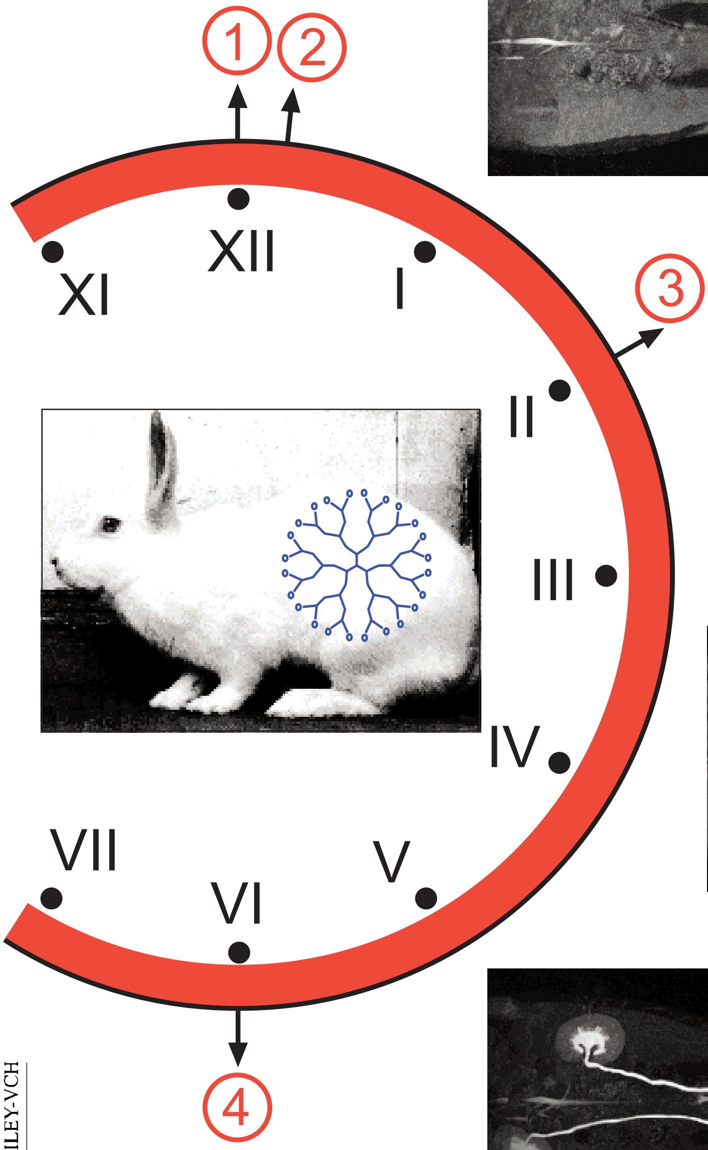
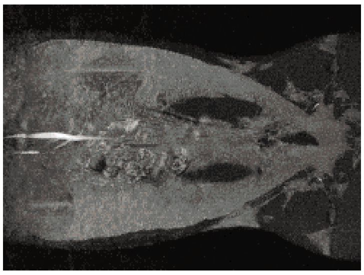
- Dendrimers -

From Design to Application

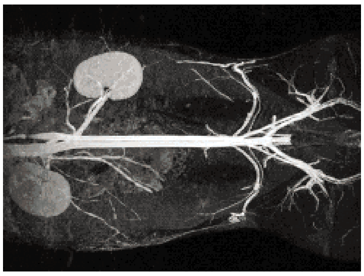
Dendrimers as Magnetic Resonance Imaging (MRI) Contrast Agents





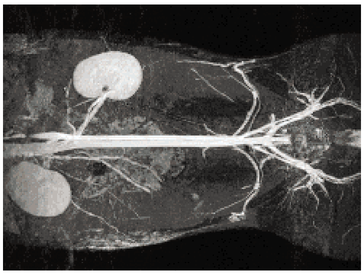
① before injection

base line, no blood vessels observable



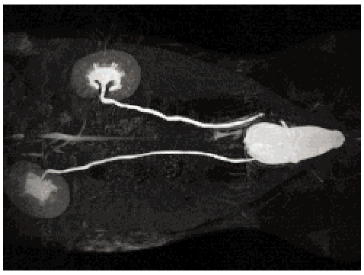
② 1 min post injection

contrasted image of the bloodstream



③ 10 min post injection

after 10 min still high contrast



④ 30 min post injection

contrast agent is almost completely washed out from the bloodstream and is only left in the kidney and the bladder

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Dendrimers: From Design to Application—A Progress Report

Marco Fischer and Fritz Vögtle*

Two decades ago a repetitive strategy for the synthesis of cascade molecules succeeded for the first time, and a rapid increase in the chemistry of dendrimers began. In the beginning the work was concentrated on the synthesis of dendrimers with new skeletons in high generations, but the tailoring of dendrimers to certain applications soon started. Here we would like to take stock and examine the latest developments in this research field. Therefore, we report on topical works to show the many facets of modern dendrimer chemistry. Dendrimers have also become commercially available, and the first applications have emerged. A contrast agent for magnetic resonance imaging (MRI) to visualize the bloodstream in the body is probably the most spectacular progress. Since specific properties of dendrimers were used for this process, this development could be at the leading edge of new applications. In the future dendrimers will generally be used more as anchor groups than they are hitherto, since dendritic building blocks allow the attachment of many substituents unlike the carbon tetrahedron (four substituents) and the benzene core (six substituents). Thus it is possible to enhance physical properties. As a tree can be full of blossoms and fruit, dendrimers can multiply functions. Undoubtedly it is more difficult to develop new functionalities for desired effects than to obtain new properties by multiplying known functions. When the orderly synthetic attachment of particular, many, selected, or different moieties on fractal central units can be controlled better than hitherto, and when analytical methods can distinguish between very similar dendritic isomers ("dendrimer libraries") and detect structure defects more easliy and more precisely, then the progress ought to be even more ingeniously tempestuous than it is currently.

Keywords: chirality · dendrimers · nanostructures · supramolecular chemistry

1. Introduction

Dendrimers, originally referred to as cascade molecules and arborols, have now been known for two decades.[1] After the publication of the first papers,[2] which dealt with the development and the realization of this fundamentally new molecular architecture but which were limited by the little developed analytical methods, the progress in this research field proceeded slowly at first and then from the early 1990s more rapidly (Figure 1).

In the meanwhile a variety of dendrimers with different cores, branching units, and end groups have been synthesized (Figures 2–4). The best known representatives, poly(amidoamine) dendrimers (PAMAM) and poly(propyleneimine) dendrimers,[3] are produced in kilogram scale and distributed commercially.

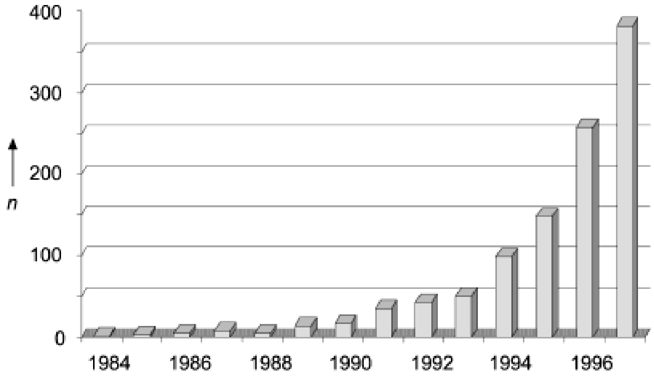

Figure 1. Number *n* of publications on dendrimers obtained from a CAS-Online search.

In accordance with the great attention that this new type of molecule has rececently attracted, reviews that summarize the whole field[1, 4a–c, i–l] and important parts[4d–h] have been published. Therefore we would like to deal mainly with the most recent works, topical structure investigations, as well as trends and applications. We hope to convey the latest developments in this still-progressing research field.

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[*] Prof. Dr. F. Vögtle, Dr. M. Fischer
Kekulé-Institut für Organische Chemie und Biochemie der Universität
Gerhard-Domagk-Strasse 1, D-53121 Bonn (Germany)
Fax: (+49) 228-73-56-62
E-mail: voegtle@uni-bonn.de

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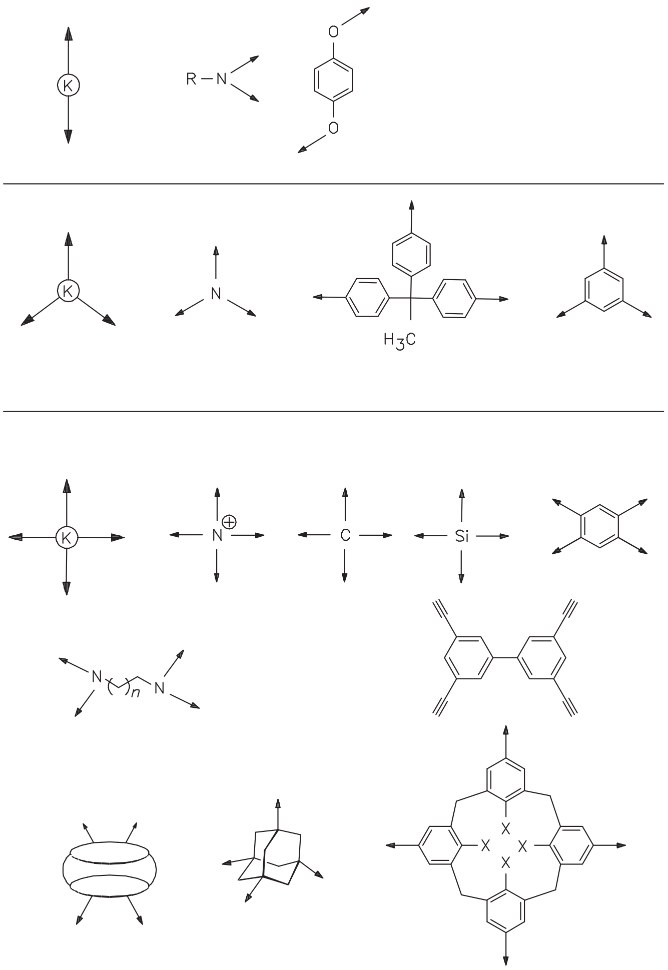


Figure 2. Overview of di- to tetracovalent core units K used in synthesis.

2. General

The term "dendrimer" (greek: dendron = tree, meros = part) graphically describes the architecture of this new class of molecule. Although the earlier name "cascade molecule" is more suitable to design their own nomenclature,[1] the expression "dendrimers" has been established in the meantime. Generally these molecules emanate from a core (Figure 2–3), and like a tree they more and more ramify with each subsequent branching unit (generation, Figure 4). There are two fundamentally different construction concepts:

1) The divergent method[2] in which one branching unit after another is successively attached to the core molecule, hence the multiplication of the number of peripheral groups is dependent on the branching multiplicity (usually 2 or 3). This way the dendrimer can be built up step by step until steric effects prevent further reactions of the end groups (starburst effect, see section 3).
2) The convergent method,[5] which takes the opposite course. The skeleton is constructed stepwise starting from the end groups towards the inside and is finally treated with a core molecule to yield the dendrimer.

Problems occur in the divergent synthesis from an incomplete reaction of the end groups, since these structure defects accumulate with the build-up of further generations. Because the by-products reveal similar physical properties, chromatographic separation is not always possible. Hence, higher generations of divergently built-up dendrimers always contain certain structure defects (see Section 3).[9] In the convergent course, however, a segment growing with each reaction step is coupled with only one branching unit. Thus, this approach facilitates the removal of undesired by-products, for example,

F. Vögtle M. Fischer

Fritz Vögtle, born in Ehingen/Donau (Germany), in 1939, studied chemistry in Freiburg as well as chemistry and medicine in Heidelberg. There he received his Ph D for research with Heinz A. Staab in 1965 on the valence isomerization of double Schiff bases. After his habilitation on steric interactions inside cyclic compounds, he was professor in Würzburg from 1969 to 1975. He then accepted a position as full professor and director of the Institut für Organische Chemie und Biochemie in Bonn. He obtained a "literature award" for his book "Supramolekulare Chemie" (translated into English, Japanese, and Chinese) and the Israeli Lise Meitner-Alexander von Humboldt-award. He is co-author of the books "Dendritic Molecules" and the eleven volume series "Comprehensive supramolecular Chemistry". His research interests are supramolecular chemistry, deformed helical molecules (cyclophanes) and their chiroptical properties, compounds with appealing architectures, catenanes, rotaxanes, and, last but not least, dendrimers.

Marco Fischer was born in 1970 in Zell an der Mosel (Germany) and studied chemistry in Bonn between 1990 and 1996. During this time he received a scholarship from the Professor-Rhein-Stiftung, Königswinter. He did his diploma thesis in the group of F. Vögtle and worked on the synthesis of new functional poly(propyleneimine) dendrimers. He is currently doing his Ph D in the same group on the synthesis, structural analysis, and supramolecular interactions of new functional dendrimers. He worked for some months on dendrimers with Professor Kari Rissanen, University Jyväskylä, and with Professor Kazuhisa Hiratani, University Tsukuba, Japan.

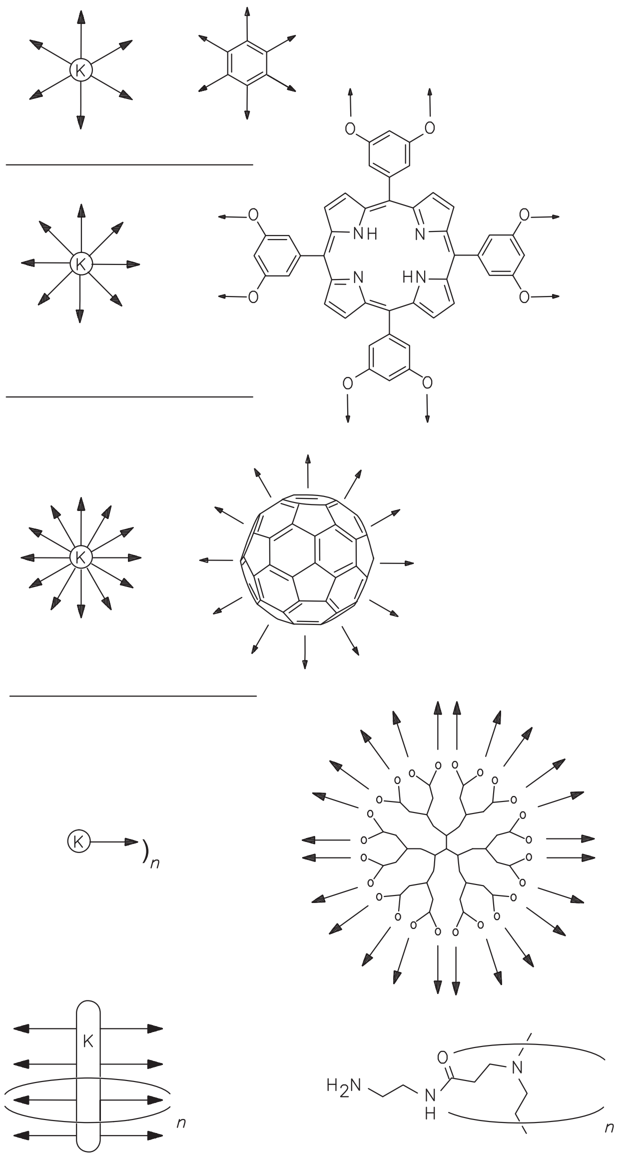


Figure 3. Overview of hexacovalent and larger core units K used in synthesis.

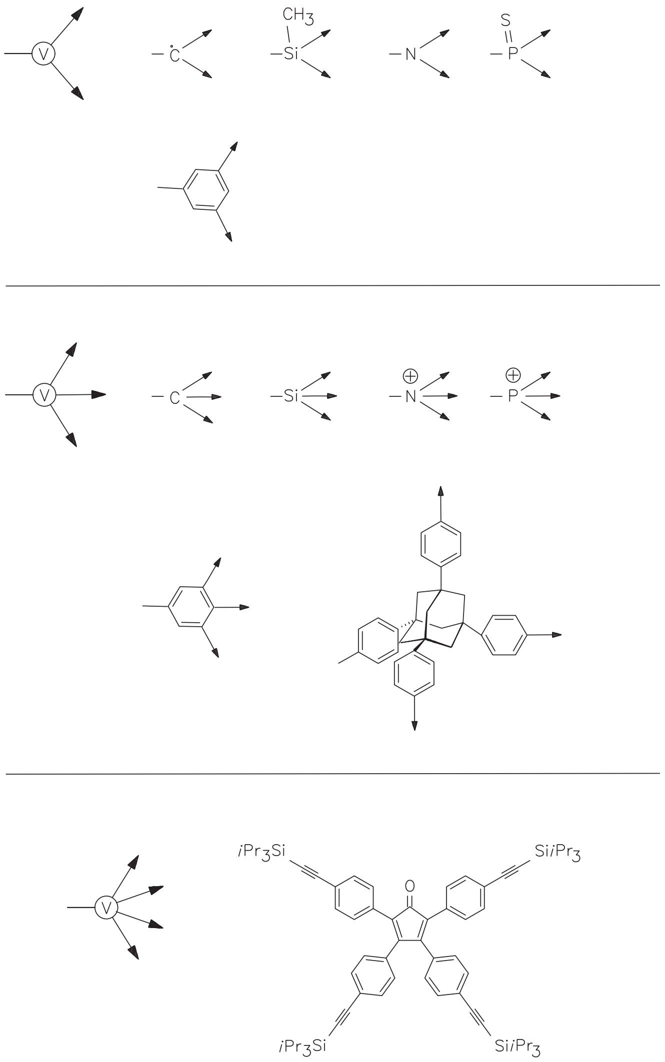


Figure 4. Overview of branch units V used in synthesis.

by means of gel permeation chromatography (GPC), though it does not allow the formation of as many generations as the divergent method because of steric problems that arise from the reaction of the segments and the core molecule.

After 20 years, a variety of dendrimer skeletons, organic, inorganic as well as organometallic ones, has now been produced; a selection of core and branch cells is given in Figures 2–4 to give a general idea of the wealth of possibilities.

3. Structural Analysis

Higher generation dendrimers reach molecular masses that in earlier days had not been accessible through directed organic reactions, apart from through polymerization reactions, which lead to products with a broad distribution of molecular masses (polydisperse).[6] They are modelled on natural globular biomacromolecules that are able to perform certain functions as a consequence of their defined three-dimensional formation through hydrogen bonds. Hence, the three-dimensional structure of high-molecular compounds, such as dendrimers, is of great interest, since the dendrimers differ from biological macromolecules, such as proteins, in their three-dimensional covalently linked skeleton. According to an early theoretical work[7] on idealized structures, it was postulated that dendrimers of lower generations take a rather flat, ellipsoidal shape. Assuming that in divergently synthesized dendrimers each branch is directed radially towards the outside and that the end groups lie on the surface of an ellipsoid, the macromolecules transform into a more spherical shape from a certain generation upwards (depending on the core molecule, branching multiplicity, and the length of the branch segment). Simple calculations[41] have shown that the area of an end group on this ellipse becomes continually smaller with an increasing number of generations until a critical branched state, the so-called “Starburst dense packing”, is reached and prevents any further reaction. Hence, the molecules are meant to be spherical constructions with a dense exterior and a loose interior with channels and cavities. Experimental results, for example, the inclusion of guest molecules and the viscosity, confirm this assumption. Thus, dendrimer chemistry has become a part of supramolecular chemistry.

More recent methods of structural analysis have revealed additional information that has revised this idea of dendrimers in some respect. In fact X-ray and neutron small-angle scattering experiments[8] have shown that the higher generations of PAMAM and poly(propyleneimine) dendrimers have a spherical shape. The electron density distribution, however, differs significantly from the model of a dense exterior and a loose interior. The electron density profile reveals a high electron density near the center and a continuous decrease towards the outside. The extension of the high density area is dependent on the generation number. These results instead correspond to the picture of a spherical construction that has the highest density in the inside and a fractal surface. Therefore, the inclusion of guest molecules can be explained by changes in the flexible dendritic arms, the terminal groups of which are observable not only on the surface, but, according to more recent calculations, also in the whole volume of the dendrimer.[8c]

Meijer et al.[9] succeeded in obtaining detailed information on the structure of poly(propyleneimine) dendrimers by means of ESI mass spectrometry. These experiments have shown that the fifth generation dendrimer is of comparatively high purity, but structural defects arise from statistical accumulation after 248 reaction steps so that in principle only 20 % of the molecules are structurally perfect. In contrast to polymers, these dendrimers with a polydispersity of 1.002 can be considered as approximately monodisperse. Consequently, a higher generation dendrimer cannot be regarded as absolutely structurally perfect, but rather as a highly ordered system with a high number of easily accessible functional groups.

4. New Types of Dendrimers

More recently most of the research groups have started to synthesize functional representatives of some established dendritic skeletons. They are particularly interested in new molecular properties that arise from the multiplicative effect of peripheral functionalities that are easily accessible or from steric shielding of the reactive center by a dendritic shell.

Nevertheless, compounds with extraordinary properties could also be produced with new molecule skeletons. Majoral et al. have shown that the preparation of particularly high generations (up to generation ten) of a dendrimer is possible based on divalent phosphor branch junctures.[10a] This molecule has the remarkable property of reacting with a large variety of functional groups. By coupling the tenth generation (3072 end groups) with a diphenylphosphanyl unit and complexing gold(I) chloride a complex could be obtained that contains up to 3072 gold ions; the size of the complex has been determined by high resolution electron transmission microscopy to be about 15 nanometers (150 Å). Correspondingly, they managed to synthesize multipalladium, -platinum, and -rhodium complexes by grafting diphosphane units onto lower generations of the dendrimer.[10b] The free accessibility to the individual binding sites of the metal complexes could be proved by means of complete ligand exchange reactions. Experiments to investigate the catalytic activity of these compounds are still required. New prospects arise from the possibility of supplying each terminal group of these dendrimers with three different functionalities so that several active units with variable properties result.[10c] Polyalkylations that were successfully carried out to yield polycationic compounds have revealed the interior of the molecule to still be freely accessible, despite the high generation numbers.[10d] Very recently the same group even succeeded in divergently building up new dendrons inside the skeleton (Figure 5).[10e]

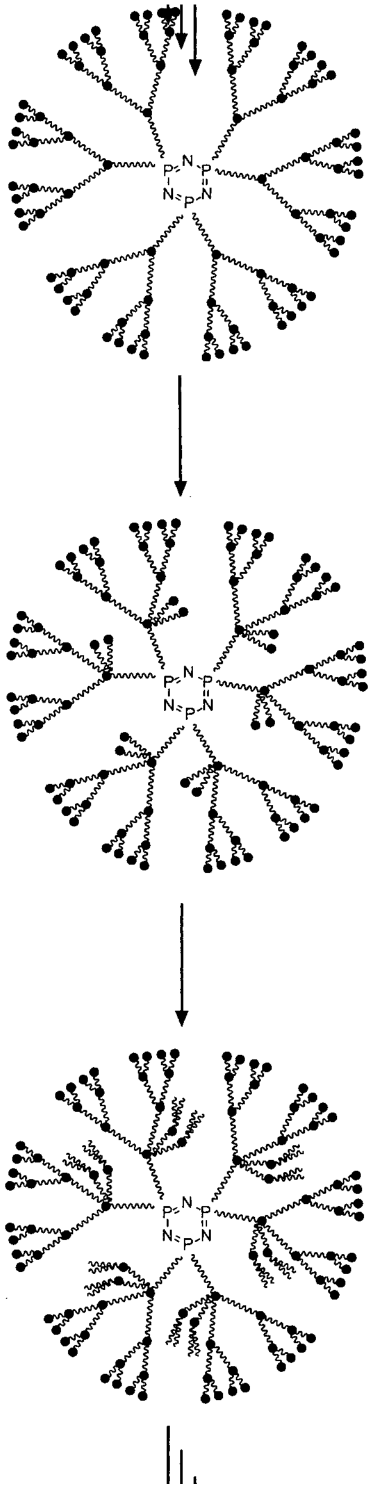


Figure 5. Divergent construction of dendrons inside a dendrimer skeleton.

This fact demonstrates the flexibility of the phosphorus dendrimer skeleton and its easily accessible interior. Therefore, a functionalization inside the covalent skeleton can be carried out in this way.

The possibility of grafting different functionalities onto existing dendritic systems has also been demonstrated by our own group.[11] The reaction of all primary amino groups on the periphery of poly(propyleneimine) dendrimers has been achieved by coupling with different sulfonic acid chlorides. The sulfonamide units obtained permit the remaining SO_2NH protons to be simply substituted by benzyl halides under mild conditions so as to variably functionalize the surface of the dendrimer. The application of various substituted sulfonic acid chlorides has been tested, and hence this way represents a method for the specific, doubly different multifunctionalization of a thoroughly examined dendritic system.

Müllen et al.[12] developed dendritic hydrocarbon skeletons of nanometer size that consist exclusively of linked benzene rings and act as interesting precursors to polycyclic aromatic systems that are difficult to access by any other way. The hydrocarbon dendrimers were constructed by Diels–Alder reactions of a substituted cylopentadienone derivative and an acetylene unit (as the dienophile). In the beginning they succeeded in the preparation of dendrimers up to the second generation with 62 benzene rings[12a] and later even the construction of dendrimers up to the third generation with 142 benzene units and a molecular mass of about 16600 amu succeeded.[12b] Further research concentrated on even using a cyclopentadienone derivative as a tetravalent branch juncture (Figure 6).[12c] This multiplicity had only been achieved previously by moieties based on heteroatoms.[13] The second generation benzene dendrimer obtained in this way already consists of 102 benzene rings, and according to force-field calculations it is of a rigidly spherical shape. Its thermal stability is remarkable, even in the presence of atmospheric oxygen it only decomposes at temperatures above 580 °C.

4.1. Synthetic Strategies

In addition to the common synthetic concepts described in the second section for constructing dendrimers there are some other approaches. In all cases the dendrimer skeleton is built up in a repetitive manner, namely, after one reaction a further step for the deprotection or activation has to be carried out.[14] The "orthogonal coupling" method is an effective synthesis that alternately uses two different branch cells with complementary coupling functionalities (Figure 7).[15] For this strategy the functionalities and the coupling products have to be inert under the reaction conditions of the second functionality pair. This way the dendrimer skeleton can be constructed either divergently or convergently depending on the target molecule.

Bradley et al.[16] reported on a solid-phase synthesis analogous to the Merrifield peptide synthesis,[17] which had earlier been applied to polylysine dendrimers by Tam.[18] This method allows the use of a large excess of reagents to achieve complete reaction without causing any purification problems. By connecting a group that was unstable to acid to the resin, the separation was guaranteed, and it was possible to synthesize a polyamide dendrimer up to the fourth generation.

Reinhoudt et al. have reported on an entirely new synthetic concept. They have carried out the synthesis of an organometallic dendrimer up to the third generation as a one-pot reaction by the controlled association of the building blocks through coordinative bonding.[19] This method is based on the self-assembly of the branching units in which an unstable coordinative cyano group and two terdentate diorganylsulfide-palladium complexes are covalently linked (Figure 8). A chloride ion that occupies the fourth coordination site of the palladium atom prevents the cyano group from being bound. After the building block has reacted with the core cell, however, the chloride ion can be removed in situ by the addition of silver tetrafluoroborate. Hence, by repeating the sequence stepwise a dendrimer of higher generation can be prepared without the usual work-up. Comparable investigations on the one-pot synthesis of polyamide dendrimers by melt polymerization of an acrylic acid derivative merely resulted in hyperbranched polymers with a broad molecular mass distribution.[20] Such a one-pot reaction is desirable for a commercial application for economic reasons, since the high expenses of a dendrimer being synthesized in many repetitive steps restricts the possible applications to a few special fields such as medicine and diagnosis (see Section 7).

4.2. Nano Structures

Nanometer-sized molecular architectures prepared by "dendronizing" linear polymers have been examined by

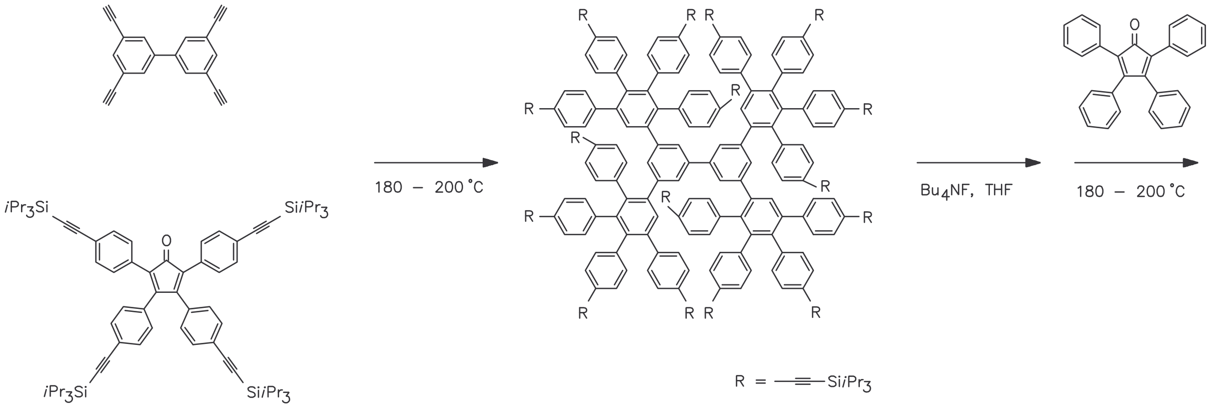


Figure 6. Divergent synthesis of a dendrimer that consists only of benzene units.

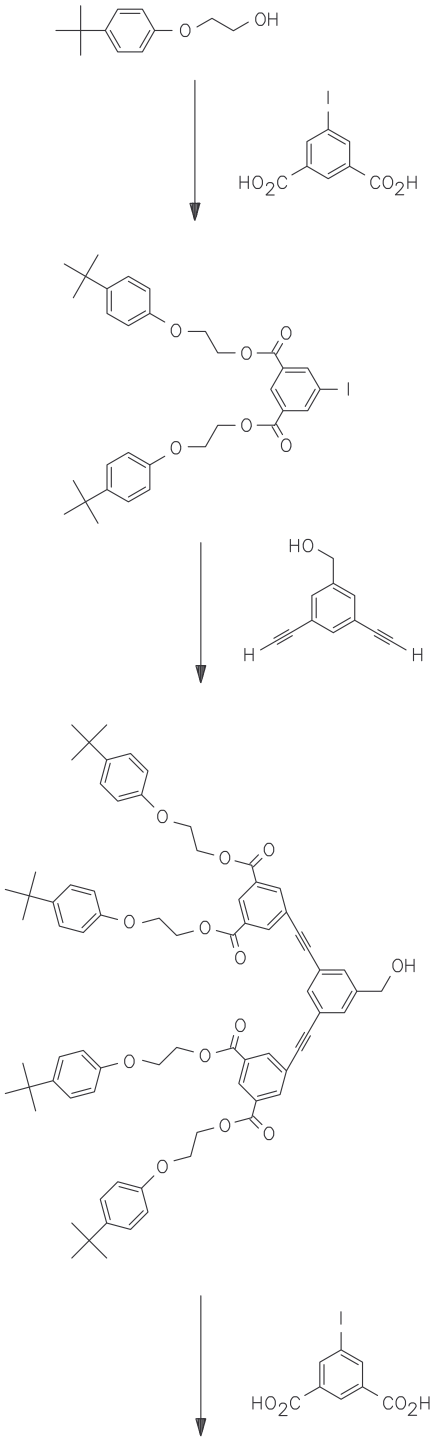


Figure 7. Orthogonal synthetic strategy (convergent and divergent).

several groups.[21] These macromolecules can be considered as dendrimers with a polymeric initiator core or—from a different point of view—as comb polymers with dendritic side arms attached to it. Two synthetic routes are employed to produce these molecules. Either a convergently prepared dendrylic substituent is coupled with each monomer moiety of the polymer chain or a dendron carrying a monomer moiety at the focal point is polymerized by standard methods. Schlüter et al. demonstrated the advantages and disadvantages of the two concepts by synthesizing poly(*p*-phenylenes) with third generation Fréchet-type dendrons (Figure 9).[22] This work has shown that third generation dendrons cannot be homogeneously connected to each monomer moiety of the polymer chain because of steric effects. Generally, this problem did not occur in the polymerization of dendriticly substituted mono-

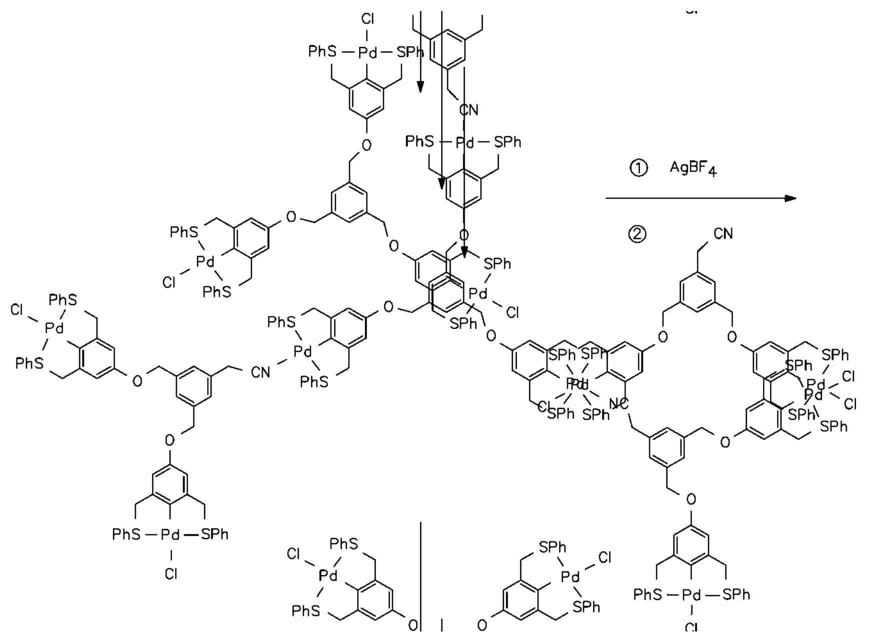
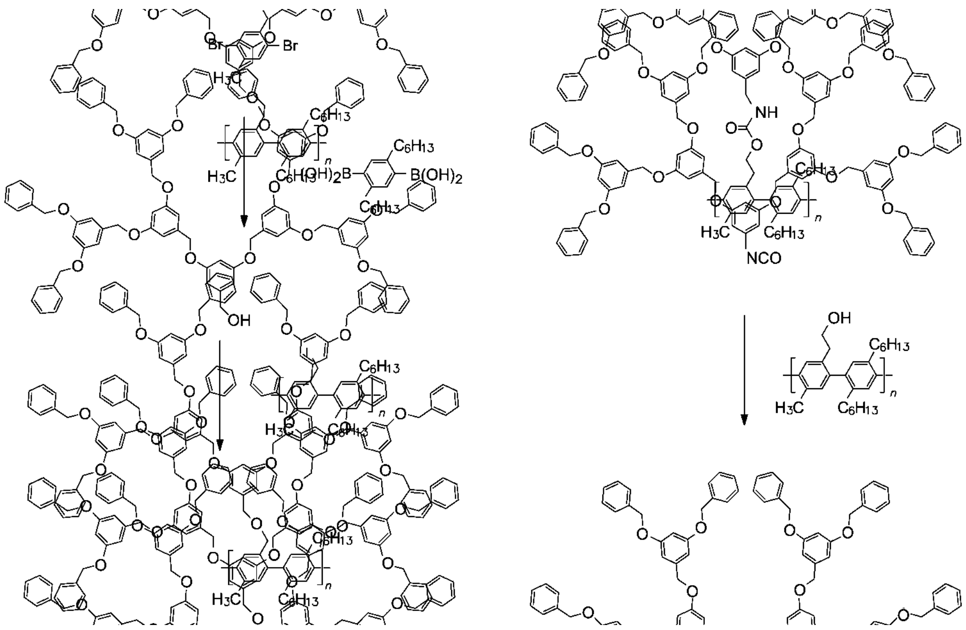


Figure 8. Construction of metallodendrimers by a one-pot reaction.



mers. In this synthetic route, however, only products with low degrees of polymerization could be obtained. The structures prepared this way have the remarkable property that as a consequence of the steric demand of the substituents the polymer chain is forced to take up a stretched form. Furthermore, the macromolecules exist as nanometer-sized rigid cylindrical particles.

Diederich et al. succeeded in preparing oligo(triacetylenes) by polymerization, as well as those substituted with first to third generation Fréchet-dendrons.[23] They build a kind of insulating layer for the conjugated oligo(triacetylene) without changing the elctronic properties of these conductive oligomers. Another preparative method has been presented by Tomalia et al. where they divergently constructed a dendrylic substituent on a linear poly(propyleneimine) with a degree of polymerization of between 100 and 500.[24] By means of electron transmission microscopy the shape of the polymer chain was observed to depend on the generation of the substituent. The shape changed from a spaghettilike entangled polymer to slightly elongated nonspheric clusters and rodlike shapes in the fourth generation. The latter line up in bunches parallel to each other, and represent an example of the self-assembly of nanometer-sized particles on a surface.

The aggregation of negatively and positively charged porphyrin dendrimers in solution through electrostatic interactions has been described by Aida et al.[25] The group noticed an increased transmission at 500 nm on mixing stoichiometric amounts of the two compounds together. Furthermore, fluorescence microscopic pictures showed 10–20 µm large aggregates that crystallized from the solution after some time. In the case where there is an excess of one of the dendrimers exact spectroscopic analyses revealed that not more than four molecules

Figure 9. Variants on the synthesis of dendritically substituted poly(*p*-phenylenes) (dendrimers with a (comb) polymer as the core cell).

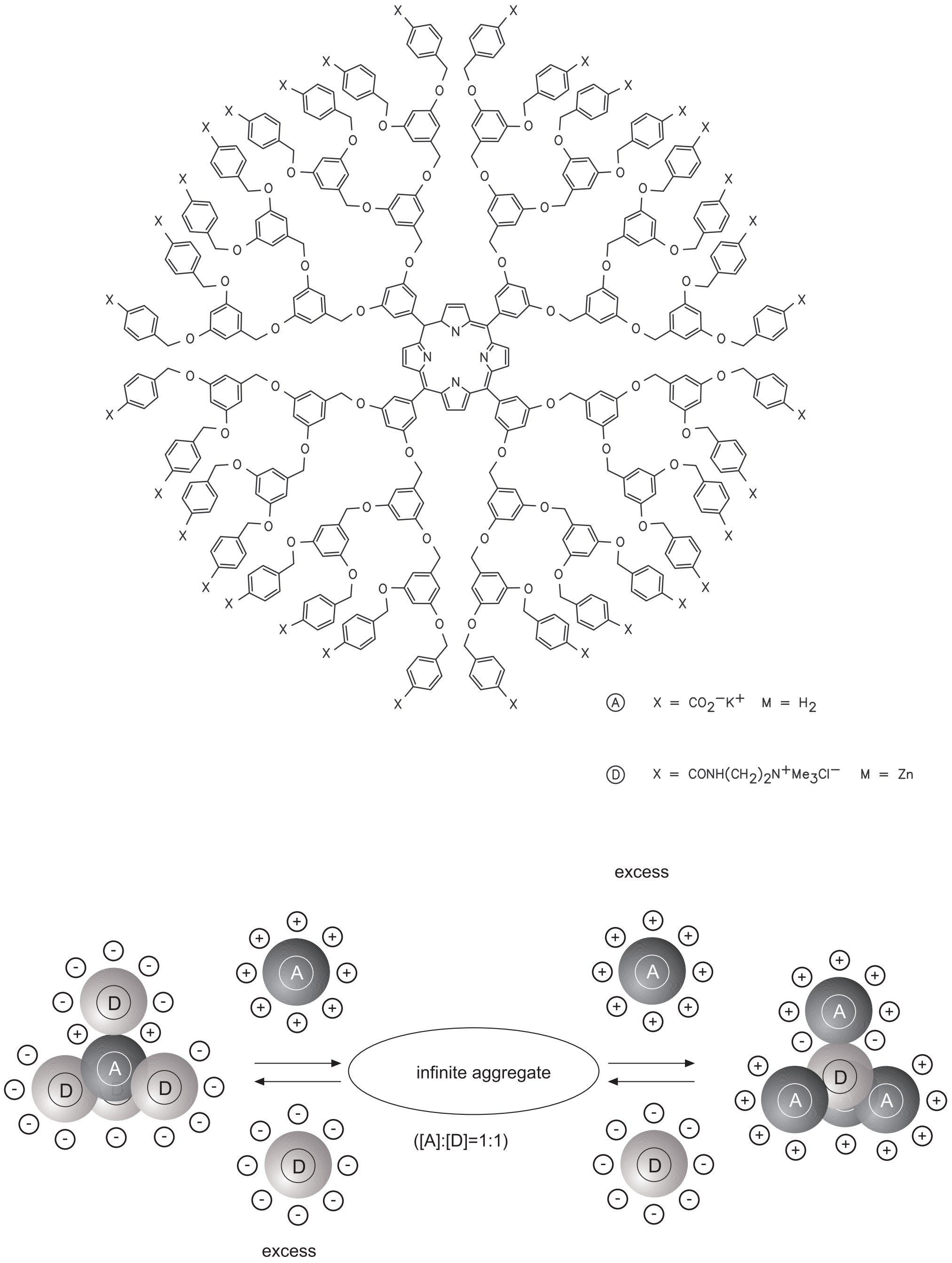


Figure 10. Electrostatic association of functionalized porphyrin dendrimers in solution.

of the excessive dendrimer interact with the other one and transfer energy (Figure 10). The formation of nanometer-sized aggregates, however, only occurs if both of the molecules that transfer energy between each other are present in stoichiometric ratios.

Percec et al. worked on the supramolecular formation of dendrons in the liquid-crystal state.[26] They described the properties of dendrons with tapered shapes and focal receptor moieties (Figure 11). This molecular architecture was obtained by using gallic acid as a branch juncture and long exterior alkyl chains. After covalently attaching a focal crown ether unit, the self-assembly of first generation dendrons to form cylindrical architectures was observable from their interaction with alkali metal ions by means of X-ray scattering experiments.[26a] In the melt these substances show liquid-crystalline behavior, the thermodynamic parameters of which allowed the formation process to be analyzed. By employing different functional groups at the focal position or on the periphery of the dendrons, different supramolecular interactions, such as hydrogen bonds, hydrophobic and fluorophobic effect, or ion complexation by crown ethers, could be compared and their energetic effect on the self-assembly could be evaluated. Based on these results, Percec and coworkers succeeded in polymerizing monomeric units that

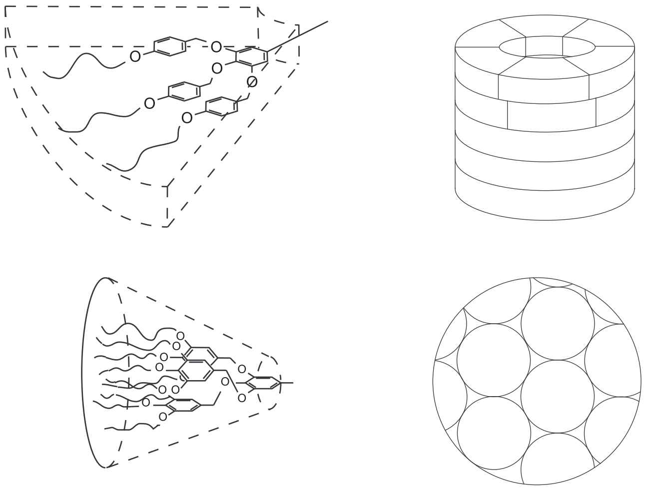


Figure 11. Self-organization of structurally different dendrons in the melt.

were focally attached to analogous dendrons to yield cylindrical structures with liquid-crystalline properties.[26b] Further construction of these gallic acid dendrons up to the fourth generation and additional studies revealed that in the melt they arrange to form supramolecular dendrimers in a form analogous to spheric micells (Figure 11).[26c] The formation of a new type of liquid-crystalline phase with cubic symmetry has been observed. The respective number of conical dendrons in these phases could be estimated by electron-densitiy measurements.

Most recently Percec et al.[26e] have successfully visualized the structures described above by electron microscopic methods. By means of atomic force microscopy,[26f] they tried to solve the geometry of polymerized, conical second generation dendrons[26d] and found a correlation between their structure and the degree of polymerization: At a low degree of polymerization a spherical molecule exists while at a higher degree a cylindrical molecule exists. This way the macroscopic architecture can be synthetically controlled.

These intermolecular associations in the liquid-crystalline state and the particular properties resulting from it are also in the focus of other research groups and under intensive investigation.[27] In addition to the main-chain and side-chain liquid-crystal polymers, dendritic systems represent a third group of liquid-crystalline, high-molecular compounds. In principal, liquid-crystalline properties can be achieved by a form-resistant, disclike skeleton,[27a–e] mesogenic, flexible units as branch junctures,[27f] or by functionalizing the dendrimer periphery with mesogenic units.[27g–i]

4.3. Combinatorial Chemistry

The idea of using dendrimers as a homogeneous soluble carrier for combinatorial libraries has been realized by Kim et al.[28] to produce a small substance collection, based on Fischer's indole synthesis, with modified PAMAM dendrimers as carrier substances. Therefore they successively employed three *N*-protected aminoacids, three keto carboxylic acids, and three hydrazine derivatives in a split synthesis. As a consequence of the solubility of the compounds the substances formed could be separated by size exclusion chromatography and resulted in a library of 27 compounds. The more reasonable ratio of carrier material used to substance yield and the possibilty of permanently controlling the reaction by spectroscopic methods is advantageous compared with the solid-phase synthesis. An automation of this process is also possible.

A strategy for specifically varying certain properties, such as solubility, viscosity, or reactivity, for desirable applications has been found by Newkome et al.[29] This group attached a triple branch juncture to poly(propyleneimine) dendrimers and were able to graft on additional functionalities (Figure 12). By using mixtures of this branch juncture and different end groups the outer layer of the dendrimer can be changed by a kind of combinatorial synthesis to result in nanometer-sized particles with numerous different shapes and functionalities. Hence, "screening methods on specific properties" can be applied to discover new materials.

4.4. Surface Coating

The peculiarities of dendritic structures offer new possibilities to manipulate the properties of surfaces by coating them. In the formation of dendrimers at interfacial areas, either gas – water or gas – solid transitions, a change in conformation compared to that in solution has been noticed. Its extent depends on the strength of the respective interaction.[4d] The stronger the attractive forces, the more flattened the spheric shape becomes and the more it resembles a disc, so that for higher generations of elliptical PAMAM dendrimers an axle ratio of 1:3 – 6 has been observed.[4f]

To examine the sensory properties of such surfaces Crooks et al. covalently linked PAMAM dendrimers to the carboxylic groups of a self-assembling monolayer (SAM) of sulfanylundecanoic acid (mercaptoundecanoic acid, MUA) on a gold surface (Figure 13).[30a] They found on the basis of acoustic wave (SAW) mass balances that dosing this modified surface with volatile organic compounds gave the essential attributes for an ideal chemical sensor. Immediately after the addition, an answer was detected which was reversible and showed a high signal-to-noise ratio. Furthermore, the sensor material guaranteed a differentiation between acids, alcohols, and hydrophobic substances by the signal intensity. In addition it was noted that PAMAM dendrimers can be irreversibly attached to gold surfaces even without covalent binding.[30b–e] By additional adsorption of hexadecylthiol the dendrimer layer was compressed, thus distorting the molecules to flattened spheroids. Cyclovoltammetric analyses revealed them to act as reversibly switchable gates for redox-active ions, which at pH 6.3 let only $[Fe(CN)_6]^{3-}$ ions pass, and at pH 11 $[Ru(NH_3)_6]^{3+}$ ions also to exchange with electrons on the gold surface. A complete, pH-selective distinction between cations and anions has been achieved by a new ultrathin multilayer structure formed from an amphoteric polymer and covalently bound PAMAM dendrimers.[30c] At low pH values these mixed membranes were permeable exclusively to anions, whereas in high pH-value regions only cations could pass.

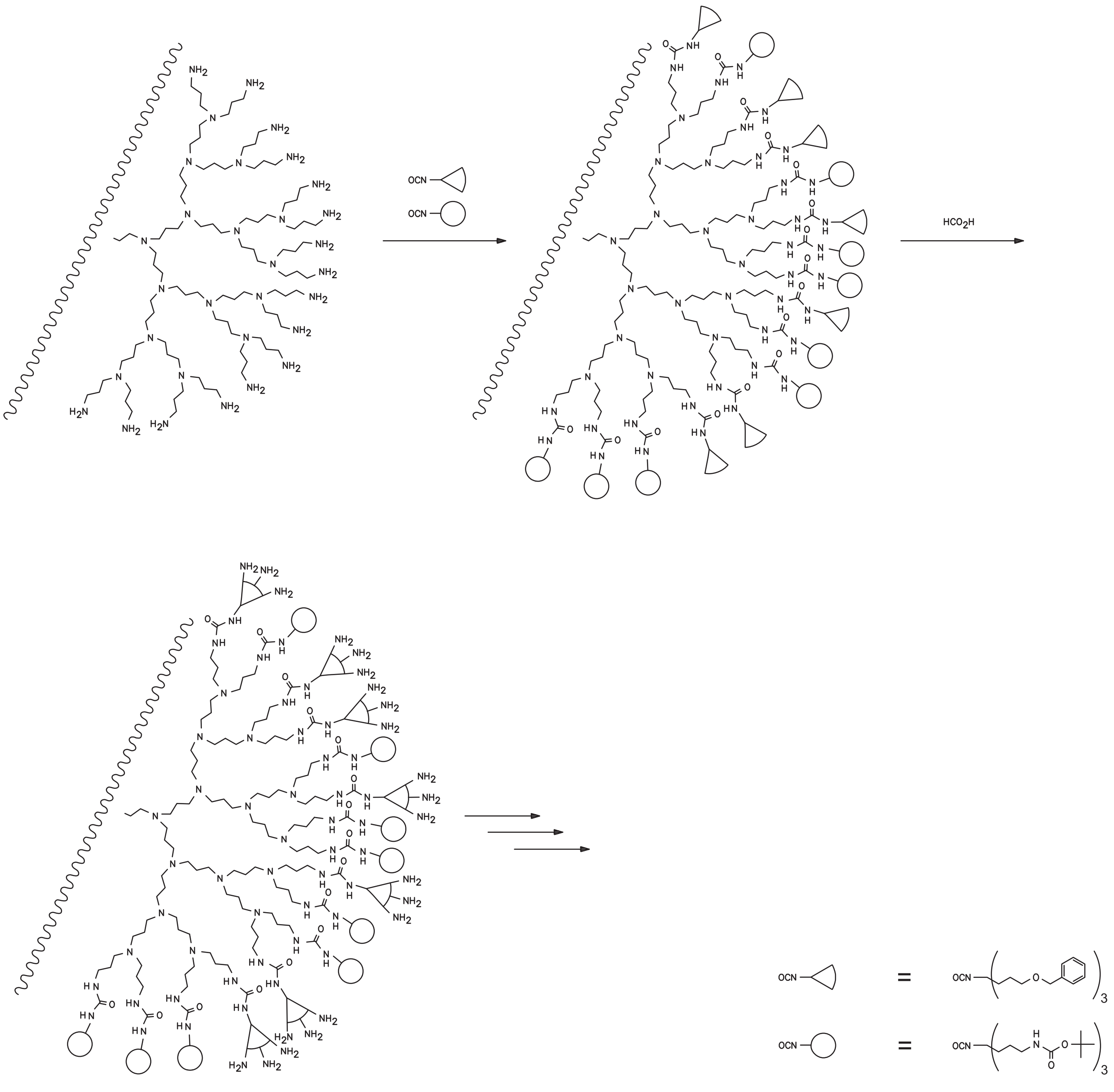


Figure 12. The grafting of additional functionalities on the surface of dendrimers.

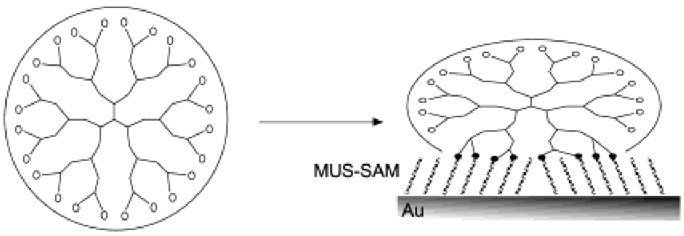


Figure 13. Covalent attachment of dendrimers to a self-assembled monolayer (SAM) of MUA molecules.

4.5. Unconventional Photoactive Systems

Molecular systems can be manipulated rapidly, mildly, and often reversibly by light. The first photo-switchable dendrimer with six azobenzene units in the periphery has been synthesized in Bonn, and the entire switching of all six groups from the *E* to the *Z* isomer has been proved.[31] Jiang and Aida,[32] as well as Junge and McGrath,[33] successfully fitted in such an azobenzene unit as the initiator core of a dendrimer with aryl ether branch junctures. The former study found a transformation into the *E* form under irradiation with ultraviolet light, although the re-isomerization under irradiation with infrared light proceeds 260 times faster than the thermal reaction at 21 °C under light exclusion. This fact has been ascribed to an antenna effect of all the peripheral aryl moieties transferring the absorbed energy through covalent bonds to the central azobenzene unit. McGrath examined the first two generations of the same system, which are not yet subject to any steric hindrance, and noted analogous photoswitchability (Figure 14).[33]

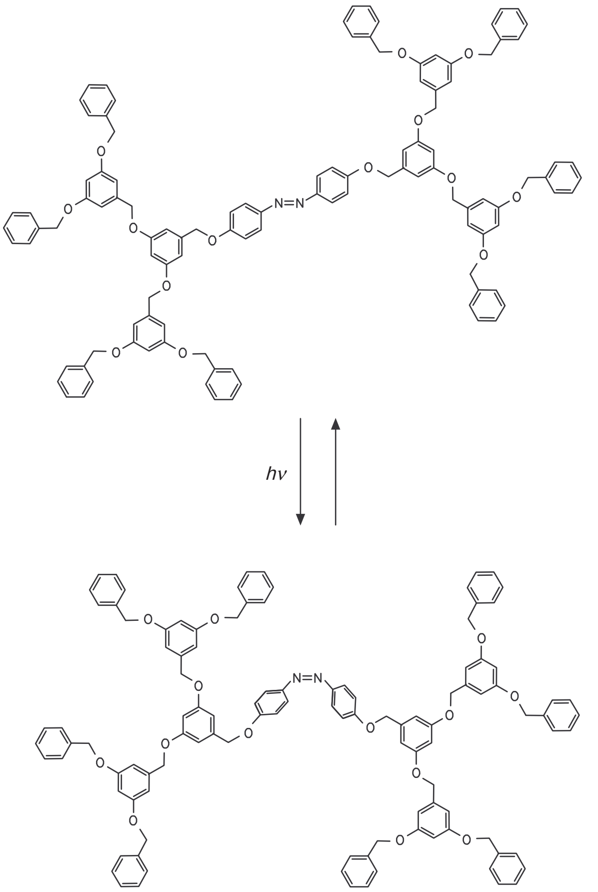


Figure 14. Photo-switchable dendrimer with a central azobenzene unit.

As recently reported by Balzani et al. and our group, no quenching effects occur even with a high number of azobenzene substituents on the periphery of a poly(propyleneimine) dendrimer and the photo-switchable units have the same properties as the monomeric azobenzene.[34] Moreover, these dendrimers with up to 32 functional groups turned out to be suitable materials for holographic data storage. Subsequent studies, that aimed to solve the host properties of the photoactive molecules, led to the discovery that in the presence of fourth generation dendrimers the fluorescence of eosin molecules is effectively suppressed.[35] This fact can be put down to the eosin being inserted into the dendrimer skeleton, since the only possible quenchers are the tertiary amino groups located there. Further evidence of this inclusion is offered by the kinetics of the photoisomerization of the azobenzene units for which eosin acts as a sensitizer. The increasing reaction rate confirms that the eosin is occluded in the dendrimer with the *Z* form of the molecule being a better host than the *E* form.

4.6. Redox-Active Dendrimers

Apart from their photochemical peculiarities, the shielding effects of redox-active moieties in the core or their multiplication on the periphery can also be subjected to further research. Whereas earlier works dealt with dendriticly substituted porphyrin or bis(terpyridine) complexes, more recently the redox behavior of dendrimers with ferrocene as the active unit has been closely examined.[4e] Morán et al. reported in 1996 on ferrocenyl-functionalized poly(propyleneimine) dendrimers with up to 64 active groups, then the highest number known for organometallic substituents on the periphery of a dendrimer.[36] The ferrocenyl functionalities do not reveal any steric effects despite the high number, and they are reversibly oxidized independently from one another at the same respective potential.[36a] By the inclusion of single ferrocenyl substituents into the the hydrophobic interior of a β-cyclodextrin host molecule, the lipophilic dendrimers have been solubilized in an aqueous solution and by this the redox properties have been changed.[36b] It turned out that all ferrocenyl units could be complexed completely up to the second generation, whereas this was impossible for higher generations because of steric effects from the large cyclodextrin molecules. Furthermore, the adsorption of the ferrocenyl dendrimers on a platinum electrode surface has been studied.[36c] Accordingly the molecules in their oxidized form are taken up in multilayers by the electrode at positive potential. On reduction they desorb into solution to leave a monolayer on the electrode. The kinetics of these processes depend on the dendrimer size. The monolayer has been examined by means of atomic force microscopy and the adsorbed dendrimers were noted to be flattened spheres (see Section 4.4). Astruc et al. observed that the ferrocenyl dendrimers can serve as supramolecular redox sensors for inorganic anions.[37] The standard redox potential changed significantly on the addition of one equivalent of salt per ferrocene unit so that it was then possible to distinguish between four different anions. To complete these analyses Cardona and Kaifer prepared monodendrons with a single ferrocene moiety at the focal position.[38] These showed a redox behavior that depended on the generation; the rate of electron transfer and the diffusion coefficient decreased with increasing generation numbers.

5. Supramolecular Interactions

The dendrimers hitherto described mainly have to be synthesized by covalently linking bonds step-by-step and as a result of this way of construction structure defects in higher generations are hardly avoidable (see Section 3). In contrast, nature uses the self-assembly of identical protein segments to give large structures that are directed by hydrogen bond formation, such as, for example, the tobacco mosaic virus, which consists of 2130 identical protein segments and a single-stranded RNA containing 6400 bases.[39] Noncovalent self-assembly combines the advantage of a minimum energetic effort in the synthesis and the possibility to tailor single segments to achieve the largest interaction.

Based on this principal Zimmerman et al. developed molecules in which two isophthalic acid moieties are connected through a rigid spacer.[40] The carboxyl groups of these compounds can interact intermolecularly through hydrogen bonds and assemble in a series of linear aggregates or in a cyclic hexamer depending on the steric demand of the spacer (Figure 15). By controlling the steric demand by Fréchet-type

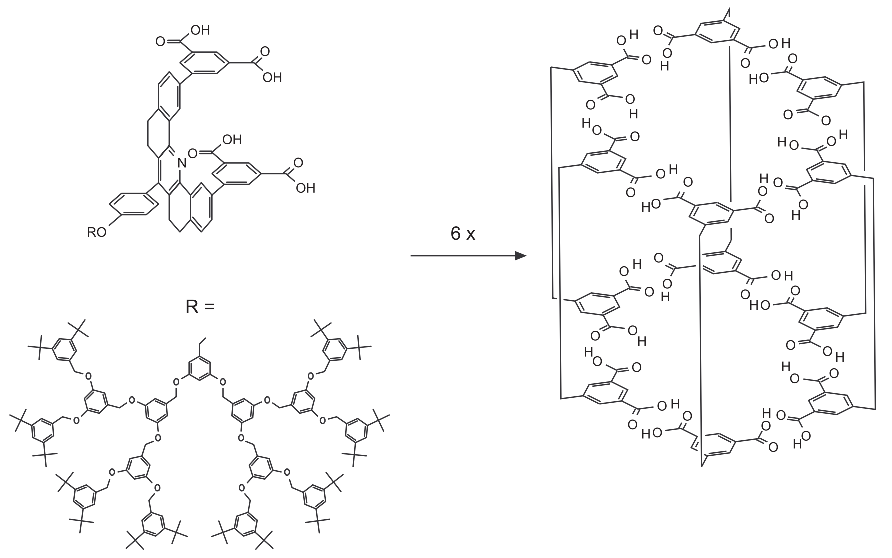


Figure 15. Supramolecular arrangement to form a hexameric dendrimer.

dendritic substituents attached to the spacer, one can influence the equilibrium of different aggregates in such a way that the cyclic hexamer structure is favored. It has been postulated on the basis of model calculations that these defined aggregates take up the shape of a flat disc that is about 9 nm in diameter and about 2 nm thick. For the first time the supramolecular construction of a nanometer-sized dendrimer by self-organization through hydrogen bonds could be demonstrated.

The same group worked on the formation of heterogeneous supramolecular structures from low-molecular guest compounds and dendritic building blocks that contained hydrogen-bonding sites that were complementary to each other.[41a] As opposed to the aggregation of equal molecules, the energetics and stoichiometry of two components self-assembling can be examined exactly by titration experiments. Again Fréchet-type dendrons of different generations, which were bound to an anthyridine core, served as the dendritic units. This core has a triple hydrogen-bonding acceptor unit whose interaction with a monomeric and a dimeric benzamidine derivative (double hydrogen bonding donor), respectively, was followed by NMR spectroscopy. In both cases the complexation was detected successfully, and the dimeric benzamidine derivative is really of a 1:2 stoichiometry. Subsequently, a recent work reported on experiments to bind analogous monomer guest molecules to a naphthyridine core (double hydrogen bond acceptor) that carried two dendryl substituents through hydrogen bonds.[41b] In these studies it was possible to examine and to compare two different dendritic systems. On the one hand the usual Fréchet-type dendrons were coupled to the naphthyridine core, and on the other hand the phenylacetylene dendrons developed by Moore[41c] were used. Both systems revealed approximately the same ability to associate guest molecules and an analogous solvent dependence in all the generations analyzed; hence no major differences either in polarity or in the free accessibility of the core unit has been registered. Only the weaker association constant of a more voluminous guest molecule for both skeletons reflects the shielding of the host molecule.

The formation of a didendron described above by means of specific hydrogen bond interactions between monodendrons and a divalent core molecule can also be achieved through the directed formation of a metal complex, as mentioned by Newkome et al.[42a] This group coupled polyamide dendrons[42b] through two alkane chains of different length to a terpyridine moiety and arranged them into heterodimers after the successful complexation of a ruthenium(II) ion (Figure 16). The dendritic surrounding of this bis(terpyridine) complex affects the redox potential significantly, with the irreversibility of the redox process increasing with higher generations. Chow et al. synthesized similar dendritic homoleptic complexes based on terpyridine[43a] by coupling polyether dendrons[43b]

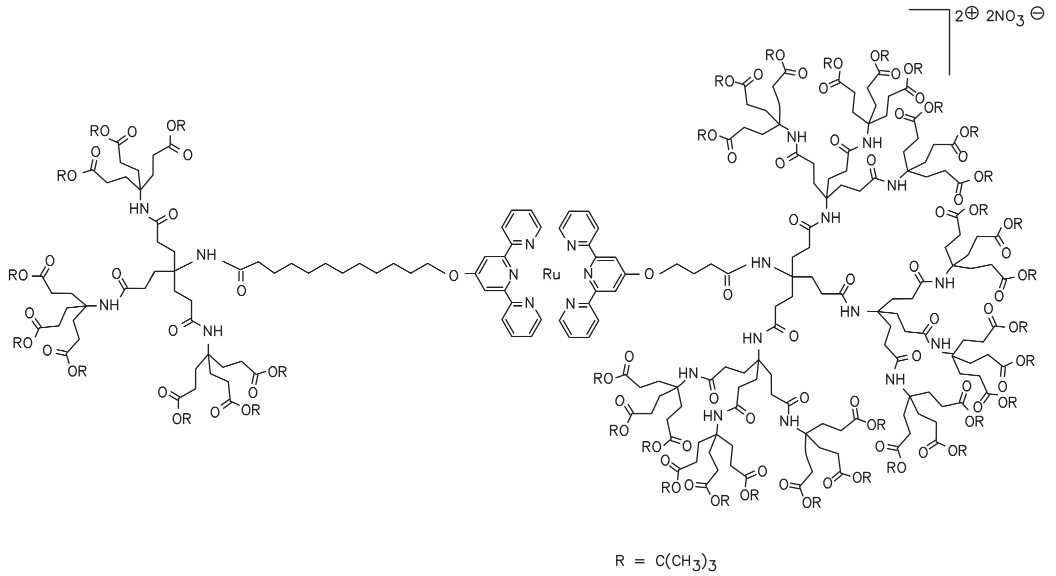


Figure 16. Synthesis of a didendron by directed metal complexation.

bearing a terpyridine core with an iron(II) ion. For these compounds the redox process was likewise irreversible with higher generations, and this has been ascribed to the comparatively large distance between the redox center and the surface of the electrode.

A different kind of self-organization that used dendritic segments was first used by Tzalis and Tor who chose a 1,10-phenanthroline ligand that was supplied with dendryl substituents in positions C3 and C8.[44] This ligand allows the stability and the spacial arrangement of the supramolecularly connected dendrimer to be directed by the coordination number and coordination geometry of the complexed metal ion. Complexation of a copper(I) ion with a phenanthroline derivative substituted with two first generation polyether dendrons yielded a tetrahedral orientation of two ligands, whereas the interaction of three ligands with an iron(II) ion led to a complex with an octahedral geometry. Such an octahedral self-organization of three ligands by metal complexation has been successfully carried out with higher generation dendryl substituents by Balzani et al. and us.[45] A 2,2′-bipyridine substituted with first to third generation polyamide dendrons and a ruthenium(II) ion served as the ligand and metal center, respectively. We only succeeded, however, in synthesizing the octahedral ruthenium complex with up to the second generation bipyridine dendrons. For higher generations steric reasons seem to prevent complex formation. In studies of the photophysical properties the second generation supramolecular dendrimer obtained with 54 peripheral ester groups showed an excited luminescence state with a remarkably high lifetime, which can be ascribed to the quenching by atmospheric oxygen as a result of steric effects.

Only recently Kawa and Fréchet reported the association of polyether dendrons up to the fourth generation by coordination to lanthanide ions.[46] This self-organization differs from the other examples described before by the ionic interaction between the tripositive erbium, terbium, and europium ions and the focal carboxylate functions predominant here (Figure 17). The preparation was carried out by simply exchanging the ligands of lanthanide triacetate by carboxylic acid dendrons. The increase in luminescence activity with higher generation polyether dendrons turned out to be a particular property of these compounds. This is caused by a strong antenna effect of the dendritic ligands and by the extremely effective insulation of each lanthanide ion.

Besides using supramolecular interactions to associate dendrons as described above, Aida et al. studied the steric effect that dendryl substituents exert on supramolecular interactions.[47a] They determined spectroscopically the binding constants between a zinc-porphyrin derivative substituted with Fréchet-type dendrons up to generation five and an imidazole group equally functionalized. As expected, the values diminished with higher generation of the substituent on either the porphyrin or the imidazole group, and for the highest number of generations studied hardly any association was detecable. This agrees with the long half-lifes of analogous porphyrin-imidazole-oxygen complexes. These are protected by the surrounding dendrimer skeleton, which forms a hydrophobic shell and prevents the complexes from being deactivated by dimerization and from being oxidized by contact with water.[47b] The use of such an apolar dendritic cover for performing liquid–liquid extraction of water-soluble dyes into organic solvents has been described by Meijer et al.[48a] They succeeded in proving that poly(propyleneimine) dendrimers substituted with long alkyl chains are able to transfer rose bengal or fluorescein from aqueous solution to an organic layer in high yield. A total re-extraction is possible because of the process being pH dependent. DeSimone et al. successfully employed dendrimers functionalized with perfluoropolyether chains to extract methyl orange into liquid carbon dioxide.[48b] Both methods are based on the fact that the corresponding dendrimer acts as a unimolecular micelle and represents a supramolecular host molecule for several dye molecules that carries them into the other layer.

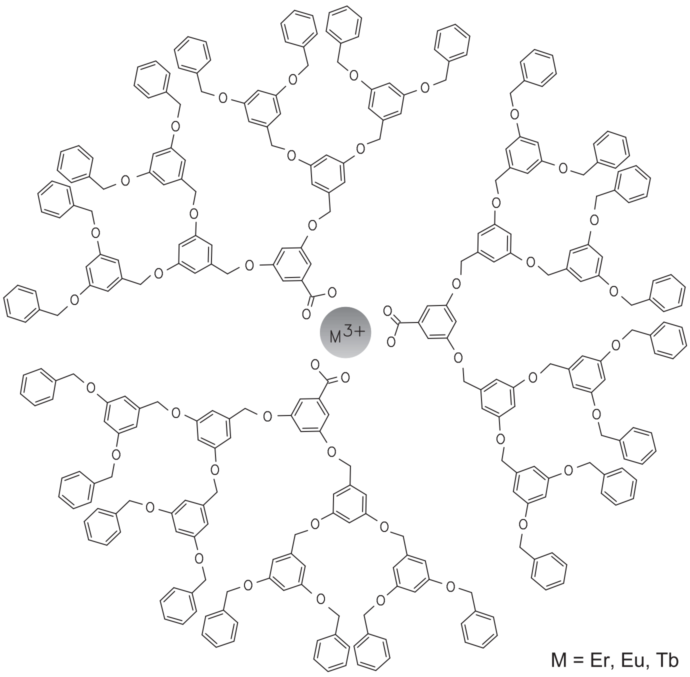


Figure 17. Synthesis of a dendrimer by ionic coordination to a lanthanide ion.

6. Dendrimers and Chirality

Even in the early days of dendrimer synthesis compounds that were constructed with lysine as a chiral branch juncture have been mentioned.[2b, 49] In these studies, however, the chiroptical properties of the compounds were not analyzed, but one expected interesting properties with respect to surface modification, metal-ion complexation, and pharmaceutical application. In the following years numerous works were published that demonstrated the varied ways in which chiral moieties can be introduced into a dendrimer. Mostly substances from the pool of optically active natural compounds were used as chiral moieties, such as amino acids and carbohydrates. Only recently Seebach et al.,[50a] Peerlings and Meijer,[50b] and Thomas and Tor[50c] summarized the work done. Peerlings and Meijer classified chiral dendrimers for the first time as dendrimers with:

1) a chiral initiator core,
2) a chiral branch juncture,

3) chiral end groups,
4) two or three of the characteristics listed above,
5) constitutionally different segments anchored to a chiral initiator chore,
6) a rigidly chiral conformation without possessing any stereogenic centers or chiral moieties, and
7) interactions with noncovalently bound chiral ligands.

For dendrimer types 6 and 7 there are no experimental examples yet. In addition, they pose many problems that have to be studied in future projects, for example, the question as to whether a chiral initiator core and achiral building blocks lead to optical activity or whether chiral moieties in a dendrimer facilitates enantioselective host–guest complexation or clathrate formation. Before one can employ dendrimers as chiral chromatography materials, catalysts in asymmetric synthesis, or for similar applications, it should be known how the molecular chirality of the dendritic building blocks and the macroscopic chirality of the compound are related to each other.

Investigations by Meijer et al.[50b, 51] on chiroptical properties of poly(propyleneimine) dendrimers with Boc-protected amino acids as terminal groups (Boc = *tert*-butoxycarbonyl) revealed that the optical activity of the compounds diminishes with an increasing number of generations until it is hardly detectable in the fifth generation with 64 end groups. This effect is not caused by racemization, concentration, temperature, or solvent influence, but arises from steric effects of the amino acid moieties that lie closely together. Their optical rotation is very sensitive to the local surroundings. If a flexible alkyl chain is introduced between the amino acid moiety and the terminal group of the dendrimer the steric tension at the end groups is reduced and the optical activity is approximately constant from the first to the fifth generation.[50b] The appearance of an induced circular dichroism by inclusion of certain dye molecules gave a remarkable indication of the presence of chiral information that was locked inside the dendritic box by 64 *N*-Boc-L-phenylalanine moieties.[51c]

Sharpless et al. observed a specific rotation that increased with the generation number in polyether dendrimers developed by them with asymmetric 1,2-diol branch units and trimesinic acid as the core molecule (Figure 18).[52] They discovered that the molar optical rotation is proportional to the number of monomer building blocks. Thus it is generated by the chiral moieties and not by a conformational arrangement of the dendrimer skeleton. Analogous results have been obtained by Chow and Mak from dendrimers containing L- or D-threitol as a connector between the phloroglucinol branch juncture units (Figure 19).[53] They also noted that in the presence of both enantiomers every D-threitol moiety exactly extinguishes the rotational effect of a L-threitol moiety.

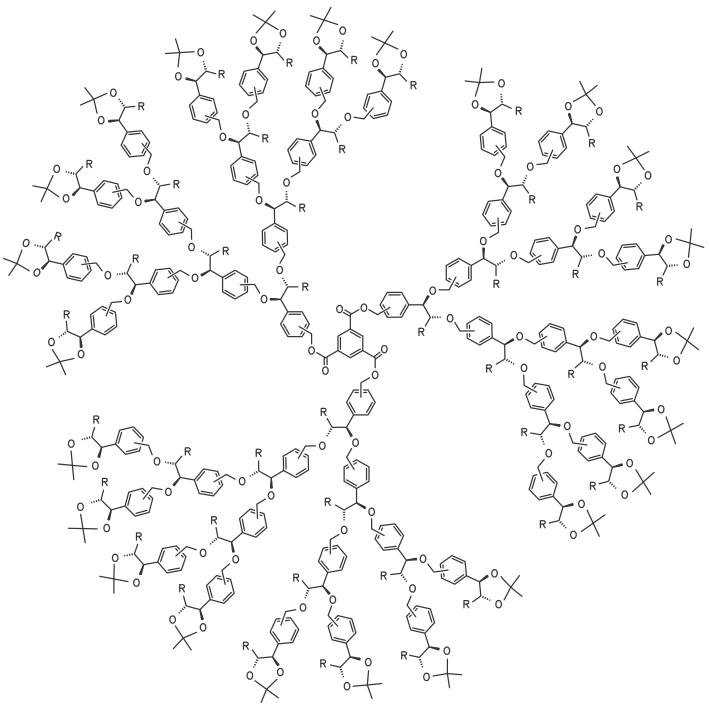


Figure 18. Dendrimers with chiral branch junctures. The optical rotation is higher with increasing generation.

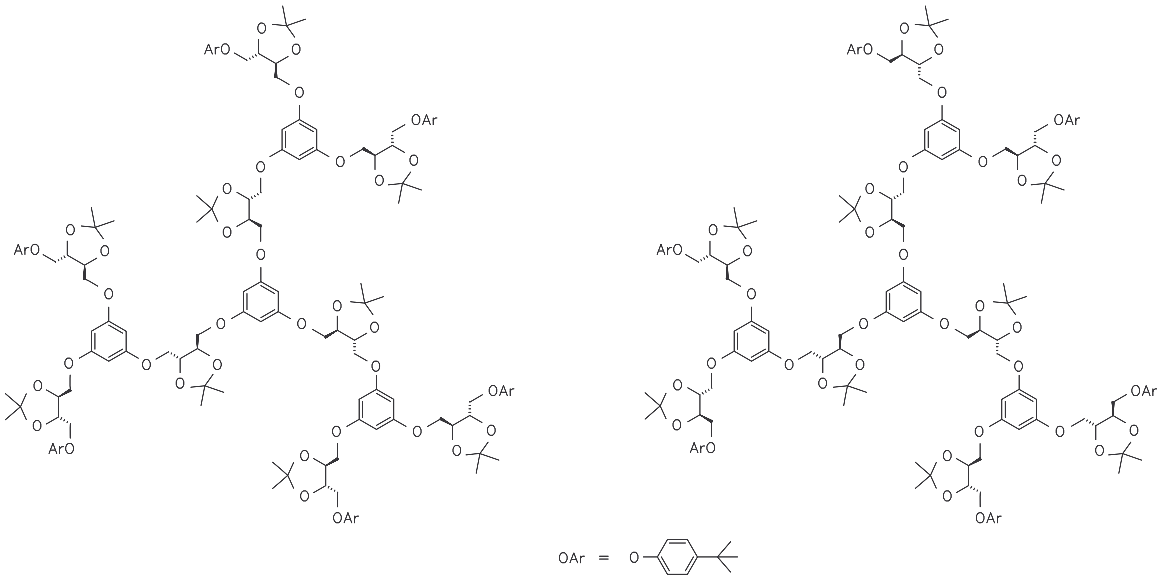


Figure 19. The rotational value can be extinguished by specifically incorporating both enantiomers of a chiral moiety.

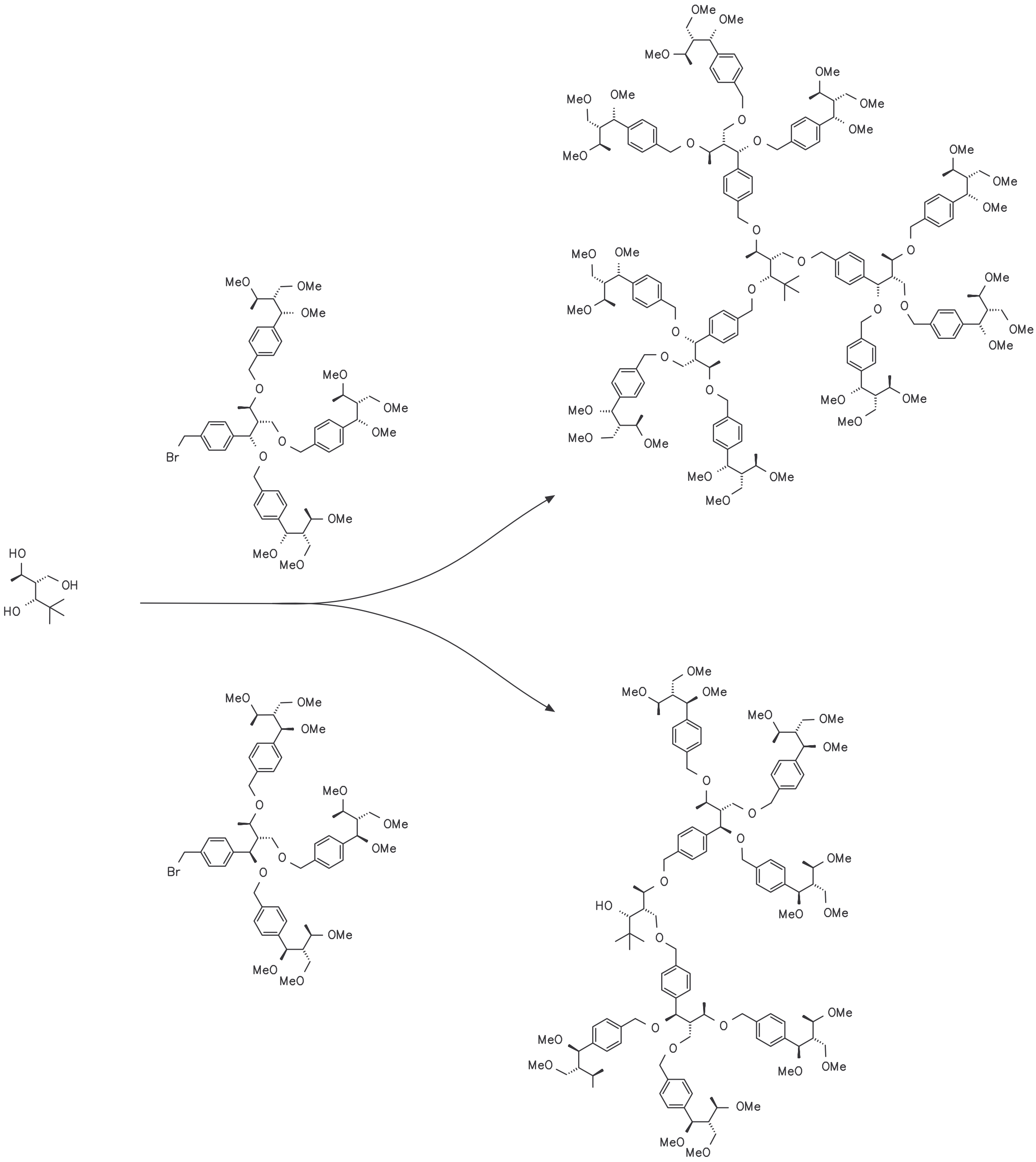


Figure 20. Diastereoselectivity in the synthesis of a chiral dendrimer.

Seebach et al. developed dendrimers based on a chiral tris(hydroxymethyl)methane derivative as the initiator core.[54] Subsequently they attached Fréchet-type dendrons of zero to second generation directly to the core or separated from it by two different spacers.[54a] For the direct anchoring, as well as for the use of a comparatively rigid spacer (*p*-xylylene), they observed a decrease in the rotational value with higher dendron generation, whereas an analogous compound with a flexible spacer (*n*-propyl) exhibited only an insignificantly low optical activity for all three generations. In successive works the same core molecule has been reacted with fully chiral, twofold and threefold branched dendrons.[54c, d] In both cases the first to third generation dendrons obtained this way show an inversed sense of optical rotation when going from one generation to the next higher one. This fact possibly indicates a conformationally chiral arrangement of the dendrons. In addition, when a threefold branch juncture with the opposite configuration on one of the three stereogenic centers is employed, a case of diastereoselectivity has been noticed (Figure 20). The corresponding second generation dendron could be attached successfully to the chiral triol initiator core only up to the doubly substituted adduct. A threefold reaction to prepare the complete dendrimer did not succeed.

The decreasing optical activity of a chiral initiator core with achiral dendryl substituents has also been studied by Meijer et al. (Figure 21).[55] Initially they did not use a chiral core for constructing the dendrimer, but they tried to produce chiral information by coupling four dendrons of different generation to pentaerythritol.[55a] They, however, failed to separate the racemic mixture chromatographically, so it was not possible to examine the optical properties. To avoid this problem the two enantiomers of a new dendrimer were synthesized by using the chiral glycerol derivative (*S*)-(+)-solketal as the core unit.[55c] This was done by specifically tethering different generation Fréchet-type dendrons. Chiroptical analyses revealed no sign of optical activity for either enantiomer. Hence, these substances can be described as "cryptochiral".[50, 56] Obviously, the conformative flexibility and the small difference in the electron density of the dendryl substituents cause the optical activity to vanish. In addition, the geometry of the two enantiomers is also only slightly different. Surprisingly, Mejier and co-workers have successfully prepared an analogous molecule (Figure 21) in a chiral form by the introduction of sterically more demanding branch units (2,6-substitution at the benzene ring).[55c] A small rotational value was measured for this molecule, and a weak signal appeared at low temperature in the CD spectrum and vanished at 30 °C. This might be a hint that the compound produced has a rigid structure as a consequence of the different branches and despite the low generation number. Because of this the molecule can take up a chiral form, though it is not favored at raised temperatures because of the higher flexibility.

The position of a chiral moiety that influences the chiroptical properties of the dendrimer has been studied by McGrath et al.[57] First four dendrons that carried their chiral branch units at different positions in the skeleton were prepared through a combination of divergent and convergent synthetic methods (Figure 22).[57a] In this synthesis compounds were also obtained that possessed a chiral moiety at the focal point of the dendron and with four different generations of Fréchet-dendrons. These did not show any remarkable difference in their molar rotations. Therefore, the size of the dendryl substituent has no distinct influence on the chirality of the individual moiety. In contrast, the molar rotation per chiral moiety rises significantly if this moiety is not located at the focal point, but is instead incorporated shell-like into the skeleton. This, however, is apparently a consequence of the position of the chiral moiety in the skeleton rather than to a conformative change in the molecule caused by it. The analysis of analogous dendrimers constructed only with chiral branch junctures and their comparison with low-molecular model compounds gave further instances of this thesis.[57b] In fact, changes in the chiroptical properties with increasing generation number have been observed, but they were ascribed to constitutional changes from chiroptical data of model compounds. It was not possible to prove that a disturbance in the conformative equilibrium, so that a certain chiral conformation is preferred, was the cause of the particular optical properties.

All these results not only show that the position and the number of chiral moieties strongly influence the resulting

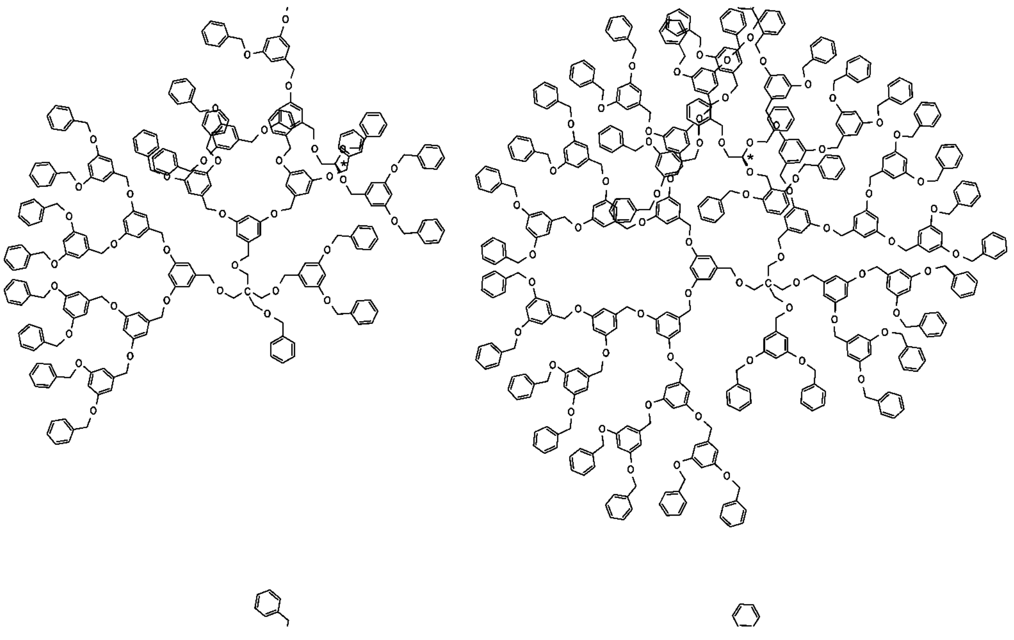


Figure 21. Dendrimers with a chiral core moiety and achiral dendritic substituents.

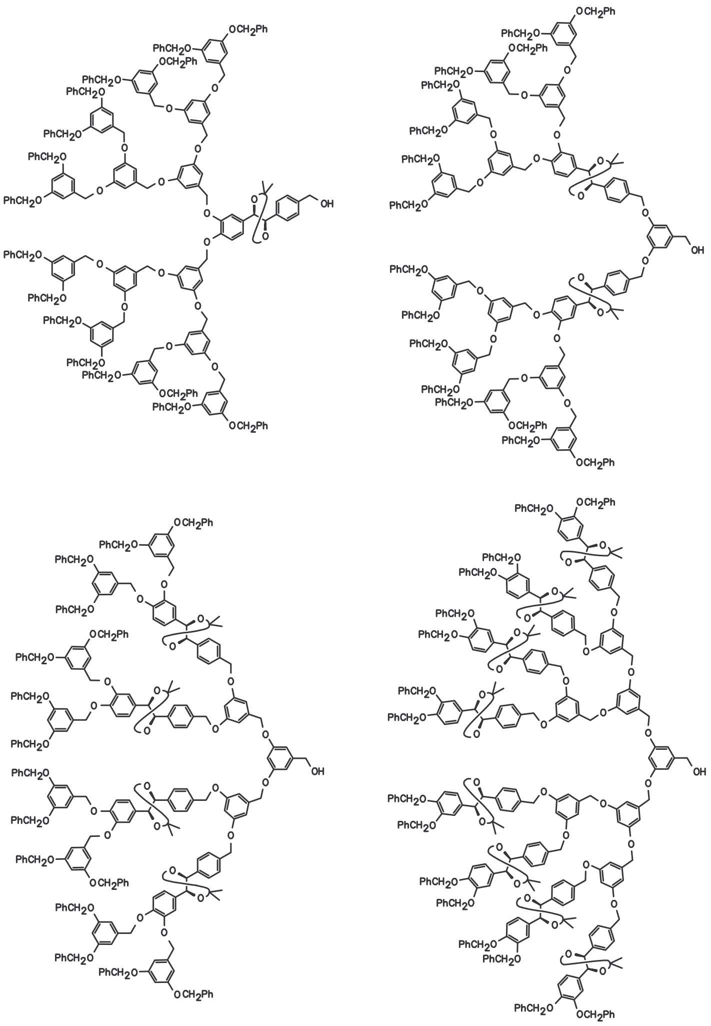


Figure 22. The position of a chiral moiety in the dendrimer skeleton significantly influences the chiroptical properties.

macroscopic optical properties of the dendrimer, but also that in all cases the optical properties are determined by the flexibility of the dendritic segments. In the search for new materials or enantioselective catalysts[58] great effort has to be made to solve exactly the influence of chiral moieties on the conformative formation of the dendrimer skeleton.[50]

7. Medicine and Diagnosis

To medicine dendrimers are substances whose possible applications as diagnostic or even therapeutic agents have been discussed and studied.[59] On the molecular level one is particularly interested in the multiplication of certain functionalities to attain high activity by multiple interaction. Thus, saccharide clusters from natural carbohydrate building blocks can compete in recognition processes on the cell surface and intervene in specific adhesive phenomena to prevent bacterial or viral infection.

Meanwhile dendrimers have repressed polymers as skeleton building blocks for the development of carbohydrate clusters as a consequence of their exactly defined structure. In this field Roy et al. have done pioneering work on the synthesis of the first lysine dendrons, which were substituted with up to 16 α-sialinic acid moieties.[60a] They found that these compounds are highly active in inhibiting the hemagglutination of human erythrocytes by influenza viruses. For a better understanding of the multivalence and its role in carbohydrate–protein interactions, glycodendrimers with variable density and conformation of the active moieties have been prepared.[60b, c] From these substances they noted that in general a larger carbohydrate–protein interaction occurred with an increase in the number of sialinic acid groups. In the same respect, Lindhorst and Kieburg developed an elegant method to react multiamino-functionalized dendrimers with different glycosyl isothiocyanates to form glycoside clusters, the carbohydrate epitopes of which can be varied as desired.[61] Furthermore, the synthesis of a dendritic carbohydrate cluster with glucose as a central building block recently succeeded.[62] Stoddart et al. reported on carbohydrate dendrimers with up to 64 peripheral groups, which were constructed convergently, divergently, or by coupling to a pre-prepared dendrimer skeleton.[63]

Dendrimers have been tested as therapeutics in boron neutron capture therapy.[64] This therapy represents a method for the treatment of presently incurable forms of cancer. The exceptionally high neutron capture cross-section of the ^{10}B isotope for thermal neutrons is used to produce a radiation energy that is lethal to the surrounding cells. The problem is that a compound as boron-rich as possible is required, which can be selectively coupled to molecules that recognize tumour cells. As well as the earlier studies on the synthesis of statistically boronated polymers, dendrimers with covalently attached boron atoms have been prepared.[65] The first lysine dendron that specifically couples to proteins and carries 80 terminal boron atoms on the end groups has been developed by Moroder et al. (Figure 23).[66] They succeeded in substituting the eight peripheral amino groups of the third generation dendron by a carboranyl amino acid and to conjugate the focal thiol group with an antibody fragment. First tests on this compound have given positive results.

Dendrimers have been applied therapeutically in gene therapy as well.[67] “Vectors” are employed to exchange a defective gene by a functioning one by the transfer of the genes through the cell membrane into the nucleus. Although viruses and liposomes have been mainly used for this, PAMAM-dendrimers have also been tested.[68] They turned out to be efficient transfection reagents and guaranteed the transfer of genetic material into mammalian cells. By means of activation by thermally generated structure defects a two to three times higher efficiency has been obtained so that the dendrimers do not necessarily have to be structurally perfect for this application. In the meantime a transfection reagent based on these studies is commercially available,[69] and is applied in the research fields of molecular and cell biology.

The use of dendritic structures for diagnostic purposes is also based on the possibility of multiplying certain functionalities and hence achieving higher sensitivities. Dendritic substances have made crucial advances and have already been tested in preclinical studies, particularly in the field of contrast media for magnetic resonance. The magnetic resonance imaging (MRI) method[70] serves to picture organs, blood

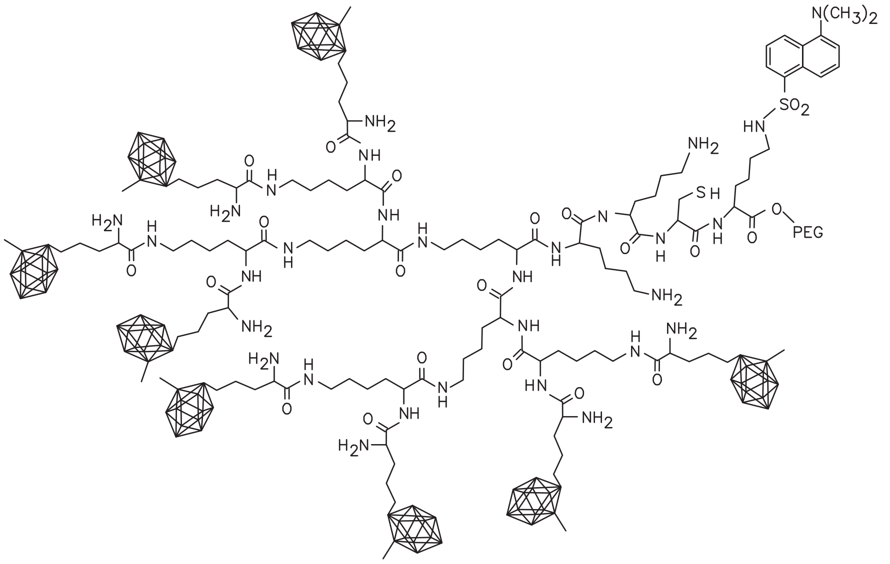


Figure 23. Lysine dendron with 80 boron atoms used in boron neutron capture therapy.

vessels, or tissue inside the human body by generating defined inhomogeneous magnetic fields that allow the nuclear resonance signal of water to be assigned to its place of origin and then to convert it into pictures. The relaxation time of the water protons are significantly shortened by application of the contrast media (paramagnetic metal cations) into the organ that is to be visualized and leads to a picture with a very good signal-to-noise ratio. However, clinically used contrast media, such as Magnevist (gadolinium salt of diethylenetriaminepentaacetic acid, DTPA),[71] reveal a disadvantage. Immediately after intravenous application they diffuse into the extravenous area as low-molecular compounds. Therefore they are only partially suitable to picture the vessels. To prevent the diffusion higher-molecular weight compounds have been developed in which several gadolinium complexes are covalently bound to albumin,[72] dextran,[73] and polylysine[74]. No preparation is on its way to clinical studies, however, because of bad renal elimination of the compounds. Several groups have turned to dendrimers as basic skeletons in their recent research,[75] including a team from Schering AG who have developed the substance most suitable to date (Figure 24).[76] This compound consists of a trimesinic acid central building block, to which second generation lysine dendrons with a total of 24 complexed gadolinium ions are anchored. Animal tests showed that the quantitative renal elimination and the higher intravascular retention time, which ensures an excellent signal-to-noise ratio, turn out to be the outstanding properties of this new contrast medium. The intravenous application of small doses of this dendrimer therefore promises a highly resolved and contrasted visualization of blood vessels (angiography, in particular coronar angiography).

8. Summary and Prospects

This review of topical works in the field of dendrimer chemistry demonstrates the great variety in this research field. The fractal molecular architecture challenges the creativity and the inventiveness of the chemists of all branches—from inorganic and organic chemistry, polymer and material chemistry, as well as analytical chemistry, biochemistry, to medicinal diagnosis. A particularly high number of publications deal with making use of the structural benefits that the dendrimer architecture offers for potential applications, compared with other substance classes. In all these studies one must not neglect the point that it has to be a very specific field of application to justify the great effort associated with the multi-step synthesis that leads to structurally perfect macromolecules. At the moment applications in molecular biology, medicine, and catalysis for which the unique combination of an exactly defined particle structure and a very high surface functionality is crucial, seem to successfully pass this cost–benefit analysis. In particular the works on transfection reagents and contrast media described in Section 7 verify this fact. On the other hand, the basic research on structurally perfect systems can examine more precisely and better

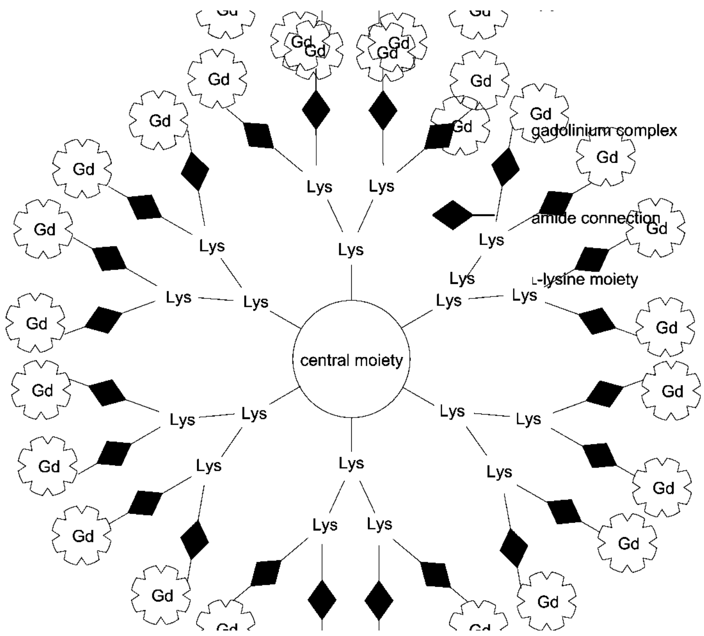


Figure 24. A dendrimer with 24 complexed gadolinium ions used as an MRI contrast agent.

understand new effects and the knowledge obtained can be applied to compounds of lower structural perfection.

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German version: *Angew. Chem.* **1999**, *111*, 934 – 955

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[3] Comprehensive information on commercially available dendrimers is given on the internet under:
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