number hosts, the host−guest interaction was complicated by the potential self-association of the host molecules and the binding of guest molecules at other hydrogen-binding sites within the host.

3. Interior Metal–Ligand Coordination

Metal−ligand interactions within coordination complexes can be as strong and robust as a typical covalent bond or relatively weak and kinetically labile. More often than not coordination geometries are well-defined and there is a selectivity inherent in the metal−ligand interaction. These features have led to the wide-spread use of metal coordination in host−guest systems and for driving self-assembly both in solution and in the solid state.[37] In this section, recent efforts to synthesize and study dendrimers with metal complexes in their interiors will be discussed. Related examples of metallodendrimer coordination chemistry will be described in the self-assembly sections.

Dendrimers with metal complexes on their interiors have been assembled either by connecting a metal ligand to the focal point of a dendron, followed by metal complexation[38] or by synthetically linking dendrons to a preformed metal complex, e.g., zinc porphyrin. As an example of the former approach, Newkome and co-workers[39] recently synthesized dendritic "lock and key" complexes such as **9** (Figure 6) based on the well-studied ruthenium−terpyridine coordination chemistry. First and second generation dendritic terpyridines were reacted with $RuCl_3$ and used as the metallo "key". Similarly, first through fourth generation dendritic terpyridines were constructed and used as the "lock". The binding of the key and the lock led to the formation of five different dendritic complexes. These complexes were characterized by NMR, UV spectroscopy, and combustion analysis as well as by electrochemical techniques. Interestingly, the cyclic voltammetry exhibited irreversible redox chemistry as the generation number increased. Similar results were reported by Chow and co-workers[40] in the study of dendritic homodimers such as **10** (Figure 7). These complexes,

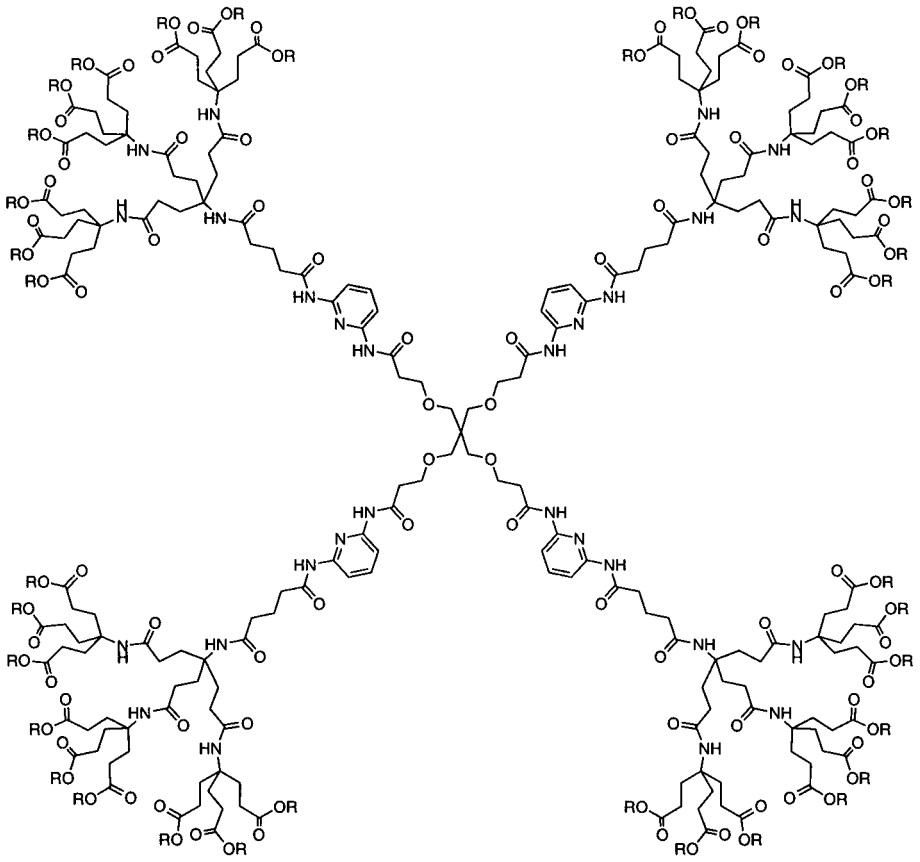


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Figure 5. Newkome's dendritic host with multiple hydrogen-bonding sites.

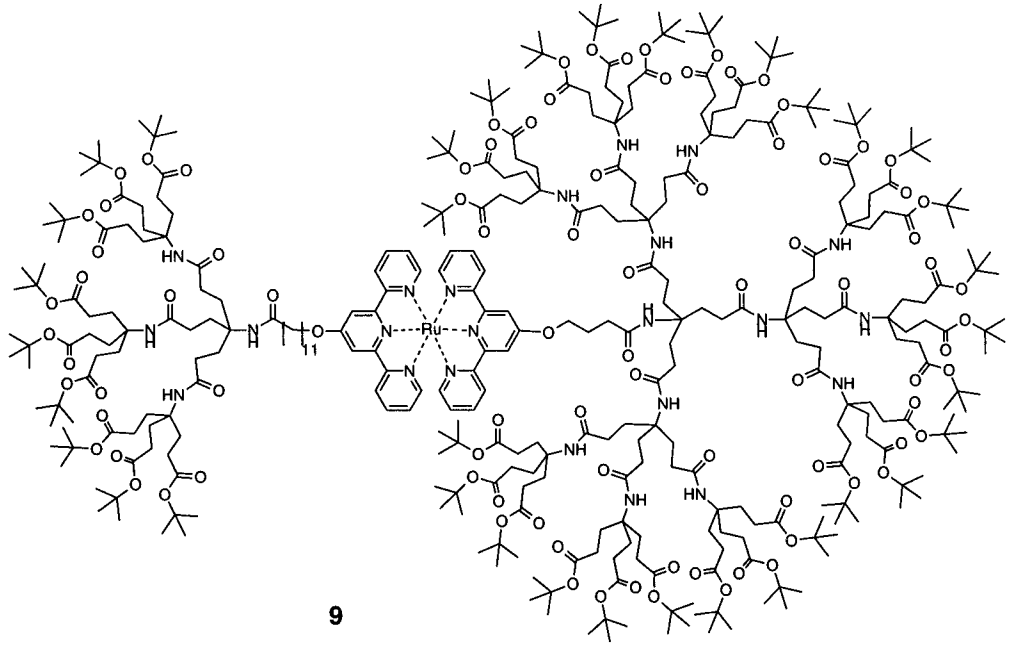

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Figure 6. Dendritic ruthenium complex reported by Newkome and co-workers.

formed from bis(terpyridine)iron(II) complexation, showed decreasing reversibility at the third generation polyether dendrimer. The Newkome and Chow observations were rationalized, respectively, by the destabilization of redox products due to steric hindrance or to an ineffective electron transfer due to the isolation of redox center from electrode surface by the dendritic shell.

Several dendrimers with metalloporphyrin cores were prepared to investigate the effect of the dendritic framework on the electrochemical or photochemical properties of the metalloporphyrin. For example, Diederich and co-workers[41] synthesized zinc porphyrin dendrimers such as **11** (Figure 8) through a divergent strategy that employed Newkome's amino triester building blocks as the dendritic shell (*vide*

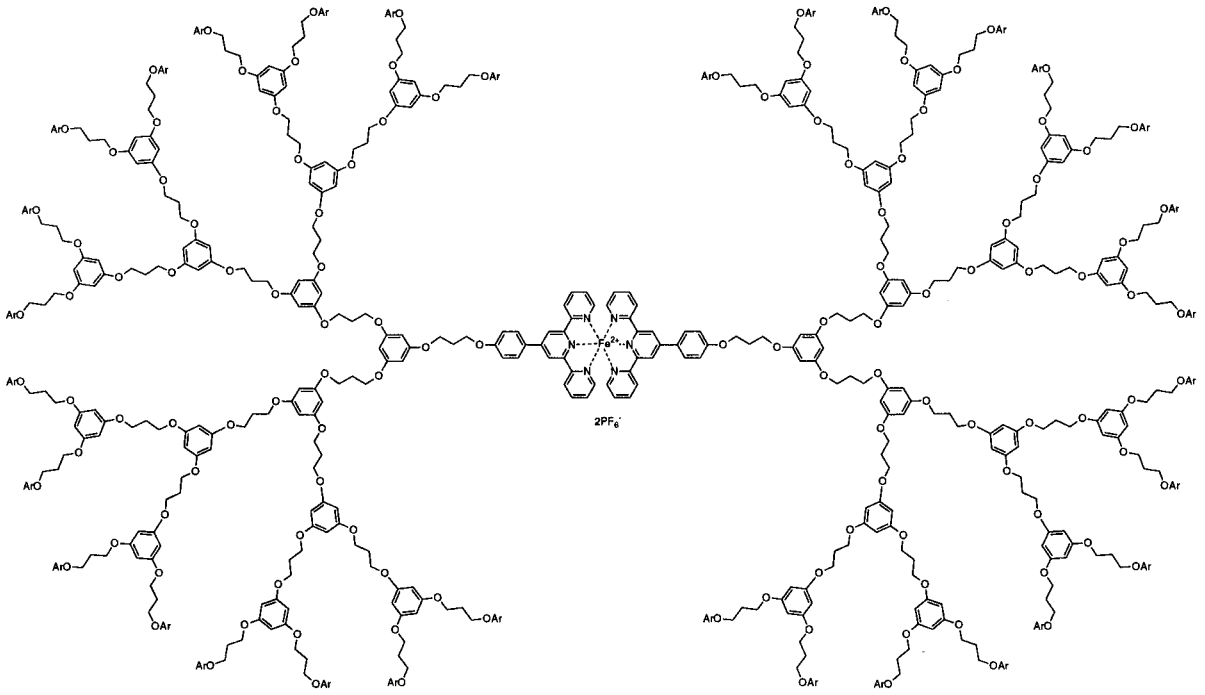

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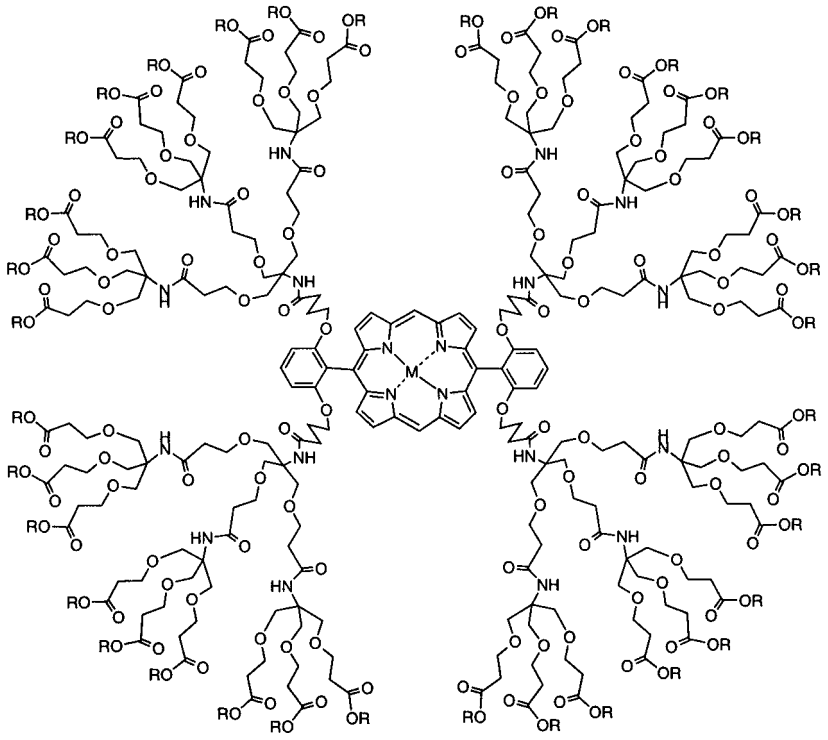
Figure 7. Dendritic iron(II) complex synthesized by Chow and co-workers.



11 M = Zn (II), R = CH_3 -
12 M = Fe (III) or Fe(II),R = $(CH_2CH_2O)_3$ CH_3 -

Figure 8. Dendritic metalloporphyrins reported by Diederich and co-workers.

supra). These novel compounds were designed to be models for electron-transfer proteins such as cytochrome *c*, in which the globular polypeptide is known to affect the metalloporphyrin redox potential. Indeed, the redox potentials of these dendritic porphyrins, determined by cyclic voltammetry (CV), were clearly affected by the dendritic substituents. As the generation number increased, the first reduction potential became more negative while the oxidation potential became less positive. This observation was rationalized by a through-space interaction between the electron-rich dendritic shell and metalloporphyrin. At higher generation numbers, the favorable interaction between the electron-rich dendrimer and the positively charged metalloporphyrin oxidation product makes the oxidation process easier, whereas the reduction product is harder to form at the higher generations.

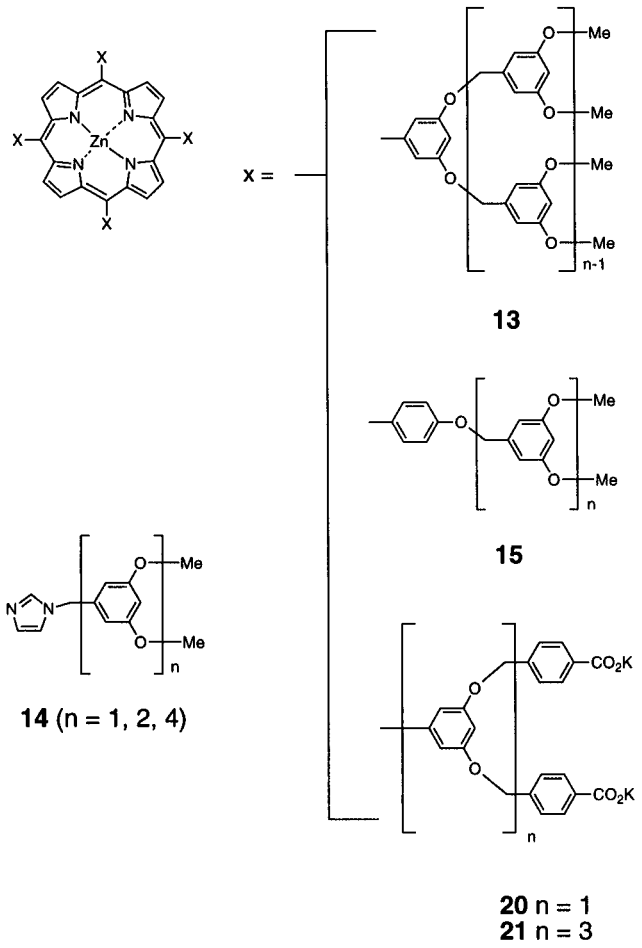


Figure 9. Dendritic metalloporphyrins and dendritic imidazoles reported by Aida and co-workers.

Diederich, Gross, and co-workers[42] synthesized similar dendritic iron(II) porphyrin complexes, e.g., **12**, but with triethylene glycol monomethyl ether groups on the surface which make them soluble in solvents whose polarity ranges from water to *p*-xylene. From the first generation to the second generation, cyclic voltammetry indicated a remarkable 0.42 V positive shift in the Fe^{III}/Fe^{II} reduction potential in water, while the change was relatively small (~0.08 V) in methylene chloride. The large potential shift in water is comparable to the difference observed between cytochrome *c* and a cytochrome *c* heme model compound possessing a more open structure.

An important event that controls the chemistry of heme-containing proteins is the coordination of a histidine residue to the metal center. Aida and co-workers[43] recently reported the attachment of a series of Fréchet dendrons both to the meta phenyl groups of a tetraphenyl zinc porphyrin and to N-1 of imidazole (see **13**−**15**, Figure 9). The UV spectra of the dendritic porphyrins were measured in both dichloromethane and 1,3-dimethoxybenzene. The wavelengths of the Soret bands were used as a measure of the microenvironment of the zinc porphyrin, a strategy which is similar to Fréchet and co-workers[44] use of a 4-aminonitrobenzene moiety as a solvatochromic probe at the dendrimer core. At the fifth generation, the λ_{max} of the Soret band (ca. $\lambda_{max} = 0.7$ nm) became solvent independent, suggesting that the zinc porphyrin core was almost completely surrounded by its dendritic shell.

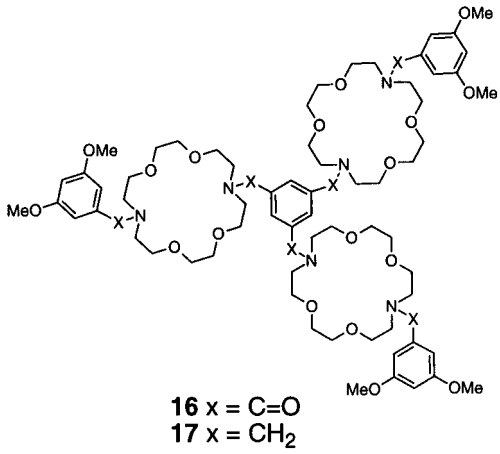


Figure 10. Crown ether-based dendrimers reported by Shinkai and co-workers.

Aida further studied the ability of first, second, and fourth generation dendritic imidazoles **14** to coordinate to dendritic porphyrin **13**. The results indicated a 1:1 stoichiometry between the host and guest with binding constants decreasing significantly as the generation number of the porphyrin increased from 4 to 5. Despite the loss of binding energy, it is remarkable that the fourth generation imidazole is able to bind the fifth generation dendritic porphyrin at all given the high degree of dendrimer interpenetration that must occur.

Shinkai and co-workers recently reported the incorporation of multiple azacrown ethers within the arms of a dendrimer and the ability of these "crowned arborols" to extract alkali metal ions from water to methylene chloride.[45] Reduction of the amide-linked crown ether dendrimers such as **16** afforded tertiary amine dendrimers such as **17** (Figure 10) which exhibited dramatically increased extraction capabilities. Surprisingly, these dendrimers extracted metal ions in a generation-independent manner and they further failed to efficiently extract Cs^+ through sandwich complexation. Both results indicate that the crown ethers inside the dendrimers function noncooperatively. The use of these same dendrimers to solubilize peptides in organic solvents through peptide−NH_3^+−crown ether interactions was also described. Only the first generation dendrimer with tertiary amine linkage was able to markedly increase the solubility of myoglobin in *N*,*N*-dimethylformamide (DMF). The solubility increase presumably occurs because this open and lipophilic dendrimer binds at the protein surface.

4. Physical Encapsulation

Meijer and co-workers[46−49] have taken the binding discussed above one step further by capping the end groups of the dendrimer host−guest complex thereby permanently encapsulating the guest molecule. The physical encapsulation was achieved in the final step of the dendrimer synthesis by reacting the terminal amino groups of a poly(propylene imine) dendrimer−small molecule complex with various activated Boc- or Fmoc-protected amino acids. In the case of the fifth generation dendrimer, NMR relaxation measurements indicated a low mobility of the surface groups, which suggests that they are sterically close packed and possibly hydrogen bonded. After exten-

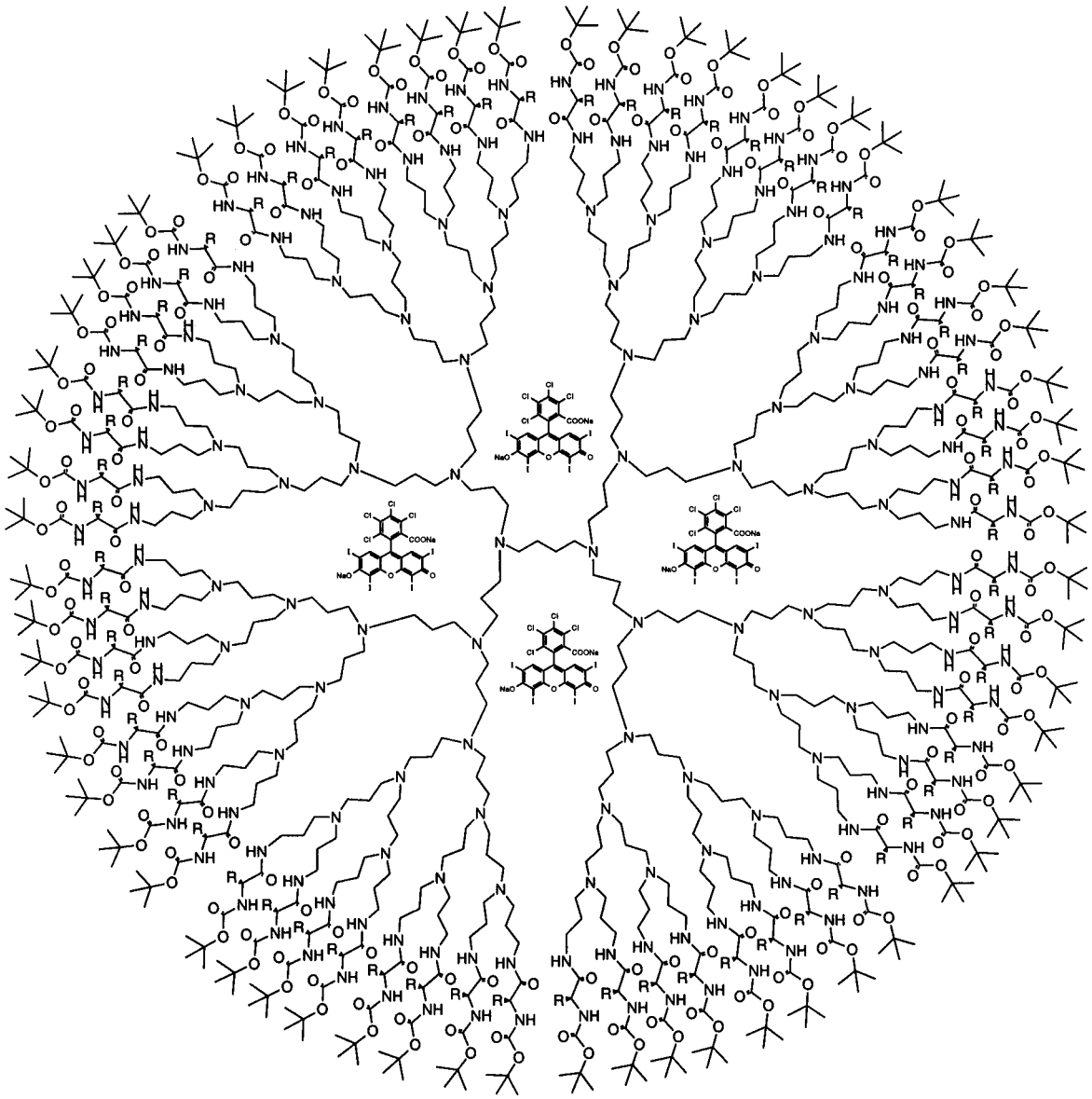


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Figure 11. Meijer's dendritic box with Bengal Rose molecules inside.

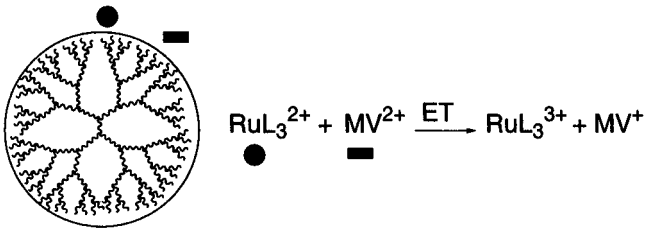
sive dialysis, spectroscopic evidence, including EPR, UV, and fluorescence studies, indicated the presence of guest molecules such as tetracyanoquinodimethane (TCNQ) and Bengal Rose within dendritic "box" **18** (Figure 11). The second generation dendrimer showed no significant encapsulation presumably due to its relatively open structure. In contrast to other molecular containers such as carcerands, macromolecular box **18** has enough space to simultaneously trap up to four molecules of Bengal Rose and 8−10 molecules of 4-nitrobenzoic acid. The potential applications of this method include its use as a drug delivery vessel, a fluorescence marker, as well as for examining the chemical and physical behavior of isolated molecules.

Meijer and co-workers[50] further demonstrated the shape-selective release of entrapped guests from the dendritic "box" by a two-step chemical approach. For example, a dendritic box containing the small EPR probe 2,2,3,4,5,5-hexamethyl-3-imidazolinium-1-yloxy methyl sulfate (**19**) and the comparatively larger dye Bengal Rose, was deprotected with formic acid to remove the surface Boc groups. Subsequent dialysis afforded a "perforated" dendrimer, in which all the small guests **19** were completely removed. Further removal of the surface amide groups by refluxing the "perforated" dendrimer with 2 N HCl resulted in the release of the dye molecules and about 50−70% of the original poly(propylene imine) dendrimer was recovered. Photochemical and enzymatic methods were suggested as alternative ways to selectively remove the dendrimer shell, approaches that offer certain advantages over the harsh chemical method used in this work. The enzymatic strategy, in particular, may be important in the development of selective drug delivery devices.

B. Complexation at Dendrimer "Surfaces"

1. Electrostatic Interactions

Molecular recognition events at dendrimer surfaces are distinguished by the large number of often identical end groups presented by the dendritic host. When these groups are charged, the surface may



4: Carboxylate-terminated PAMAM dendrimer

Figure 12. Binding and photoinduced electron transfer on the surface of PAMAM dendrimer.

behave as a polyelectrolyte and is likely to electrostatically attract oppositely charged molecules. Indeed, Turro and Tomalia[51−55] first utilized this interaction to investigate the micellar properties of PAMAM dendrimers. Medium-sized carboxylate-terminated PAMAM dendrimers, represented by **4**, were shown to facilitate the photoinduced electron-transfer (ET) reaction from tris(2,2′-bipyridine)ruthenium(II) ($Ru(bpy)_3^{2+}$) to 1,1′-dimethyl-4,4′-bipyridinium ion (MV^{2+}). This observation was rationalized by the simultaneous electrostatic binding of both $Ru(bpy)_3^{2+}$ and MV^{2+} on the dendrimer surface, as shown in Figure 12. This assumption was further supported by the observation that the Stern−Volmer constants significantly decreased upon addition of either a large amount of sodium chloride or a negatively charged quencher such as hexacyanoferrate(II) ion ($Fe(CN)_6^{4-}$). The longer emission lifetime of the $Ru(bpy)_3^{2+}$ excited state in the air-equilibrated solution also indicates the binding and protection of the excited state on the dendrimer surface.

Other examples of electrostatic interactions between polyelectrolyte dendrimers and charged species include the aggregation of methylene blue on the dendrimer surface[56] and the binding of EPR probes such as copper complexes and nitroxide cation radicals.[57,58] Recently, Aida and co-workers[59] modified a zinc porphyrin with first and third generation polyether dendrons, **20** and **21**, respectively, which carry carboxylate groups on their surface (Figure 9). Addition of MV^{2+}, or even negatively charged naphthalenesulfonate changed the UV spectra of the first generation dendritic porphyrin **20**, while no significant change was observed for the third generation dendrimer **21**. This result illustrates the shielding of the metalloporphyrin from the dyes by the dendritic shell, at least in the high generations. Fluorescence quenching experiments suggested that MV^{2+} dye molecules assemble around the carboxylate shell of **21** through electrostatic interactions and that the photoinduced electron-transfer reaction from zinc porphyrin to MV^{2+} dye takes place through the dendritic shell.

Dubin and co-workers[60] explored the possibility of complexing a linear polycation such as poly(dimethyldiallylammonium chloride) with the carboxylate-terminated PAMAM dendrimers **4**. The complexation, which usually resulted in a phase transition and was thus monitored by turbidity measurements, was dependent on the charge density of both the linear polyelectrolyte and the dendrimer surface as well as the solution ionic strength. The critical pH, defined as the pH where complex formation begins, was determined as a function of the ionic strength and dendrimer generation. For the 7.5 generation dendrimer, the critical pH increased as the ionic strength increased; however, no phase transition was observed for the 0.5 generation dendrimer regardless of the pH and ionic strength. The nature of the complexation is unknown, but the results indicate that a sufficiently large surface and charge density is required for strong complex formation between these classes of polyelectrolytes.

The electrostatic interaction of polycations and polyanions may produce a charge neutralization which can be useful in the creation of artificial gene-transfer vectors. The efficient transfer of genetic materials into an eukaryotic cell is an important requirement for effective gene therapy, which targets and potentially treats hereditary and acquired genetic disorders. Due to the potential risks in using viruses as gene-transfer vectors, artificial agents have attracted significant attention as potential replacements. Some inorganic and organic cations as well as cationic polymers such as polylysine and polyethyleneimine, were shown to precipitate and compact DNA and several were used in the development of gene-delivery devices.[61−64] On the other hand, the amine-terminated PAMAM dendrimers **1** which possess polycationic surfaces under physiological pH conditions, appear ideally suited to this purpose. Indeed their ability to bind polyanionic DNA and function as *in vitro* gene-transfer agents was recently described independently by Szoka and Baker.

Initial studies by Szoka and Haensler,[65] using a gel retardation assay showed that commercially available PAMAM dendrimers form stable complexes with DNA. The transfection efficiency of plasmids containing reporter genes that encode firefly luciferase or β-galactosidase was studied using several cell types. The transfection efficiency of firefly luciferase in CV-1 cells was highly dependent on the generation number of the dendrimers and the charge ratio of terminal ammonium to DNA phosphate groups. The maximum efficiency occurred with the sixth generation dendrimer and a 6:1 ammonium to phosphate ratio. By comparison, this assisted gene transfer is 1000-fold more efficient than that using polylysine 115. The cytotoxicity of the sixth generation dendrimer both in the presence and absence of DNA was also reported to be lower than that of polylysine 115. The fifth generation dendrimer was conjugated through a disulfide linkage to an amphipathic membrane-destabilizing peptide, GALAcys. At a low ammonium ion to phosphate ratio, this conjugate exhibited low transfection efficiency presumably due to its lowered affinity for DNA as a result of the eight negative charges in the peptide. However, when a 1:1 mixture of this conjugate and the corresponding peptide-free dendrimer was used, the transfection was enhanced compared to the peptide-free dendrimer alone.

Further study from the same group[66] indicated that the gene transfection activity described above was actually due to degraded dendrimer products resulting from a heat treatment step. Intact, commercially available PAMAM dendrimers showed low transfection efficiency. However, when the intact dendrimers were refluxed in water or butanol to promote amide

solvolysis, the transfection activity of the degraded dendrimer was enhanced significantly. Optimal activity followed heat treatment for 5−15 h depending on the initial dendrimer size, whereas further heating resulted in loss of activity. The components of the optimally degraded dendrimers were separated by size exclusion chromatography and then evaluated for their transfection activity. The results showed that high molecular weight "fractured" dendrimers were responsible for the high activity, while the low molecular weight components showed no detectable activity. These conclusions were supported by the increased transfection activity observed with a dendrimer chemically synthesized with a defective branch. Viscosity measurements as the function of pH combined with a computational study suggested that the fractured dendrimers are highly flexible compared to the intact dendrimers. This added flexibility allows them to swell and collapse, properties that were proposed to enhance their transfection efficiencies.

Recently, Baker and co-workers[67] disclosed their gene transfer studies using PAMAM dendrimers. Gel retardation studies suggested formation of a strong complex between the PAMAM dendrimer (generation number greater than 3) and DNA even in the presence of 1.5 M sodium chloride or at a comparatively high pH of 9.8. The complexes were stable under physiological conditions and could be dissociated only by strong ionic surfactants, such as SDS. Interestingly, the gene transfection efficiency is dramatically improved by the addition of (diethylamino)ethyl-(DEAE) dextran. The transfection efficiency increased exponentially with generation number up to the eighth generation where it leveled off. In most cell lines, the efficiency of a ninth generation dendrimer is 10 to 100 times higher than that of cationic lipids. The enhancing ability of DEAE-dextran is likely due to its role in disassembling large dendrimer-DNA aggregates. Indeed, the conversion to smaller complexes was indicated by electron microscopy. These smaller and compact particles probably have a high rate of cellular uptake. However, in other systems, the addition of chloroquine, a lysomotropic agent, gave much better transfection efficiency than did DEAE-dextran. In contrast to this observation, no significant enhancement was observed in Szoka's system when chloroquine was added.

In spite of the contrasting findings, the results from both groups indicate the promise that polycationic dendrimers offer as synthetic gene-transfer vectors. Further enhancements are necessary in order to develop a more powerful gene-transfer vector which ultimately might function *in vivo*. Such improvements may arise through screens for more efficient additives, or by attaching the dendrimer to a protein or other molecule which can further facilitate DNA complexation, decomplexation, transportation, or cell targeting.

Gene expression begins with the transcription of DNA into messenger RNA (mRNA) which, in turn, is translated into protein. In recent years, there have been significant efforts to design natural or synthetic oligonucleotides that inhibit either transcription or translation. The former is known as the antigene strategy, while the latter is termed the antisense DNA approach. On the basis of the approaches discussed above, Baker and co-workers[68] recently described the use of PAMAM dendrimers to deliver antisense oligonucleotides or plasmids into cells in order to inhibit gene expression. These authors showed that in a cell-free, coupled transcription−translation system, an antisense oligonucleotide complexed to a dendrimer retained the inhibitory activity of the free oligonucleotide. However, *in vitro* studies using cultured cells showed that the antisense oligonucleotide−dendrimer complexes inhibited gene expression, while no significant inhibition was detected for the free antisense oligonucleotide. In an important control study, the sense nucleotide showed no inhibitory activity in the presence of the dendrimer. Optimal inhibition (about 50%) occurred with the seventh generation dendrimer (ethylenediamine as a core) with a 10:1 charge ratio of ammonium to phosphate. Similar inhibition results were obtained with antisense cDNA plasmids complexed with PAMAM dendrimers, while a truncated antisense sequence was less effective. These results further demonstrate the ability of dendrimers to act as transport agents for oligonucleotides and their potential application to the sequence specific inhibition of gene expression. Interestingly, it was also found that the dendrimer strongly stabilizes the antisense oligonucleotide inside the cells, suggesting a role beyond that as a transport agent.

2. Multiligand Dendrimers

Because a dendrimer surface may contain multiple copies of a particular functional group, it is an ideal platform for amplification of substrate binding. Macromolecules capable of engaging in multivalent interactions may display an increased affinity with a complementary receptor either through cooperativity or a purely statistical enhancement. The presence of multiple ligands in such a close proximity on the dendritic surface may also dramatically increase the local concentration of the particular ligand in some environments wherein diffusion is a problem. This approach is particularly appealing in the area of medicinal chemistry where numerous therapeutic target receptors are multivalent.

Until recently, a variety of linear polymers were employed for this purpose. However, polymeric macromolecules are always heterogeneous and because their components are not well-defined, their reproducibility and reliability is limited. Furthermore, due to the flexibility of polymer chains, the three-dimensional structures are variable and difficult to predict. In contrast, dendrimers are often monodisperse and different sized structures can be easily obtained. In addition, the three-dimensional structures of dendrimers are better defined. For example, the surface and interior of dendrimers are considered to be segregated so that all of the peripheral ligands should be accessible for binding. With linear polymers, a substantial fraction of appended ligands may be wrapped up by the polymer depending on its conformation. Because of these potential advantages, applications of dendrimers in pharmaceutical and medicinal chemistry have been extensively explored.

2.1. Peptide Dendrimers. As early as in 1988, Tam and co-workers[69,70] reported the use of multiple

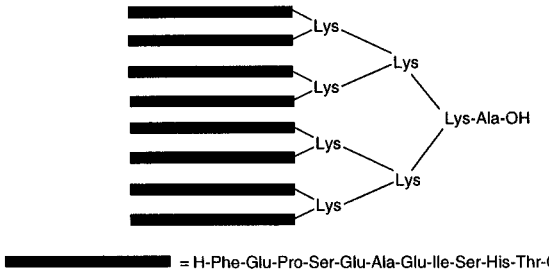


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Figure 13. Tam's multiple antigen peptide system.

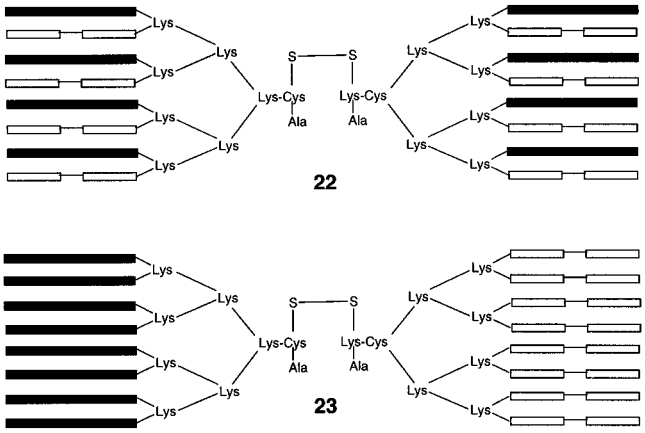

Figure 14. Peptide dendrimers with two epitopes.

antigen peptides (MAP) for the production of anti-peptide antibodies and synthetic vaccines. These peptide dendrimers were prepared by attaching multiple copies of the peptide sequences of interest to a relatively small dendritic lysine core (Figure 13). More than 80% of the total weight of these peptide dendrimers comes from the desired peptide sequence. In the traditional method in which the target peptide is conjugated to a comparatively large carrier protein the overall amount of active peptide is quite low. Thus, it is not surprising that peptide dendrimers such as **21** are found to be more immunogenic. The antibodies induced by these peptide dendrimers in rabbits and mice were not only consistently reactive, but also specific to the corresponding peptide dendrimers and monovalent peptides as well as the cognate native proteins. Neither cross-reactivity nor the reactivity toward the dendritic lysine core was observed. Thus, the peptide dendrimer provides an excellent scaffold for high immunogenicity which eliminates any undesired immunological response as may be seen when a carrier protein is used.

Tam and co-workers[71] extended the MAP concept to the synthesis of peptide dendrimers with multiple epitopes. Two independent epitopes, derived from the corresponding peptide residues in the S and pre-S(2) regions of hepatitis B virus (HBV) were incorporated either by the use of an orthogonally protected dendritic lysine core or by the heterocoupling of two homologous peptide dendrimers through a disulfide bridge (**22** and **23** in Figure 14). These diepitope peptide dendrimers induced strong immunological responses to both cognate native proteins, while the antisera from the monoepitope peptide dendrimer from the S region showed weak reactivity with the corresponding monomeric and MAP peptides as well as the S protein. The pre-S(2) peptide in these

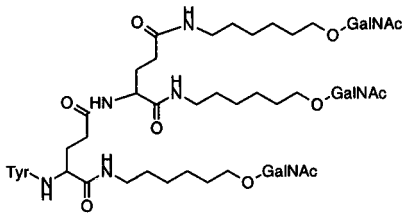

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Figure 15. A trivalent glycoside reported by Lee and co-workers.

diepitope peptide dendrimers may increase the immunogenicity of the S epitope by functioning as a T-helper epitope.

Further amplification of the MAP approach has been proposed by Tam and co-workers[72] through the design of an amphiphilic peptide dendrimer, which can potentially form liposomal or micellar assemblies. For example, a tetravalent peptide antigen containing the glycoprotein gp120 of HIV-1 was attached to a lipophilic tripalmitoyl-*s*-glycerylcysteine group. This peptide dendrimer was shown to be promising as a synthetic AIDS vaccine. Recent efforts from Tam's group[73−75] and others[76] have made it possible to efficiently synthesize large peptide dendrimers through a nonnative chemical ligation technique that involves the formation of thiazolidine, oxime, and hydrazone linkages. A variety of linear as well as cyclic peptide dendrimers[77] were prepared in this manner, in which the nonnative chemical ligation takes place on the unprotected peptide building blocks. The bioactivity of these novel peptide dendrimers and, in particular, the effect that these nonnative bonds might have on the bioactivity, have not been reported so far. Nonetheless, the new synthetic strategy does open the possibility to screen a broader range of compounds for desired properties and function.

2.2. Glycodendrimers. Carbohydrate−protein interactions are ubiquitous in biology and mediate numerous important processes such as cell recognition, adhesion, and infection.[78] However, the interaction between monosaccharides and carbohydrate-binding proteins (also called lectins) are relatively weak. Inspired by the strong binding affinity displayed by the naturally occurring neoglycoproteins and the presence of multiple binding sites in aggregated lectins, Lee and co-workers[79] designed and synthesized several divalent and trivalent branched glycosides. Although the enhancement of binding affinity is highly dependent on the structures of the multivalent ligands and the lectin, the increase in affinity (500-fold) toward rabbit hepatic lectin of $(GalNAc)_3$ **24** (Figure 15) over GalNAc is encouraging. This result was rationalized by a "cluster effect", in which the multivalent glycosides interact with more than one lectin binding site simultaneously and cooperatively.

An extension of this concept led to the design and synthesis of glycopolymers and more recently Roy and co-workers[80,81] reported the first example of "glycodendrimers". The sialic acid dendrimers such as **25** (Figure 16) were prepared by the reaction of a protected 2-thiosialic acid derivative with an L-lysine dendritic core capped with chloroacetyl groups, followed by deacetylation to free the sugar functionality.

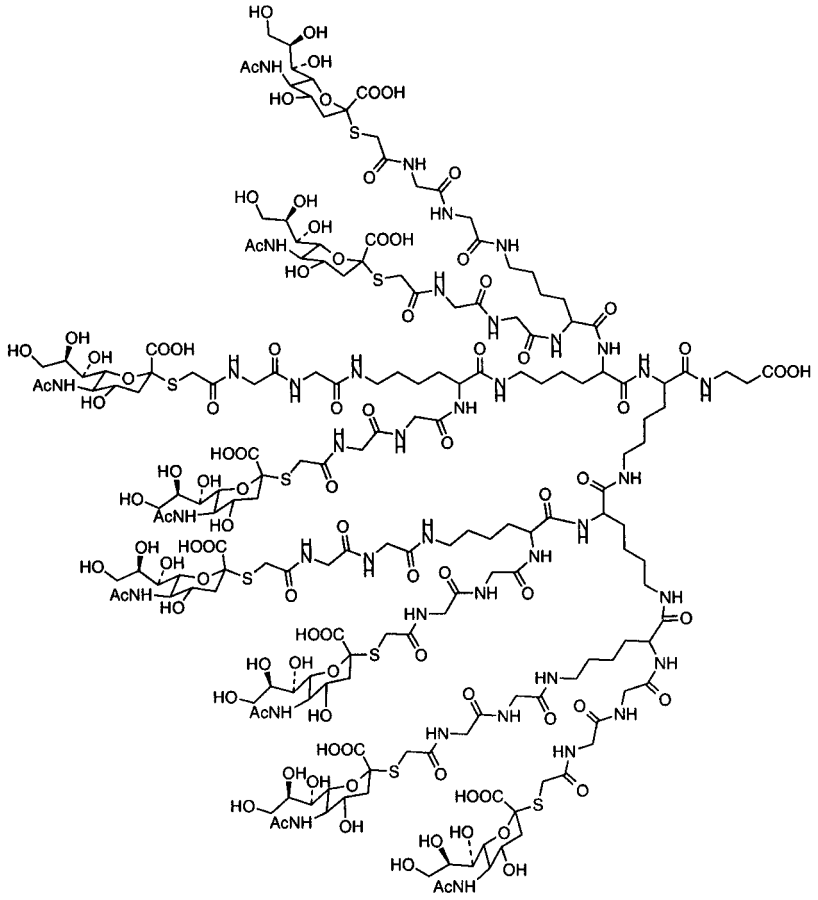

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Figure 16. A glycodendrimer based on dendritic lysine core synthesized by Roy and co-workers.

Glycodendrimers up to the fourth generation with 16 sialic acids were synthesized in this manner. The biological properties of the sialic acid dendrimers were characterized using the plant lectin wheat germ agglutination (WGA) in a direct enzyme-linked lectin assay (ELLA). The binding affinity of the third and fourth generation dendritic sialic acids was comparable to that of a sialic acid polymer with a molecular weight around 100 kD. Further studies with the influenza A virus showed a fourth generation sialic acid dendrimer to inhibit hemagglutination of human erythrocytes 158 times more effectively than the analogous monosialic acid or around 10-fold per sugar molecule. The collective evidence was taken in support of a multivalent interaction as the origin of the enhanced activity.

In addition to the sialic acid dendrimer described above, Roy and co-workers[82,83] incorporated other sugars including GalNAc, α-D-mannopyranoside, and a disaccharide onto the dendrimer surface. Other branching units such as phosphotriester, isophthalic acid, and gallic acid have been utilized. An interesting recent observation[84] from the same group shows that the sugar valency required for maximum binding capacity is not necessarily correlated to the number of binding sites in lectins. For example, the affinity of a series of mannopyranoside-containing dendrimers with Concanavalin A (Con A), which has four sugar binding sites, reached a saturation level at second generation with only four sugar residues. However, for pea lectin which has only two binding sites, a third generation dendrimer with eight sugar residues was required in order to reach the binding plateau.

The amine-terminated PAMAM dendrimers **1** were employed independently by Okada[85] and Toyokuni[86] as a platform for the construction of glycodendrimers. In work by Okada, D-glutose and D-galactose were attached to the dendrimer surface by amidation with glycosylactones. The binding ability of these glycodendrimers with Con A was investigated by quantitative precipitation experiments as well as by a competitive binding method. As expected, Con A, which specifically recognizes D-glutosyl and D-mannosyl residues, bound only the glutosyldendrimer. About a 16-fold weight equivalent of D-glucose was required to disrupt this binding interaction. In a different approach, Toyokuni and co-workers investigated the immunogenicity of a fifth generation glycodendrimer with di-Tn antigens on the surface. Surprisingly, the antibody production by this antigen was almost undetectable.

With an increasing understanding of the function of carbohydrates in biological processes, the design and synthesis of dendritic carbohydrates will continue to be an attractive area of research.[87−89] The inhibitory advantages of the multivalent glycosides relative to monosaccharides was demonstrated by Roy as well as by Lee. However, higher generation number dendritic saccharides will likely exhibit weaker protein−carbohydrate interactions due to the steric crowding on the surface. Furthermore, the binding sites in some lectins are arranged on a more or less flat or spherical surface depending on the

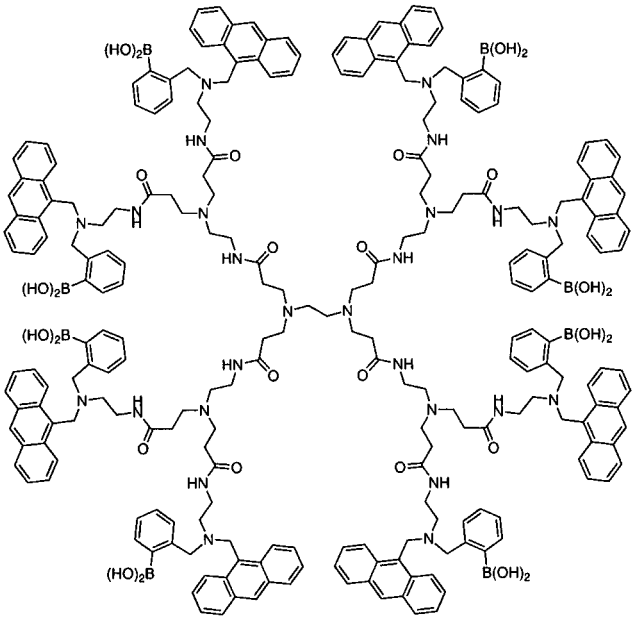

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Figure 17. A dendritic boronic acid used as a sugar receptor reported by Shinkai and co-workers.

aggregation state and structure of the particular lectin. A spherical glycodendrimer might fail to enjoy a polyvalent interaction because of a poor shape complementarity. In this case, a less spherical glycodendrimer might be employed.

3. Other Examples

The design of sugar-binding receptors has also attracted significant attention recently. For example, there remains interest in developing a convenient method for the detection of sugar levels in diabetes patients. With this objective in mind, Shinkai and co-workers[90] introduced a boronic acid-based fluorescence sensor for the sugar detection. More recently, the same group reported the attachment of "sensor units" containing an anthracene chromophore, a tertiary amine, and boronic acid group to the surface of a second generation PAMAM dendrimer.[91] For monosaccharides such as D-galactose and D-fructose which can form a 1:2 complex with boronic acid moiety, their complex with octaboronic acid **26** (Figure 17) was shown to be significantly more stable than that with a flexible diboronic acid or a monoboronic acid. The enhanced binding was attributed to a high local concentration effect where following its interaction with one boronic acid the sugar may intramolecularly bind to any of seven different boronic acids.

Wiener and co-workers[92] reported the use of dendritic polygadolinium chelates **27** (Figure 18) as magnetic resonance imaging (MRI) contrast agents. These novel dendrimers were prepared by the reaction of amine-terminated G2 and G6 PAMAM dendrimers with the gadolinium-chelated 2-(4-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid. In comparison with other polymeric or monovalent chelators, the greatly enhanced proton relaxation exhibited by these dendrimer-based polygadolinium chelators indicated their effectiveness for MRI applications. Indeed, contrast enhancement was clearly observed in several in vivo studies.

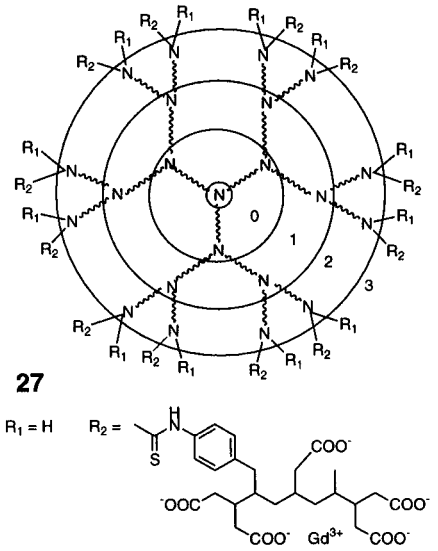

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Figure 18. Dendritic metal chelators as MRI contrast agents reported by Wiener and co-workers.

Moreover, the sixth generation polygadolinium dendrimer displayed a prolonged enhancement with a half-life of 200 min. In comparison, the half-life of the monovalent gadolinium agent is only 24 min. This prolonged enhancement time is extremely useful for 3D time-of-flight MR angiography.

Besides the examples discussed above, dendrimer surfaces have been modified with other functional groups such as boron clusters for use in imaging or radiotherapy,[93−95] imides,[96,97] and tetrathiafulvalenes[98,99] as novel redox active materials, chiral auxiliary ligands[100] for the preparation of novel catalysts, and organometallic complexes as possible electro- or photoactive materials. The synthesis of dendritic polyorganometallic complexes will be discussed in more detail in next section.

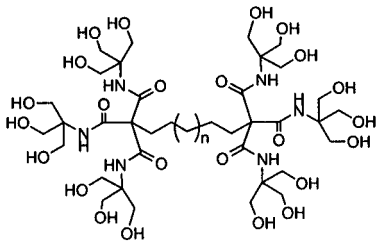
Dendrimer surfaces have also been used as a platform to facilitate the conjugation of antibodies and small molecules. For example, Roberts and coworkers[101] used PAMAM dendrimers to link a porphyrin label to an antibody. The porphyrin was attached first to the dendrimer surface, this intermediate was then conjugated to the antibody followed by the incorporation of copper-67 into the porphyrin. With the dendrimer linker, both the conjugation and the incorporation of copper-67 became more efficient, presumably due to the presence of many reacting sites on the dendrimer surface and the physical separation between the antibody and porphyrin. This antibody−dendrimer−radiolabel conjugate retained the immunoactivity of the unmodified antibody. Wu and co-workers[102] employed a similar procedure in the preparation of a dendritic antibody−metal chelate conjugate. They also found that the dendrimer facilitated the conjugation.

III. Dendrimers as Building Blocks for Self-Assembly Processes

A. Self-Assembly Mediated by Nondirectional Forces

1. Dendritic Amphiphiles

The hydrophobic effect is widely seen as a vital driving force in self-organization processes in Nature.



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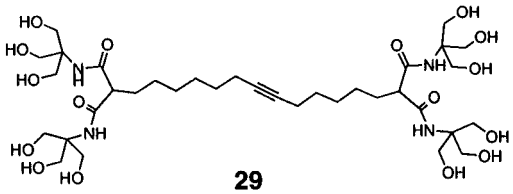

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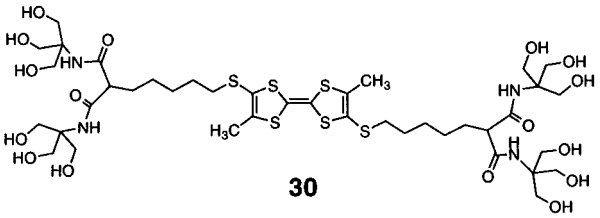

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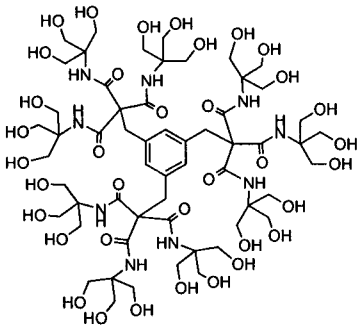
Figure 19. Bolaamphiphiles.

A paradigmatic example is the formation of lipid superstructures. Because they are amphiphilic, in water the hydrophobic and hydrophilic moieties segregate as the lipids self-assemble into micelles or bilayers. In both of these supramolecular aggregates, the hydrophilic head groups are exposed at the surface, while the hydrophobic chain ends entangle on the interior. The structure and stability of the aggregate is dependent on both internal conditions such as the critical packing parameter, i.e., the relative size of the hydrophilic to hydrophobic portions, and external conditions such as concentration and temperature.

Since their initial reports on the divergent synthesis of dendrimers, Newkome and co-workers employed dendrimers as building blocks for the construction of novel amphiphiles, including bolaamphiphiles.[103−108] Bolamphiphiles such as **28** contain two water-soluble dendritic polyols linked through a hydrophobic spacer (Figure 19).[106] A variety of spacers such as simple aliphatic chains or biphenyl or spirane units were used. The ability of these compounds to induce gel formation was shown to be affected both by the length and rigidity of the spacer. In the case of **28** (n = 1) gelation readily occurred when a 2−10% w/w aqueous solution was heated to 80 °C and then cooled to 25 °C. The resultant gel was then characterized by a combination of methods including viscometry, optical microscopy, transmission electron microscopy (TEM), and light scattering. When the gel began to form, the viscosity increased rapidly. TEM analysis of this gel indicated bundles of rod-shaped aggregates with uniform widths (34−36 Å), but variable lengths (ca. >2000 Å).

The model proposed to explain this observation involves an orthogonal stacking of the dumbbell-shaped arborols to form a long and thin aggregate. Thus, the aliphatic linkers associate hydrophobically in the interior of the rod-shaped aggregate, while the hydroxy chain ends project outward and interact with each other or with water through hydrogen-bonding interactions. It is also possible that hydrogen-bonding interactions between amide groups along the rod axis further stabilize the aggregate. Additional studies showed that the gel was stable across a wide pH range with the phase-transition temperature from gel to solution increasing as the solution became more concentrated. Fluorescence microscopy with a lipophilic probe, chlortetracycline, confirmed the existence of a hydrophobic region inside the gel.



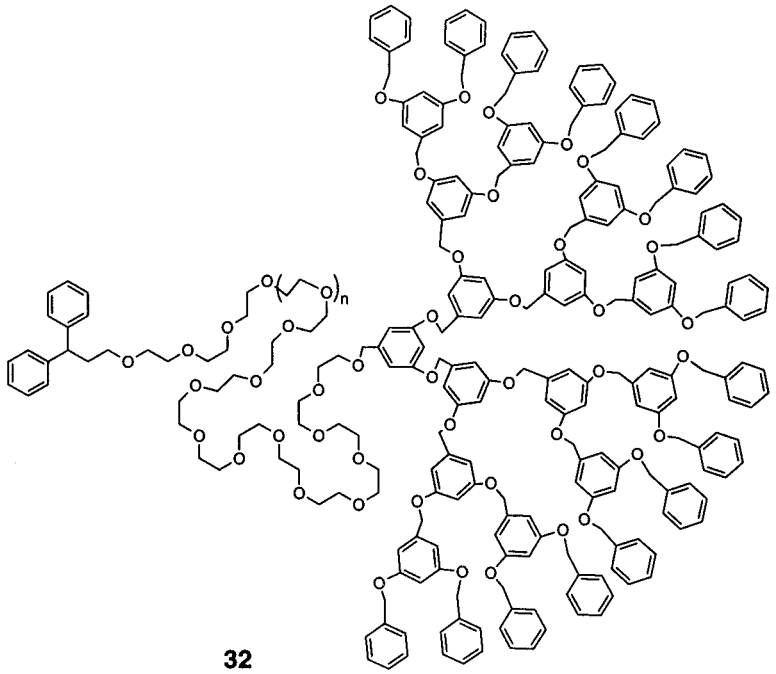
31

Figure 20. A micelle-forming dendrimer reported by Newkome and co-workers.

More recently, Newkome and co-workers[107] reported the synthesis of bolaamphiphile **29** with a central triple bond. It was hoped that the alkyne moieties aligned along the rod axis of the gel might be polymerized to form a large covalent structure. The gel formation of bolaamphiphile **29** was demonstrated. Interestingly, in contrast to the saturated analogs, a helical superstructure was detected by TEM. This novel morphology was attributed to the rigidity of the central alkyne group which prefers nonorthogonal stacking.

Jørgensen and co-workers[109] recently synthesized bolaamphiphile **30** with a tetrathiafulvalene (TTF) spacer, and explored its gel-forming ability. Gelation occurred when a hot solution of **30** in 25% (v/v) ethanol−water or DMF−water was cooled. This gel was shown to have a large bandlike structure as analyzed by phase contrast optical microscopy and atomic force microscopy (AFM). After oxidation with iodine, the gel displayed a characteristic absorption corresponding to TTF dimers or oligomers. This observation supported the conclusion that the TTF units are stacked in the gel, similar to the finding of Newkome. This type of aggregate might potentially act as a "molecular wire".

Newkome and co-workers[105] previously synthesized a tridendron **31** (Figure 20) based on a 1,3,5-trisubstituted benzene scaffold and investigated its micellar properties in aqueous solution by use of TEM and light-scattering techniques. Large aggregates were clearly visible in the electron micrographs. The critical micelle concentration (cmc = 2.02 mM) of **31** was calculated by plotting the scattered light intensity against the sample concentration. Above the cmc, the Stokes radius measured by dynamic light scattering was estimated to be about 95 nm, which remained nearly unchanged as the concentration was increased.



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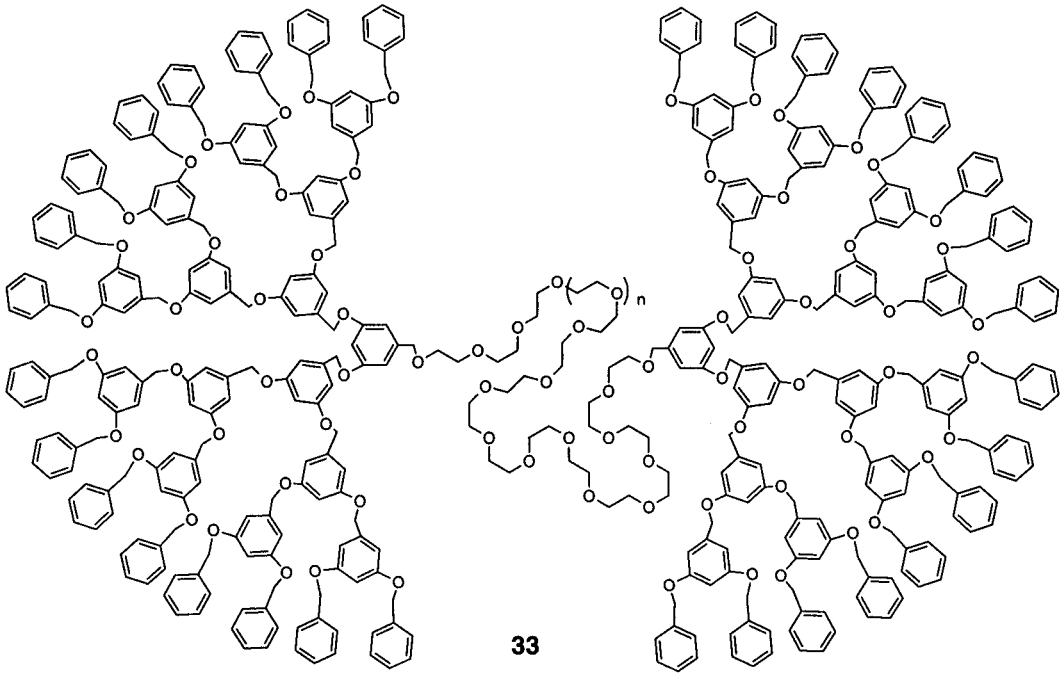
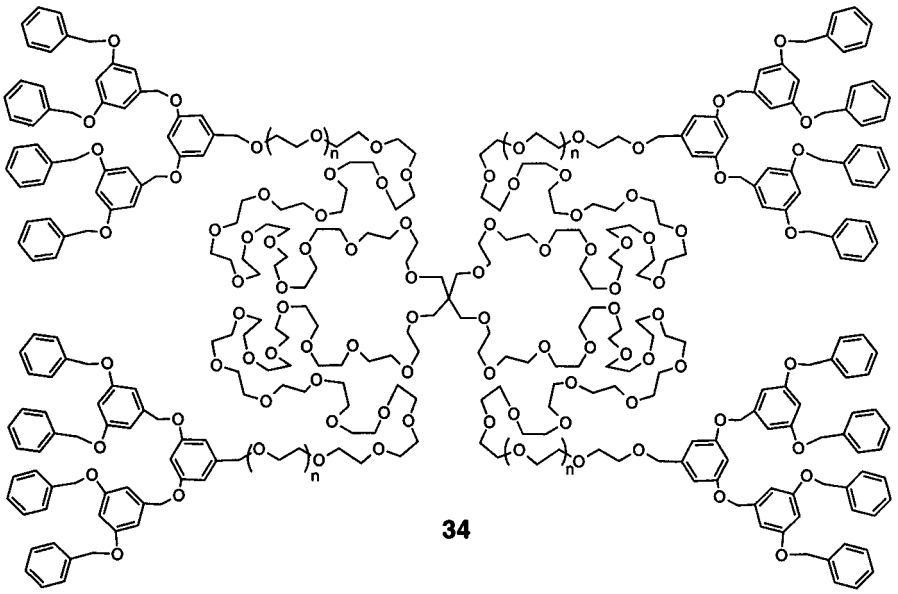


33

Figure 21. AB and ABA block copolymers reported by Fréchet and co-workers.

Fréchet and co-workers[110−113] recently reported the synthesis of a novel class of AB and ABA block copolymers (e.g., **32** and **33**, Figure 21) through the Williamson ether synthesis using a linear, hydrophilic B block such as a polyethylene glycol (PEG) or a polyethylene oxide (PEO) and a spherical, hydrophobic A block-polyether dendritic bromide. Due to the difference in shape and solubility of these two blocks, the copolymers were expected to exhibit variable solution- and solid-state properties depending on the solvents used. Copolymers were prepared with varying PEG or PEO block lengths and different dendrimer generation numbers, *m*, and these were studied by ^{1}H NMR, size-exclusion chromatography (SEC), coupled with a viscometric detector (VISC), and optical microscopy. In the case of ^{1}H NMR, the collapse and tight packing of either block was proposed to reduce its mobility, which could be qualitatively assessed by the signal broadness and weakened signal intensity. For the ABA copolymer in THF-d_8, a good solvent for the dendrimer block but a poor solvent for the PEG segment, the ratio of the PEG to dendrimer signal was lower than that in $CDCl_3$, which, in turn, was approximately equal to the theoretical value. Therefore, it was proposed that in $CDCl_3$, a good solvent for both blocks, the copolymer exists in an extended conformation, while in THF-d_8, the PEG block was tightly packed. In contrast, in methanol-d_4, which is a good solvent for PEG block but a poor solvent for dendrimer, the NMR signals from the dendrimer moiety were very broad and almost undetectable in the G4 copolymer. This



34

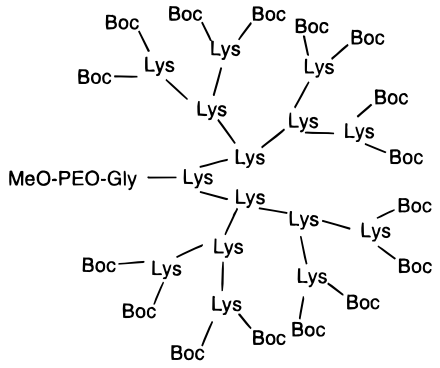
Figure 22. A star block copolymer with a solvent-dependent conformation.

observation suggests that the dendrimer block is well shielded because its surface is wrapped by an extended PEG chain.

More detailed information on the aggregation of these copolymers in solution was obtained from the SEC/VISC studies. When THF was used as an eluent, both AB and ABA copolymers gave an intrinsic viscosity ([η]) and radius of gyration (R_g) of similar magnitude to the corresponding PEO or PEG polymers alone, indicating that these copolymers are monomeric in THF. However, in aqueous methanol, some of the copolymers were shown to aggregate, forming large micellar structures. The solubility and aggregation was strongly affected by the weight ratio of the linear block to the dendrimer block as well as by the size of dendrimer. In general, copolymers containing low generation dendrons, especially G1, tended to form unimolecular micelles, whereas G2 and G3 copolymers formed multimolecular micelles, presumably driven by the hydrophobic effect and $\pi-\pi$ interactions between dendritic blocks. For example, the R_g of G2−PEG11000−G2 copolymer (the MW of PEG is 11 000 amu) was highly concentration dependent ranging from 2.3 nm at 1×10^{-3} g/mL to 8.4 nm at 6×10^{-3} g/mL. Interestingly, the coexistence of two well-separated peaks in the SEC indicated a slow exchange process between these two species of different sizes.

Using a similar approach, Fréchet and co-workers[114] recently synthesized a novel class of amphiphilic star copolymers **34** (Figure 22). To a four-armed PEG "star" scaffold derived from a pentaerythritol core were attached four polyether dendrons. Preliminary results from SEC/VISC and ^{1}H NMR studies indicated the formation of unimolecular micelles in chloroform, tetrahydrofuran, or methanol, but with strikingly different structures. Thus, the star copolymers can self-organize into different micellar structures as a function of the environment. A potential application of these "stimuli-responsive wrappers" involves their use as solvent-specific encapsulation agents.

Chapman and co-workers[115] reported the synthesis of amphiphilic copolymers such as **35** derived from



35

Figure 23. A PEO and dendritic polylysine block copolymer reported by Chapman and co-workers.

linear PEO and Boc-terminated poly-α,ϵ-L-lysine dendrimers (Figure 23). The use of PEO as a platform for the dendrimer synthesis greatly facilitated separations because products up to the fourth generation could be precipitated from the reaction mixture in ether. Surface tension measurements as a function of concentration were employed to evaluate the micelle formation of these "hydraamphiphiles". The cmc was estimated to be about 8×10^{-5} M, and the surface of the aggregates was suggested to be highly compact. Solubilization of the dye Orange-OT by the G4 hydraamphiphile in water was investigated as a function of concentration. The existence of a transition concentration for dye solubility further supported the micellar behavior of the copolymer, although this concentration was slightly different than the cmc.

As a complement to the reports by Fréchet and Chapman, Meijer and co-workers[116] recently described the synthesis of novel amphiphilic copolymers such as **36** in which the dendritic block, derived from poly(propylene imine), is both polar and hydrophilic, while the hydrophobic polymer polystyrene was used as a linear block. The micellization of these amphiphiles was investigated by a combination of conductivity measurements, dynamic light scattering (DLS), and TEM. Analogous to traditional surfac-

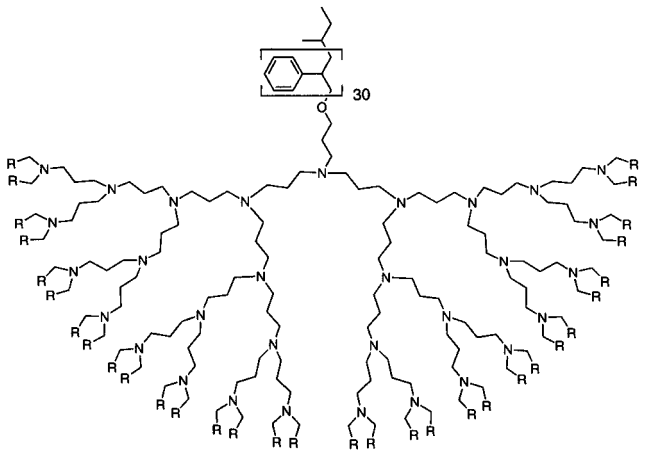


Figure 24. Meijer's amphiphilic block copolymers.

tants, which are much smaller in size, the micellar structures derived from these dendritic amphiphiles in aqueous solution were highly dependent on the dendrimer generation number, i.e., the size of head group. This observation matches well with the theoretical prediction of Israelachvili and co-workers.[117] For example, PS3000−G2, in which the hydrophilic dendritic head group is relatively small compared to the hydrophobic polystyrene block, forms an inverted micellar structure in mixtures of toluene and water as demonstrated both by DLS and its excellent ability to stabilize toluene as the continuous phase.

Vesicles were observed for PS3000−G3 by TEM, indicating that the size of the dendrimer block is comparable to that of the polystyrene section. For the G4 copolymer, both DLS and TEM clearly showed the presence of a long rod structure, suggesting the formation of a cylindrical micelle. With a further increase in dendrimer generation number, the overall shape of the monomer unit approaches that of a cone. Therefore, it was expected that PS3000−G5 **36** (Figure 24) would form spherical micelles, which was confirmed by TEM. This rational design ingeniously provides a structural bridge between traditional surfactants and amphiphilic block copolymers. Thus, these dendritic amphiphiles have a shape similar to that of traditional surfactants, but the size of amphiphilic block copolymers.

Meijer and co-workers[118] further modified the above amphiphilic copolymers with dendritic blocks terminated with carboxylic acids such as **37**. Their amphiphilic behavior was demonstrated through NMR studies in different solvents such as $CDCl_3$, D_2O, and DMSO-d_6, by monitoring the signal broadness and the integral ratio in a manner similar to that of Fréchet (*vide supra*). Conductivity measurements were used to determine the point of phase inversion from water to toluene, which as a function of pH and dendrimer size indicated the development of polar and amphiphilic properties in the copolymers. TEM studies indicated large aggregates for all block copolymers except G3 copolymer which formed wormlike micelles. Presumably, large networks are formed by further electrostatic association of smaller aggregates.

2. Self-Organization in Liquid Crystalline Phases

The self-organization of hyperbranched polymers in liquid crystalline phases has been explored by several research groups.[119] Whereas discrete aggregates are not necessarily formed, the phase-dependent organization is dependent on intermolecular interactions. Percec and co-workers[120−122] synthesized a class of flexible rodlike AB_2 monomers **38**−**40** (Figure 25) which can exist in either *anti* or *gauche* conformations. A series of hyperbranched polymers were prepared through the polyetherification of these branched monomers under heterogeneous conditions, followed by in situ alkylation of the hyperbranched products with aliphatic or benzyl bromides to give the corresponding end groups. Differential scanning calorimetry (DSC) studies showed that the glass and isotropization temperatures of these hyperbranched polymers were strongly affected by the end groups. Repeat unit **40**, with a more rigid aromatic spacer, was shown to be most effective in increasing the temperature range of nematic mesophase.

In spite of this encouraging result, there are drawbacks of the hyperbranched polymer approach, mainly due to the high polydispersities and, in this specific case, impurities resulting from intramolecular alkylation or elimination. Thus, Percec and co-workers[123,124] synthesized pure dendritic materials on the basis of the repeat unit **40** using an iterative convergent strategy similar to that of Fréchet. Mono- and tridendrons up to the fourth generation were prepared with 10-undecenyl groups on the periphery and their properties were investigated by using DSC, polarizing optical microscopy (POM), and X-ray diffraction (XRD). In contrast to the hyperbranched polymers, sharp phase transition peaks and a low degree of supercooling were observed for all dendrimers in the DSC. Except for G1OH and G1Br, which were shown to be monotropic, all other dendrimers displayed an enantiotropic nematic mesophase, and even a smectic mesophase with increasing phase transition temperatures as the generation number increased. Interestingly, (G4)3, the highest molecular weight mesogen (30863 amu) organized into a nematic texture with a rate comparable to that found with low generation dendrimers, indicating a relatively low viscosity. This result is strikingly different to that observed with linear polymers where texture formation is very slow for high MW materials. The formation of nematic instead of cubic or discotic phases for all dendrimers suggests that these particular dendrimers, even at high generation numbers,

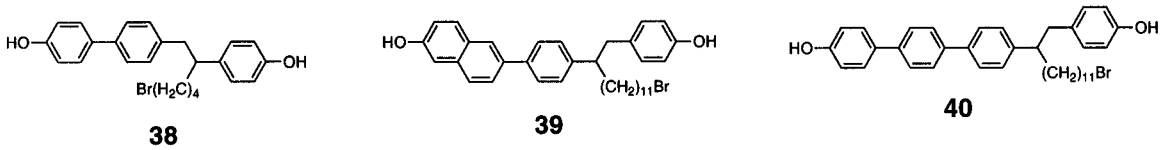


Figure 25. AB_2 monomers for the synthesis of hyperbranched liquid crystalline polymers.

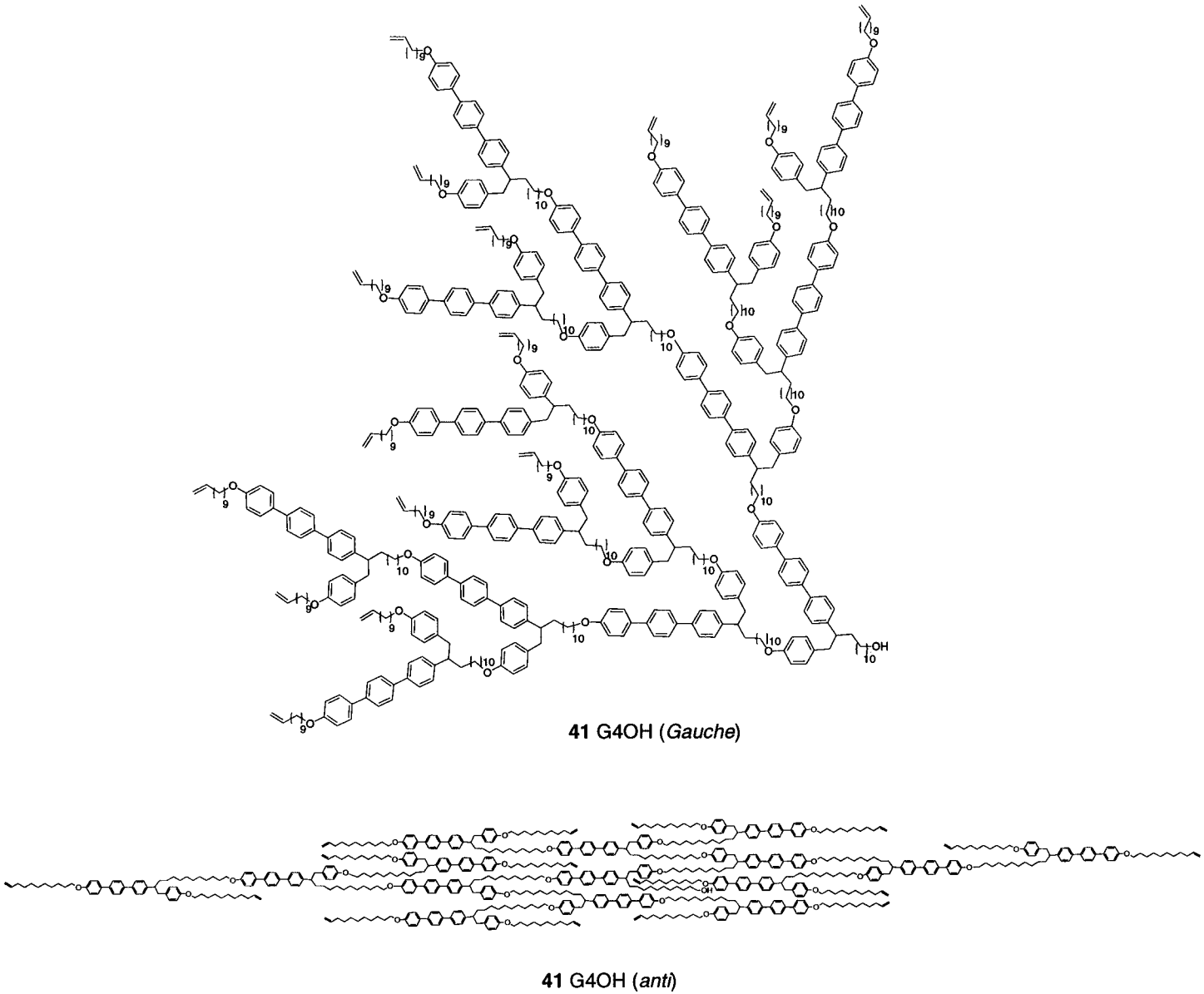
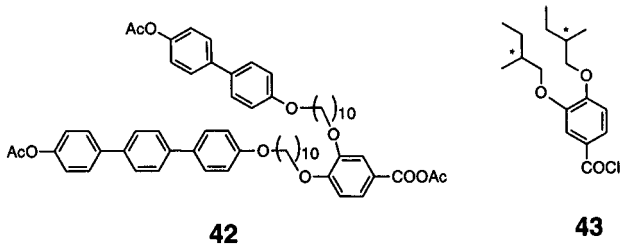


Figure 26. A monodisperse liquid crystalline dendrimer and its proposed structure in nematic phase.



42 43

Figure 27. AB_2 monomer **42** used for hyperbranched polymerization and chiral end group **43**.

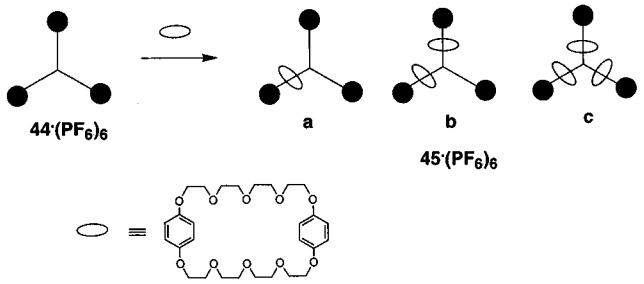


Figure 28. The synthesis of a first-generation dendritic rotaxanes.

do not exhibit a spherical or disc shape. As illustrated in Figure 26 for the fourth generation dendron **41**, it was suggested that all the repeat units adopt an *anti* instead of *gauche* conformation so that the overall shape of the dendrimers is rod-like with a compact structure that minimizes free volume.

Recently, Shibaev[125,126] and Frey[127] independently described carbosilane-based liquid crystalline dendrimers by introducing mesogenic units as end groups. In the case of Shibaev, cyanobiphenyl, methoxyphenyl benzoate, and cholesteryl groups were attached to a first generation carbosilane dendrimer, while in the case of Frey, cyanobiphenyl groups were connected to a second generation carbosilane dendrimer. These materials were shown to display smectic mesophases. Ringsdorf and co-workers[128] recently reported the synthesis of a hyperbranched polymer by polycondensation of AB_2 monomer **42** followed by capping with chiral chain end **43** (Figure 27). The polymer was shown to be chiral by polarimetry and it displayed liquid crystalline behavior. A uniform Grandjean texture was observed by POM indicating the formation of a cholesteric mesophase. Analysis of the XRD pattern led to a similar conclusion.

3. Self-Assembly by π-Stacking Interactions

Stoddart[37] and others have used the strong interaction between a π-donor and a π-acceptor in the design of a variety of aesthetically appealing self-assembling systems, including rotaxanes and catenanes. Recently, Stoddart and co-workers[129] reported preliminary results on the construction of dendritic rotaxanes by use of the so-called "slipping" method. Thus, a tris(bipyridinium) compound **44** terminated with three large blocking groups was treated with bis-*p*-phenylene-34-crown-10 (BPP34C10) at a temperature high enough to allow the crowns to slip over the blocking groups. This approach afforded mono-, di-, and trisrotaxanes **45a**−**c** with the product distribution depending on the equivalents of crown ether used (Figure 28). The formation of rotaxanes was supported by electrospray mass spectrometry and ^{1}H NMR spectroscopy wherein upfield shifts of both bipyridinium and hydroquinone protons indicated strong $\pi-\pi$ interactions.

More recently, Stoddart and co-workers prepared a series of rotaxanes with dendritic stoppers using a "threading approach".[130] The synthesis involves the alkylation of bipyridinium-based molecules with Fréchet's third generation dendritic bromide in the presence of BPP34C10. The formation of rotaxanes was confirmed by the upfield shift of both bipyridinium and hydroquinone protons. The presence of dendritic frameworks made these rotaxanes soluble in a wide range of organic solvents. The "shuttling" process of BPP34C10 molecule from one bipyridinium to the other in [2]rotaxane **46** (Figure 29) was investigated by variable-temperature ^{1}H NMR spectroscopy in several solvents. The energetic barrier to this molecular motion increased in a less polar solvent such as $CDCl_3$. It was suggested that in less polar solvents, the cationic rotaxane backbone was more surrounded by the dendritic substituent, which led to the restricted molecular motion.

B. Hydrogen Bond-Mediated Self-Assembly

Hydrogen-bonding interactions are ubiquitous in biological self-assembly processes and are also widely

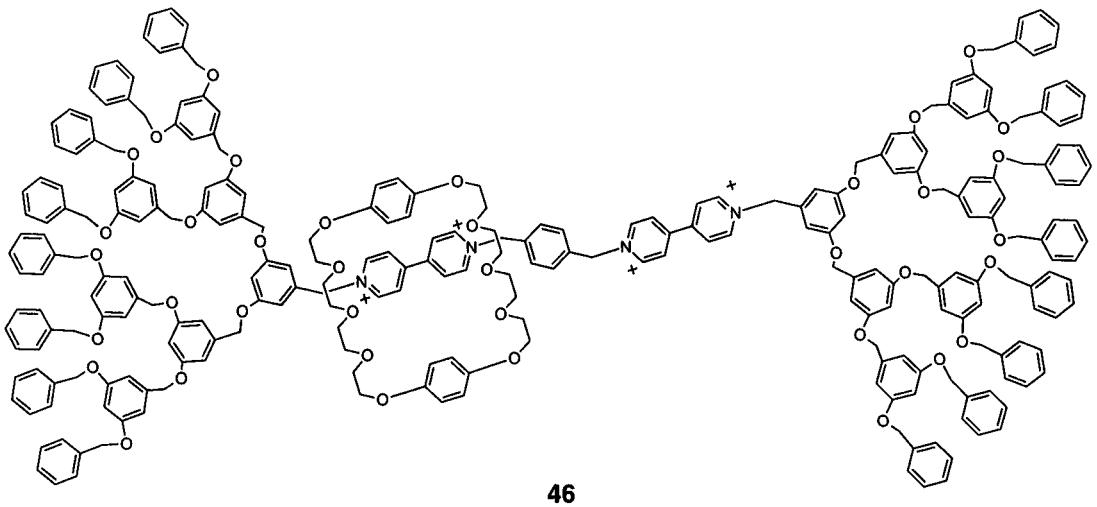


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Figure 29. A rotaxane with dendritic stoppers

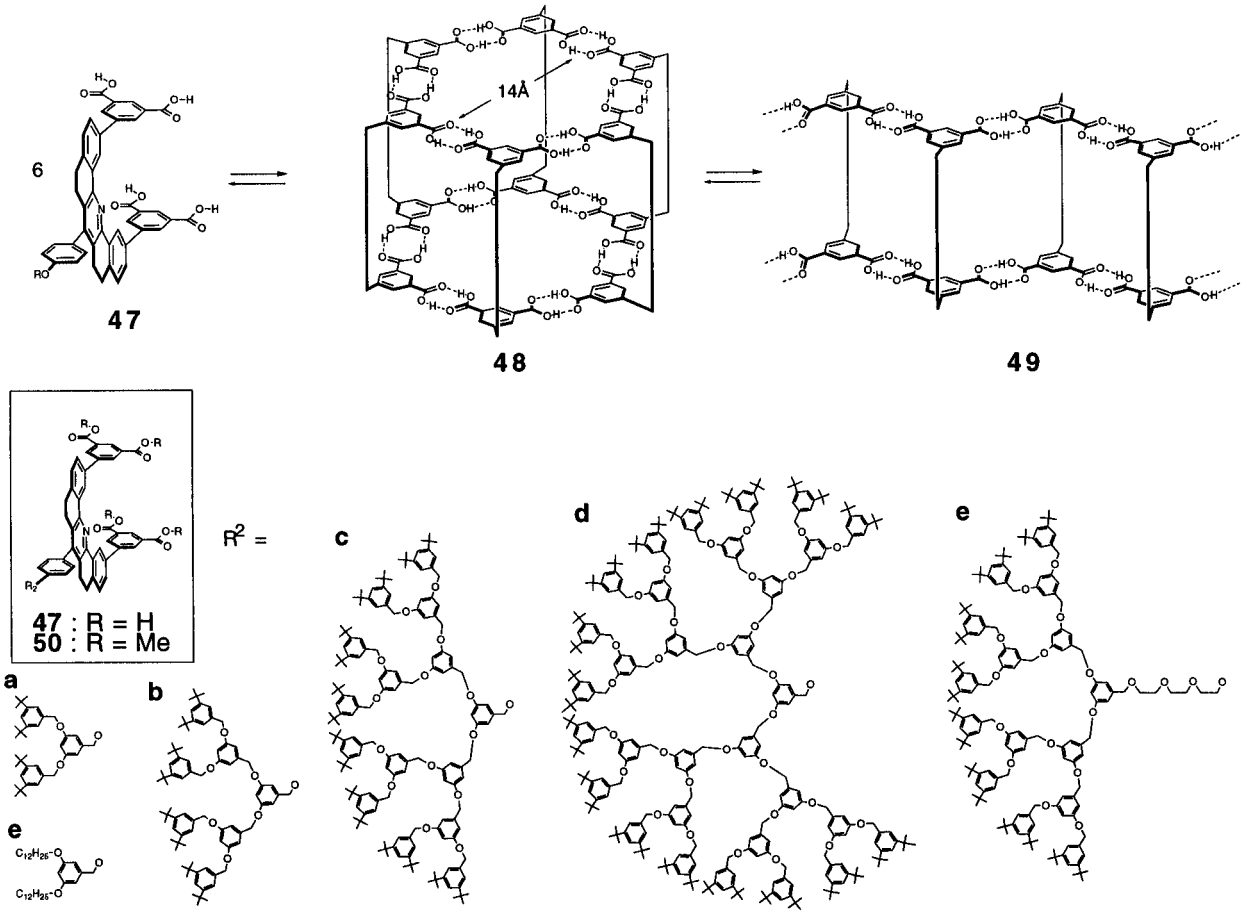


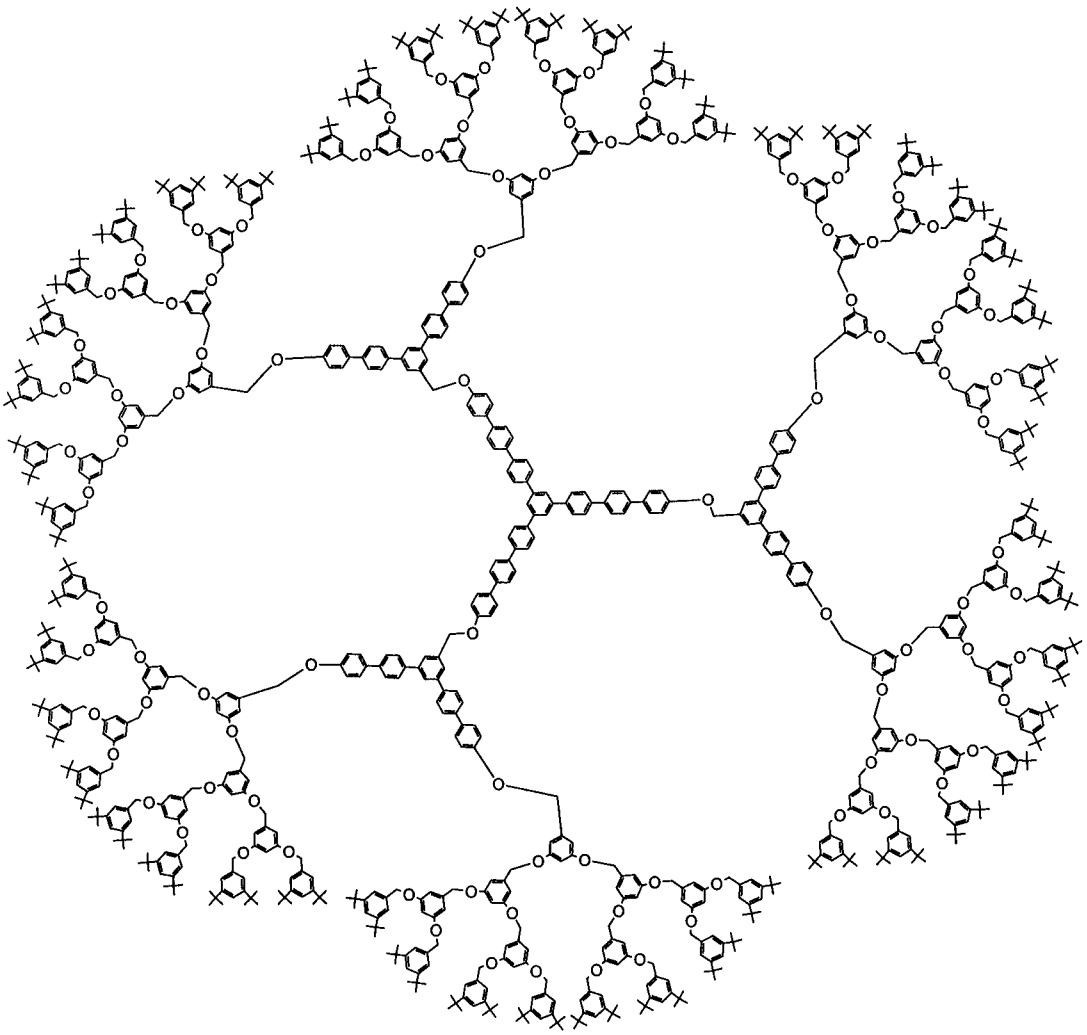
Figure 30. Self-assembling dendrimers mediated by hydrogen-bonding interactions.

employed in studies of abiotic self-assembly. The latter were extensively reviewed recently.[131] In this section, we discuss our recent efforts in the design of self assembling systems based on dendritic macromolecules using hydrogen-bonding interactions.[132] As noted above, dendrimers are well-defined macromolecules with sizes already on the nanometer scale. This makes them ideal building blocks for the construction of even larger structures. Because self-assembly processes are usually a balance between enthalpic gain and entropic loss, stable aggregates require strong hydrogen-bonding interactions and preorganized structures.

The formation of *discrete* aggregates requires a strategy for limiting growth. The generation of closed structures by cyclic aggregation is an obvious choice. Isophthalic acids can form cyclic hexamers by carboxylic acid dimer formation, or linear, zigzag polymeric aggregates. Because they did not self-assemble specifically into a hexameric aggregate in solution, an alternative approach that doubles the number of hydrogen bonds was taken. Thus, tetraacids **47**, in which two isophthalic acid units were held in a syn-orientation by a rigid spacer were designed and synthesized (Figure 30).[132] By normal pairing of carboxylic acids into hydrogen bonded dimers, these molecules can self-assemble into double-layer, cyclic hexamer **48** or a series of linear aggregates **49**. Fréchet-type polyether dendrons, up to the fourth generation, were attached to the spacer unit of tetraacids **47**. The aggregation of **47** was suggested by ^{1}H NMR spectroscopy in which the proton signals corresponding to the spacer unit of higher generation tetraacids were very broad in $CDCl_3$. The signals become sharper and well resolved as more polar solvents such as DMSO-d_6 or THF-d_8 was added to the $CDCl_3$ solution. A logical explanation for these observations is that the dendritic tetraacids exist as monomers in these polar solvents.

The self-assembly behavior of the tetraacids was characterized by SEC, laser light scattering (LLS), and vapor pressure osmometry (VPO). SEC is particularly useful in this system because of the large differences in hydrodynamic radii between monomers of different generation number and between the monomers and their putative aggregates. In addition, the precursors to the tetraacids, tetraesters **50** could be used as a standard for comparison because they cannot aggregate by hydrogen bonding yet have nearly identical sizes and molecular weights. When methylene chloride was used as the eluent, a well-defined and symmetrical peak was observed for all dendritic tetraacids except the first generation tetraacid **47a**. Importantly, the molecular weight for each tetraacid was close to that expected for a hexameric aggregate when polystyrene (PS) was used as the molecular weight standard. When THF was used as an eluent, all the tetraacids had retention times very similar to their corresponding tetraester, indicating a monomeric state in THF as was suggested by the ^{1}H NMR results.

Although SEC calibration with PS standards is commonly used for the MW determination of new polymers, the accuracy of this method depends on whether the macromolecule under investigation and its identical molecular weight PS standard have



51

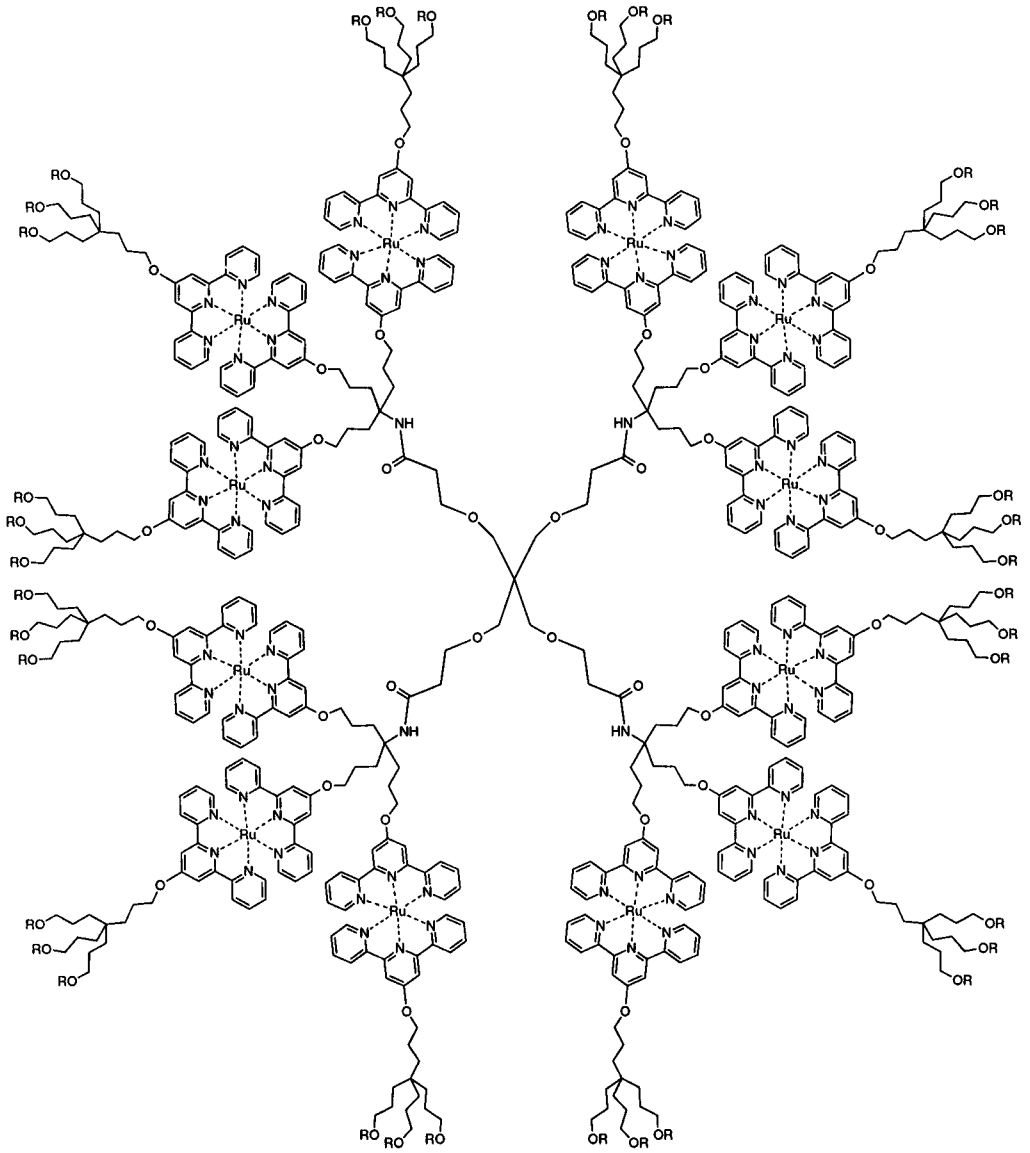
Figure 31. A covalent model of self-assembling dendrimers.

similar sizes and shapes. Therefore, it would be more conclusive to have a unimolecular analog of the hexameric aggregate for comparison. Dendrimer **51** (Figure 31), which was shown by computer modeling to have a similar size and shape as the corresponding hexamer of **47c**, was synthesized and used for this purpose. SEC showed that **47c** and **51** had nearly identical retention times. The slightly broader peak shape of **47c** compared to **51** supports the idea that **47c** self-assembles into a well-defined, discrete hexameric aggregate.

Further studies suggested that the self-assembly behavior of these tetraacids was dependent on the size of the peripheral group. The stability of **47a**−**f** aggregates was examined by SEC as a function of the injected sample concentration. It was observed that the tetraacids with small peripheral groups such as **47a** and **47e** formed unstable aggregates with concentration-dependent molecular weights, whereas **47b**−**d** formed stable aggregates across a wide concentration range. It was proposed that small peripheral group can be accommodated into the linear aggregates, whereas tetraacids with large peripheral groups are sterically compelled to form cyclic structures. This steering effect was supported by computer modeling. A large dendritic substituent alone, however, is not enough to guarantee selective formation of a hexamer because the flexibility of the tri(ethylene glycol) linker in tetraacid **47f** allowed it to form linear aggregates in contrast to the behavior of **47c**.

C. Metal Complexation-Mediated Self-Assembly

Organometallic dendrimers have received significant attention in recent years because they may contain multiple coordination sites or multi-electron transfer redox centers and thus have the potential for a range of applications including as novel catalysts, molecular electronic and photochemical devices for information storage and switching, and as energy transfer and conversion devices. A variety of organometallic dendrimers have been synthesized and can be classified into three categories: (1) dendrimers with coordination centers on the periphery, (2) dendrimers with coordination centers throughout all layers, and (3) dendrimers with coordination centers at the core. The last category has been covered in the first part of this paper and includes dendritic porphyrins of Diederich and Aida,[41−43] Newkome and Chow's terpyridine complexes,[39,40] and examples from other groups.[133−135] Thus, only the first two categories will be discussed in this section.



52

Figure 32. A metallodendrimer reported by Newkome, Constable, and co-workers.

1. Dendrimers with Coordination Centers on the Periphery

Dendrimers with coordination centers on the periphery have been assembled mostly by the divergent strategy.[136,137] The dendritic cores are first prepared by traditional dendrimer synthesis in which ligands or functional groups capable of coordinating metal ions or reacting with metal complexes are introduced in the final step of the synthesis. For example, Newkome, Constable, and co-workers[138] synthesized a dendrimer with terpyridine ligands on the surface, which was complexed with terpyridinyl ruthenium chloride to form dodecaruthenium macromolecule **52** (Figure 32).

The excellent coordinating ability of phosphines has also been utilized to prepare novel organometallic dendrimers.[139−141] For example, Dubois and co-workers[136] prepared a phosphine-containing dendrimer by iterative free-radical addition of a phosphine to diethyl vinylphosphate followed by reduction. The phosphine dendrimers were allowed to react with Pd(II) to form multivalent palladium complexes. The resultant complexes were shown to catalyze the electrochemical reduction of CO_2 to CO. On the other hand, Majoral, Chaudret, and co-workers[142] have modified their P^V dendrimers with phosphine groups (P^{III}), which complexed Au(I) ions on the periphery. The gold complexes were analyzed by high-resolution

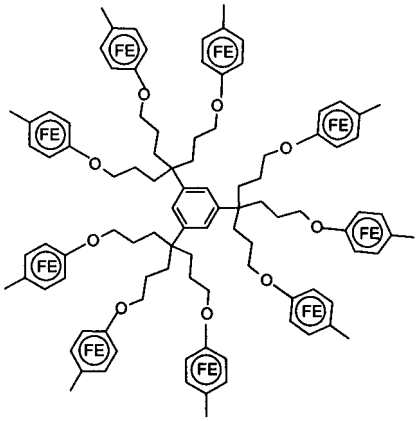


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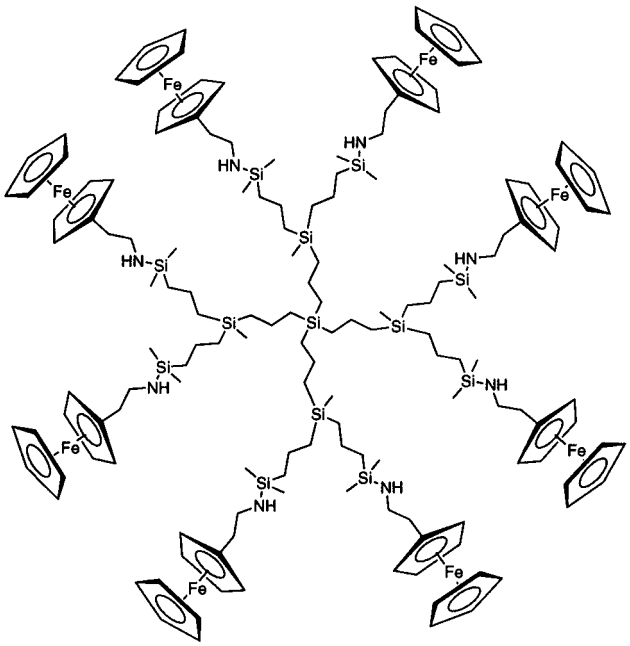
Figure 33. A nonairon complex synthesized by Astruc and co-workers.



54

Figure 34. An octairon complex based on carbosilane dendrimer.

transmission electron microscopy. In addition to observing large aggregates, individual spherical particles were observed with a size that correlated well with the dendrimer generation number.

Alternatively, reactions of dendrimer functional groups on the periphery with metal complex through displacement or oxidative addition reaction were employed. Astruc and co-workers[143] reported a synthesis of a nonairon complex **53** (Figure 33) by the aromatic nucleophilic substitution of a nonaalcohol with $[Fe(Cp)(\eta^6\text{-}p\text{-}MeC_6H_4F]PF_6$. Similarly, silicon dendrimers with reactive Si−Cl end groups can be displaced with a variety of nucleophiles. Cuadrado, Morán, and co-workers[144] reported the reaction of first and second generation Si−Cl dendrimers with [Fe(Cp)(CpLi)] or $[Fe(Cp)(CpCH_2CH_2NH_2)]$ affording tetra- and octairon complexes such as **54** (Figure 34), respectively. Seyferth and co-workers[145] modified similar silicon-based dendrimers with ethynyl groups on the periphery by chloride displacement with ethynyl magnesium bromide. The resultant dendritic polyacetylene was reacted with $Co_2(CO)_8$ to give tetrakis- or dodecakis(dicobalt hexacarbonyl) complexes. Likewise, van Koten and co-workers[146] replaced chloride groups with substituted bromophenyl alcohols and further transformed these groups into dendritic nickel complexes such as **55** (Figure 35) through an oxidative addition reaction. These tetra- and dodecanickel complexes were employed as homogeneous catalysts for the Kharasch addition reaction of CCl_4 to methyl acrylate. It was shown that the dendritic catalysts exhibited slightly lower activity but excellent regiospecificity compared to the corresponding mononickel catalyst. The advantage of these dendritic catalysts is their large size which means easy removal or recovery from reaction mixture (i.e., by dialysis or filtration).

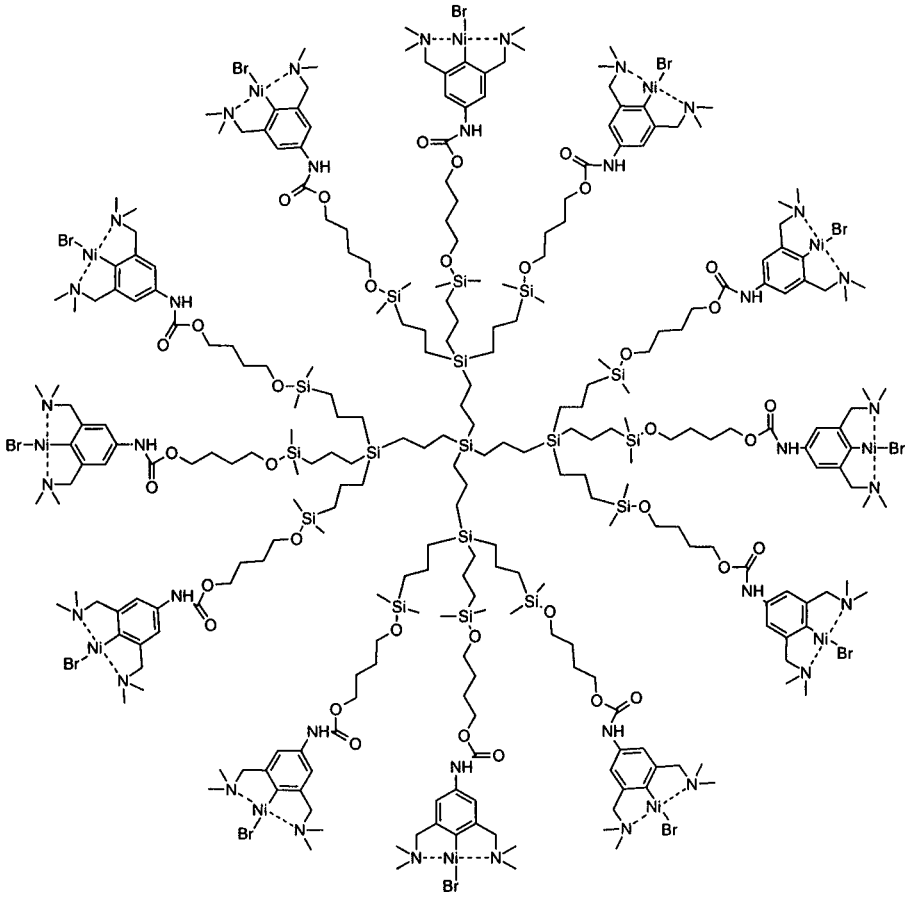


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Figure 35. A dendritic nickel complex used as a catalyst.

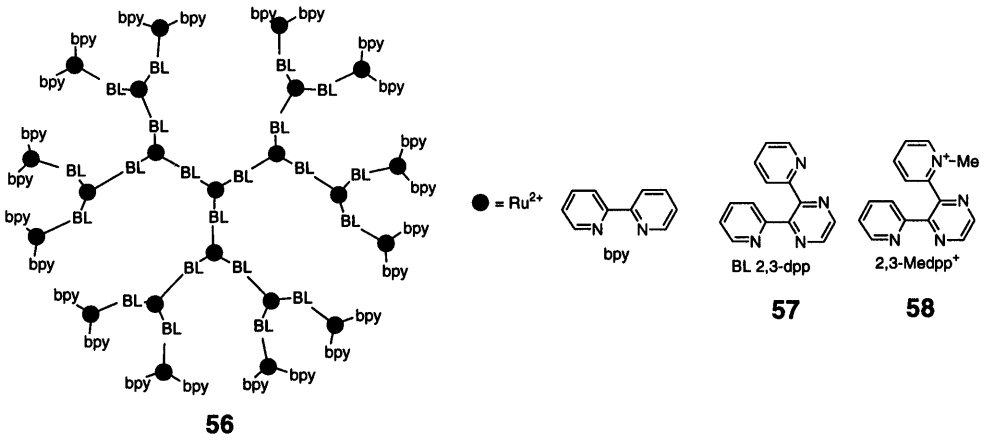

Figure 36. Dendritic ruthenium complex reported by Balzani and co-workers.

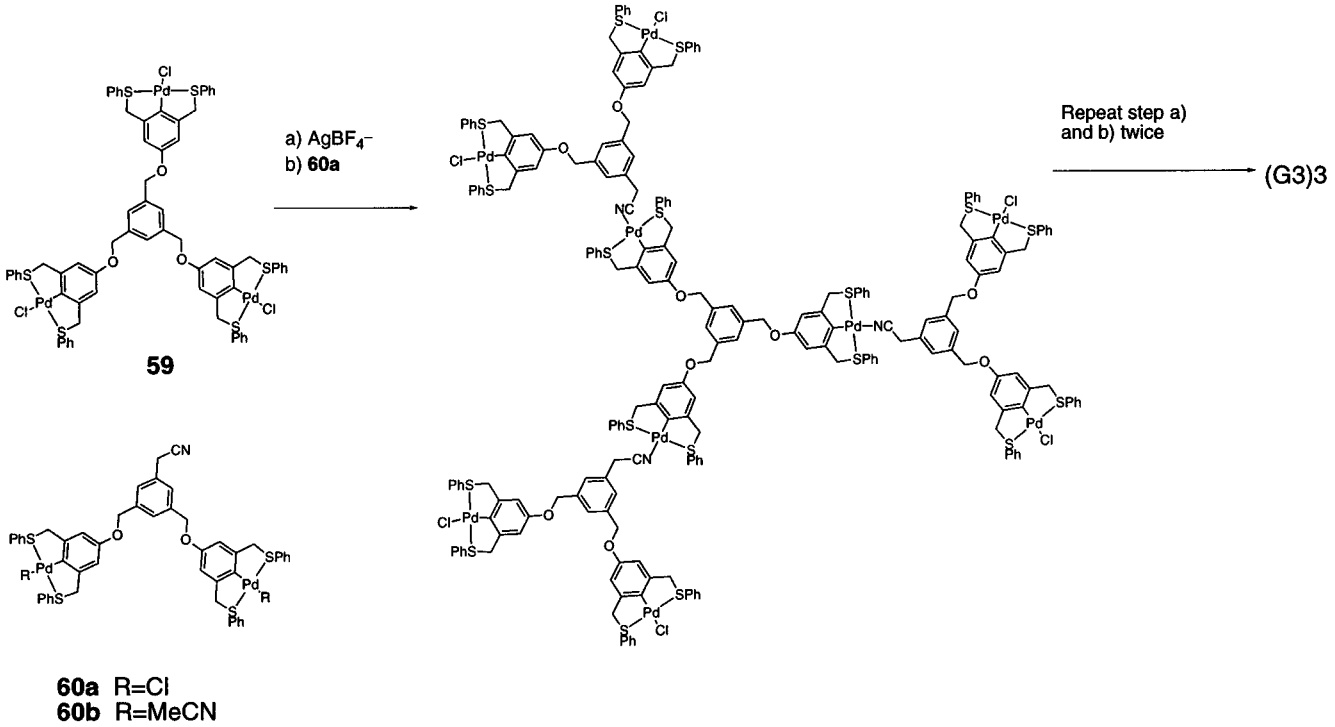

Figure 37. Iterative divergent synthesis or uncontrolled assembly of dendritic palladium complexes.

To date, only a single report has described a convergent approach to the synthesis of peripheral metallodendrimers. Moss and Liao[147−149] reported the synthesis of a fourth generation tridendron with 48 ruthenium complexes on the periphery by using 3,5-dihydroxybenzyl alcohol as a repeat unit in a approach similar to that of Fréchet. Obviously, a prerequisite of the convergent method is that the metal complex tolerate the reaction conditions used to make the dendrimer since it is introduced at the beginning of the synthesis.

2. Dendrimers with Coordination Centers throughout All Layers

Dendrimers with coordination centers in every layer were constructed by directly employing coordination complexes as building blocks for branching or bridging. Syntheses have been reported through the divergent, convergent or one-pot hyperbranched polymerization strategies. Balzani, Denti, Campagna, and co-workers[150−156] reported the synthesis of a series of dendritic ruthenium(II)−polypyridine complexes in which 2,3- or 2,5-bis(2-pyridyl)pyrazine (dpp, **57**) was employed as a bridging ligand and 2,2′-bipyridine as a terminating ligand. Balzani refers to their approach as the "complexes as ligands and complexes as metals" strategy. These novel organometallic dendrimers displayed interesting absorption and redox properties as investigated by UV−visible spectroscopy, luminescence, and differential pulse voltammetry. Recently, a more controlled assembly of organometallic dendrimers was facilitated by the preparation of a monomethylated 2,3-dpp (Medpp, **58**) ligand so that one side is temporarily protected from complexation. The methyl group of Medpp can be selectively removed so that its metal complexing ability is restored for further growth. A second generation tridendron **56** with up to 22 Ru(II) metal complexes was synthesized by this method (Figure 36). By using this more elaborate strategy, different metals and ligands are expected to be introduced without difficulty.

Similarly, Reinhoudt and co-workers[157] recently synthesized metallodendrimers with up to 47 palladium complexes through a controlled divergent approach. The assembly takes advantage of a kineti-

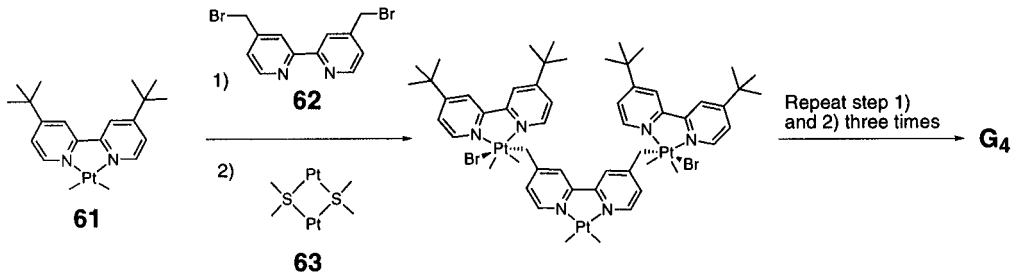

Figure 38. Convergent synthesis of dendritic platinum complexes reported by Puddephatt and co-workers.

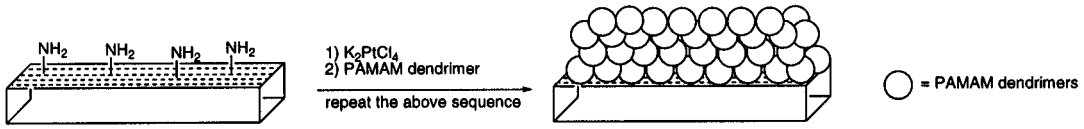

Figure 39. Construction of dendritic mutilayers.

cally inert tridentate (S−C−S) palladium complex which is labile toward substitution when the fourth ligand is a nitrile group, but is stable with chloride as the ligand. The chloride group, however, can be selectively removed by treatment with $AgBF_4$. Therefore, using tris(palladium chloride) **59** as a core, and bis(palladium chloride) nitrile **60a** as an AB_2 repeat monomer, palladium dendrimers up to the third generation can be assembled through iterative treatment with $AgBF_4$ followed by nitrile−palladium complexation (Figure 37). These dendrimers were well characterized by a combination of traditional spectroscopic techniques and combustion analysis.

On the other hand, Reinhoudt and co-workers[158] had previously reported the assembly of similar hyperbranched dendrimers through an uncontrolled polymerization of AB_2 monomer **60b**. The labile acetonitrile ligand was removed by heating **60b** under reduced pressure, thus inducing an intermolecular coordination of benzylnitrile group with the tridentate palladium, which leads to a metallopolymer. The benzyl nitrile coordination was shown by FT-IR spectroscopy and ^1H NMR studies further indicated that the self-assembly process could be reversed by addition of acetonitrile. The polymeric aggregate was shown to be spherical with a diameter of about 200 nm as characterized by the combination of quasielastic light scattering (QELS), atomic force microscopy (AFM), and transmission electron microscopy (TEM). As a control, an analogous AB monomer did not self-assemble into globular structure, although conclusive evidence for a hyperbranched structure is needed.

Puddephatt and co-workers[159−161] employed the convergent strategy in the synthesis of dendritic platinum complexes of up to the fourth generation number with 28 coordination centers. The synthesis involved a two-step iterative procedure where oxidative addition of [$PtMe_2$(bipyridine)] (**61**) into the repeat monomer 5,5′-bis(bromomethyl)-2,2′-bipyridine (**62**), was followed by treatment with [Pt_2Me_4-(μ-SMe)$_2$] (**63**) to transform the new bipyridine moieties into dimethylplatinum complexes (Figure 38). The products were characterized by UV−visible spectroscopy, NMR and GPC. Alternatively, the reaction of **62** and **63** together led to the uncontrolled assembly of a hyperbranched polyplatinum complex, although its structure was not characterized, due to insolubility.[161]

D. Self-Assembly of Dendritic Monolayers and Multilayers

Due to the their large size and globular shape, dendrimers and hyperbranched polymers are attractive building blocks for the construction of monolayer or multilayer films. For example, Regen and co-workers[162] employed amine-terminated PAMAM dendrimers to construct multilayer materials. The fabrication of these multilayers involved a repetitive activation with K_2PtCl_4 on a silicon wafer containing primary amino groups on the surface, followed by deposition of the PAMAM dendrimer (Figure 39). The film thickness was shown by ellipsometry to increase linearly as a function of the number of cycles performed. Multilayers with a thickness close to 800 Å were constructed by using the fourth or sixth generation PAMAM dendrimers with 16 or 12 cycles, respectively. The elemental composition of the multilayers was examined by X-ray photoelectron spectroscopy (XPS) after 4.5 and 5 cycles to demonstrate the incorporation of PAMAM dendrimers into the multilayers. The Pt^{2+} layer was also shown to be present and compulsory because no measurable layer growth was detected if the activation cycle was eliminated.

In a different approach, Crooks, Bergbreiter, and co-workers[163] modified a mercaptoundecanoic acid (MUA) self-assembled monolayer (SAM) by covalently linking hyperbranched dendrimers to its surface. Thus, the carboxylic acid groups of the SAM were activated and reacted with amine-terminated poly(*tert*-butyl acrylate). Hydrolysis of the ester groups with *p*-toluenesulfonic acid afforded the first layer of branched polycarboxylic acids. Repetition of this reaction sequence led to the formation of a thick and compact hyperbranched polymer layer. Each intermediate was examined by FTIR external reflection spectroscopy (ERS) and its composition was confirmed by elemental analysis using XPS. As the iterative reactions proceed, the ellipsometric thickness was shown to increase exponentially with a high density of functional groups on the surface. These modified SAMs terminated with carboxylic acids were demonstrated to be capable of further modification or to bind metal ions.

Similarly, Crooks and co-workers[164] modified the MUA-SAMs with amine-terminated PAMAM dendrimers through amide linkage (Figure 40). FTIR-

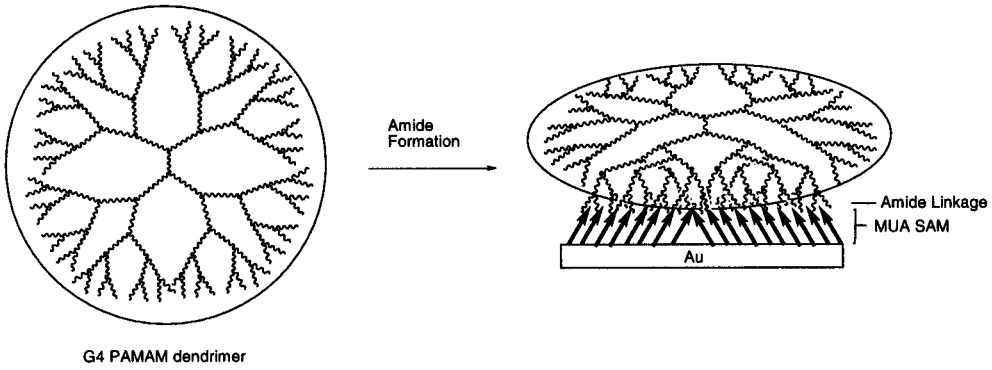

Figure 40. SAM modified with amine-terminated PAMAM dendrimers.

ERS studies indicated that the original carboxylic acid surface was almost completely reacted to form amide bonds. It was shown that the dendrimer diameter and ellipsometric thickness correlated well with amide I and II peak area, illustrating the formation of a more spherical dendrimer monolayer as the generation increases. The surface reactivity of these dendrimer-modified monolayers through the Michael addition to methyl acrylate was measured by monitoring the ester peak by FTIR. No surface reactivity was observed in the low generation monolayer, but the reactivity increased linearly as a function of dendrimer radius for the high generation dendritic monolayers. These results suggest that the smaller dendrimers are extended and fully react with the SAM, but the larger dendrimers become more globular with only a fraction of amino groups linking to the SAM. The responses of these dendrimer-modified SAMs to several volatile chemicals were evaluated through a surface acoustic wave (SAW) mass balance. The results showed that the monolayers possessed the necessary requirements for a chemical sensor: selective, rapid, and reversible responses with excellent signal-to-noise ratios.

Besides functioning as sensors, dendrimer-modified surfaces can potentially be applied to the chromatographic separations,[165−168] as catalysts, and as multiple redox reaction centers.[169]

IV. Conclusions and Future Developments

Dendrimers are a new class of aesthetically appealing macromolecules. A diverse array of repeat monomers has been used to make dendrimers, and indeed much of the initial efforts in this area have focused on synthesis. Now that such a wide range of dendritic macromolecules are available, from purely organic dendrimers (i.e., C, H containing) to those substituted with heteroatoms,[170−180] and organometallic units (*vide supra*), attention is shifting toward the properties and applications of these novel polymers. As described herein, the novel architecture of dendrimers can serve as a versatile platform for endo- or exo-receptor−substrate (host−guest) interactions. For example, the endo-receptor properties were exploited in the design of novel encapsulation agents and as models of protein function, whereas the exo-receptor properties were used in the design of artificial gene-transfer materials, multiligand arrays, and MRI contrast agents. In addition, dendrimers have been employed as building blocks for the self-assembly of several larger nano-and mesoscopic structures, including mono- and multilayers, micellar aggregates, and discrete hydrogen-bonded superstructures. The rational design of supramolecular systems that use polymers is clearly an emerging area with unlimited possibilities for fundamental new discoveries and practical applications.

The field of dendrimer chemistry is currently in an explosive growth phase. Important applications will likely emerge in the next few years in diverse areas including materials science and the biomedical sciences. The most successful new developments are likely to capitalize on a particular unique feature of the dendrimer architecture, for example, the recent use of the multiple surface groups as antennae for photoinduced energy or electron transfer.[181,182] In this regard, it will be particularly interesting to see if dendrimers built from AB_2 monomers or containing chiral surface groups are useful in chiral recognition and enantiomer separations.[183−191] New polymer architectures with dendritic components can also be expected. For example, dendrimers can be used as polymerizable building blocks for the construction of a novel type of hybrid polymer.[192,193] Dendrigrafts, including the comb-burst dendrimers, are a subclass of dendritic polymers with particularly high molecular weights yet some retain their water solubility and may be useful as high capacity unimolecular micelles.[194,195]

Despite a shift in focus toward property discovery and applications, the importance of new synthetic methods will continue to be important until dendritic polymers can be produced cheaply on industrial scale. Two areas where improvements are critically needed is in the efficiency of dendrimer construction and in monomer cost. In the former, much progress has been recorded in the last 2−3 years. For example, dendrimer synthesis via an orthogonal coupling strategy eliminates protection or activation steps, thus greatly reducing the number of synthetic and purification steps required.[196] At the same time, methods for the preparation of hyperbranched polymers with low polydispersities have appeared recently and improvements in this area are likely.[197−201] A totally unexplored area in polymer chemistry is the synthesis of combinatorial libraries. The combinatorial approach to polymer synthesis represents a particular challenge, but one which should greatly facilitate property discovery.

V. Acknowledgments

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