
Preface

Topics in Current Chemistry volume 197, entitled “Dendrimers”, turned out to be so attractive to the readers that it was extremely successful and this encouraged us to continue. In addition, the first volume was exclusively dedicated to dendrimer chemistry, which covers only a small selection of the topics in this field. Moreover, the subject dendrimers has undergone a further upturn since the publication of the first volume. The present volume “Dendrimers II” by pioneers in this new research field deals with the aspects of dendrimers mentioned in the subtitle but also touches on areas beyond chemistry.

What makes dendrimers so attractive that chemists have difficulty in avoiding them? Virtually every chemist can contribute to dendrimer chemistry, be it with a certain synthetic method which is also applicable to dendritic structures, be it with polymer chemical and analytical methods or supramolecular aspects such as host/guest interactions. Dendrimers have developed into an amalgam, into a “market place” of chemistry in which all the branches of chemistry – organic, inorganic, physical-chemical, polymer-chemical or analytical chemistry – have come together and stimulate each other. Dendrimers have become a “molecular reaction vessel” in the figurative sense.

Similarly biological and material sciences benefit, for dendrimers have proved to be useful in diagnostics, as a component of thin layers, in catalysis as well as in nano sciences. This inter-disciplinary “input” has stimulated chemistry as a whole in that it has led to the development of optimized analytical devices.

Due to the possibility of preparing a variety of different dendrimer types with perfectly or less precisely directed macroarchitecture, synergistic effects can be expected with an appropriate design. Some interesting questions such as dendritic combinatorial libraries have only been touched on as yet. Therefore properties beyond those of conventional building blocks might result.

The First International Dendrimer Symposium which took place in the DECHEMA-building in Frankfurt (3–5 October 1999) brought together many chemists who had been working in different fields. It showed that the new type of molecular cascade architecture, initiated 22 years ago, has meanwhile developed a significant potential with promising options for the future brought about by the current theoretical, computational and experimental possibilities.

We hope that this new collection of reviews will help all chemists to further develop this stimulating branching of branches in this field of research.

Polyester and Ester Functionalized Dendrimers

Sami Nummelin¹ · Mikael Skrifvars² · Kari Rissanen¹

¹ Department of Chemistry, University of Jyväskylä, PO Box 35, 40351 Jyväskylä, Finland
E-mail: Sami.Nummelin@jyu.fi; kari.rissanen@jyu.fi

² SICOMP, Swedish Institute of Composites, PO Box 271, SE-941 26 Piteå, Sweden

Former address: Neste Chemicals Research and Technology, PO Box 310, FIN-06101 Porvoo, Finland

Demand for smart and functional materials has raised the importance of the research of dendritic (Greek = tree-like) molecules in organic and polymer chemistry due to their novel physical and mechanical properties. The properties of linear polymers as well as small discrete molecules are combined in this new architectural class of macromolecules, that can be divided into two families: dendrimers and hyperbranched macromolecules, that differ in their branching sequences. Dendrimers contain symmetrically arranged branches emanating from a core molecule together with a well-defined number of end groups corresponding to each generation. This results in an almost monodisperse three-dimensional globular shape providing internal niches capable of encapsulation of guest molecules or molecular recognition. Hyperbranched macromolecules, synthesized in one-step reactions, are randomly branched and contain more defects, i.e. linear and terminal segments, being less homogenic than dendrimers. High chemical reactivity, low viscosity, high solubility and miscibility offer unique tools to modify and tailor properties in particular fields, such as adhesives and coatings, agrochemistry, catalysts, chemical and biosensors, cosmetics, inks and toners, lubricants, magnetic resonance imaging agents, membranes, micelle and virus mimicking, molecular recognition, nano devices, pharmaceuticals, self-organizing assemblies, thermoplastics and thermosets, and viscosity modifiers.

A short introduction to the first dendritic molecules is accompanied by an illustrated review of dendrimers with polyester functions. In addition future aspects and developments are briefly discussed.

Keywords: Dendrimers, Polyester, Supramolecular chemistry, Chirality, Metallodendrimers

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1

Introduction

The concept of highly branched polymers was initially proposed in the early 1940s by Flory [1–4] and Stockmayer [5]. Although synthetic efforts failed [6,7], Flory predicted the possibility of such polymers in 1952 by suggesting that it should be possible to polymerize AB_x -type monomers (where A is reactive with B and $x \geq 2$) to high molecular weight, multibranched products without gelation to an infinite network (Fig. 1) [8,9].

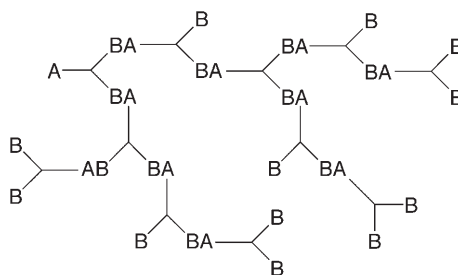


Fig. 1. Flory's randomly branched molecules based on AB_2 monomers [8,9]

Unfortunately, work in this area was not pursued until 1990 when Kim and Webster [10, 11] presented the synthesis of fully aromatic (termed “hyperbranched”) polyphenylenes. Fréchet et al. [12] followed in 1991 with the first one-step synthesis of hyperbranched polyaryl esters based on the thermal selfcondensation of 3,5-bis(trimethylsiloxy)benzoyl chloride. Since then a wide variety of structures with hyperbranched topology have appeared in the literature including polyamides [13], polyamines [14], polyaramides [15], polyesters [16–27], polyester amides [28,29], polyethers [30,31], polyether ketones [32,33], polyphenylene sulfides [34], polysiloxysilanes [35–38], polyurethanes [39–41], liquid-crystalline polymers [42,43], and metal-containing systems [44,45].

The first dendrimers, named “cascade” molecules, were introduced by Vögtle et al. [46] in 1978 (Fig. 2). “Cascade synthesis” implies that the reaction sequences can be carried out repeatedly, where a functional group is able to react in such way that it appears twice in the subsequent molecule.

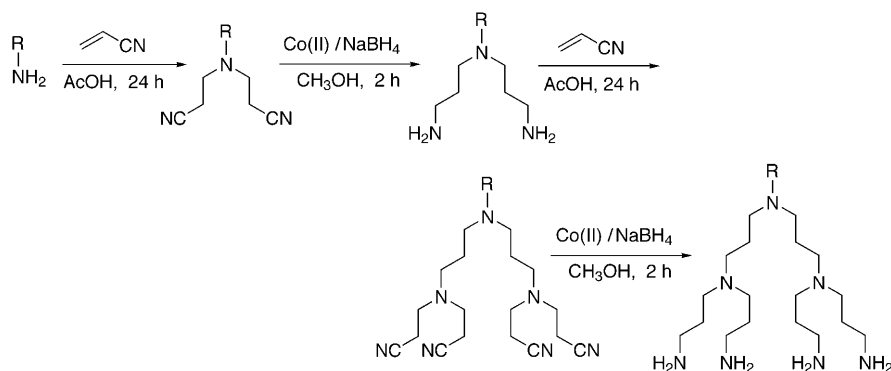


Fig. 2. Synthesis of “cascade molecules” by Vögtle et al. [46]

Since then much of the pioneering work has been credited to the research groups of Denkewalter [47–49], Tomalia [50–53], Newkome [54], Fréchet [55–57], Miller [58–60], Moore [61–64], Meijer [65, 66], and Vögtle [67–69]. Today, dendritic molecules are a topic of interest in over 150 research and development groups worldwide [70]. The growth in publications has been almost exponential since the late 1980s [71]. More than 2000 publications/patents, over 370 papers in 1997 alone [72, 73], have appeared in the literature including several extensive reviews [74–87]. For this particular reason a comprehensive review that covers all dendritic (i.e. dendrimers and hyperbranched) molecules that contain ester functions is beyond the scope of this article. Thus, the focus is on the progress of dendrimers during the past 5–10 years.

The term “dendrimer” originates from the Greek and is a combination of words “dendron” (tree, branch) and “meros” (part). Although a strict definition of the generally used term has not emerged to date, it is widely accepted that dendrimers are highly branched, yet structurally perfect molecules, prepared via iterative synthesis [88]. Further definitions, such as the number of generations, identical constitution of branches, degree of branching ($DB = 1$), and polydispersity ($PDI = 1$), should be considered separately in each case. Ultimately, each dendrimer is a mixture of similar structures rather than a molecule free of detectable faults. For instance, after 248 consecutive reactions with selectivity of $> 99\%$, the [G-5] ASTRAMOL dendrimer (Fig. 5) possesses a polydispersity of 1002, or a dendritic purity of 18% (term introduced by Meijer et al. [89]). Thus, the real amount of dendrimer with 64 terminal amine functions is only 18%, while the rest consists of imperfections with one or more branches missing [90].

The complexity of dendrimers, also known as arborols [54], cascade molecules [46], cascadol [91], cauliflower polymers [92], crowned arborols [93], dendrophanes [94], molecular fractals [95], polycules [96], silvanols [97], and “starburst dendrimers” [50], creates problems in naming. Reliance on the IUPAC nomenclature would produce extremely long names that are almost impossible to interpret. Therefore efforts aimed at a more simple nomenclature have been proposed by Mendenhall et al. [95] and Newkome et al. [98–100].

Dendrimers are constructed in a stepwise manner in repeatable synthetic steps [88]. Each repetition cycle creates an additional layer of branches, called “generation” (or “tier”). Branching multiplicity is dependent on the building block valency, although it can be generated during the growth step from a nonbranched building block as well [50, 65]. In a four-valent core the number of functional groups at the periphery follows the rate 4, 8, 16, 32, when AB_2 -type chain extenders are employed, or the rate 4, 12, 36, 108 for AB_3 -type chain extenders, providing that the branching is perfect. Defects result in branch errors. Errors that occur in the early stage of growth are generally more problematic than those occurring at higher generations, since defects in the dendrimer structure accumulate with each iteration. The problem is not the individual steps in a synthesis as much as the number of successful reactions needed to be done on the same molecule. In addition, each synthesis is only specific to one particular dendrimer.

Two major synthetic approaches have emerged: the divergent approach where growth starts from the inside (core) proceeding outwards (Fig. 3), and the convergent approach proceeding “outside-in” (Fig. 4), i.e. by first producing “dendrons” (= branches or “wedges”) which are coupled to the core (number of coupling reactions is constant throughout the synthesis). Both methods require two steps for the growth of each generation: the activation of the dendritic unit and the addition of a new monomer. Comparison of these methods show that generally dendrimers prepared by the divergent approach are more polydisperse than those prepared by the convergent approach [101]. Nevertheless, both the commercially available dendrimers (Fig. 5) are prepared by this method. Incomplete reaction arises at higher generations when large number of reactions have to occur on a sterically hindered dendrimer surface. On the contrary, the

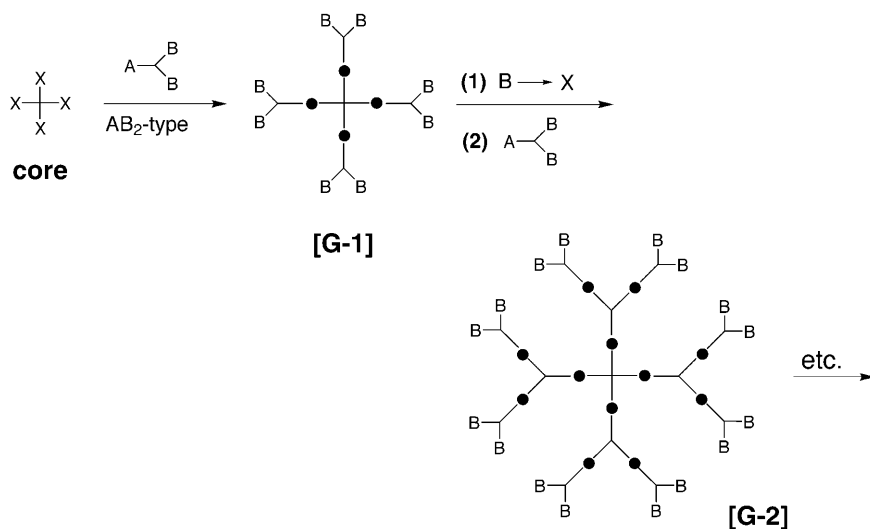


Fig. 3. Dendritic growth via divergent approach with AB_2 -type chain extenders. Protection/deprotection steps ($B \rightarrow X$) are not necessary if selective chemistry can be adapted. Dots represent the bonds formed between A and X groups [75]

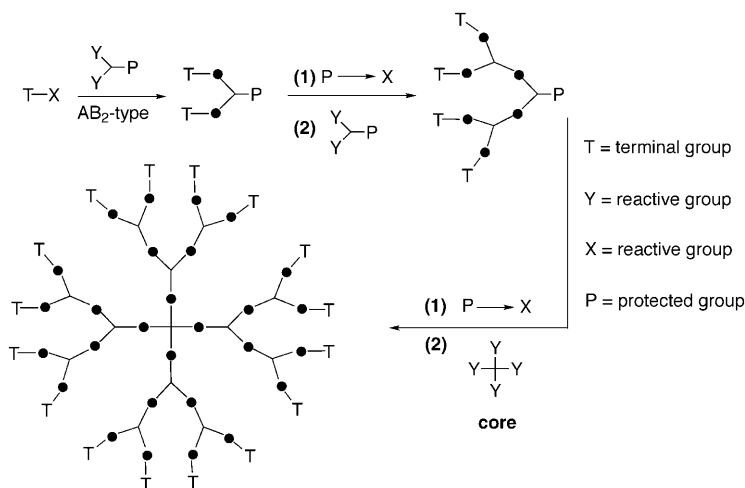


Fig. 4. Dendritic growth via convergent approach. Dots represent the bonds formed between two reactive groups Y and X [55, 56]

convergent method is usually limited to dendrimers of lower generations and yields due to the steric hindrance at the focal points of large dendrons [102]. The limits of both methods have yet to be firmly established, but critical molecular design parameters (CMDPs) of size, shape, topology, flexibility, and surface chemistry will eventually set the limits on dendritic growth (dense-packed generation) [84, 86, 92].

One limitation of dendrimers is their time-consuming synthesis. Great effort has been devoted to improving the methodologies for the accelerated construction of dendrimers in response to the need for shorter syntheses. The mixed reactivity approach [103] differs from the divergent method only in that it exploits an additional chain extender, i.e. CD_2 -type, where C can only react with B, and D cannot react with B or C. In double-stage convergent growth [104–106] monodendrons containing a single reactive group at the focal point are coupled in a divergent manner to the periphery of another monodendron or dendrimer. Both double exponential growth [107, 108] and the branched-monomer approach [109, 110] are based on an idea where AB_x -type chain extenders ($x \geq 4$) are employed reducing the number of reaction and purification steps required to reach higher generations. Accelerated dendrimer synthesis [111], also known as the orthogonal coupling method [112–114], halves the reaction steps by obviating (de)protection or activation steps by alternative use of two different building blocks in two complementary coupling reactions. Recently, papers where the divergent and convergent methods are combined have been published [115–117]. This method clearly demonstrates that functionalized dendrimers and dendrons can be employed as reagents in the synthesis of novel compounds. Thus, Vögtle et al. [118] have introduced new technical terms, suggesting the use of “{n}dendryl” for dendritic substituents of n generations and “dendreagent” referring to dendritic reagents. Solid-phase synthesis [119–122], analogous to

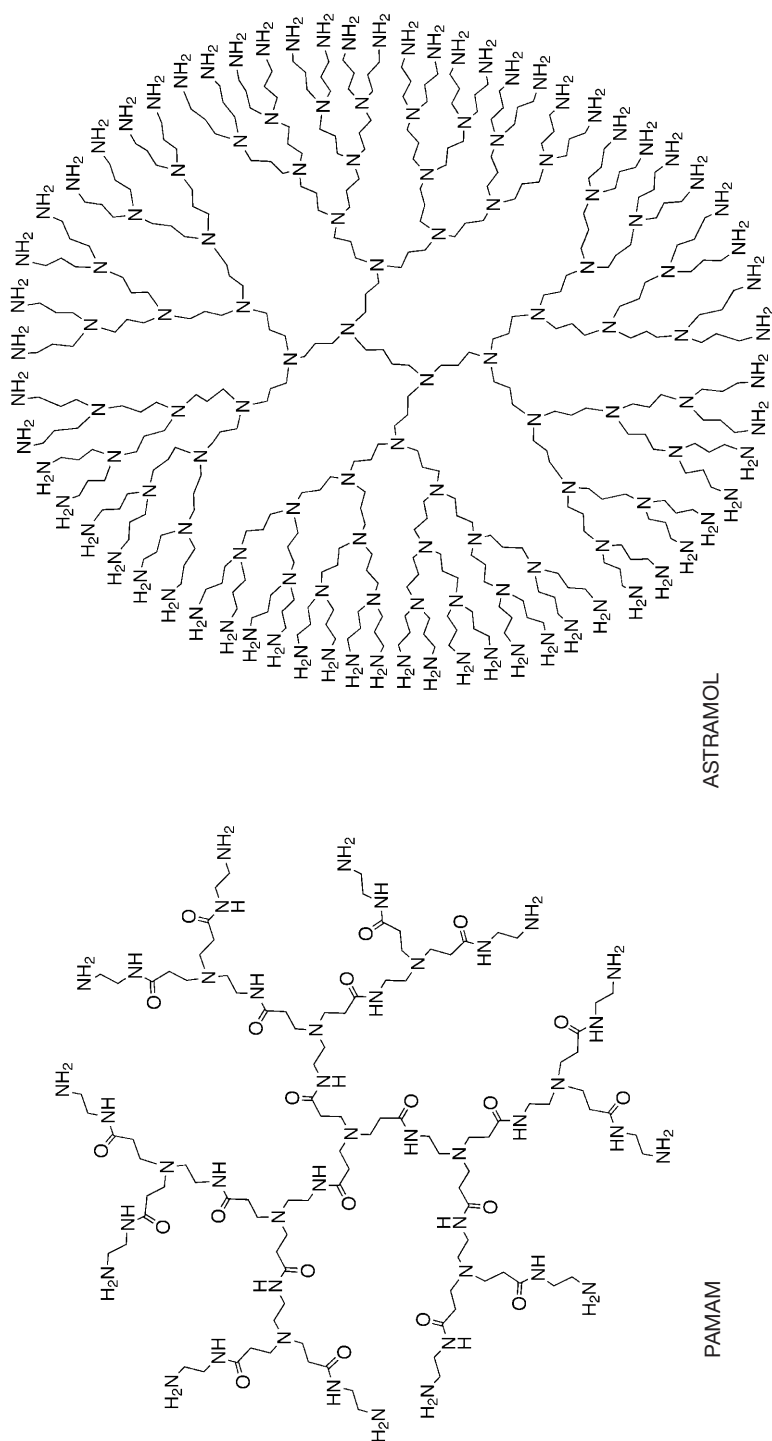


Fig. 5. The two commercially available dendrimer families [211]

the Merrifield-type peptide synthesis [123], offers advantages such as the use of large excess of reagents without any tedious purification or the use of differentially protected core molecules allowing the functionalization of a dendrimer. Bifunctionalized dendrimers can be prepared for instance by employing two differentially functionalized dendrons coupled to the core [124, 125] or via modification of functional groups within the main dendrimer [126–129]. Examples of multifunctionalized dendrimers [130–132] have also been reported, such as a combinatorial approach [133] that offers a tool to adjust dendritic properties via modification of the terminal groups. This strategy leads to dendritic materials which possess a variety of forms and terminal functions via simultaneous exploitation of mutually compatible chain extenders at different ratios. The most recent advances in dendrimer construction is the synthesis of cored dendrimers [134] and cyclotrimerization of dendrons attached to the acetylenic moiety in a $[2 + 2 + 2]$ cycloaddition process [135, 136] affording a route to fully substituted benzene-core dendrimers [137].

Dendritic fragments (A) have been linked together with well-known linear polymers (B) as hybrid-linear polymers. End-capping linear polymers, functionalized at one or both ends, with reactive dendrons leads to either AB or ABA block copolymers [138–144]. Approaches where a dendritic block is grown by a divergent method from suitably modified linear polymers [145–148], or the use of dendrons as macroinitiators for “living” radical polymerizations [149–151] leading to AB copolymers, have emerged. Recently, “dendronized” polymers (i.e. linear polymers bearing dendritic side groups) have received attention [152, 153]. With rigid rod-like backbones these macromolecules resemble a cylindrical rather than a globular shape [154–160]. Arborescent graft polymers (“dendrigrfts”) [161–166], including the comb-burst dendrimers [167, 168], are structural analogs of dendrimers. This “graft-on-graft” technique leads to soluble molecules with particularly high molecular weights.

Molecular recognition and self-assembly are important topics in supramolecular chemistry [169–173]. Structural control in the case of dendrimers makes them ideal building blocks for the assembly of larger structures from smaller subunits. Self-assembling dendrimers [174, 175] can be constructed by utilizing non-directional forces (dendritic amphiles) [176], self-organization in liquid-crystalline phases [177–181], π -stacking and intermolecular hydrogen-bonding interactions [182, 183]. Coupling of dendritic units through metal centers has been demonstrated by employing conventional synthetic strategies (i.e. divergent and convergent approaches) [184–189]. Recently, a method where covalent metallodendrimers were synthesized in a one-step reaction by exploiting the self-assembly of branching units, followed by in situ substitution of a ligand on the coordination centers, has emerged [190–194]. Structurally, metallodendrimers can be classified into four categories by the location of the metal complex(es): (1) metal complex as a core, (2) metal complexes in the branches only, (3) metal complexes on the periphery only, and (4) metals as branching centers (all layers) [195].

Use of dendritic fragments has also extended into other fields of supramolecular chemistry. First-generation dendritic rotaxanes [196] and rotaxanes bearing dendritic stoppers have been introduced [197, 198], as well as metalloporphyrin

dendrimers [199–202], C₆₀ fullerene- [203–207] and calix[4]arene-core dendrimers [208–210].

Currently, ASTRAMOL and PAMAM dendrimers [211] are being produced on a commercial scale in different generations [212]. These families are widely investigated due to their availability and they are among the most monodisperse non-biopolymers ever produced [66]. In addition, BASF AG (Germany) is producing poly(propyleneimine) dendrimers on a technical scale [213, 214] similar to ASTRAMOL for research purposes.

2

Dendrimers with Ester Functions

Dendrimers with ester functions are in focus due to easy access, facile branching, versatility [215, 216], solubility [217], processibility [218, 219], and applicability [220–225] of inexpensive raw materials. This technology is actively being developed by Neste Chemicals (Finland) [220, 221] and Perstorp Specialty Chemicals (Sweden) [222–225], for instance, in radiation-curable resin, lubricants, binders, and thermoset applications. The first polyester dendrimers are expected on the market by late 2001 from Perstorp under the trade name Boltorn [226, 227]. Related hyperbranched polyesters [228–234] are already being produced on a pilot scale.

The following discussion is organized based on the functionality present in the target structure adapting the classification of chiral dendrimers of Peerlings and Meijer [235].

2.1

Terminal

Starburst polyamidoamine (PAMAM) dendrimers [50], introduced by Tomalia et al. in 1985, were synthesized via divergent growth. Branching in the ammonia or ethylenediamine core was obtained via exhaustive Michael addition of methyl acrylate (**1**) to give the ester **2** followed by amidation with a large excess (15–250 eq.) of ethylenediamine in MeOH (Fig. 6). Higher generations (up to 10) were obtained by repetition of these two reactions. The yields reported were between 98 and 100 %. IR, ¹H-, ¹³C- and ¹⁵N-NMR, mass spectrometry (MS), size-exclusion chromatography (SEC), gas chromatography (GC), low-angle laser light scattering (LALLS), and electron microscopy were used for the characterization of the products.

Recently, Bradley et al. [121] have demonstrated the solid-phase synthesis of PAMAM dendrimers up to [G-4] by employing a two-directional acid-labile TentaGel resin-bound linker [236], which was easily cleaved by trifluoroacetic acid.

Synthesis of arborols [237] by Newkome et al. in 1985 employed a divergent approach with maximized AB₃-branching for a C-based system. The initial core, 1,1,1-tris(hydroxymethyl) pentane (**3**), was treated with chloroacetic acid in the presence of *t*-BuOK/*t*-BuOH followed by reaction of the intermediate triacid

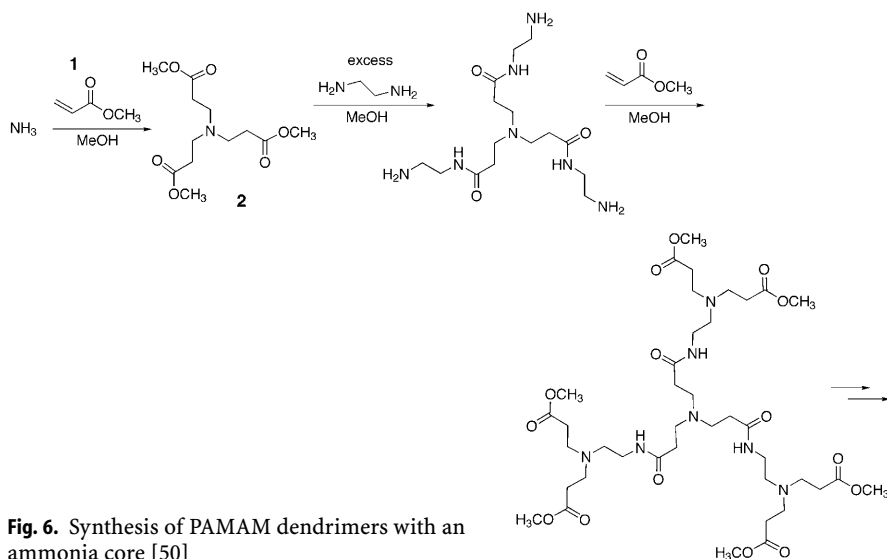


Fig. 6. Synthesis of PAMAM dendrimers with an ammonia core [50]

with methanol to afford **4** (Fig. 7). Reduction of **4** with LiAlH_4 gave the extended triol which was tosylated to yield tritosylate **5**. Treatment of **5** with $\text{NaC}(\text{CO}_2\text{Et})_3$ gave nonaester **6**. Construction of the [G-3]-dendrimer was accomplished by amide formation. Treatment of **6** with $\text{H}_2\text{NC}(\text{CH}_2\text{OH})_3$ gave the water-soluble [27]-arborol **7** (M_w 1626 amu). Products were characterized by ^{13}C -NMR.

“Dumbbell” shaped dendrimers, where two spherical groups are linked through alkyl **8** [238, 239] or alkyne **9** chains (Fig. 8) [240], were obtained by employing similar chemistry. Compounds were shown to form rod-like structures constructed by helical or scissor-like stacking. This property is reflected in the macroscopic tendency to form thermally reversible aqueous gels. However, structures with biphenyl **10** or spirane **11** cores [241] failed to aggregate in aqueous environment.

Using the same procedure branches were grown around a benzene core [242]. Mesitylene was brominated with NBS in CCl_4 to give 1,3,5-tris(bromomethyl) benzene followed by treatment with $\text{NaC}(\text{CO}_2\text{Et})_3$ in benzene/DMF to afford the nonaester **12**. The [G-2]-dendrimer was prepared by treatment of **12** with tris(hydroxymethyl)aminomethane in DMSO affording the benzene [9]³-arborol **13** (M_w 1485 amu). The highly water-soluble arborol was converted to benzoate derivative **14** for complete characterization by treatment with benzoyl chloride. All arborols were characterized by NMR and transmission electron microscopy (TEM).

Synthesis of silvanols [97] relies on the same synthetic procedure [242]. The crystalline dodecaester **15a** (Fig. 9) was obtained from the initial polytrimethylammonium [**1**₄] metacyclophane [243, 244]. In order to verify that the triester moieties were located on the upper rim, an X-ray structure of dodecaester **15a** was conducted. The [G-2] was constructed by treating the resulting ester with $\text{H}_2\text{NC}(\text{CH}_2\text{OH})_3$ in the presence of anhydrous K_2CO_3 in dry DMSO to afford

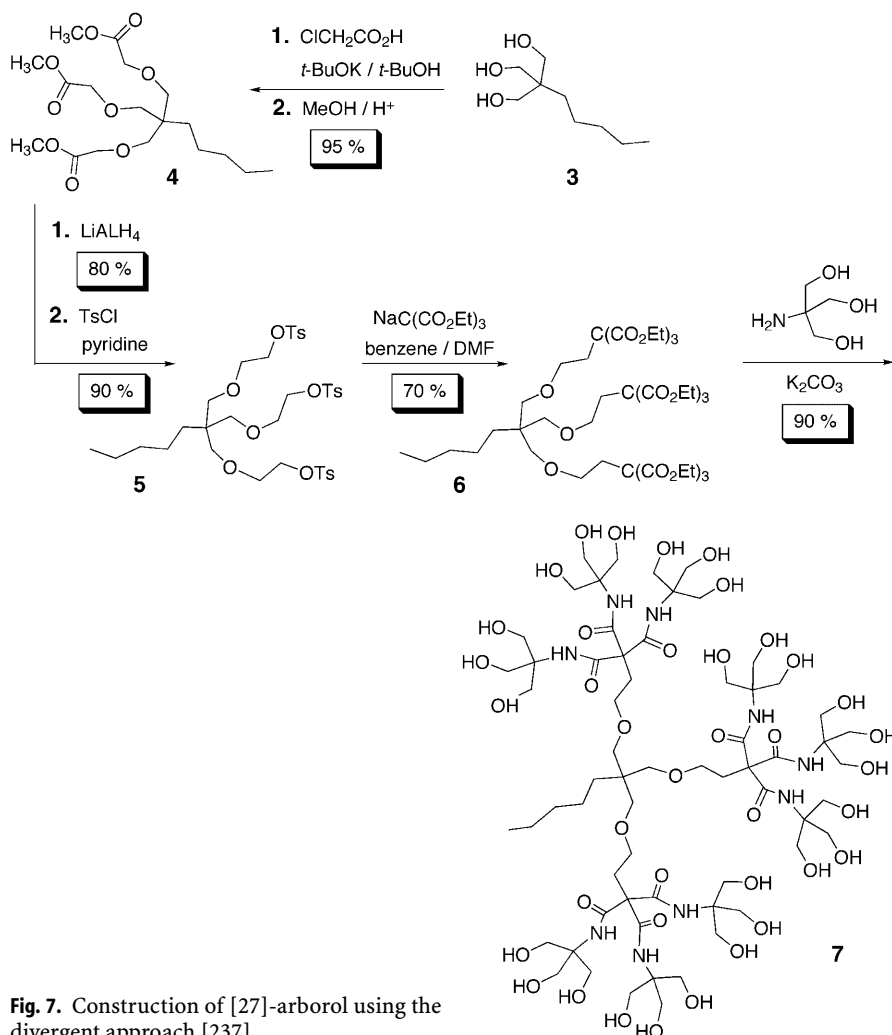


Fig. 7. Construction of [27]-arborol using the divergent approach [237]

[36]-silvanol **16a**. Similarly [72]-silvanol **16b** was obtained from the $[1_8]$ metacyclophane. The transmission electron micrograph of **16a** showed small spheres and discrete aggregates with a diameter of ~ 27 Å for a single molecule. All samples were characterized by IR, NMR, and elemental analysis.

Adamantane-core dendrimers [245] were synthesized by treatment of 1,3,5,7-tetrakis(chlorocarbonyl)adamantane (**17**) with 4-amino-4-(3-acetoxypentyl)-1,7-diacetoxyheptane (**18**) [246] in the presence of Et_3N in benzene solution (Fig. 10). Dodecaacetate **19** was converted quantitatively to the alcohol **20** by transesterification in absolute ethanol. In order to synthesize the dodecaacid a different synthetic route was developed by using di-*tert*-butyl 4-amino-2-[(*tert*-butoxycarbonyl)ethyl]heptanedioate (**21**) [247]. Treatment of **17** with

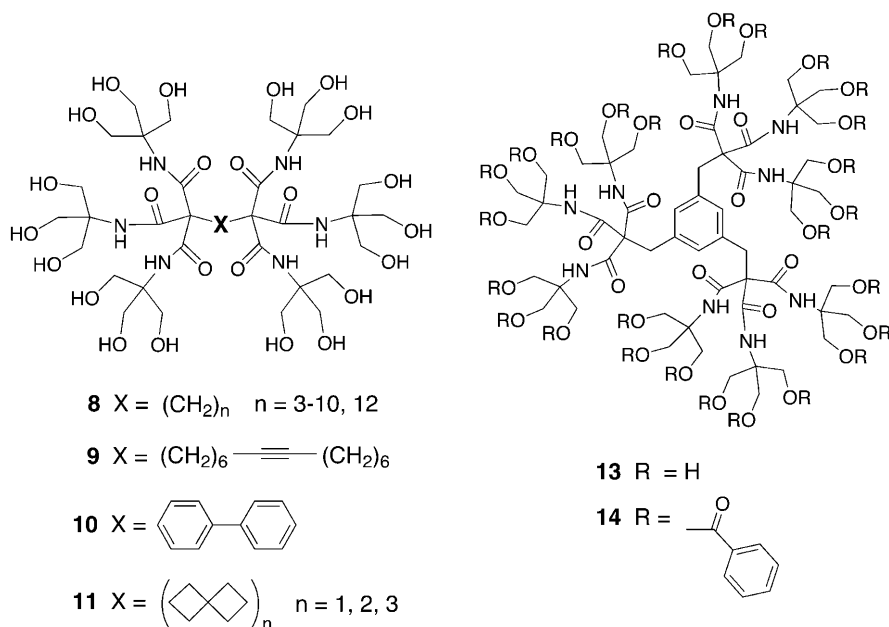


Fig. 8. “Dumbbell” $-[m]-n-[m]-$ and benzene $[9]^3$ -arborols of Newkome et al. [238–242]

amine **21** gave the solid dodecaester **22** which was hydrolyzed with formic acid. The coupling of acid **23** with amine **21** in the presence of DCC and 1-hydroxy-benzotriazole (1-HBT) in DMF gave $[G-2]$ -*tert*-butyl ester **24**. The $[G-2]$ -acid **25** was obtained by treatment with anhydrous formic acid. All products were characterized by IR, and ^1H - and ^{13}C -NMR.

A new family of “arborols” was developed to improve chemical reactivity and circumvent dense packing in the early stage of growth [248]. Tris(hydroxymethyl)aminomethane (**26**) was treated with acrylonitrile in KOH/dioxane to afford aminotrinitrile **27** which was refluxed with anhydrous EtOH and HCl to give triethyl ester **28** (Fig. 11). Nonaester **29a** was obtained by coupling with 1,3,5-benzenetricarbonyl trichloride (**30**). Reaction of amine **28** with 5-nitroisophthaloyl dichloride **31** afforded the nitro ester **32a**. The desired amine **32b** was obtained by catalytic reduction (PtO_2/H_2). The final dendrimers **34** and **35** were generated by reaction of **32b** with terephthaloyl chloride **33** or **30** in CH_2Cl_2/Et_3N . All esters were hydrolyzed to the corresponding acids with dilute NaOH in MeOH. Structures were confirmed by ^1H - and ^{13}C -NMR and IR by the appearance or disappearance of the characteristic peaks.

Fréchet et al. [249, 250] have constructed covalent micelle-like dendritic macromolecules with a methyl benzoate surface and an aryl ether interior. The synthesis was based on methyl 4-bromo-methylbenzoate (**36**) (hydrophilic layer) and 3,5-dihydroxybenzyl alcohol (**37**) as the monomer unit (Fig. 12). Coupling of **36** with **37** under standard Williamson ether synthesis conditions followed by activation with CBr_4/PPh_3 yielded, after four iterations, the dendron

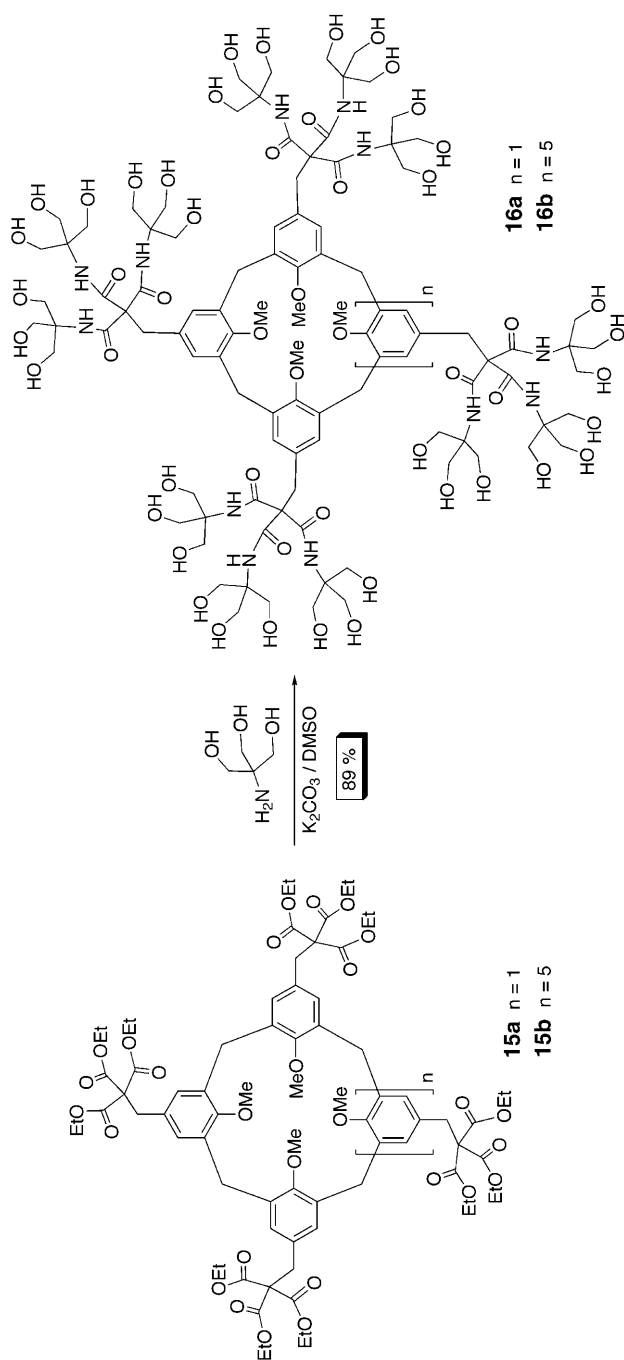


Fig. 9. Construction of water-soluble calixarenes, e.g. silvanols [97]

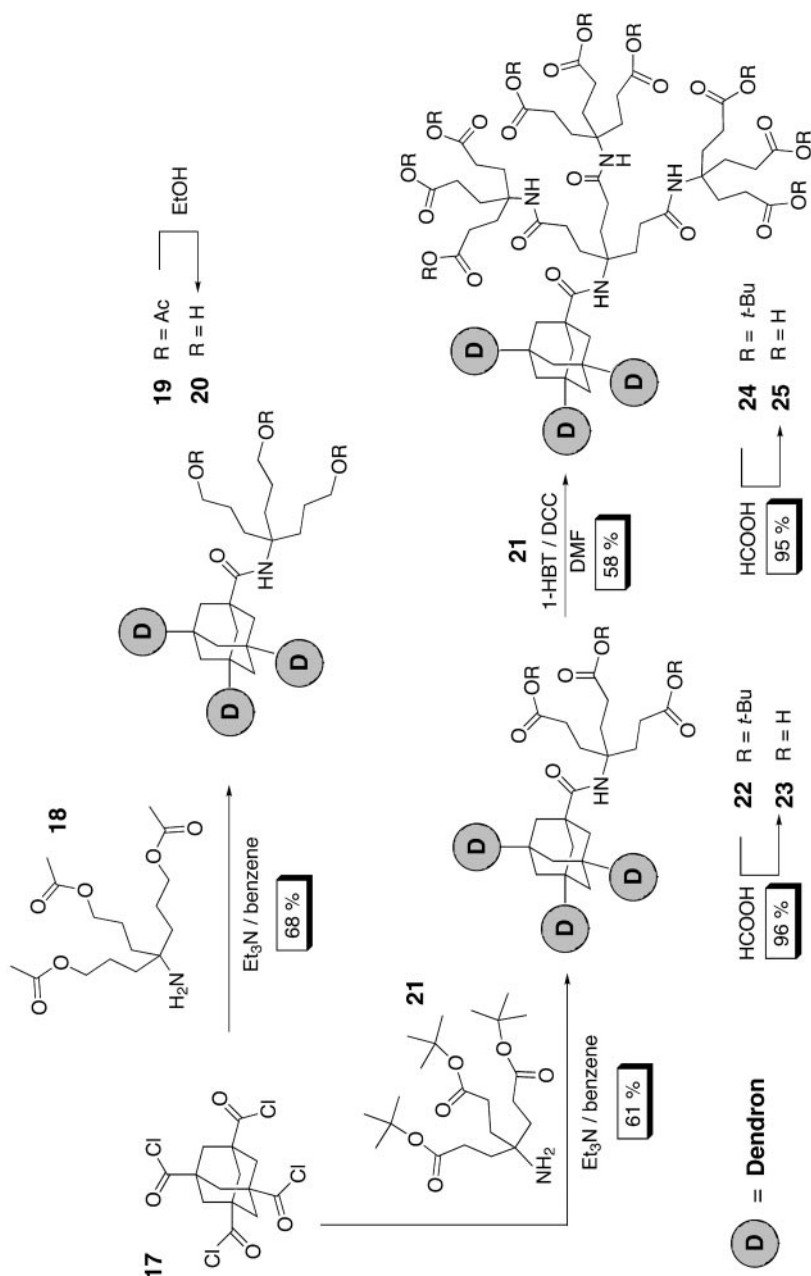


Fig. 10. Four-directional dendrimers based on an adamantane core [245]

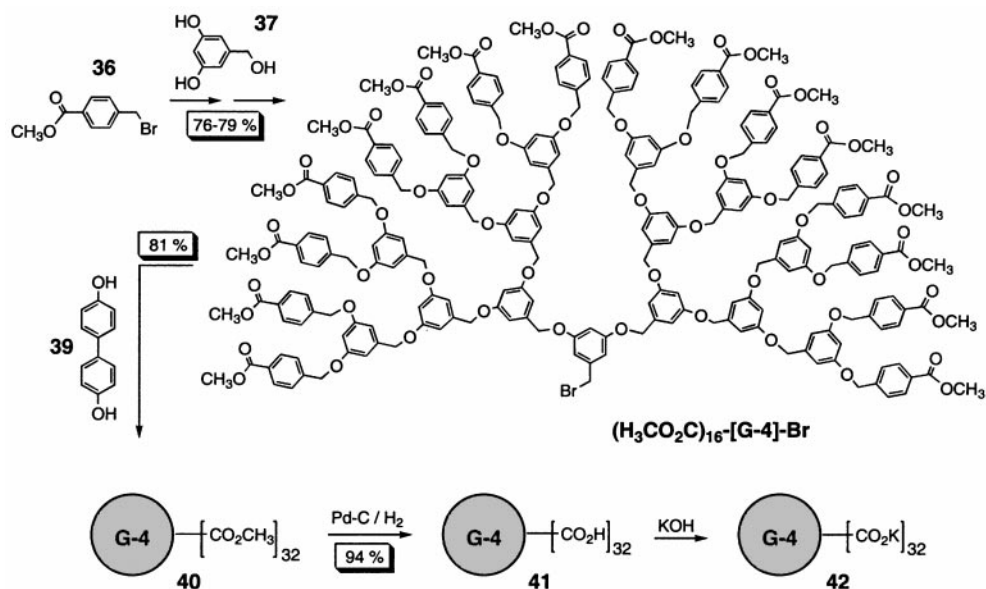


Fig. 12. Synthesis of covalent micelle-like structures based on dendritic polyethers [250]

$(\text{H}_3\text{CO}_2\text{C})_{16}\text{[G-4]-Br}$ **38**. The dendritic wedges **38** were linked to the 4,4'-dihydroxybiphenyl core **39** to afford the dendrimer **40** with 32 terminal methyl esters. Hydrogenolysis of **40** gave water-insoluble polycarboxylic acid **41**. Titration with KOH increased the solubility dramatically affording the readily water-soluble potassium salt **42**.

Similar chemistry was employed in the synthesis of poly(ethylene oxide)-coated **45** [G-2]-ether dendrimers (Fig. 13) [251]. Replacement of the methyl ester groups with poly(ethylene oxide) (PEG) oligomers (M_w 2000) was effected by a transesterification process with poly(ethylene glycol) monomethyl ether using dibutyltin dilaurate as catalyst. Excess PEG was removed followed by

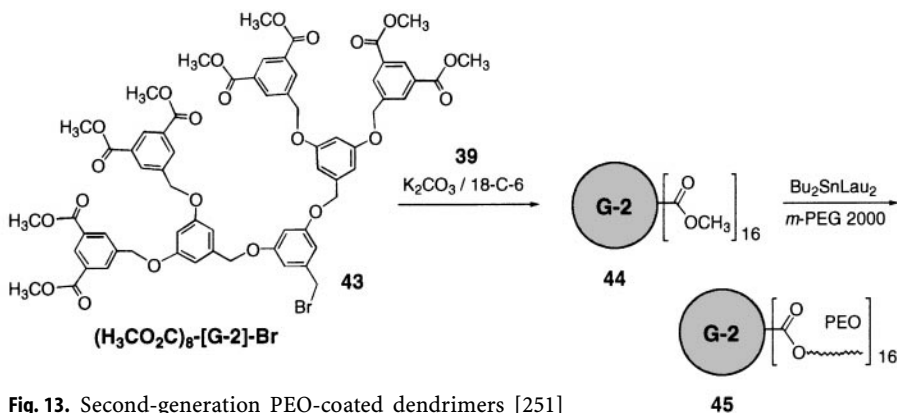


Fig. 13. Second-generation PEO-coated dendrimers [251]

extraction with CH_2Cl_2 . The final product **45** was precipitated from hexane and characterized by UV-vis absorption and fluorescence spectroscopy.

Structurally similar isophthalate ester terminated dendrimers have been synthesized [252]. Diethyl 5-(bromomethyl)isophthalate was prepared in four steps starting from 1,3,5-benzene tricarboxylic acid. Diester-terminated dendrons up to [G-4] were constructed utilizing a Williamson ether synthesis and the $\text{PPh}_3/\text{CBr}_4$ bromination reactions. Noticeably dendrons up to [G-3] were purified by recrystallization alone. Dimethyl 4-(bromomethyl) phthalate was also tested as a terminating group, but the synthesis proved to be difficult affording a mixture of products that could only be purified by column chromatography. 4,4'-Biphenol **39** was chosen as the core due to its better reactivity and shorter reaction times than 1,1,1-tris(4-hydroxy phenyl)ethane. The resulting [G-3] **46** (M_w 5644 amu) and [G-4] **47** (M_w 11,346 amu) dendrimers (Fig. 14) were obtained in ~90 % yields. The terminal ethyl ester groups of **46** and **47** were further

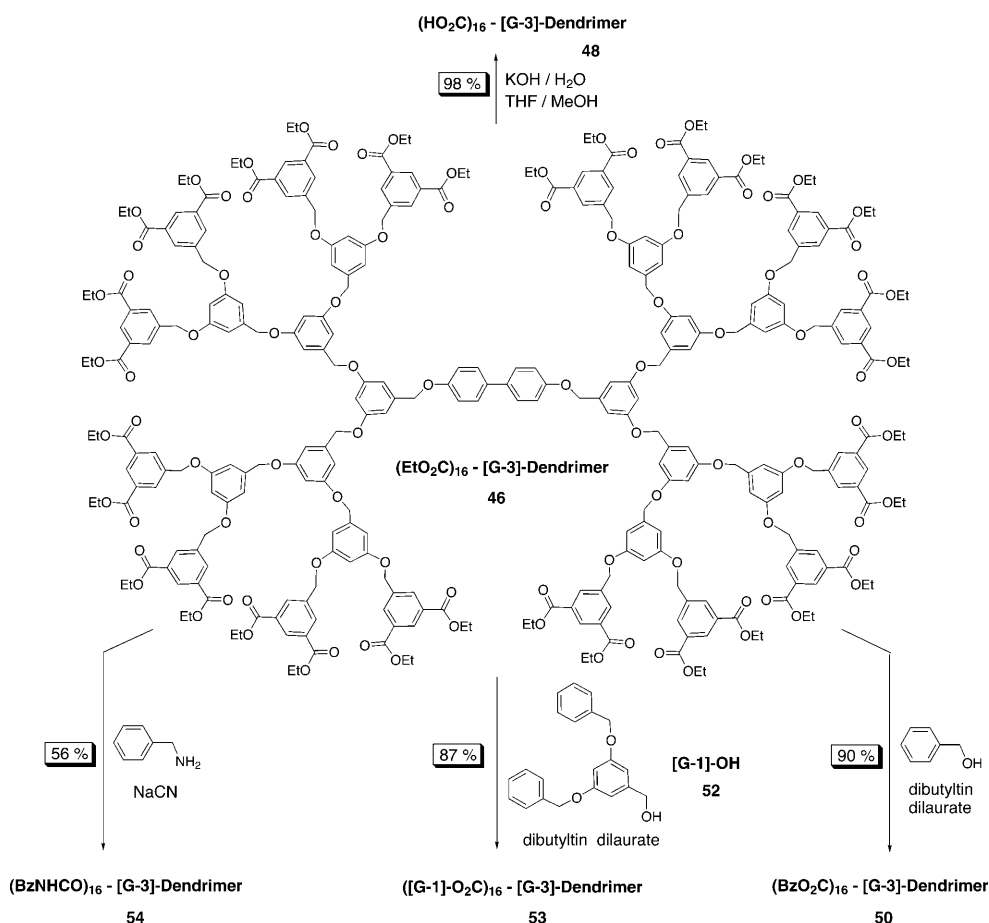


Fig. 14. Surface modification of isophthalate ester terminated polyether dendrimers [252]

modified by hydrolysis, transesterification, and amidation. Hydrolysis gave the corresponding acids **48** and **49** using a large excess of KOH in mixtures of THF/H₂O/MeOH. Reflux in neat benzyl alcohol in the presence of dibutyltin dilaurate afforded the benzyl ester terminated dendrimers **50** (M_w 7630 amu) and **51** (M_w 15,318 amu). The double-stage convergent growth approach was successfully employed by using 3,5-(dibenzoyloxy)benzyl alcohol (**52**) as reagent and dibutyltin dilaurate as catalyst yielding the [G-5]-dendrimer **53** (M_w 14,422 amu). Amidation was attempted with different amines, but only the reaction with benzylamine proved to be successful to form **54** (M_w 7600 amu). All products were characterized by ¹H- and ¹³C-NMR, IR, and matrix-assisted time-of flight (MALDI-TOF) mass spectrometry.

Vögtle et al. [253] introduced a simple divergent route to bulky dendrimers by utilizing the *N*-tosylate of dimethyl 5-aminoisophthalate **55** and 1,3,5-tris(bromomethyl)benzene (**56**) as the core molecule (Fig. 15). The resulting hexaester **57** was reduced to **58** and transformed to the bromomethyl derivative **59** followed by treatment with **55** to afford the dodecaester **60**. Increased solubility and yields were obtained by replacing the methyl group in tosylate **55** by a *tert*-butyl group. Further generations (up to 3) were constructed by repeating this three-step procedure, though problems arose due to steric hindrance. All products were characterized by NMR, MS, and fast-atom bombardment (FAB) mass spectrometry. The X-ray structure of **57** was determined showing octopus-like packing creating differently sized and shaped cavities occupied by the solvent molecules. According to the authors, this is the first reported X-ray structural analysis concerning dendritic macromolecules. As an extension of this work a series of bulky dendrimers containing 1,3,5-substituted aromatic cores or “hexacyclene” was prepared [254].

Shinkai et al. [255] have reported the synthesis of “crowned” arborols utilizing diazo crown ethers as spacers. In this case the convergent synthesis (Fig. 16) was found to be more effective than the divergent method. The diester intermediate **64** was obtained by coupling *N*-benzyloxycarbonyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**65**) with 3,5-bis(ethoxycarbonylmethoxy)benzoyl chloride (**66**). Debenzylation and hydrolysis gave the monomers **67** and **68**. [G1]-OEt **69** was obtained by coupling **67** with a 1,3,5-benzene tricarbonyl trichloride **70** core. Tetraester **71** was constructed from **67** and **68** by employing the mixed acid anhydride method with the aid of pivaloyl chloride followed by debenzylation. The resulting dendron was treated with **70** to yield [G2]-OEt **72**. [G-3]-OEt was constructed in a similar manner. Conversion of amide functions of **69** as well as the higher generation analogs to tertiary amines was accomplished by reduction with borane/dimethyl sulfide. The complexation ability of these “crowned” compounds was estimated by two-phase solvent extraction of alkali picrate salts. The [G_{*n*}]-reduced series exhibited higher metal affinity than the [G_{*n*}]-OEt series. The [G_{*n*}]-reduced series, especially **73**, was found to be a powerful reagent for the solubilization of myoglobin in organic solvents. Products were characterized by IR, ¹H- and ¹³C-NMR, MS, GPC, and elemental analysis.

Moszner et al. [256] have modified ASTRAMOL dendrimers by introducing methacrylate end groups via Michael addition. Reaction of **74**, synthesized by esterification of 2-hydroxyethyl methacrylate with acryloyl chloride, with

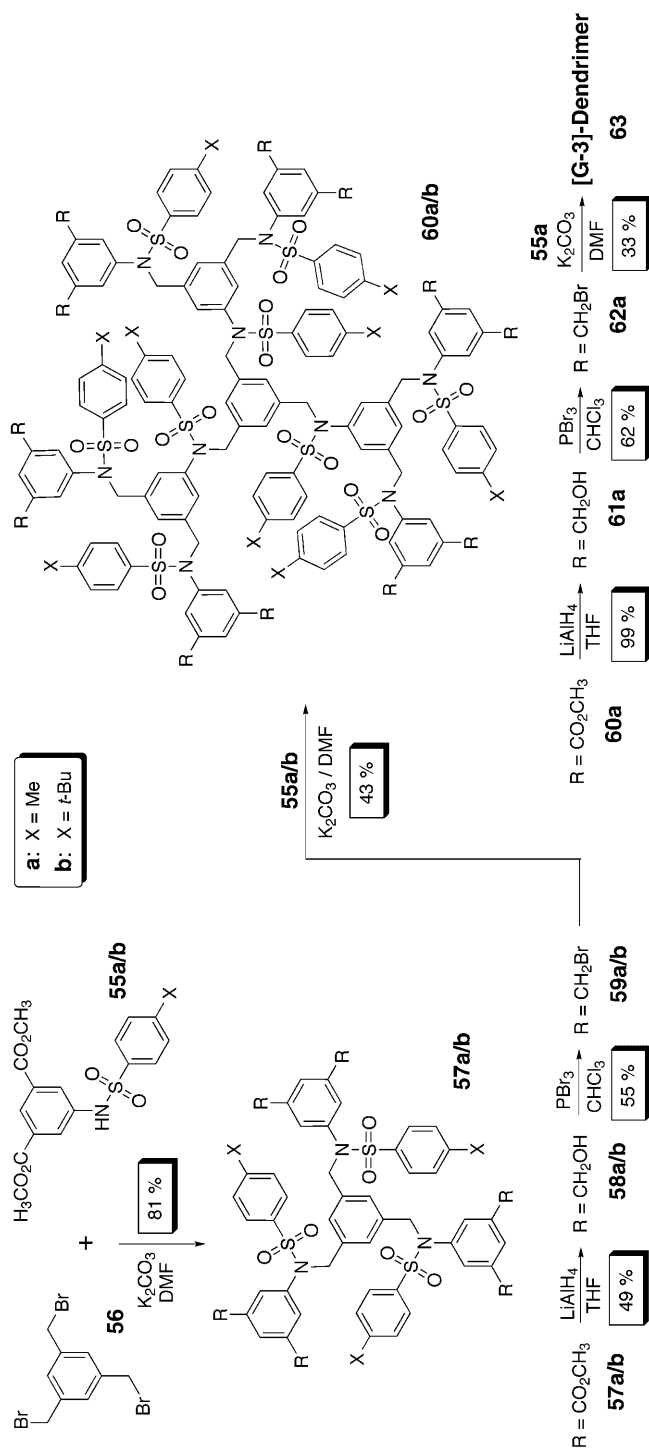


Fig. 15. Synthesis of bulky dendrimers via the divergent approach [253]

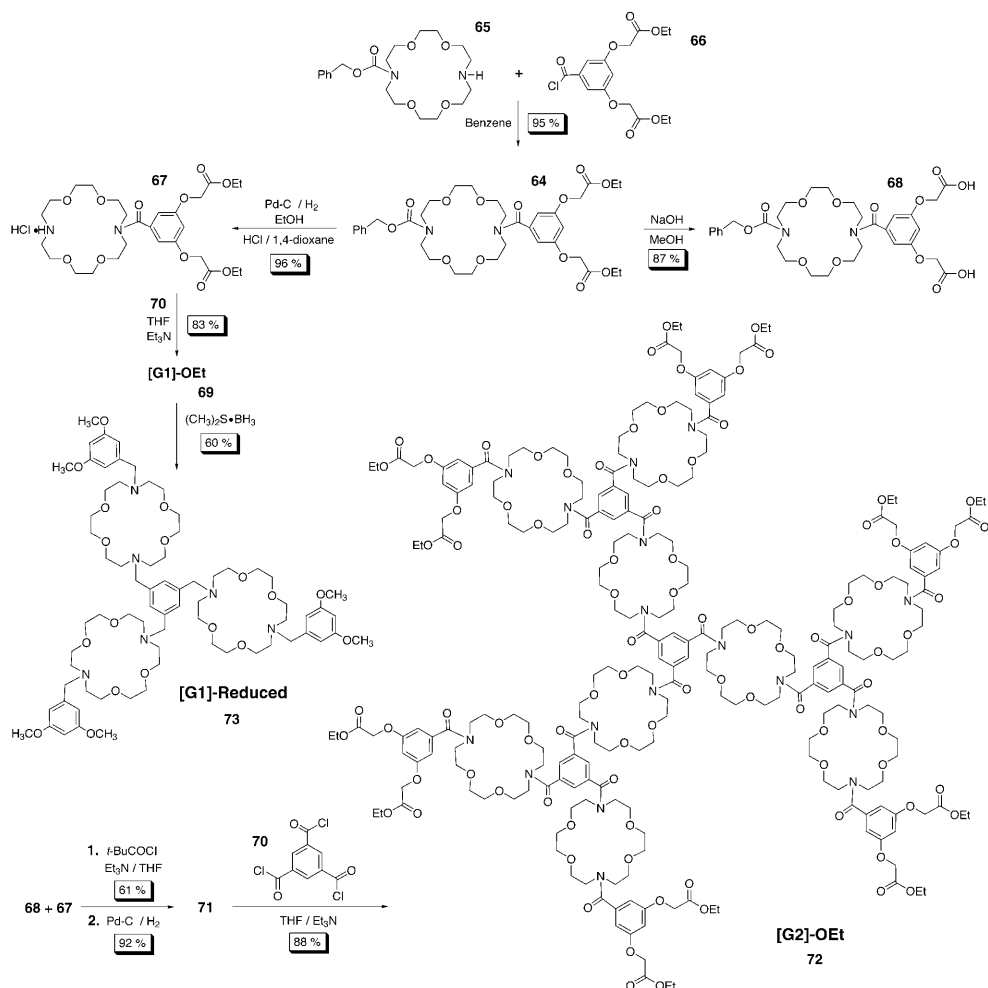


Fig. 16. Synthesis of "crowned" arborols by Shinkai et al. [255]

1,4-diaminobutane (DAB) (**75**) in MeOH gave methacrylated product **76** (Fig. 17). 2-Isocyanatoethyl methacrylate (**77**), 2-(acetoacetoxy)ethyl methacrylate (**78**) and methacrylic anhydride (**79**) were also employed as reagents, but they proved to be unsuitable for a dendrimer modification because of the poor solubility. Higher generations of DAB(PA)_x (x = 8, 32, or 64) were reacted with **74** in the dark under argon in MeOH to give poly(methacrylates) in 90–99% yields. The resulting methacrylic dendrimers were polymerized with 2,2'-azobisisobutyronitrile (AIBN) as initiator in toluene. Depending on the amount of polymerizable end groups, gelation occurred soon after. It was concluded that the majority of methacrylic groups were crosslinked intermolecularly and the rest were connected "intramolecularly" on the surface of the dendrimers. Products were characterized by ¹H- and ¹³C-NMR, IR, direct scanning calorimetry (DSC),

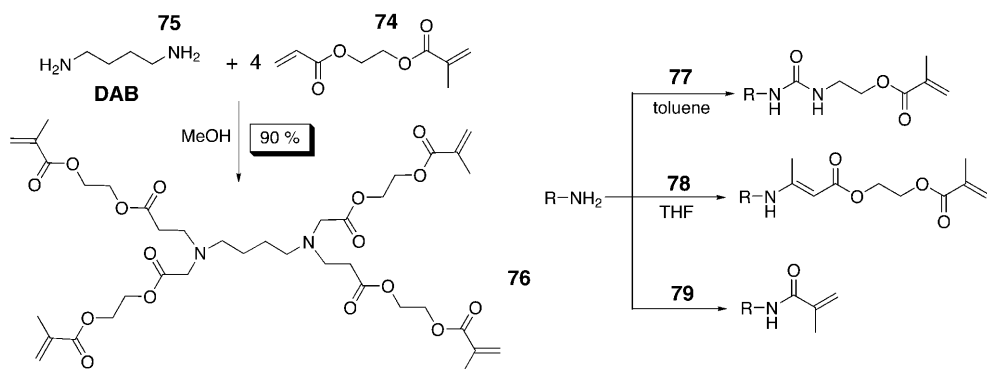


Fig. 17. Methacrylated dendrimers with a poly(propyleneimine) skeleton [256]

and GPC. Differences in the glass transition temperature (T_g) were not observed unless the end group was changed to phenyl or stearyl acrylate ($\rightarrow$ increase in T_g).

Diederich et al. [94, 257] have reported the construction of “dendrophanes”, i.e. dendritic cyclophanes. The aim was to build a model system for apolar binding sites located in the center within globular proteins by linking together water-soluble cyclophanes (major synthetic receptors for apolar and aromatic substrates [258, 259]) and dendrimers and to study the influence of the shielding effect of growing dendritic structures on the kinetics and thermodynamics of inclusion complexation by a cyclophane. Branches up to [G-3] **80–81** (Fig. 18) were grown in a divergent manner around a [6.1.6.1.]paracyclophane core [260] employing the procedure of Newkome et al. [248, 293]. The X-ray structure of the paracyclophane ester derivative exhibited an open 8.0×9.5 Å wide rectangular cavity (distances between the centers of opposite benzene rings). The cavity of the [G-1]-ester (ca. 7×10 Å) was slightly distorted but remained open for host–guest complexation. All ester-terminated “dendrophanes” were purified by preparative GPC. Hydrolysis of esters to the corresponding acids proceeded quantitatively using LiOH in aqueous THF/MeOH. All compounds were fully characterized by IR, ¹H- and ¹³C-NMR, electron ionization (EI)-MS, FAB-MS, or MALDI-TOFMS.

Binding studies of carboxylic acid terminated compounds were performed with naphthalene derivative titrations. ¹H-NMR titrations with naphthalene-2,7-diol in aqueous buffer demonstrated the formation of 1:1 complexes possessing similar stability to those formed by the non-branched cyclophane core. The results suggest that the cavity in the cyclophane core remains open even with the densely packed generation **81**. The observed host–guest exchange kinetics for all compounds (except for **81**) was remarkably fast. Fluorescence titrations with the fluorescent probe 6-(*p*-toluidino)naphthalene-2-sulfonate (TNS) showed that the micropolarity around the cavity binding site decreases with increasing generation number.

Another “dendrophane” family was introduced by Diederich et al. [261, 262] to explore inclusion complexes with steroids in aqueous solutions. The novel cyclophane core with four carboxylic acid linkers was prepared in a total of ten

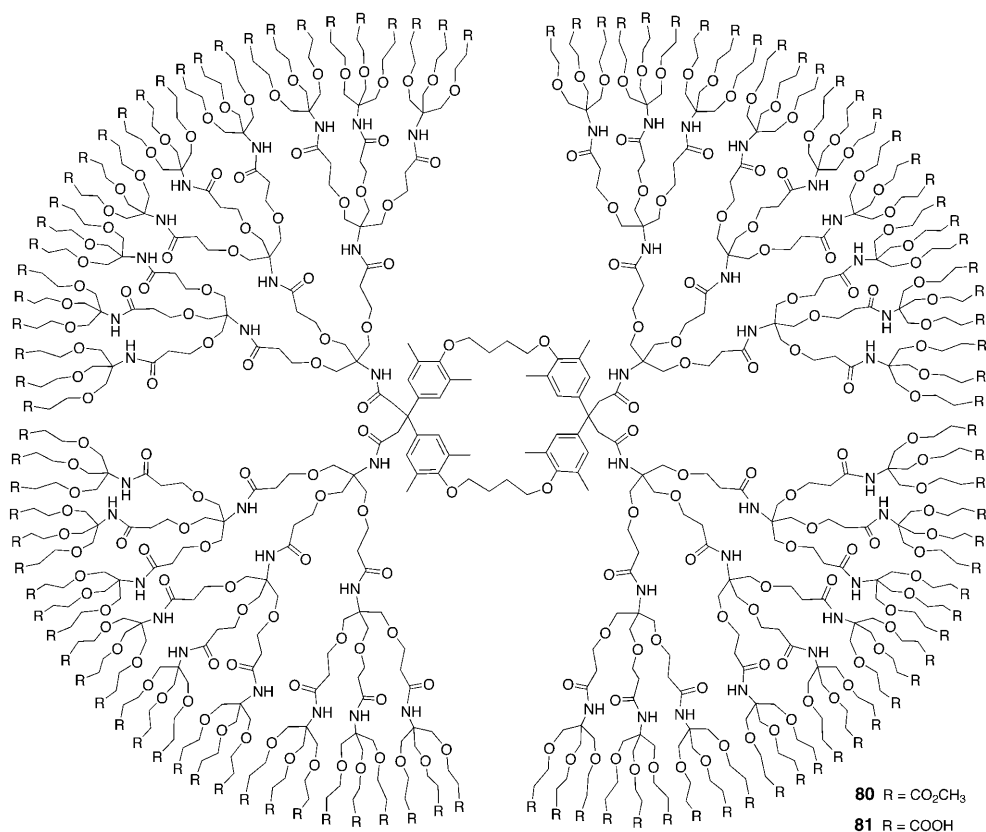


Fig. 18. The water-soluble [G-3]-“dendrophanes” of Diederich et al. [257]

steps. Construction of poly(ether amide) dendrons up to [G-3] **82–83** was accomplished by the method developed by Newkome et al. (Fig. 19) [248, 293]. All esters were purified by preparative GPC and hydrolyzed to the corresponding acids in quantitative yields. Characterization was performed by IR, ¹H- and ¹³C-NMR, FAB-MS or MALDI-TOFMS. Steroid recognition by the carboxylic acid terminated compounds (generations 1–3) was investigated by ¹H-NMR binding titrations in basic borate buffer in D₂O/CD₃OD.

All “dendrophanes” formed 1:1 axial complexes with testosterone indicating that the binding site within the dendritic structure is accessible. The stability of these complexes was comparable to that of non-branched core cyclophanes. Fast host-guest exchange kinetics on the ¹H-NMR scale was observed for all compounds.

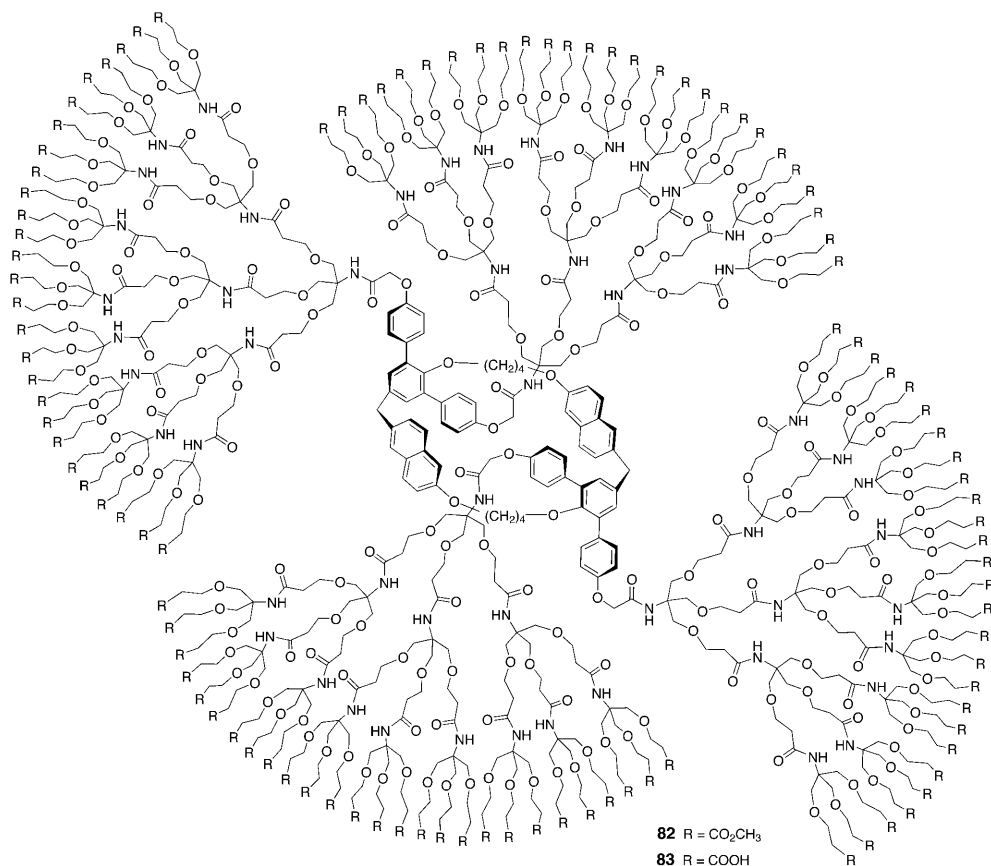


Fig. 19. The [G-3] steroid-recognizing “dendrophane” receptor of Diederich et al. [261, 262]

2.2

Core

Chapman et al. [96] have constructed dendrimer-type “polycules” **84** using unsymmetrically substituted tetraphenyladamantanes **85** as branching units and acid chloride derivative **86** as the core molecule (Fig. 20). Detailed data was not given.

2.3

Core and Branching

Hawker and Fréchet [263] have introduced dendrimers with an aromatic polyester inner structure and a readily modified hydrophobic/hydrophilic surface. The synthesis involved the convergent growth process of trichloroethyl 3,5-dihydroxybenzoate (**87**) as the monomer and 3,5-bis(benzyloxy)benzoic

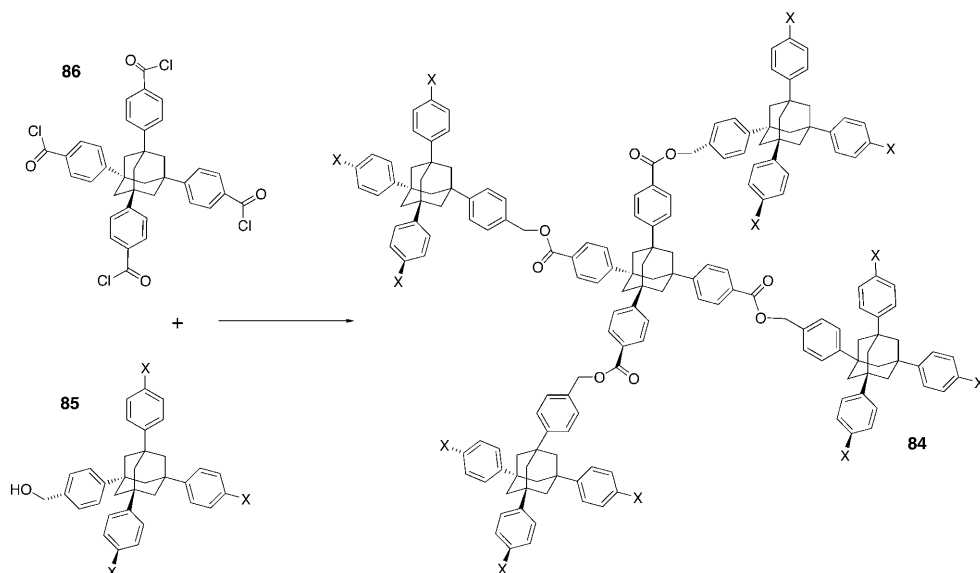


Fig. 20. Synthesis of “polycules” by Chapman et al. [96]

acid (**88**) as the terminal unit (Fig. 21). Dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridium *p*-toluenesulfonate (DPTS) or 4-dimethylamino pyridine (DMAP) [264] were utilized as condensing agents in CH_2Cl_2 affording the [G-2]-ester **89**. Removal of the trichloroethyl ester group with zinc in THF/acetic acid solution gave the desired acid **90**. Repetition of this two-step process afforded the [G-4]- CO_2H dendron **91**. Coupling of **91** (30% excess) to the 1,1,1-tris(4'-hydroxyphenyl)ethane core **92** was carried out using the same DCC/DPTS chemistry to afford the [G-4]-dendrimer **93** (M_w 10,746 amu). The phenolic-terminated polyester **94** was obtained by removal of the benzyl ethers at the chain ends using catalytic hydrogenolysis ($\text{Pd-C}/\text{H}_2$).

Comparing the properties of **93** and **94** showed significant differences in glass transition (T_g) temperatures (~ 130 K) and solubility. Modification of **94** with excess of the monobenzyl ester of adipic acid **95** in the presence of DCC and DMAP afforded the polyester **96** (Fig. 22). NMR experiments showed that ca. 90% of the phenolic groups had been esterified. The corresponding acid **97** was obtained after removal of the benzylic esters at the chain ends. Titration with NaOH confirmed the change in functionality and gave the water-soluble salt **98**. Excess of NaOH caused hydrolysis of the interior ester bonds. All dendrimers were characterized by ^1H - and ^{13}C -NMR, IR, MS, SEC, and DSC.

Haddleton et al. [265–267] have prepared three geometric series of aromatic polyester dendrimers via divergent growth in order to investigate their physical properties. In particular, interest was focused on three aspects: (1) the nature of the end groups (hydrophobic or hydrophilic), (2) the effect of the degree of branching of the core both on dendrimer properties and on synthetic access to higher generations, and (3) luminescence studies on dendrimers.

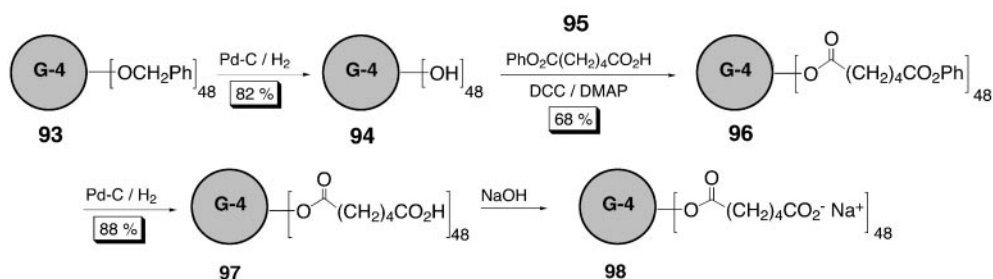


Fig. 22. Surface functionalization of a benzyl ether terminated dendrimer [263]

Two different synthetic routes were employed using hydroquinone **99**, phloroglucinol (1,3,5-trihydroxybenzene), and naphthalene-2,6-diol **100** as core molecules. Esterifications were carried out at ambient temperature by activating benzyl-protected 3,5-dihydroxybenzoic acid monomer with DCC/DPTS in dry acetone or using the corresponding acid chloride in dry CH_2Cl_2 with DMAP as catalyst (Fig. 23). Removal of the benzyl protecting groups of [G-4]-OBn

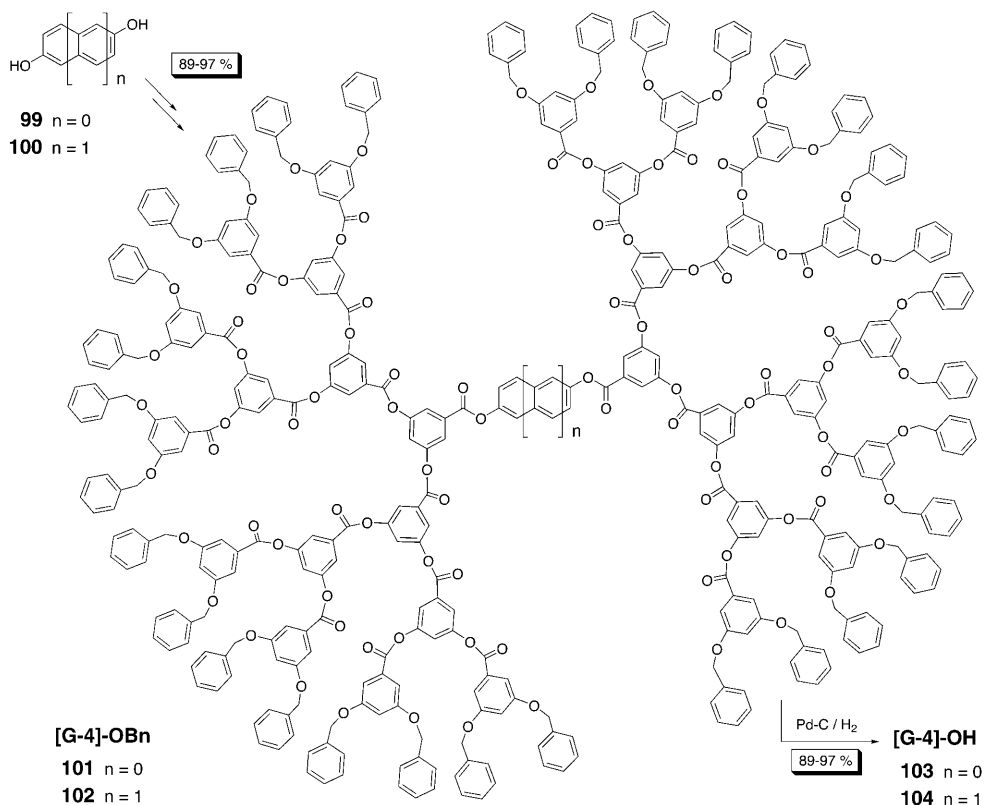


Fig. 23. Two-directional aromatic polyesters of Haddleton et al. [265]

101–102 by catalytic hydrogenation ($\text{Pd-C}/\text{H}_2$) afforded hydroxy-terminated polyesters **103–104**. Products were characterized by ^1H - and ^{13}C -NMR, IR, GPC with polystyrene narrow molecular weight standards, and MALDI-TOF. GPC results for all purified [G-4]-dendrimers indicated the presence of $\sim 5\%$ of higher oligomers. An interesting phenomenon, yet unexplained, was the clearly higher yield of the DCC method over the acid chloride approach in preparation of higher generations and vice versa for lower generation dendrimers. The densely packed generation emerged after [G-3] for three-directional dendrimers and [G-4] for two-directional dendrimers. As an extension of this work a series of poly(alkyl ester) dendrimers are under construction [268]. According to the authors, alkyl or alkyl/aryl analogs are expected to possess better processing properties.

Zeng and Zimmerman [112] have demonstrated the use of an orthogonal protecting group strategy (widely used in peptide chemistry) in dendrimer synthesis. Construction of the [G-4]-dendron **111** begins with the synthesis of AB_2 -monomers which contain two pairs of a complementary coupling functionality. Monomer **105** was prepared by diazotization of 5-aminoisophthalic acid followed by treatment with NaI. Monomer **106** was obtained from methyl 3,5-dibromobenzoate by reduction, coupling to (trimethylsilyl)acetylene, and deprotection with K_2CO_3 .

Monomers were designed to couple by the Mitsunobu esterification [269] and the Sonogashira reaction [270]. Coupling of (4-*tert*-butyl phenoxy)ethanol (**107**) to monomer **105** gave the [G-1]-dendron **108** (Fig. 24). The [G-2]-dendron **109** was constructed via Sonogashira reaction of monomer **106** and **108**. Repetition of both reactions led to the [G-4]-dendron **111** in four steps. By employing the branched monomer approach to increase the efficiency of the synthesis, two new monomers (**112** and **113**) were prepared (Fig. 25). With these new monomers the [G-6]-dendron **118** (M_w 20,896 amu) was obtained in three steps using similar conditions to those described above. All products were characterized by standard spectroscopic methods, SEC, and MALDI-TOFMS.

Bryce et al. [271] have introduced dendrimers containing thermodynamically stable redox-active tetrathiafulvalene (TTF) units at the periphery using convergent growth. Reaction of 4-(hydroxymethyl)tetrathiafulvalene (**119**) with 5-(*tert*-butyldimethylsiloxy)isophthaloyl chloride (**120**) gave compound **121** which was deprotected to afford the dendron **122** (Fig. 26). Coupling of **122** with benzene-1,3,5-tricarbonyl chloride (**123**) in the presence of DMAP gave the [G-1]-dendrimer **124**. No reaction occurred when Et_3N was employed. The [G-2]-dendron **125** was constructed by repetition of this procedure. Compounds were characterized by NMR and plasma desorption mass spectroscopy (PDMS). Charge-transfer interactions were investigated by cyclic voltammetry (CV). The stability of the $(\text{TTF})_x$ aryl esters was increased by changing the trifunctional core **123** to a bifunctional core such as benzene, biphenyl, or biphenyl ether. All compounds were stable at room temperature in air and daylight for at least one year, although readily soluble products were obtained only when the biphenyl ether core was employed [272].

As a continuation of the work described above, Bryce et al. [273] have prepared polyester dendrimers **128** (Fig. 27) that contain both π -donor (TTF) and π -acceptor (AQ) groups. These dendrimers show reversible switching between

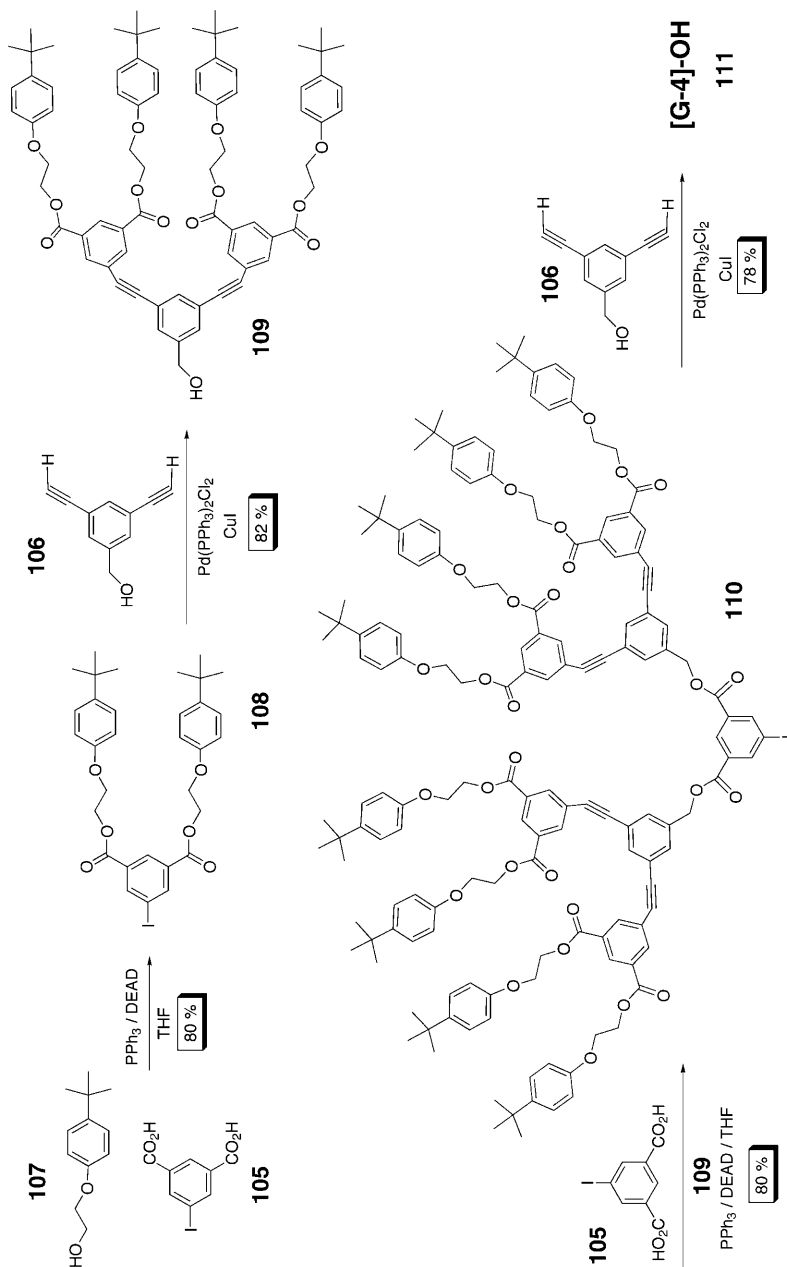


Fig. 24. Orthogonal coupling strategy [112]

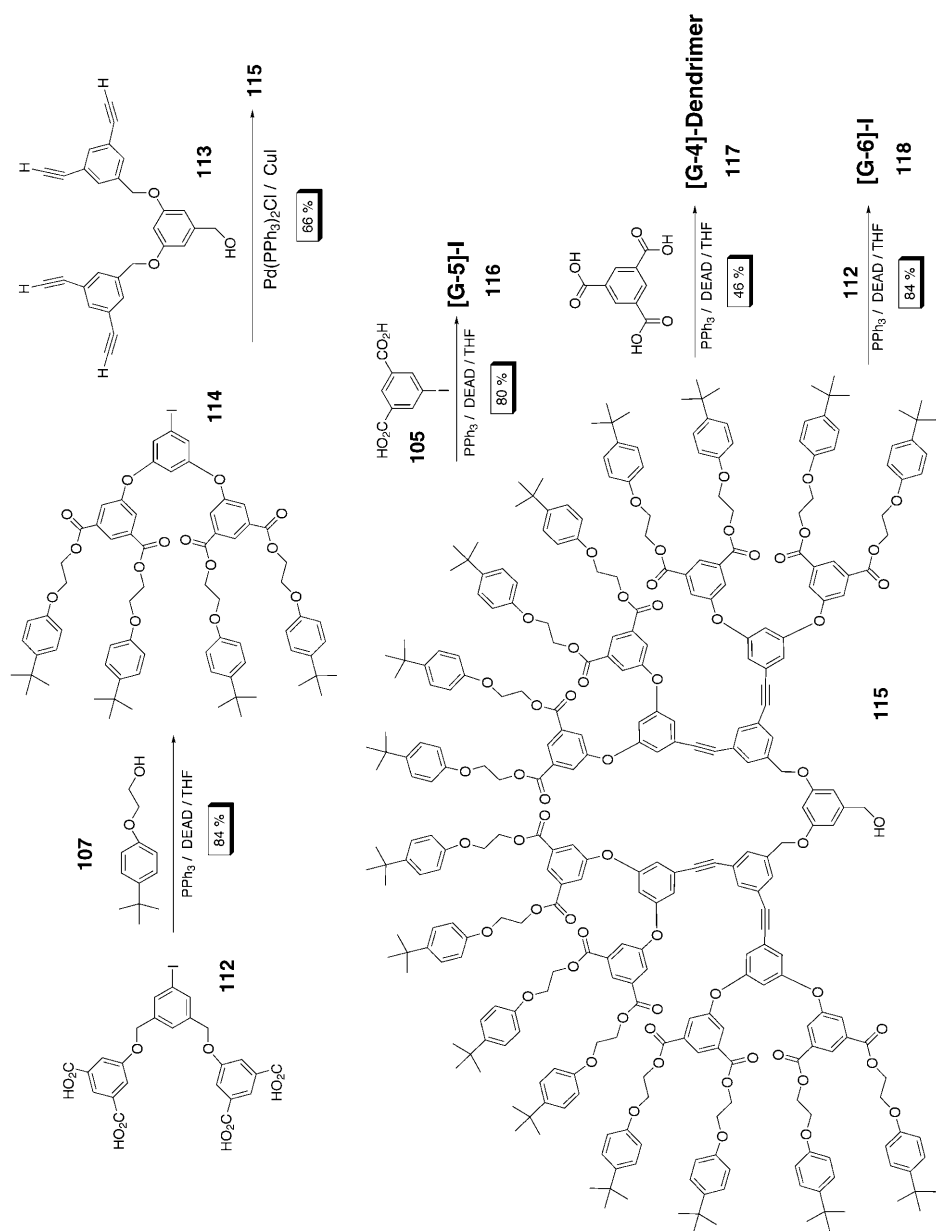


Fig. 25. Orthogonal coupling strategy with a branched monomer approach [112]

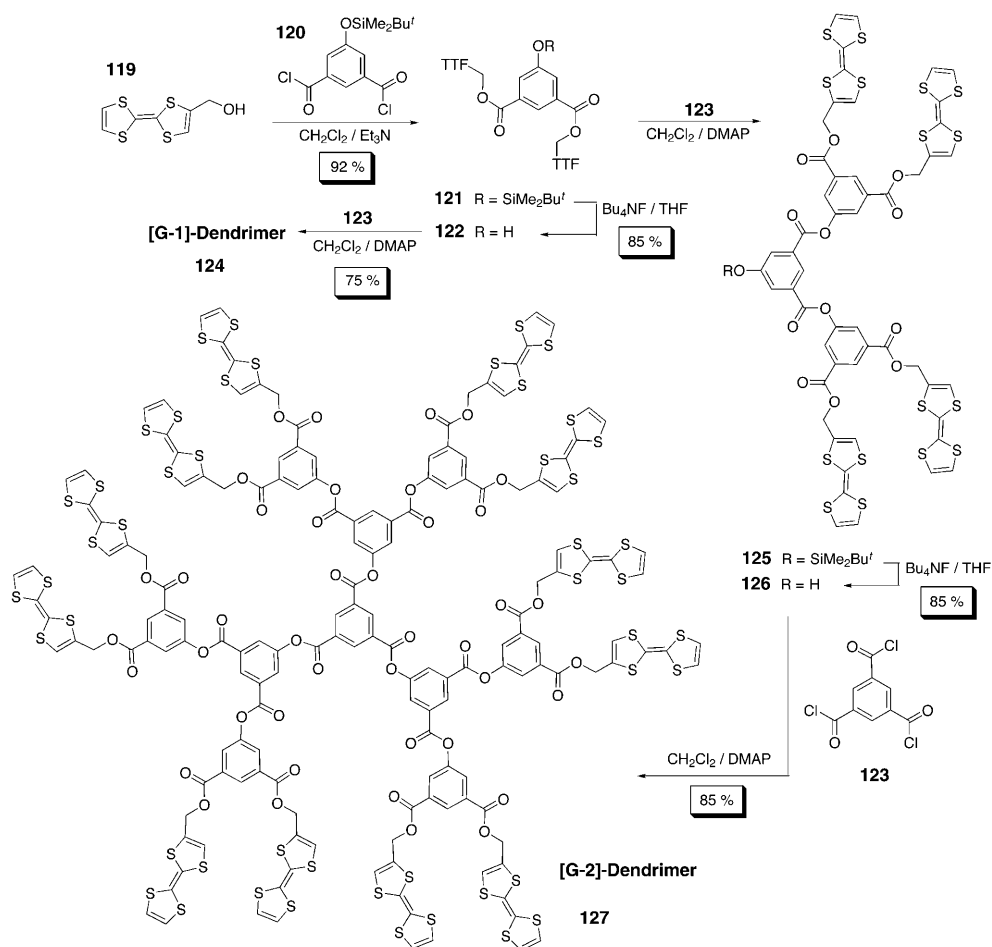


Fig. 26. Redox-active polyester dendrimers containing tetrathiafulvalene units [271]

cationic and anionic states under electrochemical control. The sparingly soluble $(\text{AQ})_2$ dendron **132** was prepared by the reaction of 2-(hydroxymethyl)anthraquinone (**129**) with silyl-protected isophthalic acid **130** followed by deprotection with HCl/THF (7:1). The $(\text{TTF})_4$ dendron **135** was obtained from the reaction of phenol derivative **133** (2.1 eq.) with benzene-1,3,5-tricarbonyl chloride (**123**). The unreacted acid chloride was hydrolyzed during workup but could be regenerated using oxalyl chloride. Reaction of **135** with **132** gave the [G-1]-dendrimer **128**. The [G-2]-dendrimer $(\text{TTF})_8(\text{AQ})_4$ was constructed by a similar iterative method. All compounds were characterized by ^1H -NMR, FAB-MS and UV-vis spectroscopy. The main difference between the [G-1]- and the [G-2]-dendrimers was the intramolecular π - π charge transfer from TTF to AQ units, as observed in the UV-vis spectra. This phenomenon is due to the more congested structure of the [G-2]-dendrimer. Such interactions in a dendritic

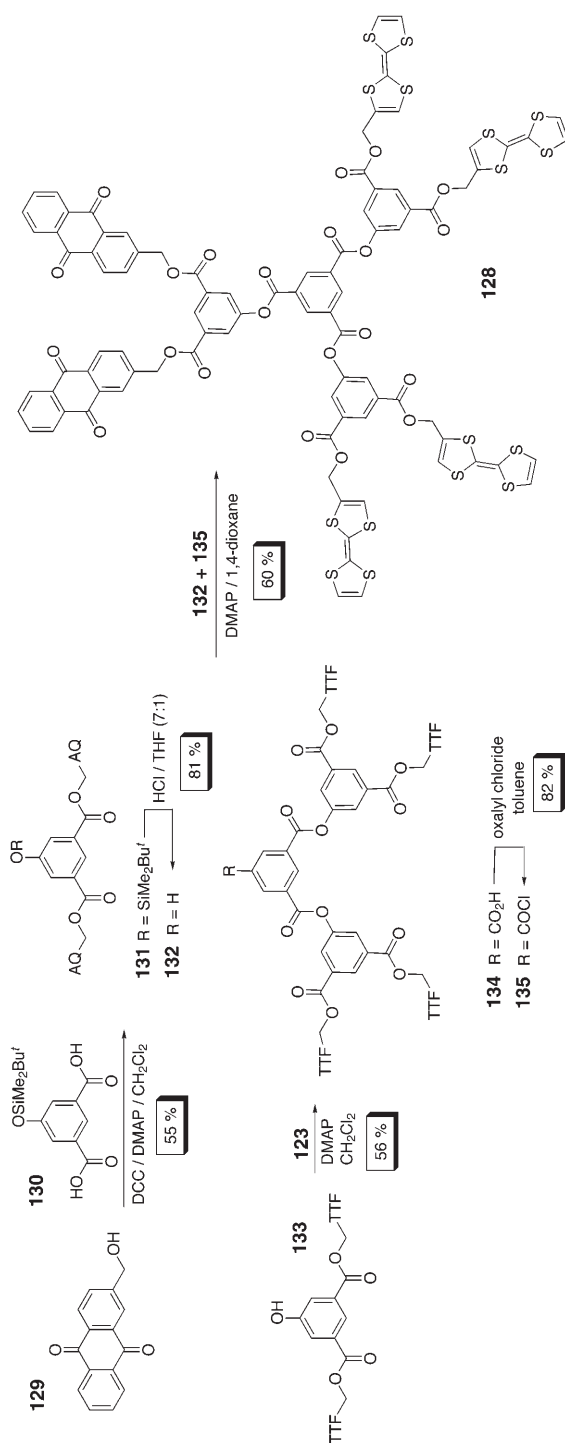


Fig. 27. Redox-switchable dendrimers containing both *p*-donor and *p*-acceptor groups [273]

microenvironment could open up new possibilities for the construction of electrooptical switches.

2.4

Core and Terminal

Twyman et al. [274] have reported a synthesis of small dendrimers with possible pharmacological applications. The convergent synthesis (Fig. 28) involved an exhaustive Michael addition of suitable α,β -unsaturated carbonyl compounds **130af** to 1,3-diaminopropan-2-ol (**129**) under an atmosphere of nitrogen. The resulting dendrons were coupled to the core **123** in THF using Et_3N as catalyst. All dendrimers **132a–f** were fully characterized by ^1H - and ^{13}C -NMR, IR, FAB-MS and SEC.

2.5

All Layers

Miller et al. [275–277] have prepared a series of monodisperse dendrimers based on the convergent synthesis of symmetrically substituted esters. The synthesis (Fig. 29) proceeded in a stepwise manner requiring at first the synthesis of dendrons which were subsequently attached to the 1,3,5-benzenetricarbonyl trichloride **123** core. The key intermediate in the syntheses of [G-1]–[G-3]-dendrons was 5-(*tert*-butyldimethylsiloxy)isophthaloyl dichloride (**133**), prepared in three steps. Molecular weights up to 5483 amu (**134**) were observed, with diameters up to 45 Å, as determined from examination of space-filling models. The resulting polyesters were readily soluble in typical organic solvents and were characterized by ^1H - and ^{13}C -NMR, GPC using polystyrene standards and thermogravimetric analysis (TGA) exhibiting stability up to 500 °C under an atmosphere of nitrogen.

The globular shape of dendrimers offers unique possibilities for constructing novel block copolymers compared with the linear analogs. Controlled placement of different chemistries in a radial or concentric fashion around the core molecule offers a route to either segment-, layer-, or surface-block copolymers (Fig. 30) [278].

Hawker et al. [279, 280] have employed dendritic ether **135a** and ester **135b** fragments in copolymer construction (Fig. 31). The fragments chosen were based on 3,5-dihydroxybenzyl alcohol and 3,5-dihydroxybenzoic acid. The reaction scheme employs the same procedure as that described in Fig. 21 [263]. The copolymer dendron **139** was coupled to the core **140** under standard DCC/DPTS conditions affording the dendritic segment-block macromolecule **141** (M_w 5370 amu). Numerous conformations are possible due to free rotation about the single bonds; however, constraints arising from the branching sequence do not allow a structural isomer where all three polyester fragments are adjacent.

Dendritic layer-block copolymers were constructed in a similar manner employing the same building blocks (Fig. 32). Reaction of **135a** (2.1 eq.) with **136** followed by deprotection (Zn/AcOH) gave the ether-[G-3]- CO_2H **142**. The ester blocks were constructed via coupling of **142** with **136**. Deprotection of the tri-

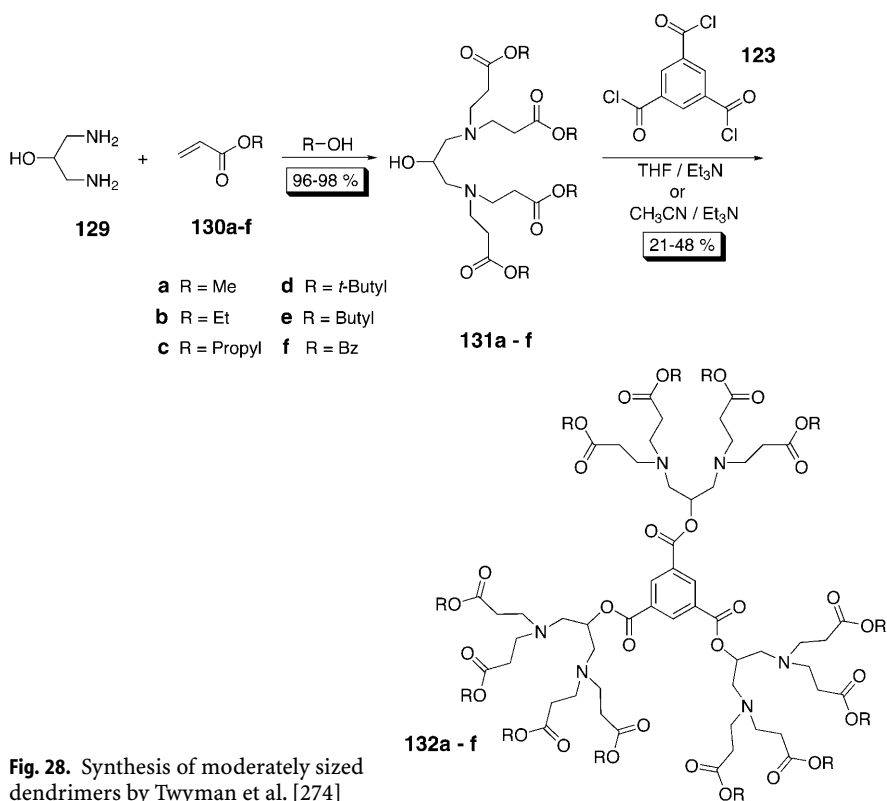


Fig. 28. Synthesis of moderately sized dendrimers by Twyman et al. [274]

chloroethyl ester at the focal point afforded [G-4]-CO₂H **144** which was coupled with **140** under standard conditions to afford the dendritic layer-block copolymer **145**. For all copolymers, a combination of ¹H- and ¹³C-NMR, MS, and SEC proved to be useful in detecting impurities and defects.

Ihre et al. [281, 282] have synthesized dendritic aliphatic polyesters based on 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) **146** monomer via convergent growth (Fig. 33). The corresponding hyperbranched system has been studied and thoroughly characterized previously [229, 232, 283]. The hydroxyl groups of **146** were deactivated by acetate formation using acetyl chloride (**147**) in the presence of Et₃N and DMAP. The acid **148** was then converted to the acid chloride **149** by oxalyl chloride in CH₂Cl₂. Reaction with the benzyl ester protected monomer **150** gave the [G-2]-dendron **151**. Deprotection was accomplished by selective catalytic hydrogenolysis (Pd-C/H₂). Higher generations were obtained in a similar fashion. The final dendrimers, up to [G-4], were obtained by coupling of acid chloride dendrons to the 1,1,1-tris(hydroxyphenyl)ethane core **154**. Characterization was performed by ¹H- and ¹³C-NMR, SEC, elemental analysis, and pulsed field-gradient spin echo (PGSE) ¹H-NMR. The effective radii of the dendrimers were estimated from the diffusion coefficients by assuming a spherical geometry for all dendrimers.

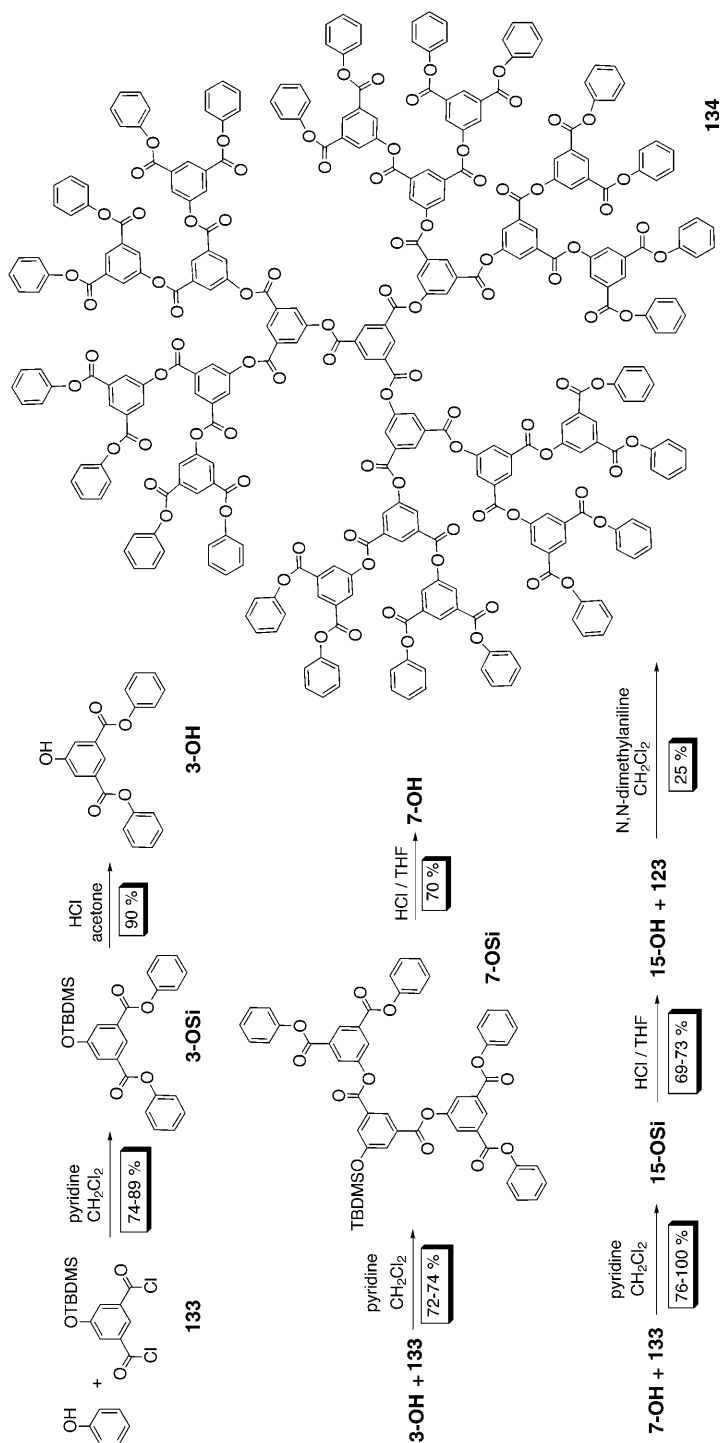


Fig. 29. Synthesis of dendritic arms and their coupling to the core [275–277]

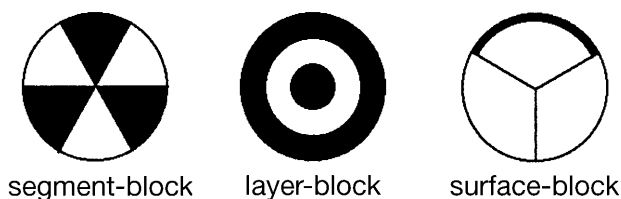


Fig. 30. Novel architectures of the dendritic block copolymers [278]

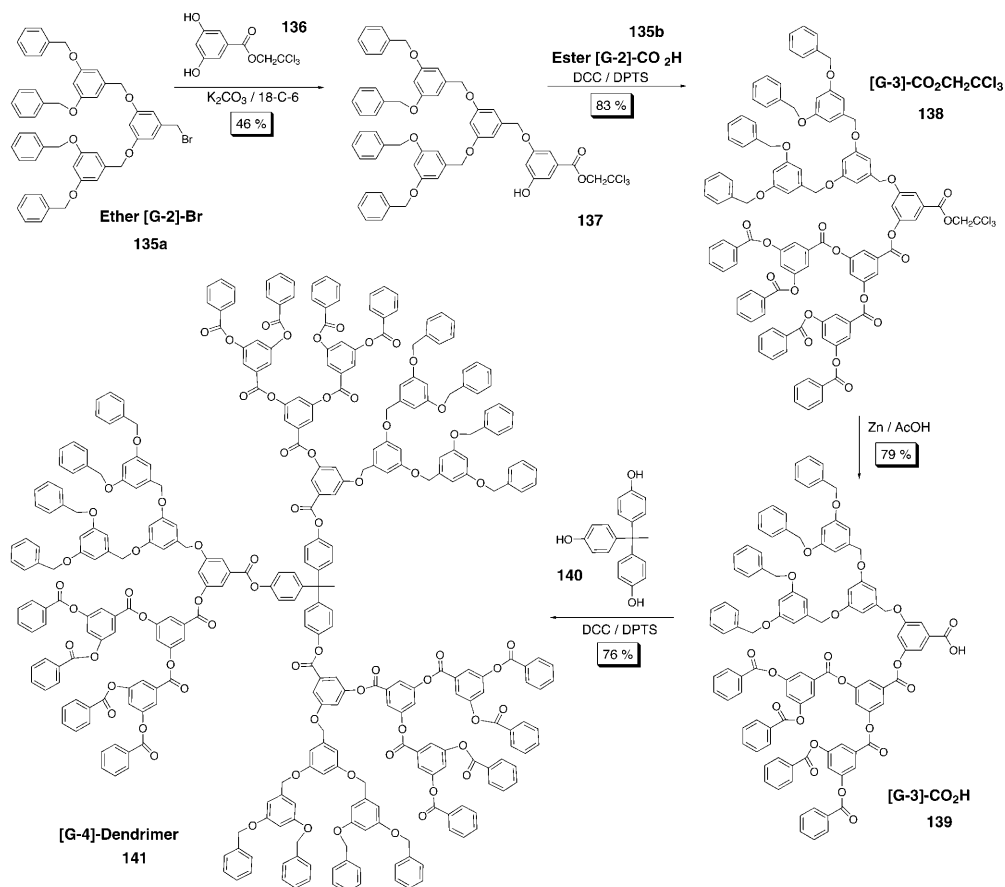
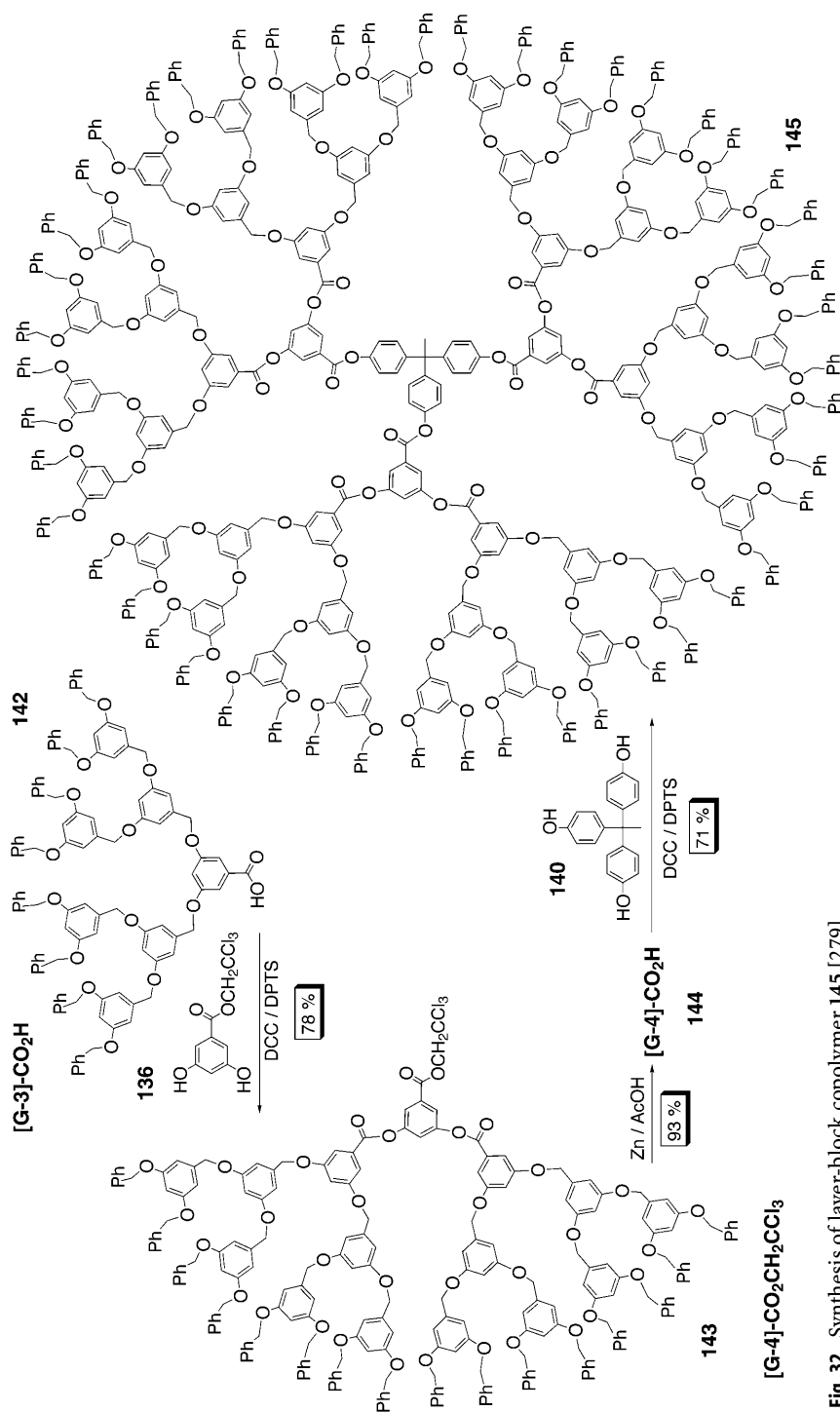


Fig. 31. Synthesis of segment-block copolymer 141 [279]

Surface modification of the acetate functional dendrimers was not successful due to the lack of selectivity in the hydrolysis of the acetate ester groups. A better synthetic route was applied by employing double-stage convergent growth and acetonide protecting groups [284]. The bis-MPA 146 was protected by reaction with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic

Fig. 32. Synthesis of layer-block copolymer **145** [279]

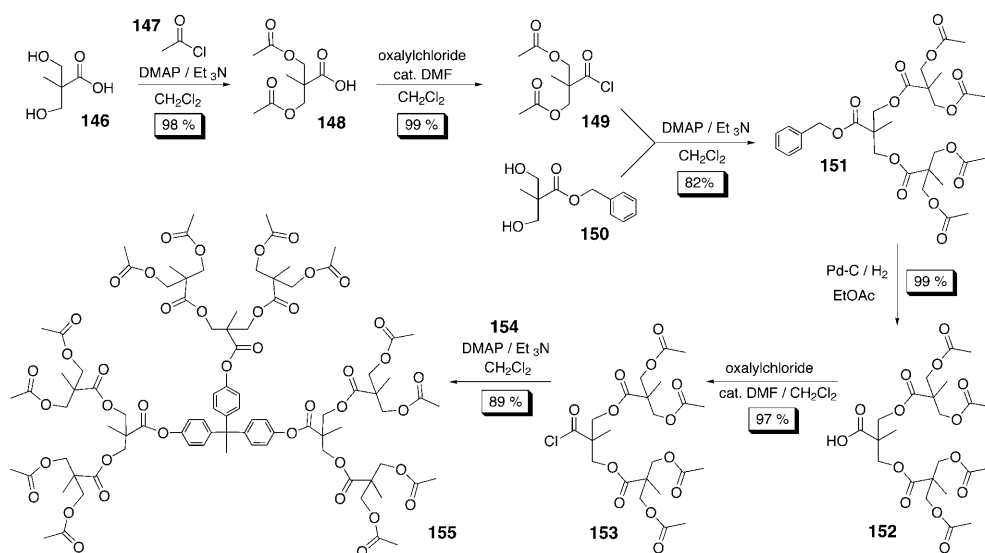


Fig. 33. Synthetic route for the bis-MPA-based dendrimers [282]

acid in dry acetone. Protection of the acid function was accomplished by reaction of the potassium salt of **146** and benzyl bromide. Deprotection of the benzyl ester group was achieved by catalytic hydrogenolysis (Pd-C/H₂). The protecting acetonide groups were removed by refluxing in MeOH with an acidic Dowex 50W-X2 resin. All esterifications were carried out under an argon atmosphere in CH₂Cl₂ by employing DCC/DPTS chemistry. The [G-4]-dendron was obtained by a double-stage coupling of the [G-2]-acid and the [G-2]-alcohol followed by deprotection. Coupling with the 1,1,1-tris(hydroxyphenyl)ethane core **154** gave the three-directional [G-4]-dendrimer in 85% yield, which is substantially higher than in a previous example [282]. Surface modification [285] of the hydroxy functional dendrimer was accomplished by reaction with benzoyl, octanoyl, and palmitoyl chloride in the presence of Et₃N and DMAP in CH₂Cl₂. According to ¹H- and ¹³C-NMR, SEC, and elemental analysis only fully substituted products were obtained whereas employing the corresponding acids under DCC/DPTS conditions gave only partially reacted compounds. This phenomenon is probably due to the hydrogen bonding between the hydroxyl groups of the dendrimers and Et₃N. As expected, the thermal and solution behavior was strongly dependent on the nature of the end groups. The glass transition temperature (*T_g*) of the dendrimers varied from -4 °C (acetate) to +57 °C (hydroxy).

Bo et al. [110] have employed the branched monomer strategy to prepare polyester dendrimers. AB₄-monomer **156** was synthesized (Fig. 34) in five steps with a protecting methyl group as the focal point. Monomer **156** was reacted with benzoic acid (**157**) to give [G-2]-CO₂Me dendron **158** which was deprotected as **159** and further reacted with **156** to give [G-4]-CO₂Me **160**. The methyl-protected [G-3] building block **161** was obtained by reaction of **156** with [G-1]-CO₂H **162**. Removal of the protecting methyl group by refluxing with

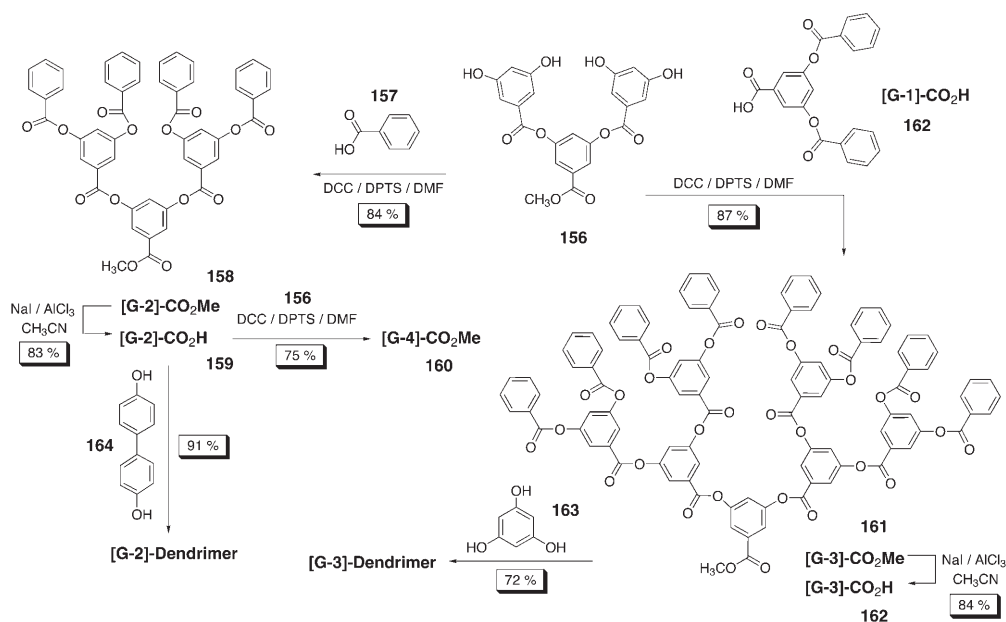


Fig. 34. Construction of polyesters via the branched monomer strategy [110]

AlCl₃/NaI in acetonitrile gave the corresponding acids **159** and **162** without any side reactions. The final dendrimers **165** and **166** were obtained by coupling of the dendrons with either phloroglucinol **163** or 4,4'-dihydroxybiphenyl **164** core under DCC/DPTS conditions. All products were characterized by ¹H- and ¹³C-NMR, IR, GPC, and MALDI-TOFMS.

Shi and Rånby [286–289] have prepared radiation-curable dendritic resins based on the pentaerythritol **167** core and the 1,2,4-benzenetricarboxylic anhydride **168** monomer using the mixed reactivity approach (Fig. 35) [103]. The

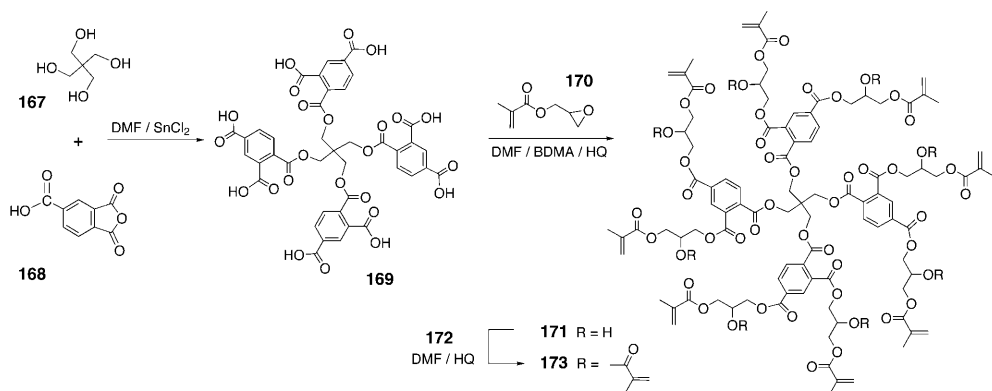


Fig. 35. Synthesis of radiation-curable dendritic resins [286–289]

resulting octaacid **169** was further reacted with glycidyl methacrylate **170**. The hydroxyl groups of **171** were esterified with methacrylic anhydride **172** affording the polyester **173** with 16 double bonds at the chain ends. The resulting esters were largely a mixture of *meta* and *para* isomers due to the reactivity of anhydride **168**. A small amount of the *ortho* isomer was expected to form via the hydrolysis reaction of the carboxylic acid group of **168**. All reactions were carried out in DMF using SnCl_2 or *N,N*-dimethylbenzylamine (BDMA) as catalyst and hydroquinone as inhibitor under N_2 . Operation at 70–100 °C was necessary due to the readily crosslinkable double bonds. Products were characterized by titration, GPC, and IR. Rheological behavior was studied on UV-cured samples.

3

Chiral Dendrimers

There are various ways to build chiral dendrimers [290]. Seebach et al. [291] were the first to differentiate dendrimers based on the position of the chiral centers in the molecule. Later Peerlings and Meijer [235] modified and expanded the classification by introducing two additional classes (6 and 7), although no concrete examples of such structures are known to date. Thus, all chiral dendrimers can be categorized into seven classes [292]: (1) chirality of the core only, (2) chirality of the branching unit only, (3) chirality of the terminal group only, (4) chirality of two or three building blocks mentioned above, (5) constitutionally different branches attached to a chiral core, (6) a rigid chiral conformation without any stereocenters or chiral units, and (7) interactions with non-covalently attached chiral ligands.

3.1

Terminal

Newkome et al. have reported a series of four-directional poly(ether amide) cascade dendrimers [293, 294]. The tetraacid chloride core **174** was synthesized in four steps starting from pentaerythritol (Fig. 36). The [G-1]-dodecaester **176** was obtained by reaction with tris(carboxyethoxymethyl)aminomethane (**175**) using a standard DCC peptide formation method. Hydrolysis of **176** gave the [G-1]-acid **177**. Chirality [295] was introduced by treatment of **177** with tryptophan methyl ester hydrochloride **178** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC) and Et_3N affording the [12]-tryptophan methyl ester **179**. The [36]-tryptophan methyl ester **180** was constructed in a similar manner from the [G-2]-analog of **177**. IR, NMR and SEC were used for characterization. A direct relationship between the optical rotation and the number of surface tryptophans was observed.

Synthesis of a fully chiral dendrimer **181** with 15 chiral centers has been reported by Twyman et al. [296]. The procedure is based on the repeat unit L-glutamic acid using convergent growth (Fig. 37). Benzyloxycarbonyl-protected L-glutamic acid was treated with *N*-hydroxysuccinimide, DCC and dimethylaminopyridine (DMAP) to give the active ester **182**. Treatment with L-glutamic

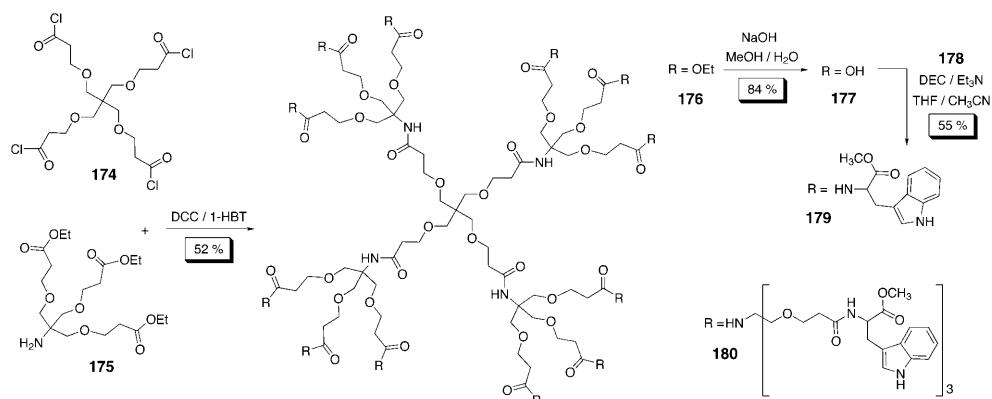


Fig. 36. Chiral polytryptophan methyl ester dendrimer of Newkome et al. [295]

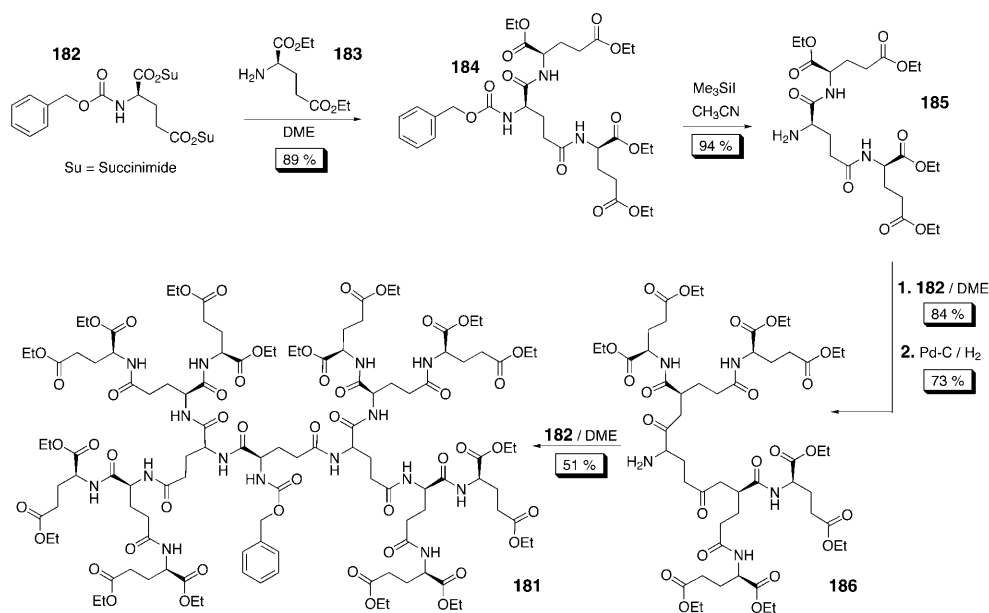


Fig. 37. Chiral dendrimer based on the repeat unit L-glutamic acid [296]

acid diethyl ester (**183**) in dimethoxyethane (DME) afforded **184**. Deprotection was carried out with iodotrimethylsilane (ISiMe₃) in CH₃CN at -5°C and was immediately stopped when no more starting material could be seen by TLC, since the ISiMe₃ reagent is capable of cleaving other esters as well. After purification amine **185** was isolated as a single diastereoisomer. The next generation was introduced by treatment of **185** with active ester **182**, to give the larger protected dendron **186**. Several deprotection attempts failed, but direct hydrogenation (Pd-C/H₂) increased the yield of amine **186** to 73%. The final dendrimer

180 (M_w 2537 amu) was then obtained as a single diastereoisomer after reaction of **186** with **182**. The structure and the purity of these compounds were verified by ^{13}C -NMR, FAB-MS and SEC.

Ranganathan and Kurur have constructed chiral dendrimers for the design of globular protein mimics based on glutamic (Glu) **187** (Fig. 38) or aspartic (Asp) acid building blocks [297]. In order to generate a compact spherical conformation, hydrophobic 1,3-adamantane dicarboxylic chloride **188** was chosen as the core molecule after molecular modeling studies. Dendrons were synthesized in a convergent two-step sequence involving first the quantitative coupling of *N*-protected L-Glu/Asp with L-Glu/Asp-diOMe followed by hydrolysis of the methyl ester to the acid and condensation with Glu/Asp-diOMe to a [G-3]-dendron with seven chiral centers. Final coupling of the deprotected dendrons with the core **188** were performed in dry CH_2Cl_2 in the presence of Et_3N affording [G-1]-compounds in nearly quantitative yields. In the case of the [G-2]-dendrons the yields dropped from 67 to 33% (Glu) and 59 to 10% (Asp) for [G-3] as anticipated. The lower yields of the Asp dendrimers were due to comparatively more steric congestion. Results from ^1H - and ^{13}C -NMR, and MS studies were in agreement with the assigned structures.

Kim et al. have introduced a new methodology for the construction of combinatorial libraries, termed dendrimer-supported combinatorial chemistry (D-SCC) [298]. The approach, where a dendrimer is employed as a soluble support, combines classical solution-phase synthesis with facile homogeneous purification with SEC or ultrafiltration. The PAMAM dendrimer was chosen for the dendritic unit due to its availability, reactivity, and highly symmetric nature. Indoles were chosen because of their biological and pharmacological significance [299]. 4-Hydroxymethylbenzoic acid (HMB) (**189**), which served as a base-labile handle, was reacted with PAMAM-[G-2] under standard carbodi-

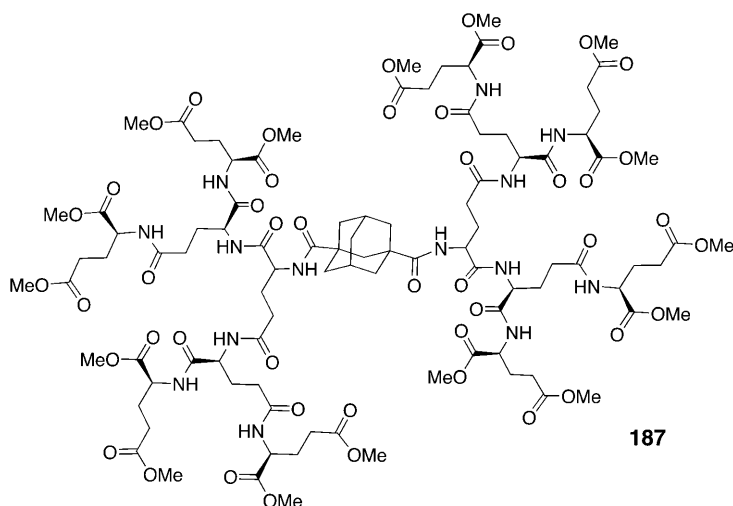


Fig. 38. Protein-mimicking dendrimer based on glutamic acid (Glu) [297]

imide conditions to form a compound **190** with eight cleavable attachment sites (Fig. 39). Further steps and cleavage of the indole **194** from the dendrimer support are outlined below. All products were characterized by ^1H - and ^{13}C -NMR, IR, UV, SEC, and MS.

To demonstrate the feasibility of D-SCC a small $3 \times 3 \times 3$ (27 compounds) library was constructed by employing split synthesis. Essential to such an approach is the ability to separate mixtures of compounds from reagents and solvents. Throughout the combinatorial library construction, identical reaction conditions (as mentioned in Fig. 39) were employed. Three equal pools contain-

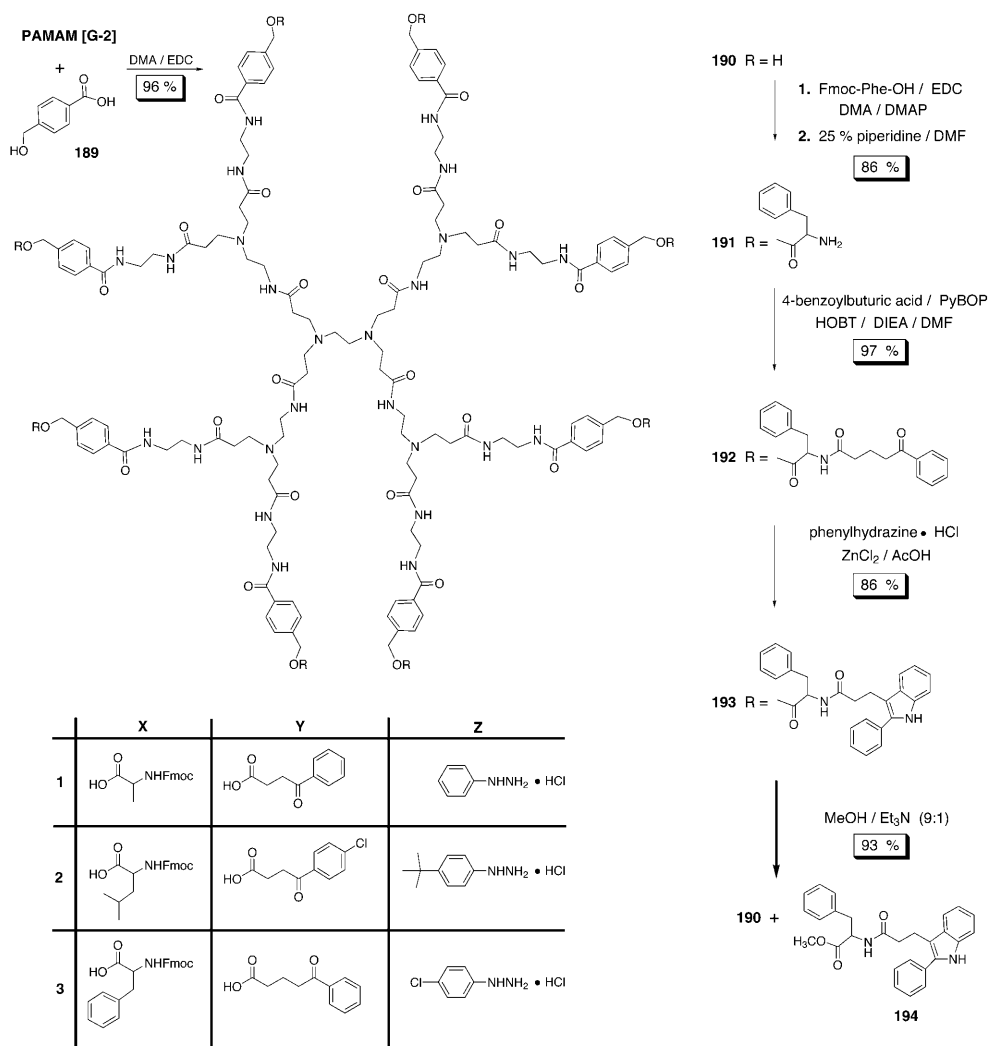


Fig. 39. Dendrimer-supported indole formation via the Fischer synthesis [298]

ing PAMAM-HMB **190** were coupled with Fmoc-protected amino acids X_1 – X_3 . The reaction mixtures were combined, purified by SEC, and deprotected to give PAMAM–HMB– X_1 – X_3 as yellow foams in approximately equimolar amounts (84% yield from **190**). Splitting into three equal pools and sequential acylation of each pool with keto acids Y_1 – Y_3 afforded PAMAM–HMB– X_1 – X_3 – Y_1 – Y_3 as tan foamy solids (98%) after workup. Again split into three pools (each containing ideally nine compounds) and treatment with arylhydrazine hydrochlorides Z_1 – Z_3 gave, after purification of each pool separately, three mixtures containing nominally nine compounds each (66–83% yield). The three sublibraries were cleaved (90–96%) from the dendritic support and the recovered dendrimer **190** was removed by filtration. All compounds in the library were analyzed by high-performance liquid chromatography (HPLC) and no side products were observed.

Results of this publication show that D-SCC offers several advantages to combinatorial chemistry. These include operation in the solution phase, reproducible separation and relatively easy characterization of compounds (due to the homogeneity of the dendrimer support), and extremely high loadings compared with resin-bound compounds thus reducing reaction volume. According to the authors, D-SCC provides a general strategy on constructing libraries or a variety of single compounds. In addition, by employing dendrimer supports, properties such as chemical stability, solubility, and loading capacity can be tailored towards the desired direction. A further goal of the group is to design new dendrimer supports and linkers and to develop automated procedures for D-SCC.

Dubber and Lindhorst [300] have prepared chiral carbohydrate-core dendrimers. D-Glucose was converted in four steps into the per-*O*-(2-aminoethyl) functionalized derivative **195** in 43% overall yield (Fig. 40). The resulting amine **195** was used as the core in PAMAM-type dendrimer construction. Branching was achieved by exhaustive Michael addition of methyl acrylate affording the decaester **196** followed by amidation with a large excess (600 eq.) of ethylenediamine. The [G-2]-dendrimer **198** was constructed by repeating this reaction sequence.

Research in the field of carbohydrate dendrimers (i.e. glycodendrimers) is fairly new [301], but is rapidly growing [302, 303]. The research groups of Stoddart and Meijer [304–311], Roy [312–318], Lindhorst [319, 320], Okada [321, 322], and Schlüter [323] have introduced various approaches to carbohydrate-containing dendrimers. Such compounds, possessing highly symmetrical structures with biologically active moieties, can provide a novel approach to multivalent ligands involved in carbohydrate–protein interactions [324].

3.2 Core

Seebach et al. [325–327] have synthesized dendrimers which possess chiral central unit and achiral branches. The [G-1]-dendrimer **201 a/b** was synthesized from triol **199 a/b** by esterification with 3,5-dinitrobenzoyl chloride (**200**) in pyridine (Fig. 41). The six nitro groups of **201 a/b** were reduced (PtO_2/H_2) to

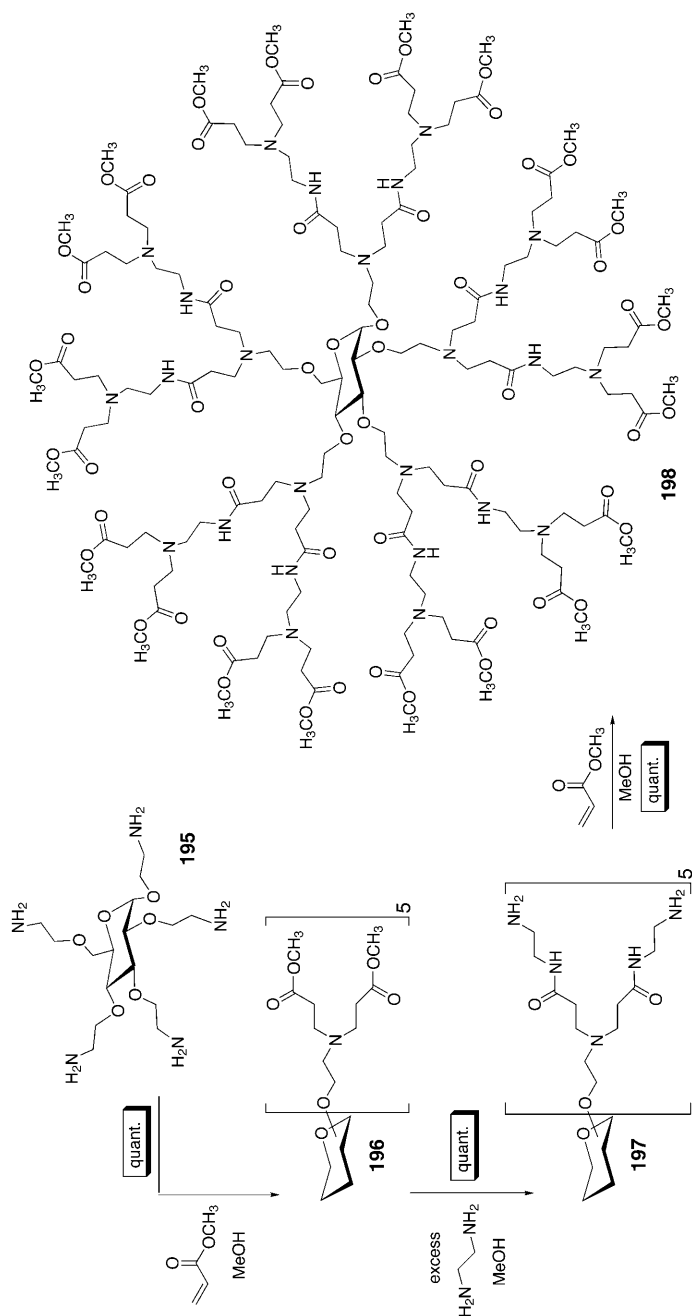


Fig. 40. PAMAM dendrimer with a chiral D-glucose core unit [300]

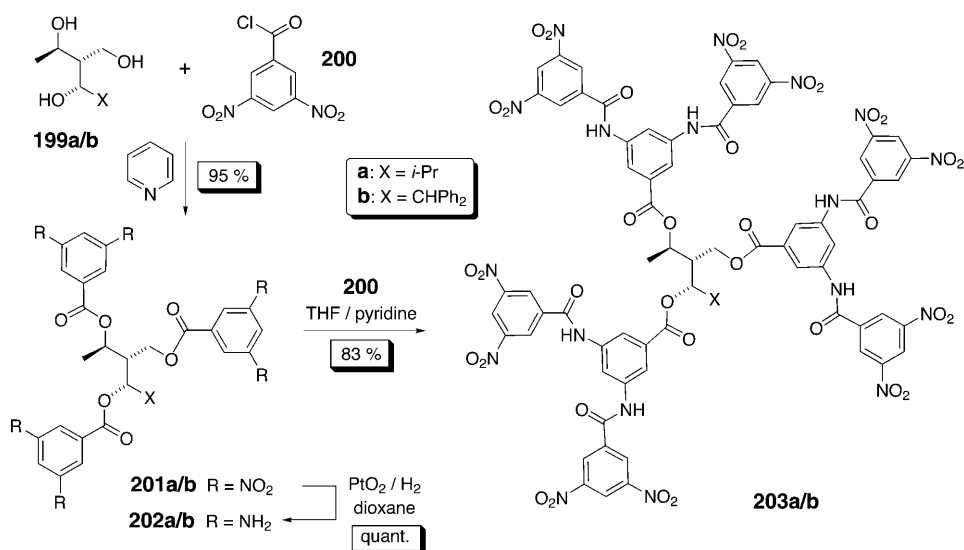


Fig. 41. Divergent synthesis of dendrimers with a chiral ester core [325–327]

amino groups **202a/b**, then acylated with **200** to afford the [G-2]-dendrimer **203a/b** with 12 nitro groups on the surface. Compounds were characterized by IR, ¹H- and ¹³C-NMR, MS, and elemental analysis. A remarkable change in the optical activity was observed for nitro-terminated compounds in proceeding from the **201a** to **203a** ($[\Phi]_D^{25}$ from –124 to +155) and from the **201b** to **203b** ($[\Phi]_D^{25}$ from –827 to –282) center piece suggesting considerable contributions to the optical activity from the conformationally chiral chromophores at the dendritic surface. Compounds **202a/b** and **203a/b** were found to have a tendency to form clathrates with other molecules (e.g. dioxane). The [G-2]-dendrimers **203a/b** were also shown to act as hosts in the formation of host–guest complexes. Inclusion complexes with acetone, acetonitrile, and ethyl acetate were observed.

3.3

Branching

Brandi et al. [328] have prepared enantiopure dendrimers up to [G-2] based on a chiral *trans*-3,4-dihydroxypyrrolidine and the convergent approach (Fig. 42). The [G-1]-compound **207** was prepared in one step by treatment of TBDMS-protected pyrrolidine **204** with terephthaloyl chloride (**205**) in pyridine followed by addition of benzyl alcohol **206**. The debenzylated $[\text{Pd}(\text{OH})_2/\text{H}_2]$ compound **208** was reacted with protected pyrrolidine **209** to yield the [G-2]-dendron **210**. Debenzylation of **210** and coupling with either terephthaloyl chloride (**205**) or mesitoyl chloride (**212**) under standard Schotten-Baumann conditions gave the final dendrimers **213** and **214**. All compounds were analyzed by ¹H- and ¹³C-NMR, IR, MS, and elemental analysis.

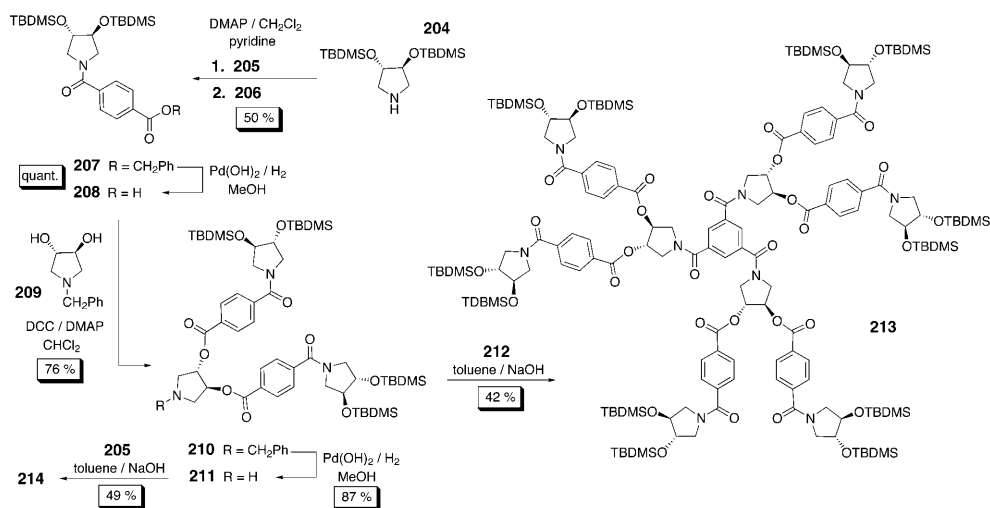


Fig. 42. Enantiopure dendrimers based on *trans*-3,4-pyrrolidine [328]

The chiroptical properties of compounds **213** and **214** were analyzed by UV and circular dichroism (CD) spectra. The Φ/N values (molar rotatory power divided by the number of chiral units) suggest linear growth for **214** and radial growth for the three-directional dendrimer **213**. The observations from the CD analysis confirm that the chiroptical properties are additive when growth is linear (**214**). For the radial-growth dendrimer **213** such additivity was not observed.

3.4

All Layers

Seebach et al. [329,330] have introduced the first examples of biodegradable [331] dendrimers constructed from (*R*)-3-hydroxybutanoic acid (HB) and trimesic acid via convergent growth. The benzyl ester protected dimer **215a** and tetramer **215b** of HB were employed as elongation units (Fig. 43). The triacid cores **218a/b** were obtained by debenzilation ($\text{Pd-C}/\text{H}_2$) of **217a/b** obtained from the reaction of **215a/b** with trimesic acid **216**. The benzyl-protected [G-1] branching units **220a/b** were synthesized by acylation of **215a/b** with in situ activated TBDPS-protected 5-hydroxymethyl-1,3-benzenedicarboxylic acid **219**. The [G-2] building blocks **223a/b** were constructed by the reaction of **221a/b** with **222a/b** obtained by desilylation ($\text{HF}/\text{pyridine}$) and debenzilation of **220a/b**. The final coupling of desilylated dendrons **221a/b** and **224a/b** with cores **218a/b** followed by removal of the benzyl ester protecting groups gave the [G-1]- and [G-2]-dendrimers **227a/b** and **228a** as viscous oils. The characterization of all compounds were performed by ^1H - and ^{13}C -NMR, IR, MALDI-TOFMS, elemental analysis, and optical rotation.

The biodegradability of the compounds was studied with various hydrolases using tetrameric HB **229b** as standard substrate for a PHB-depolymerase, since

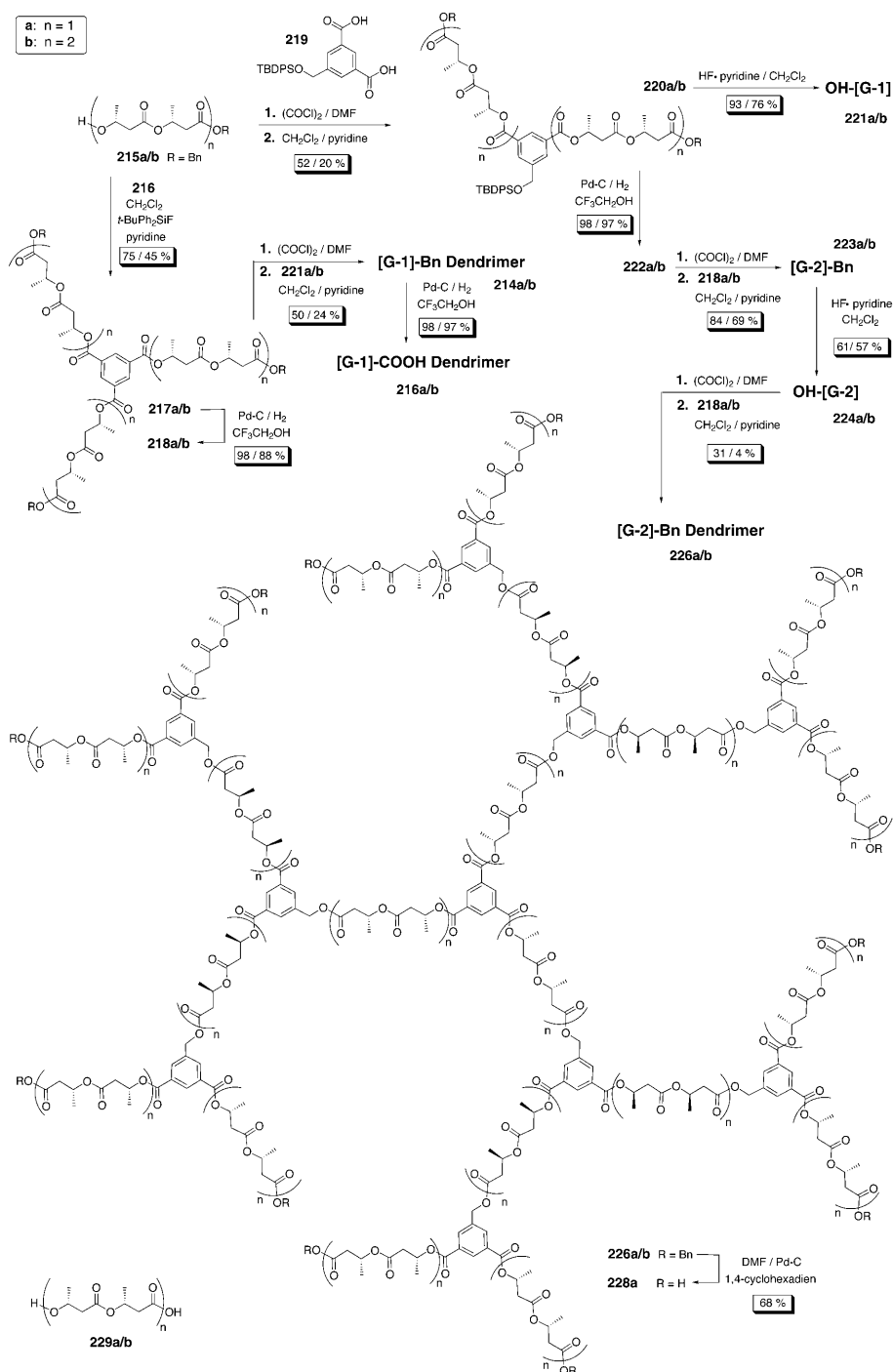


Fig. 43. Biodegradable dendrimers of Seebach et al. [329, 330]

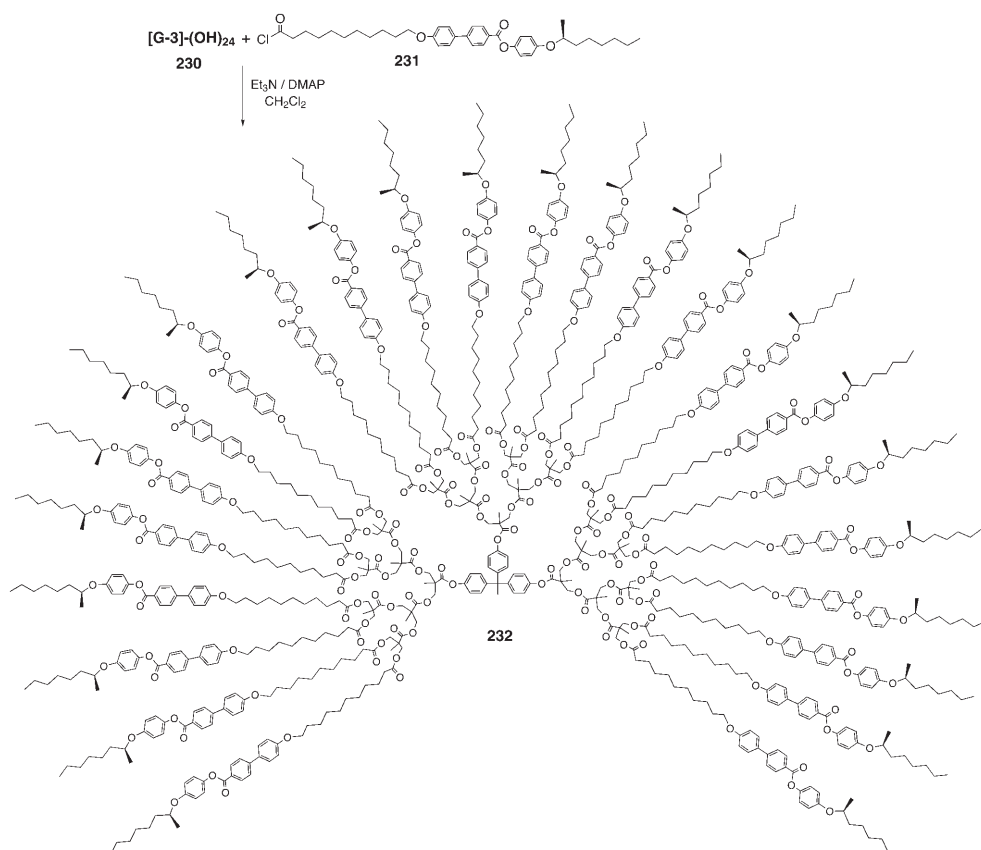


Fig. 44. Novel ferroelectric dendritic liquid-crystalline polymer (FDLCP) [332]

the dimeric HB **229a** is not biodegradable. No degradation was observed for benzyl-protected dendrimers with dimeric HB building blocks (**a**), whereas the acid-terminated compounds were found to be moderately good substrates for this enzyme. All deprotected dendrimers with tetrameric HB building blocks (**b**), like **229b**, were good substrates for the depolymerase exhibiting a rate for the first degradation step about hundred times faster than the degradation of compounds possessing a dimeric HB skeleton. In addition, degradation by an esterase, lipase, and protease was observed for the dendritic compounds as well.

Based on the skeleton introduced in Fig. 33 [282, 284], the first ferroelectric dendritic liquid-crystalline polymer (FDLCP) **232** has been prepared [332]. The [G-3]-polyester **230** bearing 24 terminal hydroxyl groups was coupled with the mesogenic group 4'-[(R)-1-methylheptyloxy]phenyl-4-{4'-[10-(hydroxycarbonyl)decyloxy]phenyl}benzoate (**231**) via acid chloride reaction in CH_2Cl_2 using DMAP as catalyst (Fig. 44). The purity of the compound was confirmed by $^1\text{H-NMR}$ and SEC measurements. DSC and optical polarized light microscopy studies of the mesogen showed the presence of chiral SmA^* and SmC^* phases

(Sm = smetic). By applying a direct current (DC) electric field, it was possible to obtain an induced tilt angle that was a linear function of the applied voltage for the SmA* phase, whereas the high viscosity of the SmC* phase resulted in a decrease in the tilt angle. When the electric field was turned off, no relaxation process was observed indicating that the macroscopically polar ferroelectric state of the SmC* phase stays locked. The ability to synthesize dendrimers exhibiting a ferroelectric SmC* phase offers an alternative to main-chain and side-chain ferroelectric liquid-crystalline polymers (FLCPs). Thus, novel structures in the fields of dendritic polymers and FLCPs can be expected in the future.

4

Metallo dendrimers

Preparation of branched polymeric structures possessing sites capable of molecular recognition at specific locations on the dendritic superstructure is limited by monomer availability. From the chemist's point of view, the development of versatile building blocks with the potential to incorporate a wide variety of functionality is desirable, especially in mimicking biological processes. Dendritic topology can produce distinctive microenvironments (core, branches, or surface) analogous to those found in biological systems, each of which can exhibit functional properties modulated by the dendrimer as a whole [333, 334]. For instance, constructing a dendrimer around a porphyrin core could modify its chemical behavior by altering the polarity of the surroundings of the electrophore. Thus, dendritic porphyrins could serve as synthetic models of electron-transfer heme proteins such as cytochrome c that are of particular interest in biological systems.

4.1

Terminal

Diederich et al. [335–337] have reported the divergent synthesis of dendritic porphyrin compounds by employing Newkome's polyether amide "cascade" **233** [293, 295] and its triethylene glycol monomethyl ether derivative as dendritic units. The tetraacid porphyrin **234**, prepared in four steps, exhibits a spatial arrangement in which the carboxylic acid linkers are above and below the zinc-porphyrin plane, confirmed by X-ray analysis. The [G-1]-porphyrin **235** was synthesized from **234** by employing **233** with peptide coupling methodology (Fig. 45). Hydrolysis with LiOH in MeOH/H₂O gave the solid dodecaacid **236**. Iteration led to the [G-3]-porphyrin **237** (viscous oil) which has 108 methyl esters at the surface (*M_w* 19,054 amu).

Molecular modeling studies suggest that the structure of **237** is globular (~4 nm) and densely packed, resembling the dimensions of cytochrome c. In order to investigate the influence of the dendritic structure on porphyrin redox potentials, (poly)carboxylic acids up to [G-2] were esterified with triethylene glycol monomethyl ether. Demetallation of **238** gave the free-base porphyrin **239** which was reacted with FeCl₂ followed by in situ oxidation to yield water-soluble

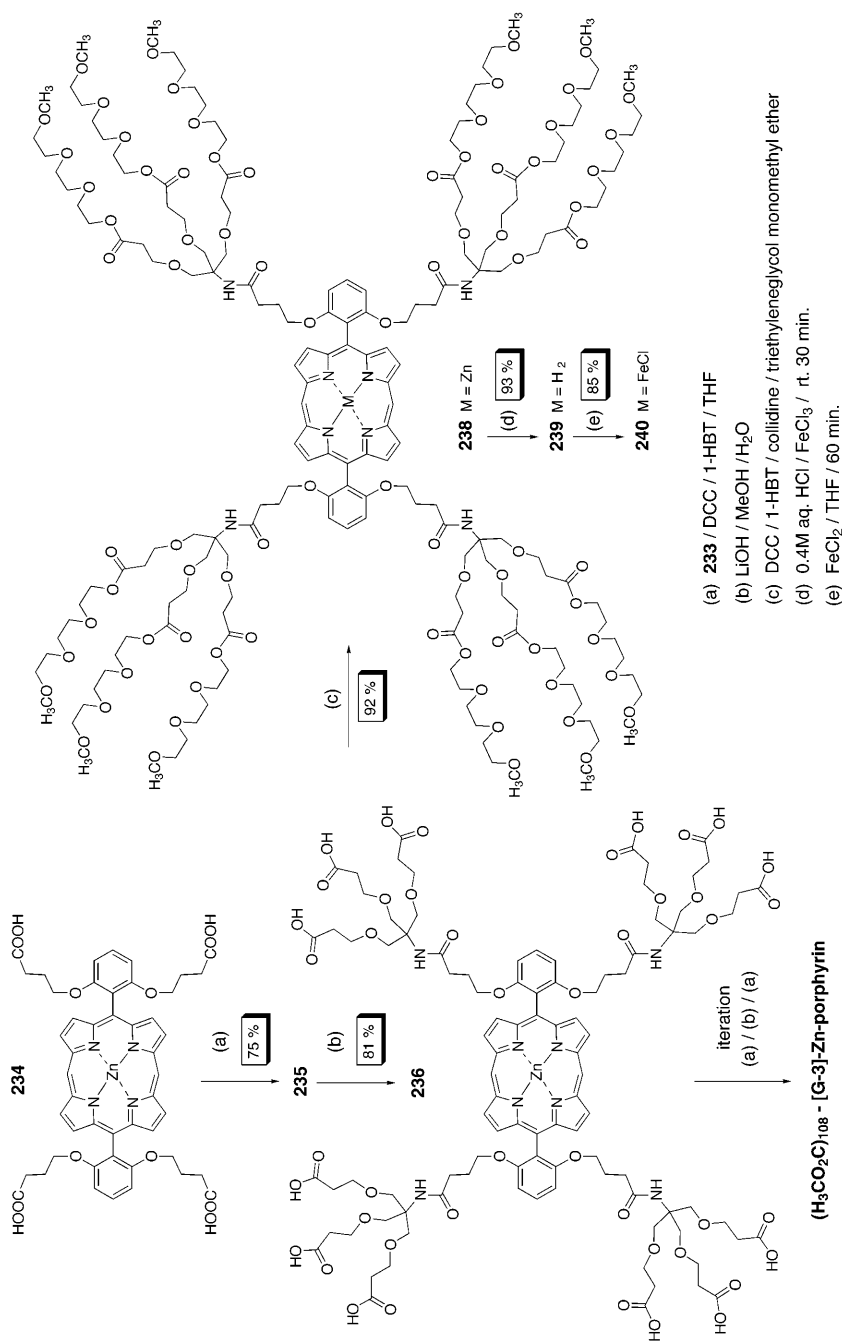


Fig. 45. Synthesis of Zn- and Fe-porphyrin dendrimers by Diederich et al. [335–337]

dendritic Fe^{III} porphyrin **240**. The same reaction sequence was utilized for the synthesis of the [G-2]-analog **241**. Structures were confirmed by IR, ¹H- and ¹³C-NMR, FAB-MS, MALDI-TOFMS, GPC, and UV-vis spectroscopy.

The electrochemical properties were investigated in THF, CH₂Cl₂ and aqueous solutions by cyclic voltammetry. In the Zn-porphyrin series the redox potentials (in THF) become more negative with increasing generation. This was attributed to the more electron-rich microenvironment around the porphyrin core. In the Fe-porphyrin series the oxidation/reduction potentials of the biologically relevant Fe^{III}/Fe^{II} couple remained practically unchanged in CH₂Cl₂, whereas in aqueous solution the [G-2]-derivative **241** displayed a potential 420 mV more positive than **240**. This difference was explained by solvation of the core electrophore. Steric hindrance of **241** blocks the access of the external solvent to the central core while the less hindered **240** stays relatively open. As a result, the more charged Fe^{III} state is destabilized relative to the Fe^{II} state.

Dioxygen and carbon monoxide binding studies were performed on the Fe^{II} porphyrins **240** and **241**. Both compounds exhibited reversible O₂ and CO binding activities. The behavior was compared to the heme proteins, tetrameric hemoglobin (Hb) and monomeric myoglobin (Mb), that are responsible for dioxygen storage and transport in biological systems. The O₂ affinities of **240** and **241** were ~1500 times greater than those of T (tense)-state Hb approaching the high affinity of the blood worm *Ascaris*. The CO affinities were found to be close to the T-state Hb values, but lower than “picket fence” porphyrin [*meso*-tetra(α,α,α-*o*-pivalamidophenyl)porphyrin] [338].

Newkome et al. [339, 340] have introduced a novel synthesis of bisdendrimers **242** by coupling of “cascade” macromolecules through metal centers (Fig. 46). Previously synthesized AB₃-branched monomers [341] provided the basis for the construction of dendritic “locks” and “keys”. The use of a ruthenium(II) metal center allowed the formation of stable complexes between the discrete terpyridine receptor units attached to different “cascade” molecules. Due to the paramagnetic nature of the ruthenium “cascades” definitive NMR spectra could not be obtained. However, elemental analysis and MALDI-TOF mass spectra supported the structures.

“Locks” and “keys” were connected via a single Ru^{II} center in MeOH with 4-ethylmorpholine as the reducing agent to give a two-directional, crystalline bisdendrimer complex. Five different Ru^{II} complexes were synthesized. Characterization was performed by NMR, elemental analysis, UV spectroscopy and electrochemistry data. NMR signals of the interior were partially masked due to the presence of numerous *tert*-butyl groups at the surface. In addition, Ru^{II} complexes appeared to be unstable under the conditions used for the MALDI-TOF mass spectrometry.

Vögtle et al. [342] have presented various synthetic strategies to prepare dendrimers with a tris(bipyridine)ruthenium(II) complex as their core. A procedure reported by Newkome et al. [240, 245] was employed starting from 4,4'-bis(bromomethyl)-2,2'-bipyridine (**243**) by treatment with HC(CO₂Et)₃ in DMF. Due to the decarboxylation reported previously [240], further reaction of **244** with TRIS afforded dodecaol **245** as a hygroscopic colorless solid instead of the desired octadecaol. Complexation of **245** with Ru^{II} failed probably due to the

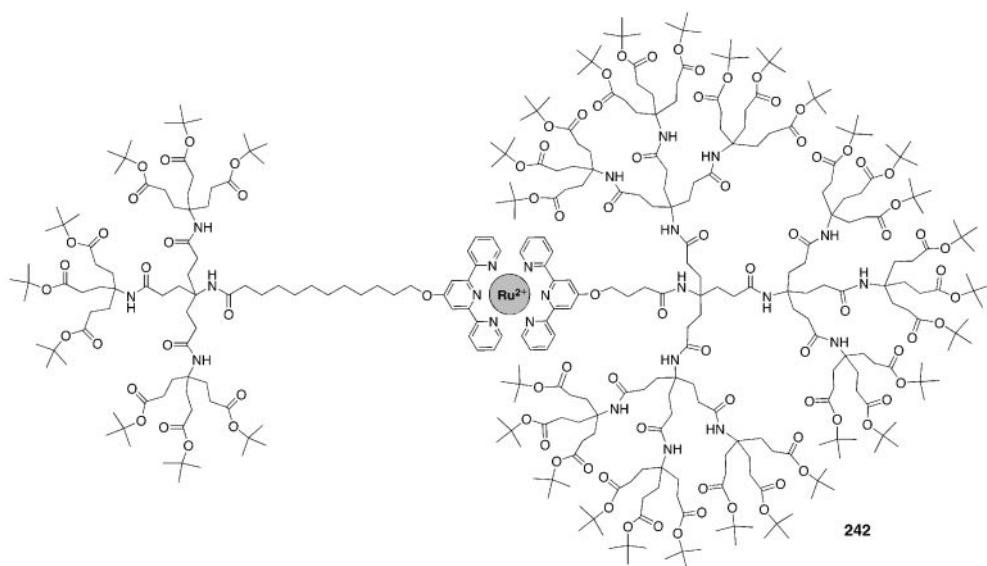


Fig. 46. Dendritic “lock and key” of Newkome et al. [339, 340]

strong interactions between the hydrophilic surface and the Ru^{II} ion or possible aggregation of the ligand which prevents the coordination of the Ru^{II} cation. Thus, a different pathway was developed by complexing the dendritic hexaester **244** with Ru^{II} to yield **246** followed by reaction with TRIS in DMSO (Fig. 47). The dendritic complex **247** was obtained as an orange-red solid. Further growth of generations was not successful.

The [G-3]-bipyridine ligand was obtained by an alternative route [248]. 2,2'-Bipyridine-4,4'-dicarboxylic acid (**248**) was treated with **249** using standard peptide chemistry (DCC/HOBT) in THF to obtain hexaester **250** (Fig. 48). Hydrolysis of **250** with NaOH in MeOH/ H_2O afforded the corresponding acid **251**. Generations [G-2] **252** and [G-3] **254** were synthesized in a similar fashion.

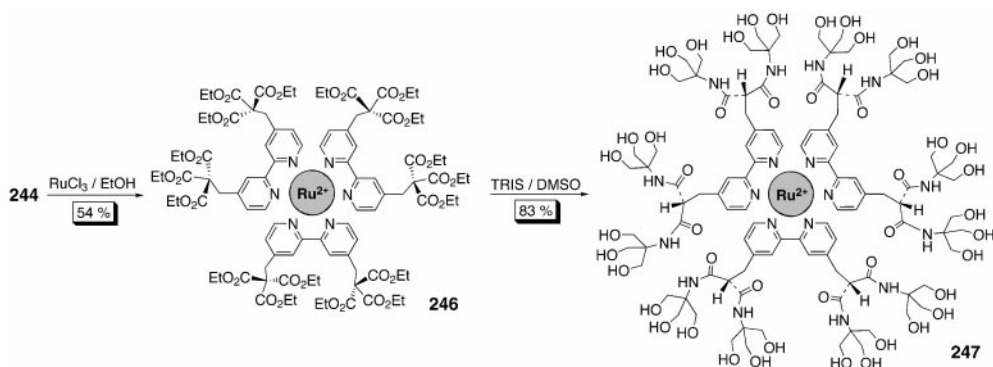


Fig. 47. [G-2]-tris(bipyridine)ruthenium(II) complex [342]

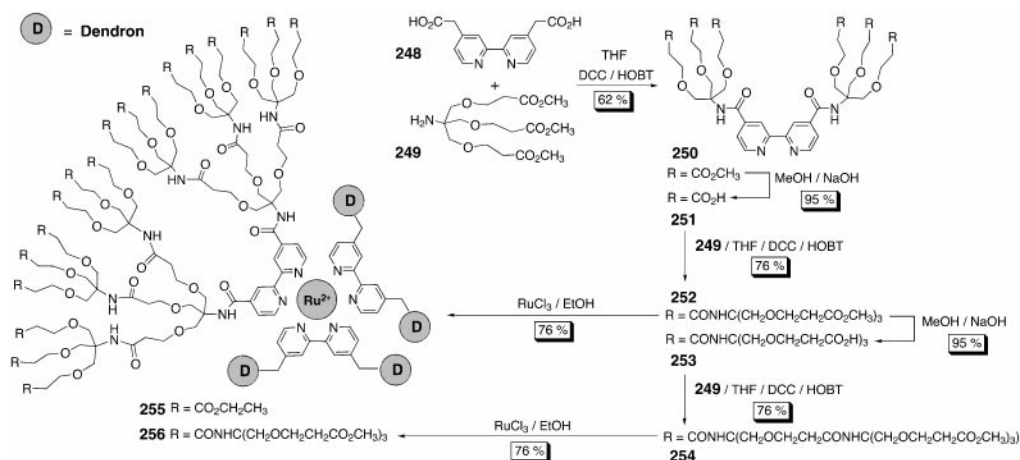


Fig. 48. Construction of [G-3]-bipyridine ligands [342]

Compounds were characterized by ¹H- and ¹³C-NMR, positive FAB-MS and MALDI-TOFMS.

The bipyridine ligands 251 and 253 were refluxed with Ru^{II} chloride in EtOH for 14 d to yield tris(bipyridine) chelates 255 and 256 (Fig. 48). Complete transesterification occurred (OMe → OEt) with the [G-1]-product. The [G-2]-compound was only partly transesterified probably due its denser surface compared with its [G-1] counterpart. In the case of the [G-3]-ligand 254 complexation did not proceed in the desired manner.

The characteristic metal-to-ligand charge-transfer (MLCT) bands in the visible region could barely be observed. The reason suggested for this behavior is the competition of the donor centers in the dendritic part of the ligand with the bipyridine nitrogens or steric hindrance by the dendritic branches which prevent conversion to the ciscoid conformation needed for metal chelation. An investigation of the spectroscopic and photophysical properties showed that absorption and emission spectra of Ru^{II} dendritic complexes, as well as unsubstituted parent Ru^{II}-bipyridine complexes, are very similar. However, the large dendritic complexes exhibit a more intense emission and a longer excited-state lifetime in aerated solutions than [Ru(bpy)₃]²⁺. This was explained by the shielding effect of the large dendrimer branches on the Ru-bipyridine core. A long lifetime of the luminescent excited state is important for immunoassay applications, since the signal of the label can be read after the decay of the background fluorescence of the sample, whose lifetime usually is on the nanosecond time scale.

Cardona and Kaifer have prepared a series of novel dendrimers containing a single redox-active ferrocene subunit as the core moiety [343]. The [G-1]-compound 257 was synthesized by reaction of chlorocarbonyl ferrocene with Behara's amine 258 (Fig. 49) [344]. The next generation was obtained by hydrolysis of the terminal *tert*-butyl ester groups followed by reaction of amine 258. Instead of repeating this two-step process the [G-3]-dendrimer 259 was con-

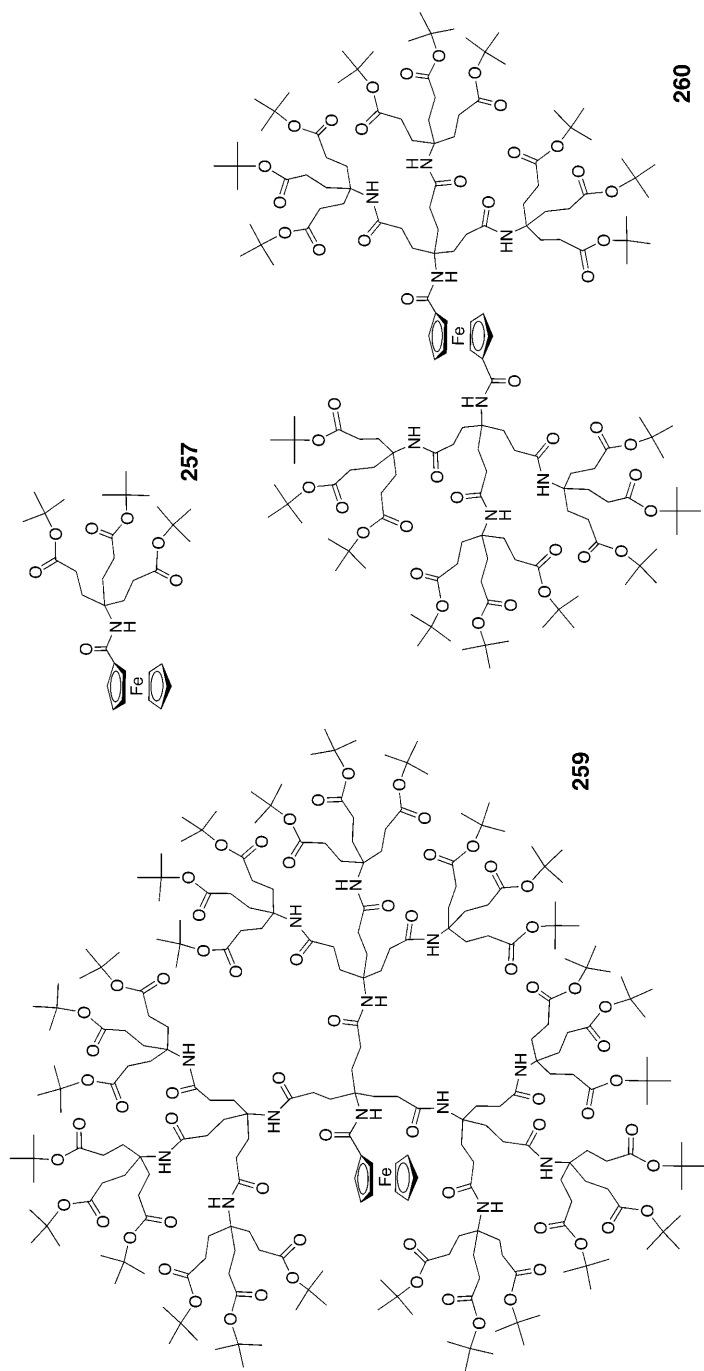


Fig. 49. Asymmetric redox-active dendrimers containing a ferrocene subunit [343]

structed by a combination of the convergent and divergent methods. Direct reaction of a [G-2]-analog of Behara's amine with the triacid of **257** afforded **259** more efficiently. All products were characterized by ^1H - and ^{13}C -NMR, UV-vis, IR, and MALDI-TOFMS.

The electrochemical properties were in agreement with the previously published results on electroactive dendrimers. As anticipated, a correlation between the increasing molecular mass of the dendrimers (1–3 generations) and the decrease in the values of the heterogeneous electron transfer rate constant (k°) was observed. The bisdendritic compound **260** exhibited slower kinetics than its monodendritic analog. This is due to the asymmetric character of monodendrons which may approach the electrode surface either with the ferrocene side (fast) or with the dendritic side (slow) facing the electrode. By contrast, the more symmetric shape of **260** results in slower kinetics and, when approaching the electrode, its dendritic moieties set the minimum distance between the ferrocene core and the electrode surface. As such, the synthesized monodendrons may exhibit orientation-dependent rates of electron transfer; this possibility is under investigation.

4.2

Branching

Suslick et al. [345] have synthesized sterically hindered dendrimer-metalloporphyrins for use as shape-selective oxidation catalysts. [G-1]- and [G-2]-dendrons were prepared according to a known procedure [279] except that 3,5-dihydroxybenzoic acid was replaced by 3,5-di-*tert*-butylbenzoic acid to increase steric hindrance. Dendrimer-porphyrin Mn^{III} complexes **262** and **263** were synthesized in two steps (Fig. 50) by the DCC-coupling reaction [346] of a [G-1]- or [G-2]-acid with $\text{Mn}[\text{T}(3',5'\text{-OHPh})\text{P}](\text{Cl})$ **261** with DPTS as catalyst under an atmosphere of argon. THF was employed as the solvent for the first 12 h after which it was removed. The residue was redissolved in CH_2Cl_2 and the reaction was complete in 72 h. This was essential due to the low solubility of $\text{Mn}[\text{T}(3',5'\text{-OHPh})\text{P}](\text{Cl})$ **261** and its rate dependence on the solvent. After evaporation and extraction with *n*-pentane the green viscous complex **262** was obtained.

A similar procedure was employed for the [G-2]-analog **263**. Products were analyzed by HPLC, UV-vis spectroscopy, and MALDI-TOFMS. Use of these complexes as regioselective epoxidation catalysts for both intra- and intermolecular selectivities was examined. Dendrimer-porphyrins showed greater regioselectivity than the corresponding unhindered parent metalloporphyrins, although the selectivities were not as high as those achieved with bis-pocket porphyrins [5,10,15,20-tetrakis-(2',4',6'-triphenylporphyrin)]. This phenomenon was explained using molecular modeling studies on the metal-free porphyrins. In the bis-pocket system side access is completely blocked while top access ($\approx 4 \text{ \AA}$) remains available. In the dendrimer-metalloporphyrins the results were the complete opposite, exhibiting a significant side opening of $10 \times 7 \text{ \AA}$ (van der Waals surface to surface) that limits the extent of regioselectivity. From the synthetic point of view *meta* substitution of a tetraphenylporphyrin is more

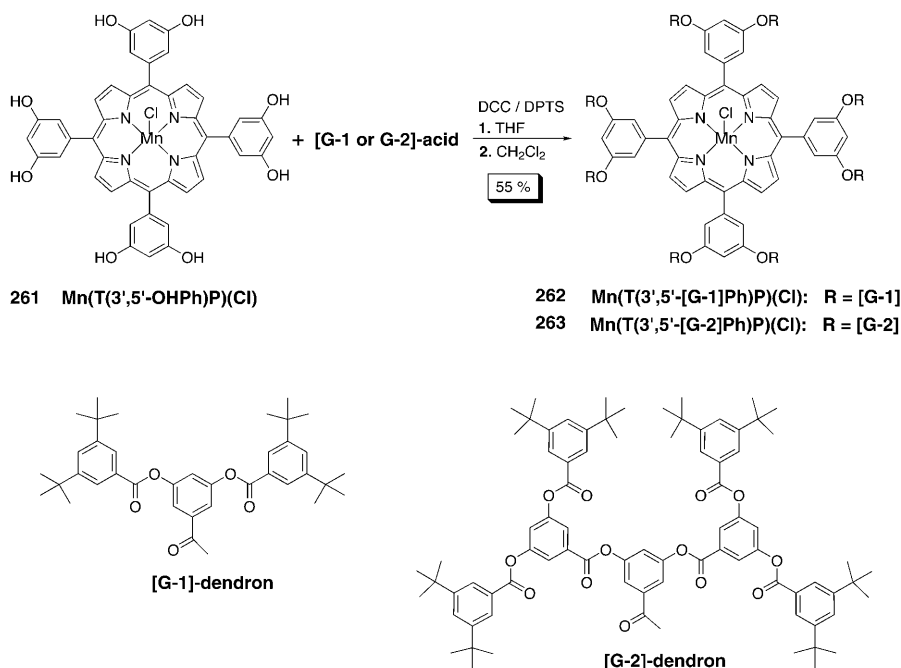


Fig. 50. Construction of manganese^{III} complexes of dendrimer-porphyrins [345]

favorable than *ortho* substitution which does not yield completely esterified products.

Later Suslick et al. [347] reported shape-selective ligation to dendrimer-metalloporphyrins. The dendritic fragments mentioned above were coupled to the *m*-phenyl position of Zn-porphyrins using the DCC/DPTS coupling reaction. Substitution to the *o*-phenyl position was now achieved via amide linkage [G-1A]. Improved solubility properties were reported compared with the dendrimer-porphyrin Mn^{III} complexes. Compounds 264–266 (Fig. 51) were characterized by ¹H-NMR, UV-vis spectroscopy, MALDI-TOFMS, and HPLC.

Zn-porphyrins were chosen as binding sites due to their ability to bind generally only a single axial ligand. Ligand-binding constants (K_{eq}) for a series of various amines of different sizes and shapes were measured using standard procedures [348]. The differences in ligand selectivity arise from the size and shape of the side-accessible cavity since top access to the porphyrins is completely hindered. Differences of 10^3 – 10^5 in the values of K_{eq} were observed for *o*-phenyl-substituted $\text{ZnT}(2',6'\text{-[G-1A]Ph})\text{P}$ 264, especially with nonlinear amines. The *m*-phenyl-substituted compounds showed a remarkable increase in K_{eq} for all the amines relative to nonsubstituted Zn-porphyrins probably due to attractive interactions between the dendrons and the ligand.

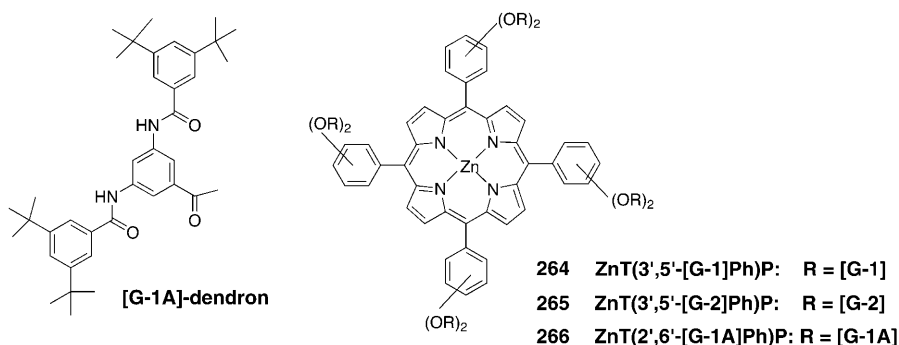


Fig. 51. Shape-selective dendrimer-metalloporphyrins [347]

4.3

Core and Branching

Albrecht et al. [349] have introduced periphery-functionalized metallodendrimers **268** with an aryl ester backbone (Fig. 52). These molecules reversibly bind SO₂ and therefore have potential for use as sensors. Dendrimers containing a platinum^{II} functional unit were constructed from **267** using the methodology developed by Miller et al. [277]. These materials showed low solubility properties. Aryl ester units have been calculated to be planar molecules and, thus, are the reason for the solubility problems. When the metallodendrimer **268** was exposed to SO₂ gas, the SO₂ adduct **269** was formed instantaneously. Enhanced solubility and drastic color changes were observed and verified by ¹H-NMR and UV-vis spectroscopy.

5

Conclusions

This review article, along with others, clearly shows that the research and development of dendrimers has really “mushroomed” over the last twenty years and will undoubtedly continue to grow with the same vividness. In this short time we have witnessed the shifting of the focus from the synthesis of novel structures which possess a number of generations to the tailoring of the properties of dendrimers applicable to a variety of targets and the commercialization of dendrimers [211]. Absolutely amazing work has been carried out in many research groups but, in general, the yield of products has been on the gram scale or less. For this reason, and also due to a lack of practical and reliable characterization methods, the material properties have not been studied thoroughly [350, 351]. Thus, the full potential of dendrimers is yet to be discovered. A scale-up process is crucial for commercialization and in order to make dendrimers competitive with other products on the market. Until these requirements are fulfilled the methodology of dendrimer synthesis and identification must be pursued further, allowing convenient and facile access for inexpensive, precisely controlled and characterized materials.

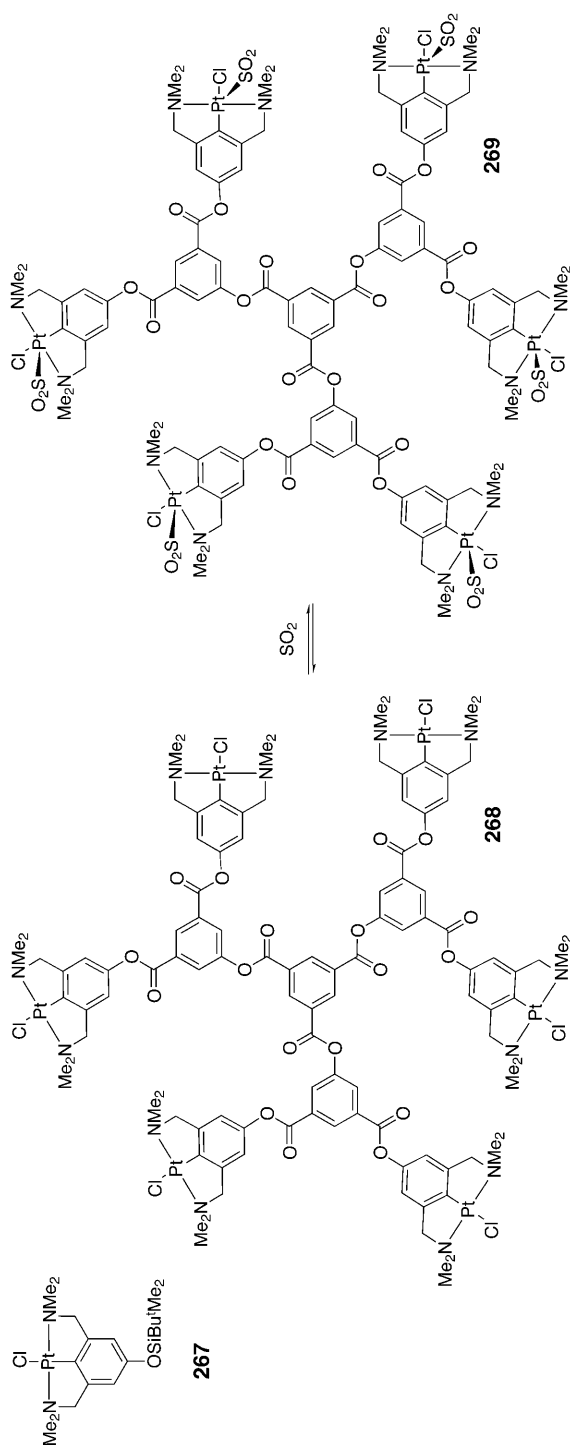


Fig. 52. Formation of SO_2 adducts from periphery-functionalized metallodendrimers [349]

As described here, a diverse array of dendrimer skeletons with organic, chiral, and organometallic moieties has been discovered. Current techniques allow a high degree of control over structural and functional properties [352] that can be integrated into a dendrimer at desired locations providing almost unlimited potential in applications and discoveries never seen before. Recent advances in areas such as catalysts [353–360], chromatographic separations [361–364], extraction and transport [365–369], light harvesting and energy transfer [370–372], magnetic resonance imaging (MRI) [373–375], photo-responsive dendrimers [376–380], self-assembled monolayers [381–383], biologically active dendrimers [384–387], and more, are likely to capitalize apace.

One advantage of dendrimers over nonbranched materials lies in the fact that by multiplying existing, known functions, rather than developing novel functionalities, chemists are able to modify and tailor properties more successfully. For this reason (poly)esters are an attractive class of substances since they are widely employed in “conventional” materials ranging from adhesives and coatings, cordage, cosmetics, fibers and textiles, films and packaging materials, laminates, medical accessories, oil additives to plastics, and resins [388–390].

This compilation of polyester dendrimers has established that pure ester skeletons are scarce. Instead ester functions are frequently merged either on surfaces, in branch junctures, or at the core because of easy access, facile branching, stability, and solubility properties [276, 277, 284]. Besides applicability [220–225], some compounds are reported to be nontoxic [226, 391–393] and biodegradable [329, 330]. This aspect might provide a boost towards environmentally friendly, highly branched materials, and could make ester dendrimers superior to other structures. Generally speaking, dendrimers will definitely have a role in the evolution of nanotechnology and, thus, will in the long run compete with, and probably replace, a wide range of existing materials and products.

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6

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Silicon-Based Dendrimers

Holger Frey · Christian Schlenk

Freiburg Materials Research Center and Institute for Macromolecular Chemistry, Albert-Ludwigs-University, Stefan-Meier-Strasse 21/31, 79104 Freiburg, Germany

E-mail: holfrey@mf.uni-freiburg.de

This review focuses on dendrimers with Si-atoms as branching point, aiming at a comprehensive summary of the state of the art of the field. Carbosilane, siloxane, silane, silazane, and silatrane dendrimers are considered. The important features common to Si-based dendrimers are: (i) almost all of the Si-based dendrimers known at present are prepared divergently; (ii) most of the known Si-based dendrimers exhibit high flexibility, manifested by low glass transition temperatures; (iii) the use of Si as branching connectivity permits one to vary the branching multiplicity between 2 and 3, allowing one to tailor the density of the structures. Hyperbranched polymers based on silicon that fulfill the structural criterion are also considered, since it is likely that many of the applications discussed for structurally perfect dendrimers at present will eventually be realized with well-defined hyperbranched polymers obtained in one reaction step.

Keywords: Silicon, Dendrimers, Hyperbranched polymers, Synthesis, Application potential.

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1

Introduction

Since the first description of a “cascade” synthesis in the late 1970s by Vögtle et al. [1] and the seminal work by Tomalia et al. [2] and Newkome et al. [3] in the mid-1980s, dendrimers, perfectly branched, highly symmetrical tree-like macromolecules have evolved from a curiosity to an important trend in current chemistry. Amply demonstrated in this volume, a wide variety of dendrimer construction strategies has been developed on the basis of classical organic chemistry. The state of the art in the synthesis, nomenclature, and terminology in use as well as various unusual features of this still relatively young class of macromolecules have been summarized in excellent reviews by various authors [4–11].

Dendrimers based on heteroatoms offer several peculiar features, such as variable branching multiplicity, high flexibility, and unusual electro-optical properties. The main emphasis in this field to date has been placed on phosphorus- and silicon-based dendrimer topologies. Some of the developments in the general area of heteroatom-based dendrimers have been summarized in previous reviews, documenting the enormous increase in activity in recent years [12–14].

This review focuses on Si-based dendrimers, i.e., dendrimers with Si-atoms as branching point between the generations. We aim at a comprehensive summary of the state of the art in the field, focusing on carbosilane, siloxane, silane, silazane, and silatrane dendrimers. Only in a few cases, when analogies to other classes of dendrimers are important, are the respective works cited. Hyperbranched polymers that fulfill the structural criterion are considered in the final part of this review, since it is likely that many of the applications discussed for structurally perfect dendrimers will eventually be realized with well-defined hyperbranched polymers obtained in one reaction step, possessing a certain polydispersity and a randomly branched structure.

Silicon chemistry offers several quantitative (>99% yield) reactions suitable for the preparation of dendrimers. Most of the various classes of Si-based

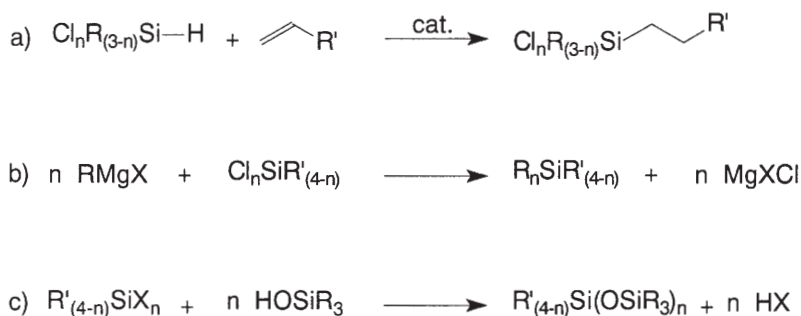


Fig. 1 a–c. Set of basic construction reactions used for the synthesis of most Si-based dendrimers

dendrimers known have been prepared on the basis of the relatively small set of reactions shown in Fig. 1, which comprises hydrosilylation, Grignard-reactions, and controlled condensation of silanols. In the case of silazane structures, the aminolysis of chlorosilanes replaces the hydrolysis used for the preparation of carbosiloxane structures. Complete conversion is an essential prerequisite for the construction of structurally perfect dendrimer molecules, since the preparation of higher dendrimer generations requires the transformation of a large number of functional groups at one macromolecule.

There are some important features common to all Si-based dendrimers: (i) almost all of the Si-based dendrimers known at present are prepared divergently; (ii) most of the known Si-based dendrimers exhibit high flexibility, manifested by low glass transition temperatures; (iii) the use of Si as branching connectivity permits to vary the branching multiplicity to a certain extent, rendering the structures ideal for the investigation of the correlation of the branching density with materials properties.

2 Carbosilane Dendrimers

2.1 Synthesis and Characterization

2.1.1 General Synthetic Strategy

Among the Si-based dendrimers, polycarbosilane structures, recently briefly reviewed [15], have received by far the strongest attention to date, due to their straightforward synthesis and the possibility to tailor the dendrimer structures by variation of (i) core functionality, (ii) branching multiplicity, and (iii) the segment length between the branch points, respectively. Furthermore polycarbosilanes are kinetically as well as thermodynamically very stable molecules owing to the dissociation energy of the Si-C bond (306 kJ mol^{-1}), which is similar to that of C-C bonds (345 kJ mol^{-1}) and the low polarity of the Si-C bond. So

far, almost all reported carbosilane dendrimers have been synthesized via the divergent approach. Generally, the synthesis starts from a core molecule possessing alkenyl groups with a hydrosilylation step using either trichlorosilane or dichloromethylsilane as hydrosilylation reagent, depending on the desired branching multiplicity. The following alkenylation step is usually carried out with either vinyl- or allylmagnesium halides, depending on the desired spacer length. Although hydrosilylation as well as Grignard reactions are well-known and widely studied reactions, they are not unproblematic for the construction of carbosilane dendrimers. It is obvious that the major problem in the divergent synthesis of dendrimers is the fact, that very high conversions have to be reached in each reaction step. Since the yields of Grignard reactions decrease with increasing size of the Grignard reagent, only short alkyl spacers between the branch points can be employed. The main problem associated with the hydrosilylation step lies in the control of the regioselectivity of the Si-H addition to an unsymmetrically substituted olefin. In the reaction of a terminal olefin $R'CH=CH_2$ with a silane of the structure R_3SiH , the α -adduct, $R_3SiCH(R')CH_3$, and the β -adduct, $R_3SiCH_2CH_2R'$, can be formed. Although the presence of both units in the hydrosilylation product should not affect the further growth of the dendrimer, usually the β -adduct is desired in order to obtain a dendrimer of maximum symmetry. The other problem related to the hydrosilylation step is the isomerization of the terminal double bonds in the case of allyl end groups. This isomerization leads to internal double bonds, which are no longer amenable to hydrosilylation and therefore this side reaction produces dendrimers with defective branching structure. The extent of isomerization depends strongly on the solvent used and can thus be disfavored by careful choice of the solvent. Depending on the chlorosilane used, the branching multiplicity of the dendrimers is either 2 or 3. As it has been shown by MALDI-TOF studies [16–18], a branching multiplicity of 2 leads to lower steric hindrance and hence more perfect structures can be obtained in higher generations ($> G_2$) than in the case of a branching multiplicity of 3. Unfortunately, in most reports on carbosilane dendrimers, MALDI-TOF mass spectrometry has not been employed, which renders it difficult to compare the perfection of the structures attained.

A typical reaction sequence leading to a carbosilane dendrimer of the first generation with allyl end groups and a branching multiplicity of 3 is shown in Fig. 2.

As early as 1978 Fetters et al. reported the use of a branched carbosilane structure that may be viewed as a dendrimer of the first generation with 12 end groups. This molecule was used for the preparation of a 12-arm star polymer [19]. However, van der Made et al. [20, 21], Zhou et al. [22, 23], and Muzafarov et al. [24] independently reported the first syntheses aiming at carbosilane dendrimers of various generations. Van der Made et al. used tetraallylsilane as core, trichlorosilane as hydrosilylation reagent, and allylmagnesium bromide as ω -alkenylation reagent to obtain dendrimers up to the fifth generation. The authors also report the use of undecenylmagnesium bromide to prepare dendrimers with a less dense structure. However, it has to be mentioned that the molecular weight and the structural perfection of these dendrimers were not substantiated by appropriate analytical methods. In addition, the use of long

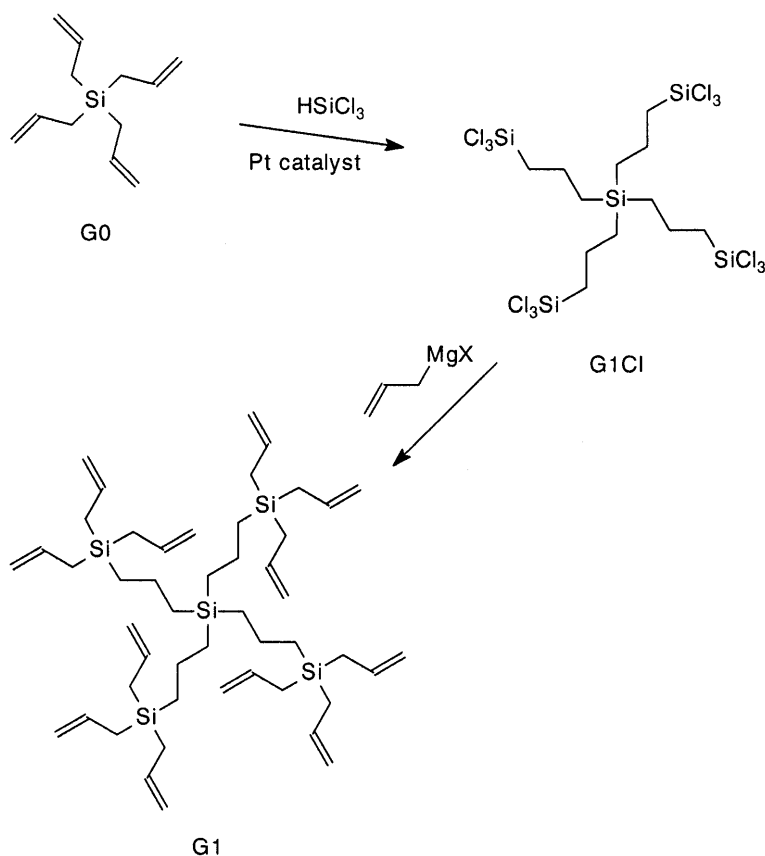


Fig. 2. Typical reaction sequence for the preparation of a G1 carbosilane dendrimer

alkylmagnesium bromides for quantitative conversion at tetrahedral silicon has been reported to be problematic [25] and therefore dendrimers with perfect structure are unlikely. In contrast, Zhou and Roovers started from tetravinylsilane and built up dendrimers up to the fourth generation by hydrosilylation with dichloromethylsilane and alkenylation with vinylmagnesium bromide. This route leads to a slower increase of the number of branches and therefore to a more open structure compared to van der Made's approach. The molecular weights of each generation were determined by vapor pressure osmometry and laser light scattering, the results being comparable to the calculated values. Using SEC, Zhou and Roovers showed that there are no gross structural imperfections, such as dimers, in the dendrimers prepared. Furthermore, they showed that SEC is not well-suited for the judgment of the structural perfection of dendrimers, owing to the broadening of the SEC traces by diffusion and the insensitivity of the method to small imperfections in the globular topology. Muzafarov et al. reported the use of triallylmethylsilane as core, methyldichlorosilane in the hydrosilylation step, and allylmagnesium bromide in the alkenyla-

tion step [24]. However, experimental data were not given in this report. In a more recent publication by this group, carbosilane dendrimers obtained by similar reactions, however starting from tris(methyldiallylsiloxy)methylsilane have been described [26]. Dendrimers up to the seventh generation were obtained and characterized with respect to thermal properties.

Seyferth et al. presented a strategy that – starting from tetravinylsilane as the core molecule and using a succession of alternate hydrosilylations of the vinyl groups with trichlorosilane, followed by reaction of the silyl chloride end groups with vinylmagnesium bromide – provided four generations of carbosilane dendrimers. These represent the most dense structures available employing this approach [27]. In addition Seyferth et al. reduced the chlorosilanes of each generation with LiAlH_4 to the corresponding Si-H terminated dendrimers, which were employed as pyrolytic SiC precursors. The ceramic residue yields obtained after pyrolysis of these precursors in argon at 950 °C (TGA experiments) increased with generation number. For the fourth generation a yield of 66% was obtained, which is generally considered to be satisfactory in pre-ceramic polymer chemistry. However, the authors state unambiguously that in practice the utility of these materials as ceramics precursors is very limited due to the laborious synthesis.

Numerous reports on the synthesis of carbosilane dendrimers with allyl end groups have been published by Kim et al. [28–32], who used various core molecules containing allyl- or vinyl groups, for instance 2,4,6,8-tetramethyl-2,4,6,8-tetravinyltetrasiloxane, diallylphenylmethylsilane, 1,2-bis(triallylsilyl)ethane, and triallylmethylsilane. Kim et al. constructed the dendrimers with allylmagnesium bromide as Grignard reagent and either HSiCl_3 or HMeSiCl_2 as hydrosilylation reagent. Characterization of the dendrimers relies on NMR spectroscopy and elemental analysis only. In further publications these authors reported the synthesis of carbosilane dendrimers terminated with phenylethynyl, *p*-bromophenoxy and *p*-phenylphenoxy groups, respectively [33–38]. In some cases, the obtained products were characterized by MALDI-TOF mass spectrometry. In addition to carbosilane and siloxane cores, use of a glucose derivative as a chiral building unit for the construction of carbosilane dendrimers has been reported recently by Boysen and Lindhorst [39]. Tetra-*O*-allylglycosides were prepared and subjected to the hydrosilylation/Grignard reaction sequence to afford G1 dendrimers.

In recent work, van Leeuwen et al. developed a promising strategy for the divergent preparation of carbosilane-based dendrons with focal amine functionality (G1–G3). The approach is based on a bromopropyl-trichlorosilane core used for the dendrimer construction and subsequent reaction with ammonia under pressure to generate the focal amine functionality. Coupling of the amine with trimelic acid has been employed to obtain hybrid topologies with polar triamide core that may serve as a binding site for polar guests in the receptor-like structure [40, 41]. Jaffrès and Morris chose the polyhedral silsesquioxane octavinylpentacyclooctasiloxane as core and trichlorosilane, dichloromethylsilane, and chlorotrimethylsilane as hydrosilylation reagent [42]. Applying vinylmagnesium bromide as well as allylmagnesium bromide, a variety of dendrimers up to the second generation, differing in the number and the type of end groups,

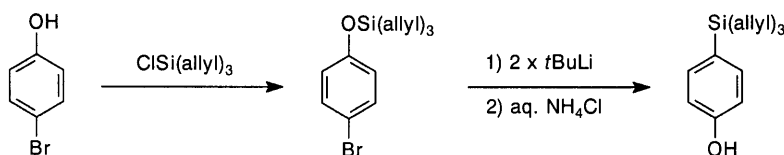


Fig. 3. Synthesis of 4-triallylsilylphenol by means of a low temperature (0 °C) [1,4]-silyl migration (Gossage, van Koten et al.)

was obtained. Characterization relies on NMR spectroscopy. In the case of the first generation possessing 24 vinyl groups, single crystals could be grown that were characterized by X-ray diffraction, showing disorder of the vinyl end groups in the crystal. The materials were used for the synthesis of silanol-terminated dendrimers (cf. Sect. 2.2.2).

A carbosilane dendrimer with a functionalizable core has recently been described by van Koten et al. [43, 44]. In an elegant way they obtained 4-triallylsilylphenol by means of a low temperature (0 °C) [1,4]-silyl migration from 4-(tri(allylsiloxy)phenyl)lithium which was obtained by lithiation of 4-(tri(allylsiloxy)bromobenzene (cf. Fig. 3). The use of the molecule obtained for the convergent synthesis of a carbosilane dendrimer has been demonstrated by the formation of [1,3,5-tris{4-(tri(allylsilyl)phenylester}benzene]. Furthermore novel trifurcate carbosilane dendrimers up to the second generation have been synthesized divergently, starting from the phenolic hydroxy group protected derivative of 4-triallylsilylphenol. These new materials were thoroughly characterized using NMR spectroscopy, SEC as well as mass spectrometry (ESI and MALDI-TOF).

Only recently an interesting study on carbosilane dendrimers using $^1\text{H}/^{13}\text{C}/^{29}\text{Si}$ triple resonance 3-D NMR methods has been published by Tessier and co-workers [45, 46]. Starting from tetraallylsilane as core the authors obtained G0 by hydrosilylation with chlorodimethylsilane, followed by reduction using LiAlH_4 . In order to obtain G1 (designated G2 by the authors), tetraallylsilane was hydrosilylated with dichloromethylsilane. The resulting product was converted with vinyl Grignard reagent prior to hydrosilylation with chlorodimethylsilane. Subsequent reduction led to the desired second generation. The dendrimers were characterized using $^1\text{H}/^{13}\text{C}/^{29}\text{Si}$ triple resonance, 3-D, and pulse field gradient NMR techniques. Signals from one-bond and two-bond connectivities among ^1H atoms coupled to both ^{13}C and ^{29}Si at natural abundance were detected selectively. The spectral dispersion and the atomic connectivity information present in the 3-D NMR spectra provided resonance assignments and a definitive structure proof.

2.1.2

Unusual Carbosilane Systems

Besides the carbosilane dendrimers with aliphatic units based on the repeating sequence of alternating hydrosilation and ω -alkenylation with Grignard reagents, only a few other systems have been developed: Nakayama and Lin

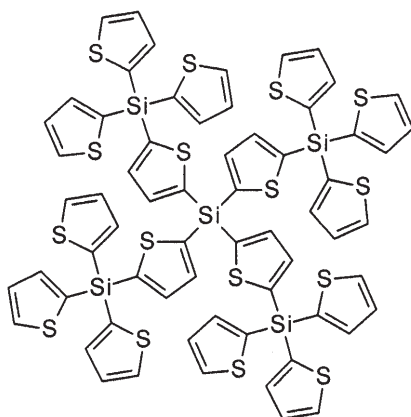


Fig. 4. Si-based dendrimer (G1) composed of thiophene rings connected by silicon (Nakayama and Lin)

synthesized the first generation of an organosilicon dendrimer composed of thiophene rings, connected by silicon [47]. The tetralithiation of tetra-2-thienylsilane followed by reaction with methyl tri-2-thienylsilyl ether gave the desired first generation, 5,5',5'',5'''-tetrakis[tri-2-thienylsilyl(tetra-2-thienyl)]silane which is shown in Fig. 4. The structures were confirmed using NMR spectroscopy and elemental analysis. It is noteworthy that the obtained dendrimer forms inclusion complexes with CCl_4 , CH_2Cl_2 , benzene, and acetone, when crystallized from these solvents.

Another so far uncommon carbosilane dendrimer has been obtained by Kim and Kim [48]. They started from tetrakis(phenylethynyl)silane and prepared dendrimers up to G3 via a repeated sequence of hydrosilylations with dichloromethylsilane and subsequent ω -alkynylations with lithium phenylacetylide. NMR and MALDI-TOF-MS support the successful synthesis. As expected, the glass transition temperatures are considerably higher than those of common carbosilane dendrimers based on alkenylation [49]. The obtained dendrimer possessing double bonds in the interior and triple bonds at the periphery has been used to prepare a dendritic Co complex whose properties are discussed below (Sect. 2.2.1) [50]. Another intriguing, recent development in this area are silylacetylene-dendrimers reported by Sekiguchi and coauthors [51]. These molecules, characterized by alternating silicon-acetylene units, were built up in a convergent type synthesis, that, however, is limited to G2 possessing 12 end groups. A crystal structure was obtained for G1, which shows a nearly planar structure due to the rigid acetylene units.

A hybrid dendrimer structure was obtained by Brüning and Lang by replacing the Grignard alkenylation step by an alcoholysis employing allyl alcohol [52]. As a core tetraallyloxysilane was used, which was hydrosilylated with dichloromethylsilane followed by the alkenylation with allylmagnesium bromide, yielding the first generation. Hydrosilylation resulted in the silylchloride-terminated second generation, which was subjected to alcoholysis with allyl alcohol. Accord-

ing to the authors the formation of uniform and analytically pure dendrimers was supported by NMR spectroscopy as well as elemental analysis.

2.2

Modification and Application Potential

2.2.1

Metal Complexes and Catalysis

One of the most promising applications of carbosilane dendrimers, based on their inertness, is the use as scaffolds for catalytically or redox active metal complexes. Dendrimer-bound catalysts combine the advantages of heterogeneous and homogeneous catalysis: on one hand they allow the accurate control of the number and structure of active sites, comparable to homogeneous catalysts, on the other hand they are conveniently removed from a product-containing solution using ultrafiltration as known from heterogeneous catalysts. This process can be carried out in a continuous manner, using a membrane reactor. The technique is considered to be promising for the synthesis of various fine chemicals. The first example of a homogenous catalyst based on a dendritic carbosilane scaffold was reported by van Koten et al. in 1994 [53, 54]. The authors connected 4-amino substituted 2,6-bis[(dimethylamino)-methyl]-1-bromobenzene (NCN-Br), a precursor for the potentially multidentate monoanionic 1-[C₆H₂(CH₂NMe₂)₂-3,5]⁻ (NCN) ligand, to the periphery of the zeroth generation with 4 chlorodimethylsilyl end groups and the first generation with 12 chlorodimethylsilyl end groups, respectively by a 1,4-butanediol linker. The first generation was obtained by hydrosilylating tetraallylsilane with trichlorosilane followed by alkenylation with allylmagnesium bromide. Conversion of the zeroth and first generation with chlorodimethylsilane led to the chlorodimethylsilyl derivatives. To achieve the connection between the scaffold and the NCN-Br ligands the 4-amino substituted NCN-Br was reacted with triphosgene to afford the isocyanate derivative, which was subsequently reacted with an excess of 1,4-butanediol. Reaction of the chlorodimethylsilyl functionalized dendrimers with the modified ligands yielded dendritic precursors with 4 and 12 binding sites for transition metals, respectively. The desired nickel containing dendrimers were produced by oxidative addition of these precursors to the zerovalent nickel complex Ni(PPh₃)₄. Figure 5 shows the dendritic nickel complex of the first generation.

The prepared dendrimers were successfully employed as homogeneous catalysts for the Kharasch addition reaction. Mechanistic considerations concerning the use of such diaminoarylnickel(II) complexes have been given in [55]. A drawback of the dendritic catalyst obtained in this fashion is the carbamate linker used, due to the additional synthetic steps required as well as the sensitivity towards organometallic reagents, such as alkyllithium or Grignard compounds. To improve the stability and to simplify the synthetic methodology, the attachment of the catalytic ligand-metal moiety directly to the outermost silicon atoms was targeted. Treating the biphosphinoaryl ligand 3,5-(Ph₂PCH₂)₂C₆H₃Br (PCP), a phosphorus analogue of the NCN ligand described above, with

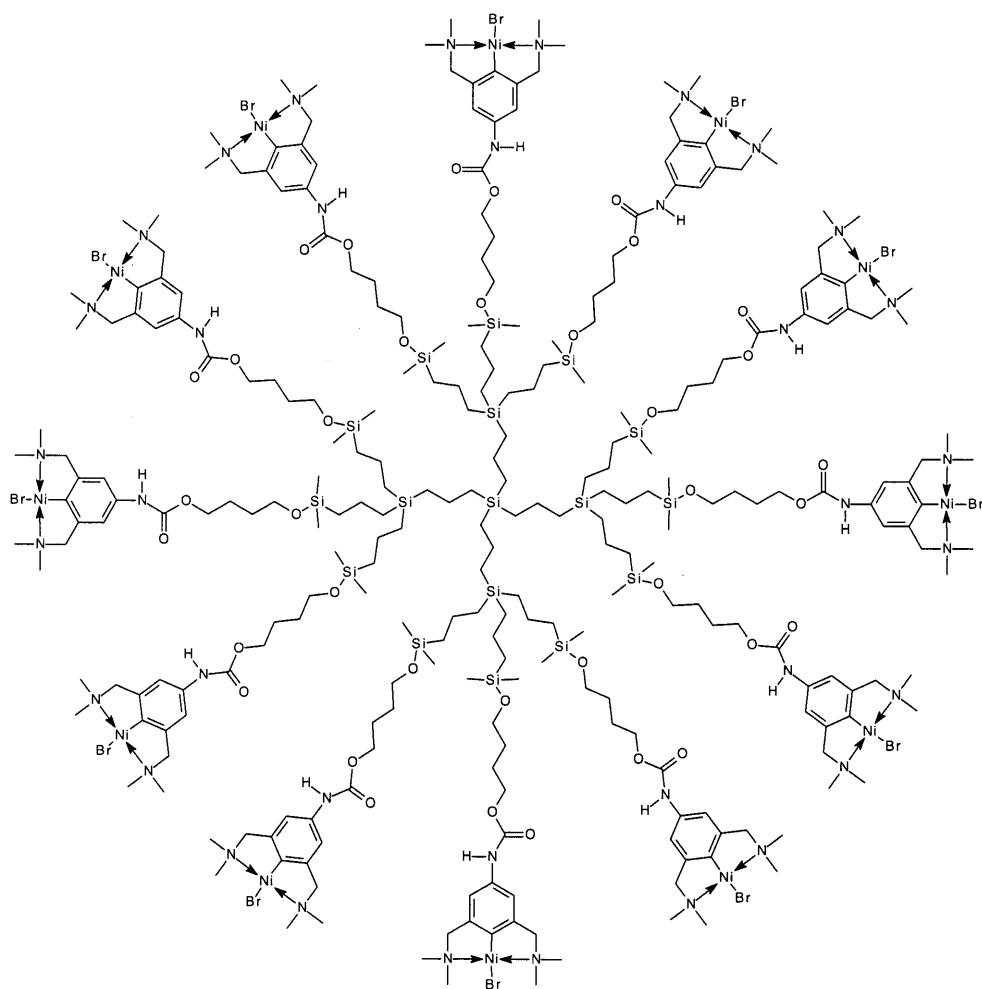


Fig. 5. Dendritic Ni-catalyst suitable for Kharasch addition reactions (van Koten et al.)

tert-butyllithium and quenching the resulting lithium derivative with chlorotrimethylsilane, van Koten et al. showed that this route allows a facile direct linking of these ligands to carbosilane dendrimers [56]. Furthermore it could be shown by model compounds that the incorporation of reactive Ru(II) PCP' complexes into carbosilane dendrimers can be accomplished by a ligand displacement of an NCN ligand, avoiding the use of the traditional precursor $\text{RuCl}_2(\text{PPh}_3)_3$, which leads to aryl-Si bond cleavage and hence to degradation of the carbosilane dendrimer. Dendritic carbosilanes functionalized with NCN-H end groups directly attached to the scaffold have been obtained via the reaction of a zeroth and a first generation dendrimer bearing chlorodimethylsilyl end groups with 3,5-bis[(dimethylamino)methyl]phenyllithium [57, 58]. Their multilithiated derivatives, representing the first examples of multilithiated den-

dimer systems with stable C-Li bonds, have been prepared by treatment with an excess of *tert*-butyllithium. These compounds can be used to introduce various metals via lithiation/transmetalation sequences. This has been exemplified by transmetalation of the tetralithiated, NCN derivatized zeroth generation carbosilane dendrimer with $\text{PtCl}_2(\text{SEt}_2)_2$ affording the desired Pt-metallated dendrimer. Further investigations concerning this new approach demonstrated its usefulness for the synthesis of (catalytically active) metal-containing carbosilane dendrimers [59].

A carbosilane dendrimer with 12 peripheral iodoarene groups has been prepared on the basis of carbosilane polyol precursors by van Koten et al. [60]. In this case, the iodoarene groups were attached to the polyols by esterification with 4-iodobenzoyl chloride. The obtained compound was reacted with $\text{Pd}(\text{dibenzylideneacetone})_2$ in presence of *N,N,N',N'*-tetramethylethylenediamine to yield periphery-palladated complexes. The prepared dendrimer represents the first example of an exclusively σ -bonded completely periphery-palladated dendrimer. In subsequent work, attachment of the iodoarene groups via esters was avoided, since the ester function appeared to prevent the transmetalation of the complex to a diorganopalladium(II) complex [61]. The reactivity of the dendritic organopalladium(II) and -(IV) complexes has been studied in detail and a crystal structure was obtained for the bipyridyl complex $[\text{PdMe}(\text{C}_6\text{H}_4(\text{OCH}_2\text{Ph})-4(\text{bpy}))]$.

Only recently, the first hydrovinylation of styrene carried out in a membrane reactor, catalyzed by Pd complexes with hemilabile P,O ligands attached to a carbosilane dendrimer has been reported by Vogt et al. [62]. A carbosilane dendrimer of the zeroth generation bearing four chlorodimethylsilyl end groups was converted with the protected lithium derivative of [4-bromo]-*tert*-butyldimethylsilylbenzyl ether to yield a dendritic polyol after deprotection. Coupling of this polyol with $\text{ClC}(\text{O})\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{Ph}_2$ followed by reduction with trichlorosilane and subsequent reaction with $[(\eta^3\text{-C}_4\text{H}_7)\text{Pd}(\text{cod})]\text{BF}_4$ afforded the star-shaped Pd catalyst shown in Fig. 6. The dendritic catalyst proved to be active in the hydrovinylation of styrene with ethylene to 3-phenylbut-1-ene. However, isomerization to the E/Z mixture of the achiral 2-phenylbut-2-ene was also observed. To suppress this reaction, the hydrovinylation was carried out in a continuous process in a membrane reactor. This led to the highly selective conversion of styrene in low yields. The authors expect improved catalyst retention by nanofiltration membranes for the G1 dendrimer-supported Pd catalyst. In a recent publication van Leeuwen et al. reported the synthesis of phosphine functionalized carbosilane dendrimers and the corresponding palladium complexes as well as the use of the latter in the allylic alkylation reaction of allyl trifluoroacetate and sodium diethyl methylmalonate performed in a continuous flow membrane reactor [63]. Unfortunately, decomposition of the Pd-complex during the reactions complicated the analysis of the catalyst retention. Nevertheless, the authors were able to confirm that carbosilane dendrimers carrying catalytically active moieties are suitable for the use in continuous processes and that these molecules combine the advantages of homogeneous and heterogeneous catalysis. A remarkable result is the first X-ray analysis of a G2 carbosilane dendrimer.

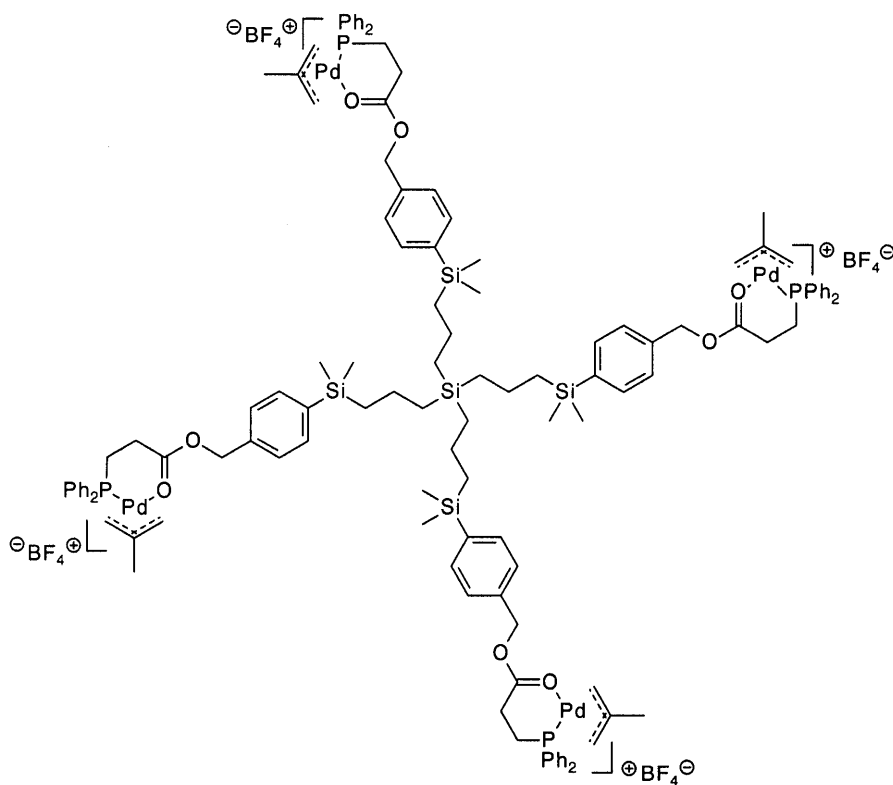


Fig. 6. G0-Pd catalyst used for the hydrovinylation of styrene in a membrane reactor (Vogt and van Koten)

A new concept in the use of functionalized carbosilane dendrimers as soluble supports is the ester enolate-imine condensation reaction leading to β -lactams, which has been developed by van Koten and co-workers [64]. In order to obtain a functionalized dendrimer suitable as a support in this reaction, the authors coupled dendritic chlorosilanes with a linker group, i.e., either [4-bromo]-*tert*-butyldimethylsilylbenzyl ether or (*S*)-[4-bromo]-*tert*-butyldimethylsilyl- α -methyl-benzyl ether. Desilylation afforded dendritic polyols, which were reacted with phenylacetyl chloride. In the zinc-mediated ester enolate-imine condensation the resulting dendrimers were treated with LDA and zinc chloride prior to addition of an imine. The reaction turned out to be highly *trans*-selective and led to high conversions. However, only a modest level of stereoselection was achieved.

Dendrimers offer interesting potential for electrochemistry, since they permit one either to isolate one single electroactive group internally or to load a large number of electroactive moieties on a single molecular nanoparticle [65]. The latter approach has been explored for carbosilane dendrimers in several laboratories and is based on the high redox-stability and flexibility of the carbosilane scaffold. The synthesis, characterization, and properties of redox-active carbo-

silane dendrimers containing ferrocenyl groups were reported by Casado and co-workers in several publications over the last few years, which have been summarized recently [66]. The electronic properties of these dendrimers containing a controlled number of equivalent redox centers render them promising materials for use in multielectron redox catalysis. The first example of this interesting class of organometallic dendrimers was published as early as 1994 by Cuadrado et al. [67]. Hydrosilylating tetraallylsilane with chlorodimethylsilane afforded the silyl chloride terminated G0. In order to obtain the corresponding first generation, tetraallylsilane was hydrosilylated using dichloromethylsilane followed by the allylation with allylmagnesium bromide. Subsequent hydrosilylation with chlorodimethylsilane yielded the targeted carbosilane dendrimer with eight silyl chloride end groups. The silyl chlorides have been replaced by reaction either with ferrocenyllithium resulting in direct attachment of the ferrocenyl groups to the outermost silicon atoms or with β -aminoethylferrocene resulting in ferrocenyl groups separated from the outermost silicon atoms via an ethylamino group. Electronic properties have been studied by cyclic voltammetry, revealing that the ferrocenyl moieties are noninteracting redox centers. Besides this, it was found that the dendrimers based on the first generation, i.e., eight ferrocenyl moieties, undergo "oxidative precipitation" upon oxidation to polycations. This results in thin films adsorbed on the Pt electrode surface. Further investigation concerning the preparation of electrode surfaces modified with dendrimers containing directly attached ferrocenyl groups revealed that the modified Pt electrodes are extremely durable and that the redox response is practically unchanged without loss of electroactive material [68]. More detailed cyclic voltammetry, differential pulse voltammetry, and bulk coulometry showed that the observed reversible oxidation waves represent a simultaneous multielectron transfer of four or eight electrons respectively, as expected for four or eight independent reversible one-electron processes at the same potential. Carbosilane dendrimers containing electronically communicated ferrocenyl moieties have been obtained by one of the few convergent approaches to carbosilane dendrimers reported so far [69]. Cuadrado et al. prepared the G0-dendron diferrocenylmethylvinylsilane by reaction of ferrocenyllithium with dichloromethylvinylsilane. Further growth of this dendron was achieved by hydrosilylation with phenylchlorosilane followed by alkenylation with allylmagnesium bromide affording a dendron with four ferrocenyl units. Coupling these dendrons to tetrakis(dimethylsilylpropyl)silane via hydrosilylation resulted in carbosilane dendrimers containing 8 or 16 ferrocenyl moieties on the dendritic surface, respectively. The electrochemical behavior supports the existence of significant interaction between the two ferrocenyl units linked by the bridging silicon. In another study Losada et al. reported the synthesis of similar structures and their use as mediators in amperometric biosensors [70]. G0 bearing four ferrocenyl units was obtained by hydrosilylation of tetrakis(dimethylsilylpropyl)silane with vinylferrocene. Also the corresponding first generation has been prepared containing eight ferrocenyl moieties. The structure is depicted in Fig. 7.

Using these dendrimers, dendrimer/glucose oxidase/carbon-paste electrodes were constructed, whose electrochemical behavior has been investigated by cyclic voltammetry. Also the steady-state response of the ferrocene-mediated

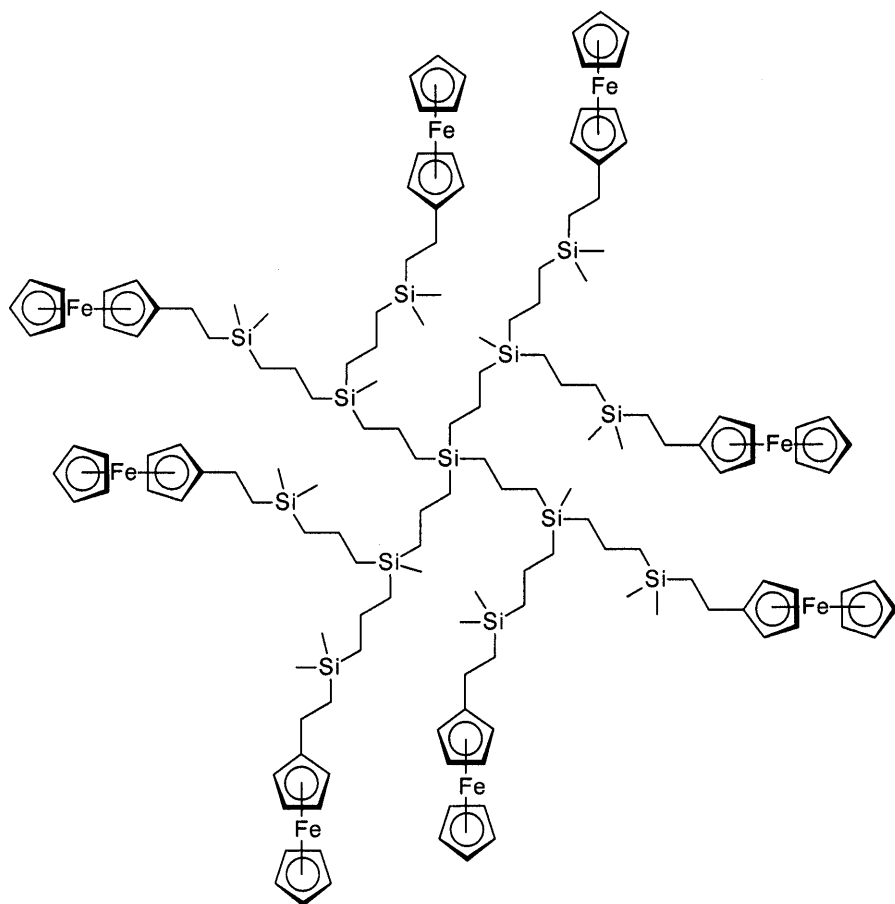


Fig. 7. Redox-active carbosilane dendrimer (G1), bearing 8 ferrocenyl units (Losada et al.)

glucose oxidase electrodes to glucose has been measured, demonstrating that ferrocenyl-functionalized dendrimers are capable of acting as mediators for carbon-paste electrodes. The results suggest that the flexibility of the dendritic mediator is an important factor in the ability to facilitate the interaction between the mediating species and the redox centers of glucose oxidase. Only recently, Losada et al. reported the use of Si-NH group containing dendrimers, the synthesis of which is described above [67], as anion receptors in solution and immobilized onto electrode surfaces [71]. Electrochemical investigations showed that the ferrocenyl functionalized dendrimer recognizes and senses anionic guests, i.e., HSO_4^- and H_2PO_4^- , via significant cathodic perturbations of the oxidation potential of the ferrocene couple. It has been demonstrated that the anionic guests are coordinated via hydrogen bonding interactions in the neutral state and electrostatic attractions after the electrochemical oxidation of the ferrocenyl moieties in the receptor. The impressive collection of ferrocenyl-

containing carbosilane dendrimers was further enlarged by Cuadrado et al. [72]. Dendrimers with similar branching structures but 1,3,5,7-tetramethylcyclotetrasiloxane as core were synthesized up to the second generation. As expected, in this case the ferrocenyl redox centers attached to the periphery behave as independent, electronically isolated units.

Jutzi and co-workers reported the preparation of a polyferrocene-branched dendrimer-like construct, which was obtained by hydrosilylation of decaallylferrocene with $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{Si}(\text{Me}_2)\text{H})]$ [73]. Although the structure is not based on silicon as branching point, it is based on a Si-containing spacer and has therefore been included in this review. The structure is shown in Fig. 8.

An interesting communication describing the synthesis of a core-functionalized carbosilane dendrimer has been published by van Leeuwen and co-workers [41]. Starting from *p*-bromostyrene, dendrons up to the third generation have been constructed by iterative hydrosilylation with trichloro-

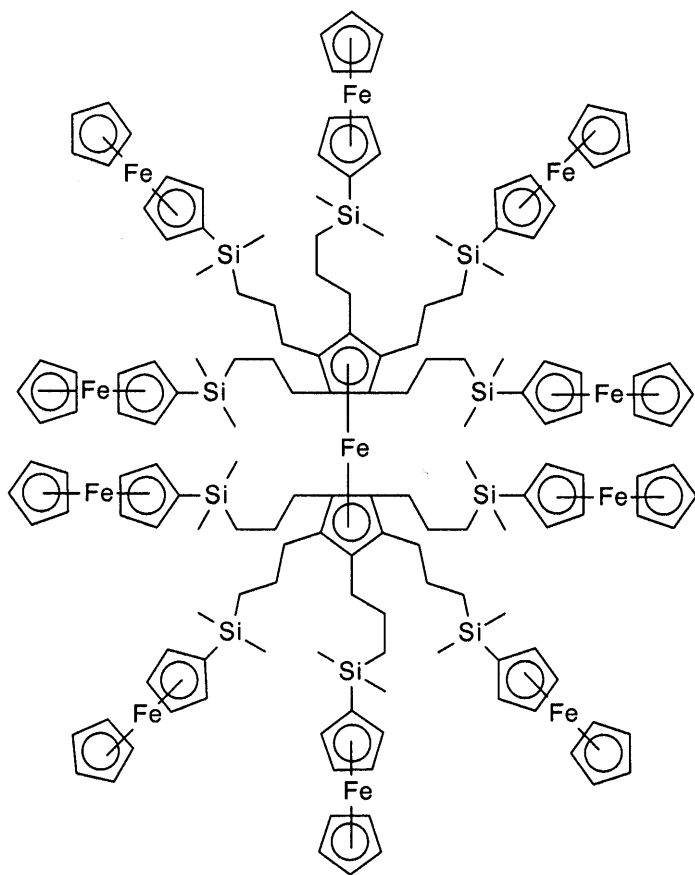


Fig. 8. Polyferrocene structure, obtained by hydrosilylation of decaallylferrocene with $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{Si}(\text{Me}_2)\text{H})]$ (Jutzi et al.)

silane and alkenylation with allylmagnesium bromide. The obtained dendrons were characterized by NMR spectroscopy, elemental analysis, FAB-, and MALDI-TOF-MS. After lithiation at the bromobenzene moiety, the dendrons were reacted with tetraethylferrocene-1,1'-diylbis(phosphonite), yielding the bidentate ligands with molecular weights up to 8567 g mol⁻¹. PdCl₂-complexes have been prepared by reaction of the different ligands with Pd(MeCN)₂Cl₂. In further experiments the catalytic activity of these unusual structures was tested in Pd-catalyzed allylic alkylation. All dendritic Pd complexes were found to be catalytically active. As expected, the rate of the reaction decreased when using the higher generation catalysts. Also, the selectivity of the allylic alkylation reaction was influenced by the generation: with increasing generation number of the dendrons, the selectivity decreased, which is tentatively explained by steric arguments, but also by a change in the polarity of the microenvironment.

Carbosilane dendrimers of the first generation peripherally functionalized with phenyl rings have been prepared by Cuadrado et al. [74]. The π -coordinating ability of the arene rings located at the dendrimer surface towards transition metals allows the synthesis of organometallic dendrimers containing η^6 -coordinated Cr(CO)₃ moieties at the periphery. The reaction of G0 with chromium hexacarbonyl afforded the desired dendritic tetranuclear complex. However, in the case of G1 only 4 of the 8 phenyl groups could be converted into the chromium complexes. Once more, cyclic voltammetric studies of metallated G0 revealed the tricarbonylchromium moieties to be noninteracting redox centers.

Organometallic carbosilane dendrimers (G0) with peripheral Si-cyclopentadienyl groups, Si-Co, and Si-Fe σ -bonds resulted from the reaction of tetrakis(chlorodimethylsilylpropyl)silane with alkaline cyclopentadienides, with LiAlH₄ followed by dicobalt octacarbonyl, and with Na⁺[(η^5 -C₅H₅)Fe(CO)₂]⁻, respectively [75]. All compounds were characterized by NMR and mass spectrometry.

Carbosilane dendrimers bearing acetylene-dicobalt hexacarbonyl units at the periphery have been reported by two groups: Seyferth et al. prepared small vinyl-terminated dendrimers based on previous work of this groups [27], which were then hydrosilylated with chlorodimethylsilane, followed by conversion with ethynylmagnesium bromide to yield carbosilane dendrimers with ethynyl groups at the periphery [76]. Reaction of these dendrimers with dicobalt octacarbonyl afforded the desired dendrimers with 4 (or respectively 12 in G1) acetylene-dicobalt hexacarbonyl complexes in the periphery. X-ray diffraction showed that the bond distances of the tetrahedrane cluster fall within the limits reported for other acetylene-dicobalt hexacarbonyl complexes. The reaction of dicobalt octacarbonyl with a dendrimer possessing two ethynyl substituents on each peripheral silicon atom failed. The authors attributed this failure to steric factors. Kim and Jung used dendrimers based on tetrakis(phenylethynyl)silane as core molecule with bis(phenylethynyl)methylsilyl end groups [48] to obtain the acetylenedicobalt hexacarbonyl terminated dendrimers [50]. Figure 9 shows the first generation. In contrast to Seyferth et al., apparently they did not encounter problems concerning the reaction of dicobalt octacarbonyl with the employed dendrimers possessing two phenylethynyl substituents on each peripheral silicon atom. However, a MALDI-TOF mass spectrum of the second

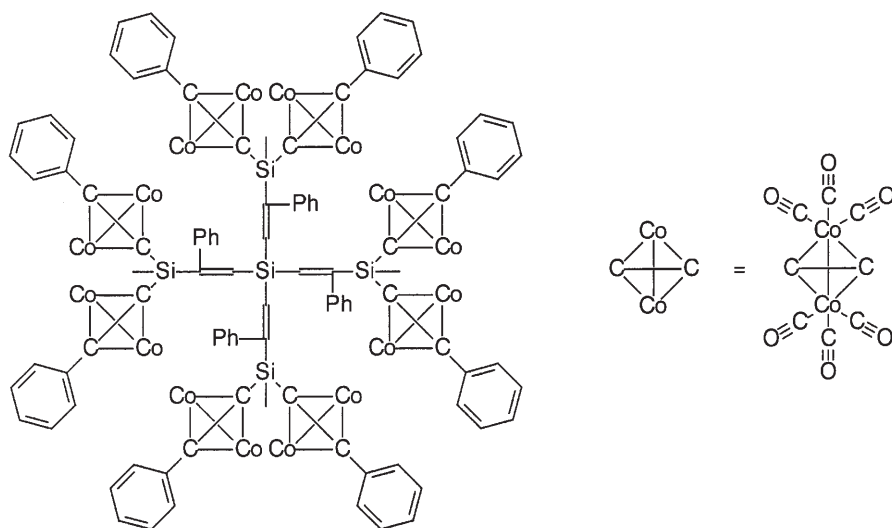


Fig. 9. Acetylene dicobalt hexacarbonyl terminated carbosilane dendrimers based on tetrakis (phenylethynyl)silane as core molecule (Kim and Jung)

generation ideally containing 32 dicobalt clusters could not be obtained. Similar work based on alkoxysilane dendrimers has been published by Lang and co-workers recently [77]. The results will be discussed in the alkoxysilane section of this review.

A very interesting report concerning the synthesis of highly charged organo-metallic carbosilane dendrimers and their characterization by mass spectrometry as well as X-ray diffraction was published by Tilley et al. [78]. They prepared G1 and G2 of benzyl-terminated dendrimers by hydrosilylation with trichlorosilane, followed by addition of benzylmagnesium chloride. The materials were characterized by NMR spectroscopy and MALDI-TOF-MS. Cationic ruthenium centers were introduced by the reaction of the corresponding benzyl terminated dendrimers with $[\text{Cp}^*\text{Ru}(\text{NCMe})_3]^+\text{OTf}^-$. The structure of the first generation is shown in Fig. 10.

The authors' intention was to obtain charged, spherically shaped dendrimers, possessing cationic or anionic end groups for the construction of superlattice structures. In the case of G1, electrospray ionization Fourier transform-ion cyclotron resonance (ESI FT-ICR) mass spectrometry confirmed the formation of the perfect structure. Further support was obtained from the X-ray diffraction analysis. However, in the case of the second generation the ESI mass spectra revealed that a mixture of the perfect structure containing 36 Cp^*Ru^+ units and dendrimers with only 35 Cp^*Ru^+ units had been isolated. The hypothesis that steric congestion at the periphery prevented complete complexation of all 36 terminal benzyl groups was confirmed by preparing a second generation with 24 benzyl groups only. Reaction with $[\text{Cp}^*\text{Ru}(\text{NCMe})_3]^+\text{OTf}^-$ led to the desired structure with 24 Cp^*Ru^+ units. A third generation dendrimer bearing 72 Cp^*Ru^+ units has also been prepared.

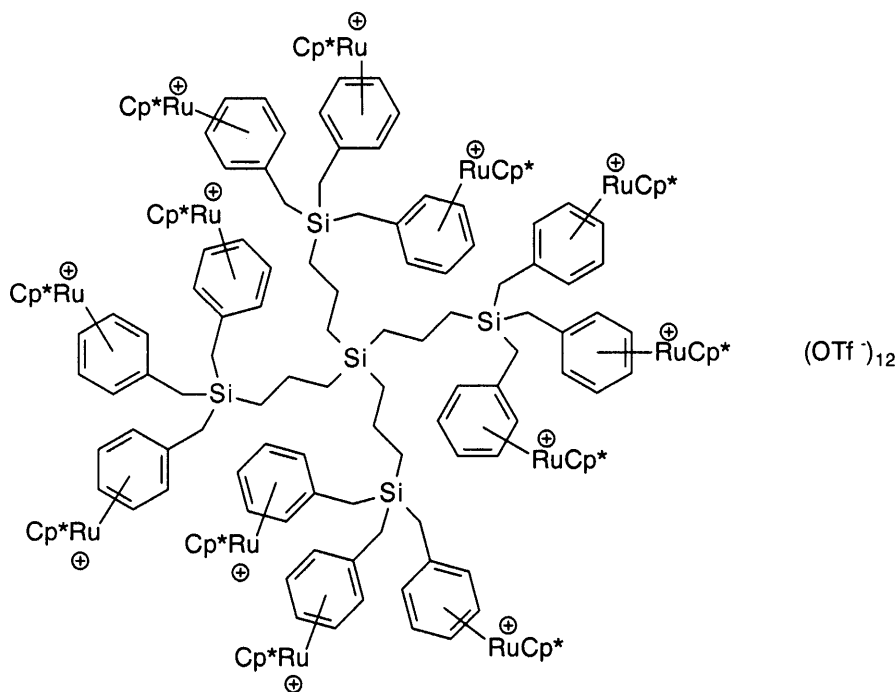


Fig. 10. Benzyl-terminated dendrimers with $[\text{Cp}^*\text{Ru}(\text{NCMe})_3]^+\text{OTf}^-$ complexes (Tilley et al.)

Attachment of transition metal clusters represents another novel facet of carbosilane dendrimer chemistry. The mixed gold/iron cluster fragment $[\text{AuFe}_3(\text{CO})_{11}]$ has been attached to a phosphino-terminated G1 carbosilane dendrimer by Rossell et al. [79]. In this manner, dendrimers with high metal density on the periphery can be obtained.

Seyferth et al. patented the preparation of group 4 metal-containing carbosilane dendrimers and their use as catalysts for the polymerization of olefins and silanes [80, 81]. As an example, polyethylene was prepared using a methylaluminumoxane-activated catalyst prepared by the reaction of a second generation carbosilane dendrimer with a vinyl derivative of a zirconocene.

2.2.2

Dendritic Carbosilane Polyols

Dendritic carbosilane polyols are intriguing materials, since they represent a versatile platform for the construction of a variety of unusual dendrimer-based polymer architectures. Therefore, this class of carbosilane dendrimers is reviewed in a separate section. Possessing a completely hydrophobic scaffold in combination with strongly polar end groups, the dendritic carbosilane polyols are expected to resemble micelles in their behavior.

Our group reported the first synthesis of these compounds [18, 82]. We prepared a series of carbosilane dendrimers, which were converted into dendritic

carbosilane polyols by hydroboration using 9-BBN and subsequent oxidation with $\text{H}_2\text{O}_2/\text{OH}^-$. This formally led to quantitative anti-Markovnikov addition of H_2O to the terminal double bonds of the carbosilane dendrimers. The second generation of the prepared carbosilane dendrimer bearing peripheral hydroxy groups is depicted in Fig. 11.

The dendritic polyols were characterized by NMR spectroscopy and MALDI-TOF mass spectrometry, demonstrating not only the quantitative hydroboration/oxidation reaction, but also the suitability of the MALDI-TOF mass spectrometry for the molecular characterization of dendritic structures in general. Glass transition temperatures of the carbosilane dendrimers with allyl end groups indicated high flexibility (-100°C to -80°C). Glass transition temperatures and flow temperatures of carbosilane dendrimers were also determined by Muzafarov et al., confirming this result [26]. These authors showed that the T_g s for dendrimers with a branching multiplicity of 2 were in the range of -90°C to -80°C , becoming constant above the fourth generation. In contrast, the

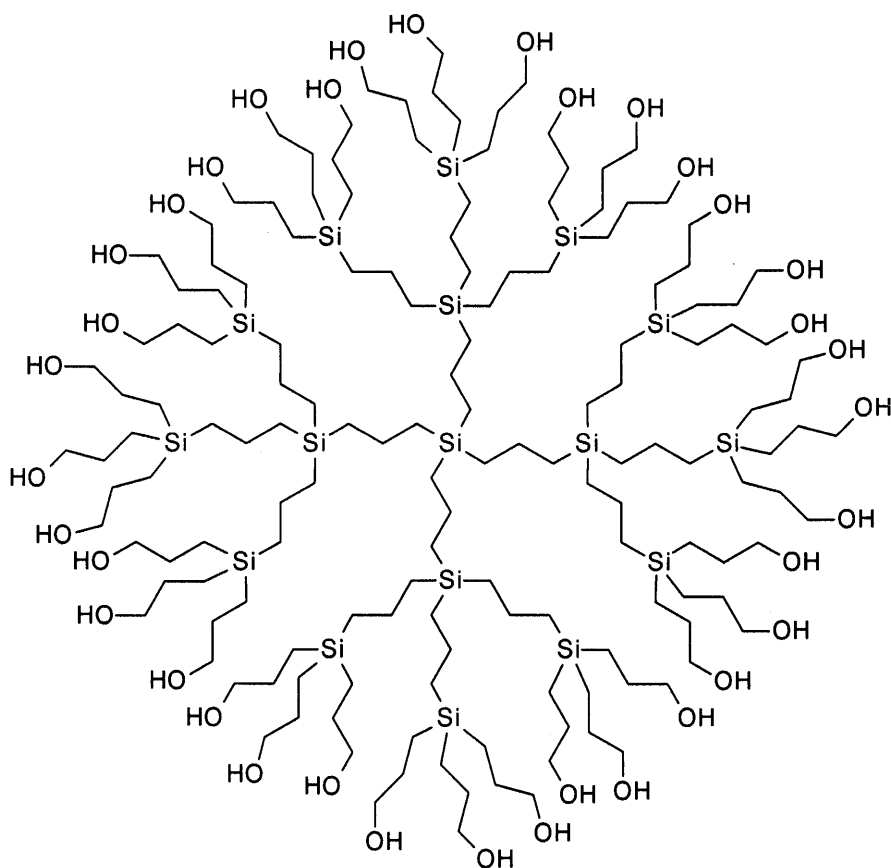


Fig. 11. Dendritic carbosilane polyol (G2) obtained by hydroboration/oxidation of allyl-terminated carbosilane dendrimers (Frey et al.)

glass transition temperatures of the dendritic polyols prepared in our group are approximately 60 K higher (-30°C to -40°C). This strong increase is explained by hydrogen-bonding, resulting in a network-like structure and by a possible exclusion of the polar hydroxyl end groups from the lipophilic carbosilane interior.

In an alternative approach, Getmanova et al. obtained dendritic carbosilane polyols by hydrosilylation of an allyl-terminated carbosilane dendrimer with an organosilane bearing a trimethylsilyl protected hydroxyl group [83, 84]. Hydrolysis of the trimethylsiloxy groups afforded the desired polyols. IR spectroscopic investigation in bulk and solution showed that the hydrogen-bond network formed in both cases is rather sensitively dependent on temperature and concentration. Sheiko et al. studied the spreading of these hydroxy functional materials at the air/water interface [85, 86]. The dendrimers formed a monolayer on the interface. Depending on the molecular area, three equilibrium states have been identified: (i) over a remarkably broad range of molecular areas a stable monolayer was formed; (ii) upon compression of the monolayer with decreasing molecular area a transition into a bilayer structure occurred, which is considered to be a first-order transition; (iii) finally, an isotropic liquid film was formed. In the same work a carbosiloxane dendrimer was also investigated (cf. Sect. 3.2). Sheiko and co-workers also employed tapping mode scanning force microscopy to examine the hydroxy-functional dendrimers [87]. The dendrimers showed two types of wetting behavior, depending on the substrate used. Due to preferential adsorption of the hydroxyl groups, the dendrimer displayed autophobic spreading on mica, whereas a substrate coated with a semifluorinated polymer was only partially wetted. On both substrates, submicrometer-size droplets were observed.

Comparison of the measured microscopic contact angles and macroscopic values revealed a difference, which was explained by deformation of the droplets caused by the tapping tip.

In an elegant approach, using nucleophilic reactions of mercapto-substituted amphiphiles and carbosilane dendrimers bearing (chloromethyl)silyl groups on their terminal branches, Krska and Seyferth obtained amphiphilic dendrimers with hydrophobic carbosilane cores and, among others, hydroxyl groups at the periphery [88]. The synthesis and properties of these compounds will be discussed in more detail in Sect. 2.2.4 dealing with host-guest chemistry.

Only recently Comanita and Roovers reported an alternative synthetic approach to dendritic carbosilane polyols [89]. Hydrosilylation of vinyl-terminated carbosilane dendrimers, synthesized by successive hydrosilylation and nucleophilic displacement starting from tetravinylsilane, methyldichlorosilane, and vinylmagnesium bromide [22], with bis-(6-(2-tetrahydropyranyloxy)hexyl)methylsilane led to the THP-protected polyols. After deprotection, the desired polyols with 4, 8, 16, and 32 hydroxy groups (G0–G3), respectively, were obtained. The purity of the compounds was established via NMR-spectroscopy and SEC.

Kuzuhara et al. used carbosilane polyols, using the approach of Terunuma et al. [90], to attach cyclodextrin moieties to a core molecule [91]. Although only G0 has been reported so far, the methodology should be applicable to carbosilane dendrimers of higher generations as well.

Silanol functionalized carbosilane dendrimers were obtained by Morris and co-workers [92]. Although silanol groups are, in general, hydrolytically unstable,

these molecules are of interest since they may be used to mimic silica surfaces to study the attachment of catalytically active metals to silanol groups. To obtain silanol derivatives, the vinyl end groups of the dendrimers were hydrosilylated with chlorodimethylsilane. Subsequently, the silyl chloride was reduced, using LiAlH_4 . Catalytic hydrolysis employing water over Pd/C yielded the desired silanol-functionalized carbosilane dendrimer. The compounds were characterized by NMR spectroscopy and CHN microanalysis. According to the authors, even upon standing for 6 months in air the dendrimers showed little evidence for intermolecular condensation.

Earlier disclosed patent literature by researchers at Bayer A.-G. had also described the synthesis of carbosilane dendrimers with silanol end groups and their use for the preparation of coatings with improved scratch resistance and toughness [93–95]. These materials were prepared by hydrolysis of chlorosilyl terminated dendrimers of low generations. Compared to ethoxysilyl or methoxysilyl end group containing dendrimers, the prepared dendritic silanols are considered to be advantageous because they do not release ethanol or methanol upon condensation.

As already mentioned above, due to their chemical stability carbosilane polyols permit a wide variety of modification reactions on the dendrimer periphery. For instance, the polyols can be coupled with mesogenic, i.e., rigid, units. This has been used to prepare dendritic liquid crystalline polymers, discussed in the following section.

2.2.3

Dendritic Liquid Crystalline Polymers (DLCP)

Carbosilane dendrimers were among the first dendrimers whose solid state properties and mesophase formation have been considered. Currently, there is growing interest in the combination of branched structures and mesogenic units, motivated by the fact that the globular shape might reduce the bulk viscosity, and hence the switching times of such materials. Coupling of the flexible, dendritic carbosilane scaffolds with rigid mesogenic units as end groups results in dendritic liquid crystalline polymers (DLCPs). It is a peculiarity of this class of LC polymers that the attachment of mesogenic units to the flexible carbosilane dendrimer scaffold leads to a structural conflict between preferential anisotropic order of the mesogenic units and the spherosymmetry of the dendrimer. The construction principle demonstrated first for carbosilane dendrimers has meanwhile also been realized for poly(propyleneimine) and PAMAM dendrimers [96, 97].

The first work on dendrimers with a large number of mesogenic end groups was reported by our group [82, 98, 99]. Carbosilane dendrimers with 12, 36, and 108 cholesteryl end groups were prepared via esterification of dendritic carbosilane polyols with cholesteryl chloroformate. Self-assembled ultrathin films of carbosilane dendrimers with these mesogenic units at the periphery, obtained after deposition on mica surfaces, were studied with atomic force microscopy [100]. At high dendrimer concentrations, flat, homogeneous films of 2–4 dendrimer layers were found. For low concentrations, a single dendrimer monolayer

exhibiting an irregular cellular pattern of holes was observed. Interestingly, the third generation dendrimer, i.e., the highest generation examined in this study, did not show dewetting or reorientation upon annealing, which was ascribed to lower molecular mobility. In further studies we investigated the influence of (i) generation, (ii) spacer length, and (iii) type of mesogen coupled to the dendrimer on the phase behavior of the dendritic liquid crystalline polymers [101–103]. We attached cyanobiphenyl units to dendritic carbosilane polyols of G0 to G2 via esterification of the hydroxyl end groups, obtaining DLCPs with the mesogenic groups connected by spacers of different length to dendritic scaffolds of different generations. In Fig. 12 a dendrimer of this type is depicted,

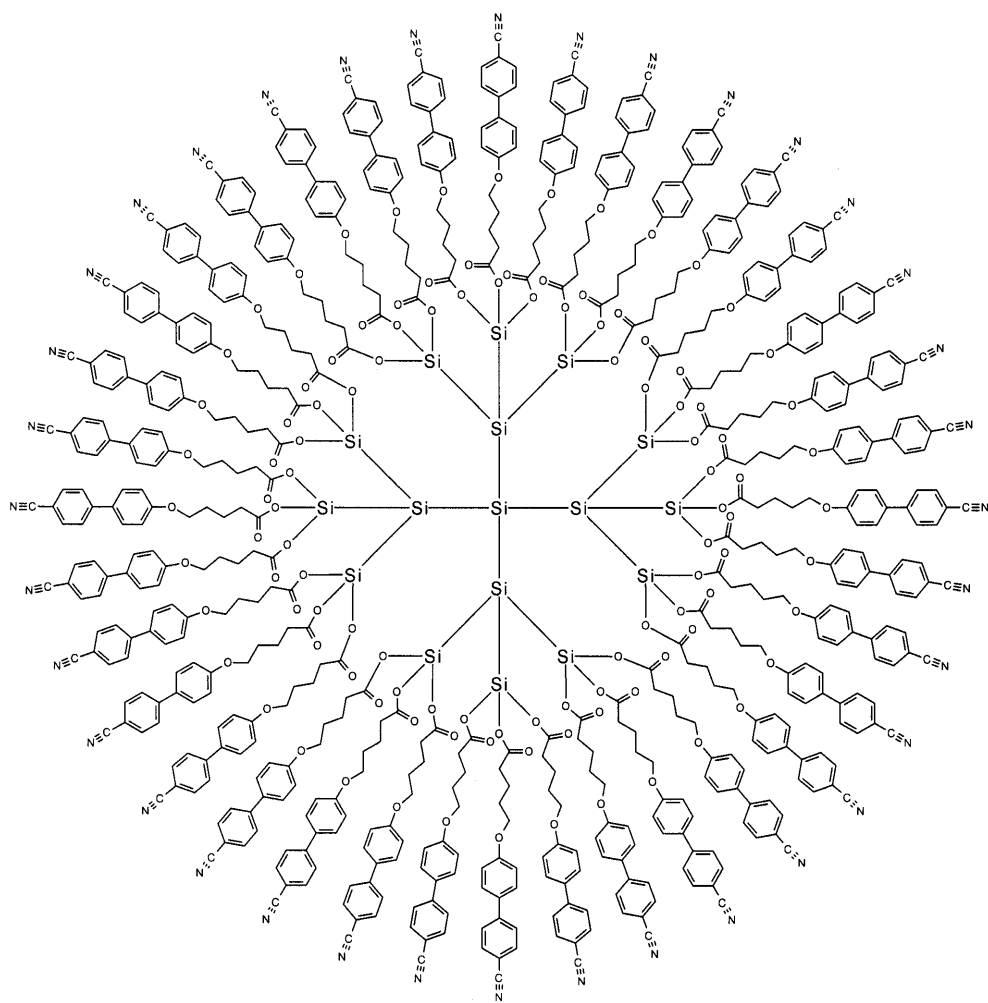


Fig. 12. Dendritic liquid crystalline dendrimer (DLCP) bearing 36 cyanobiphenyl moieties that are attached to the scaffold via a short spacer (Frey et al.) (— represents C_3H_6)

bearing 36 cyanobiphenyl moieties that are attached to the scaffold via the short spacer. The DLCPs were characterized by polarizing microscopy, DSC, WAXS, and SAXS with respect to their thermotropic phase behavior. All of the DLCPs except for G1 develop layered (smectic) structures, which are explained by separate ordering of the calamitic surface groups and the core which, however, requires a deformation of the dendritic scaffolds in order to adjust to the smectic order. Reducing the spacer length and/or increasing the number of end groups (i.e., the generation number) complicates the formation of well-developed smectic phases. Furthermore, if dendrimer scaffolds with a branching multiplicity of 3 are used, in higher generations (usually above G2) no liquid crystalline phases were observed [104]. This is explained by the dense packing of the mesogens at the dendrimer surface, disabling the formation of smectic layers.

Concurrent to the evolution of higher order within the smectic layers on cooling G1 and G2, microphase separation of the dendritic carbosilane scaffolds from mesogen and spacer-containing domains occurs. From SAXS data the resulting morphology is concluded to be lamellar with a periodicity showing distinct increase with generation. Thus, surprisingly, these LC-materials, although being composed of constitutionally isotropic molecules, are capable of developing nanophase-separated morphologies in a certain analogy to block copolymers. This is supported by TEM-images (Fig. 13), showing a lamellar morphology with stained mesogen-rich domains of 2–3 nm thickness and domains containing the dendrimer cores [105].

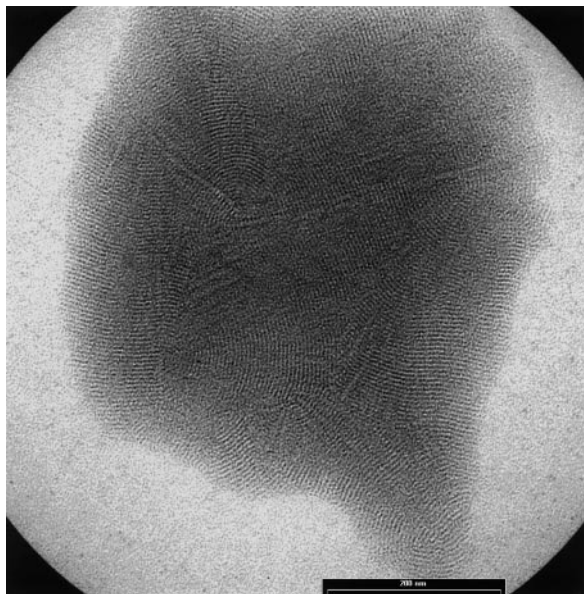


Fig. 13. TEM-image of the nanophase-separated morphology of a liquid crystalline dendrimer with mesogenic cyanobiphenyl end groups; mesogen-rich domains are stained preferentially and appear dark; scale-bar: 200 nm (Thomann et al.)

Shibaev and co-workers used cyanobiphenyl, methoxyphenyl benzoate, and cholesteryl groups as mesogenic units [106] in a number of works on liquid crystalline dendrimers. Generally, dendrimers with a branching multiplicity of 2 have been used by this group. The mesogenic units were coupled to carbosilane dendrimers bearing eight allyl groups by hydrosilylation. The LC properties of the obtained dendrimers were determined by polarizing optical microscopy in combination with DSC-measurements and X-ray diffraction. It could be shown that the type of the mesophase depends essentially on the chemical nature of the mesogenic group attached. Furthermore, a phase transition between two different smectic phases (S_C and S_A) was observed for the cyanobiphenyl-terminated dendrimer. In further work the electric birefringence (Kerr effect) and the dielectric polarization of the prepared DLCPs have been measured [107]. In accordance with the Kerr law, the dielectric polarization was found to be proportional to the second power of the electric field. It was shown that the electric birefringence of DLCP solutions is mainly determined by the electro-optical properties of the mesogenic groups oriented in the electric field independently of the scaffold. Shibaev and co-workers also prepared liquid crystalline carbosilane dendrimers containing terminal cyanobiphenyl groups up to the fifth generation [108] using dichloromethylsilane as branching reagent. The cyanobiphenyl groups were attached to the dendritic scaffold via a spacer consisting of 11 methylene units. In preliminary experiments all obtained dendrimers exhibited birefringence over a wide temperature range. The phase behavior of the fifth generation of the above described series of carbosilane liquid crystalline dendrimers has recently been studied in detail [109]. Polarizing optical microscopy, DSC, and X-ray diffraction revealed an unusual phase behavior. At room temperature the dendrimers form a lamellar (smectic A) phase which develops in-plane ordering above 40 °C. Above 121 °C the material transforms into a more disordered mesophase, probably a disordered hexagonal columnar phase. Since lower generations of liquid crystalline dendrimers form smectic (layered) structures only, this behavior shows that the dendrimer core becomes significant for the structure of the LC phase. Furthermore the existence of a smectic mesophase up to the fifth generation shows that the structural conflict between the mesogenic units and the spherosymmetry of the scaffold is less pronounced in these carbosilane dendrimers with a branching multiplicity of 2, compared to structures possessing a branching multiplicity of 3 [102].

Smectic phases have also been found for carbosilane dendrimers substituted with mesogenic units based on azobenzene by Zhang et al. [110]. In subsequent work these authors reported on the attachment of further mesogenic units [111] and formation of nematic as well as cholesteric phases. Terunuma et al. recently reported the synthesis of cyanobiphenyl-terminated carbosilane dendrimers based on triallylphenylsilane as a core [90]. The prepared DLCPs were characterized by DSC and polarizing optical microscopy. X-ray diffraction data were not given. In a subsequent report, the same authors reported carbosilane dendrimers with mesogens bearing a chiral tail (G1, G2; branching multiplicity 3). Again, the materials exhibited smectic A phases only. Interestingly, these dendrimers could be used as chiral dopants, leading to the formation of Sc^*

phases. The response times for switching of these phases in electric fields increased with molecular weight, as commonly seen in the case of ferroelectric liquid crystals [112].

Besides classical calamitic mesogens, perfluoroalkyl groups ($-\text{C}_6\text{F}_{13}$) have been attached to carbosilane dendrimers in our group [113]. The attachment of the perfluorinated alkyl groups to the allyl end groups of the dendrimers was performed via free radical addition of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-*n*-octyl mercaptane, which affords the corresponding fully thioether-functionalized end groups. Perfluorinated dendrimers of G0 to G3 with 4, 12, 36, and 108 perfluoroalkyl end groups, respectively, have been prepared. As an example, G2 is shown in Fig. 14.

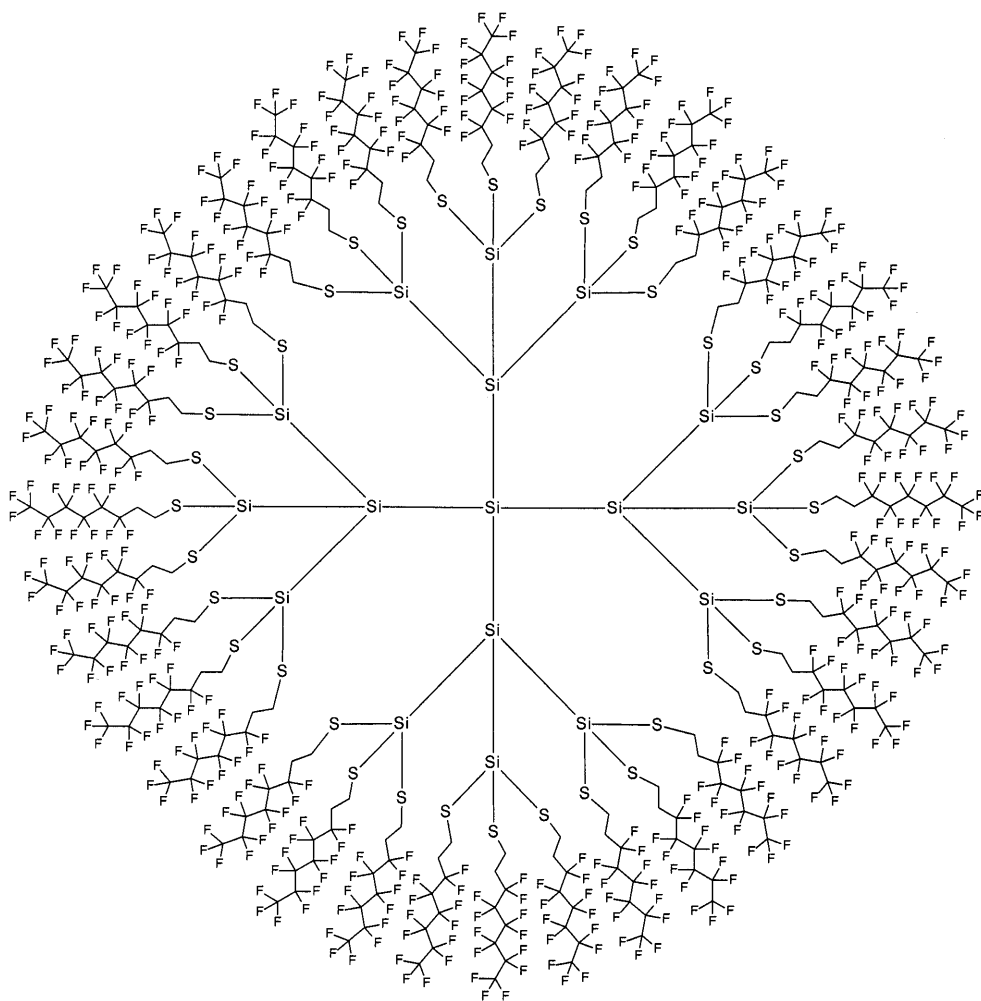


Fig. 14. Perfluorinated carbosilane dendrimer (G2) with 36 perfluoroalkyl end groups (Frey et al.) (— represents C_3H_6)

The “fluorophilic” periphery of these dendrimers is immiscible with the “lipophilic” carbosilane structure. Such core-shell-type dendrimers also exhibit generation-dependent mesophase formation. Whereas G0 was obtained as a crystalline material that did not show the formation of a mesophase, G1 formed a highly ordered smectic phase at low temperature. The layered structure of G2 was considerably less well developed and G3 displayed a WAXS pattern that indicated a hexagonally packed array of cylindrical domains. This generation-dependent thermal behavior is ascribed to the increasingly dense packing of perfluorohexyl groups on the dendrimer surface. The obtained dendrimers have been studied in further detail by Stühn et al. using X-ray scattering techniques as well as quasielastic neutron scattering [114]. As a result of the microphase separation between the end groups and the carbosilane core, the perfluorinated dendrimers form generation-dependent superstructures. It has been found that the helical end groups tend to arrange in layers between the carbosilane domains, the layers possessing a local order similar to that observed in the crystalline state of perfluorinated alkanes. Independent of the generation number the dendrimer core has to deform to adjust to the order of the end groups. Furthermore, segmental dynamics, as studied with quasielastic neutron scattering, revealed a dynamic heterogeneity caused by the demixing of end groups and dendrimer core. Only recently Stühn and co-workers examined the dielectric relaxation in these perfluorinated carbosilane dendrimers [115]. The dendrimers showed a fast relaxation with an Arrhenius-type temperature dependence and an activation energy of 17 kJ mol^{-1} . In all generations a dominant α -process was found, which was split into a slow and a fast part. For G1 a transition from a smectic to a nematic state was observed at -15°C . This transition is observed in the dielectric relaxation as a discontinuous increase of the relaxation times for both components of the α -process. Further studies concerning the dielectric relaxation of carbosilane dendrimers with cyanobiphenyl end groups have also been carried out [116]. An unusually narrow α -process was observed, indicating a clear separation between the relaxation times of the dendrimer scaffold and the end groups. The distortion of the dendrimer scaffold as a consequence of the smectic order within the end groups was reported to be responsible for a shift of its relaxation times.

In summary, carbosilane dendrimers have permitted one to obtain a detailed understanding of the behavior of end-group induced liquid crystallinity in flexible dendrimers. In most cases, the topology leads to smectic phases. Key parameters for the supramolecular order developed are the branching multiplicity as well as the spacer length between mesogen and dendrimer.

2.2.4

Host-Guest-Chemistry and Solubilization Properties

Due to their structural density gradient leading to inner cavities and their fixed spherical topology, dendrimers with an amphiphilic structure are regarded as micelle-analogues. The first dendrimer that acts like a micelle of usual amphiphiles was reported by Newkome et al. [117]. Newkome et al. prepared a carboxylate-terminated hydrocarbon dendrimer, which shows solubilization behavior

for apolar molecules in polar media, yet no critical micelle concentration was observed. As already mentioned above, carbosilane dendrimers are similarly well-suited for application in the field of host-guest-chemistry and solubilization, since they likewise possess a completely hydrophobic scaffold. In addition the route to these dendrimers is flexible, permitting to control the size of the inner cavities. This has been demonstrated by our group in a molecular force field study concerning the host properties of carbosilane dendrimers [118]. Based on these results, the dimensions of the inner cavities can be controlled from 5–15 Å by variation of the branching multiplicity and/or spacer length. The density of the periphery has also been investigated. It was found that the higher generations possess a dense outer shell with holes in the range of 2–3 Å. On the basis of the results obtained, predictions concerning the size of molecules that can be trapped inside the dendrimers are possible. Besides, the calculations showed that with increasing generation number the tendency of the dendrons to interpenetrate increases greatly, eventually forming a dense molecular surface in higher generations. This is in agreement with the Monte Carlo model reported by Mansfield and Klushin [119]. Structural analyses of carbosilane dendrimers possessing different branching multiplicities and therefore cavities of different sizes have also been performed using molecular dynamics modeling techniques [120]. A simple equation for the calculation of the maximum possible dendrimer generation was derived.

Further insight into the carbosilane dendrimer structure has been gained from fluorescence spectra and the excimer formation of pyrenyl-labeled dendrimers [121–123]. The investigated dendrimers possessed a pyrenyl group, i.e., a fluorescent probe, at the central silicon atom. It was found that excimer formation did not occur with mere carbosilane dendrimers, whereas carbosiloxane dendrimers showed the formation of excimers, evidenced by time-correlated single-photon counting techniques and steady-state fluorescence spectroscopy. These results yielded information on the conformational mobility and steric hindrance of the investigated dendrimers. This may permit one to tailor new carbosilane dendrimers for the selective inclusion of guest molecules.

Only recently Krska and Seyferth reported the synthesis of water-soluble carbosilane dendrimers [88]. Nucleophilic reactions between mercapto-substituted amphiphiles and carbosilane dendrimers bearing (chloromethyl)silyl groups on their terminal branches yielded amphiphilic dendrimers with hydrophobic carbosilane cores and alcohol, dimethylamino, or sodium sulfonate amphiphilic groups at the periphery. To render the dimethylamino-terminated dendrimers water-soluble, they have been reacted with methyl iodide, providing quaternary ammonium iodide salts. The structure based on the first generation is exemplified in Fig. 15.

A detailed study of these dendrimers using MALDI-TOF mass spectrometry has been reported by Wu and Biemann [124]. Dendrimers terminated with tertiary amino groups have been detected as their $[M + H]^+$ ions. Dendrimers with chloroalkyl end groups required the addition of silver trifluoroacetate to produce $[M + Ag]^+$ ions. Interestingly, for the first and second generation with quaternary ammonium groups, complexes with three or seven matrix anions have been observed. This investigation once more confirms the importance of

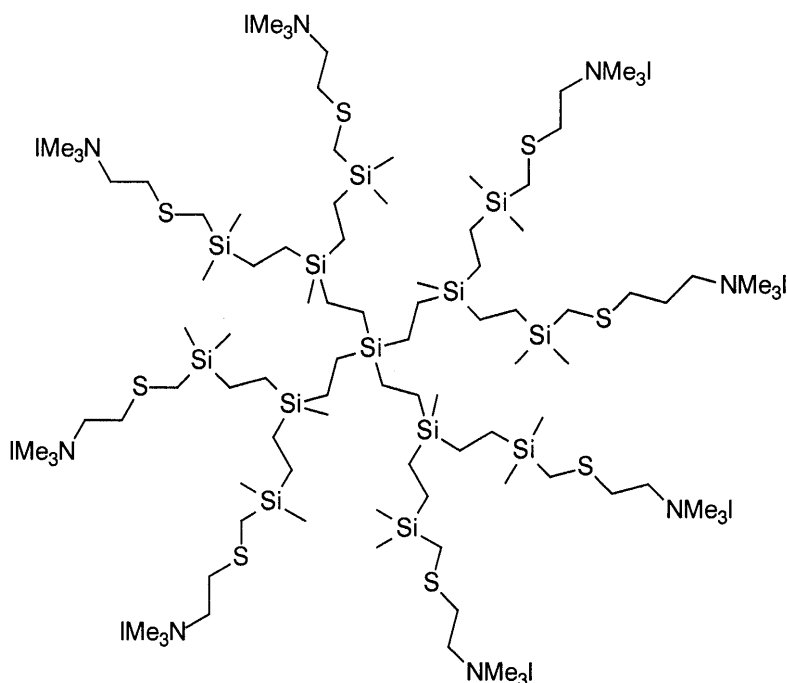
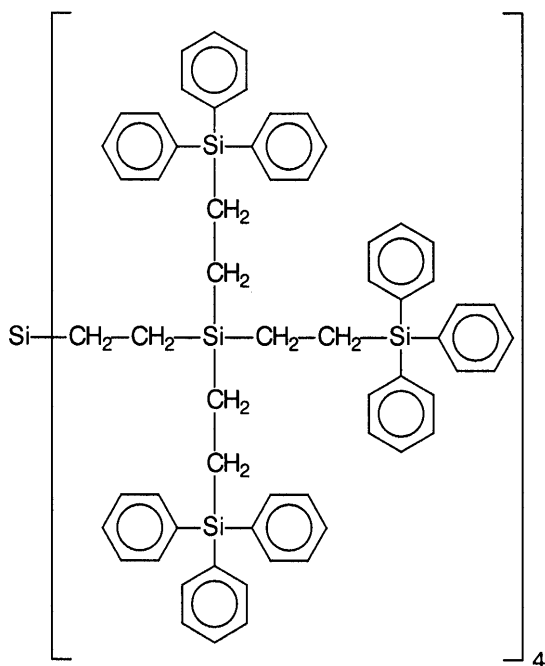


Fig. 15. Water soluble, dimethylamino-terminated dendrimers, reacted with methyl iodide lead to dendrimers with quaternary ammonium iodide salt end groups (Seyferth et al.)

MALDI-TOF mass spectrometry for the characterization of dendrimers. Both the negatively charged sulfonate terminated dendrimers as well as the positively charged ammonium terminated dendrimers were soluble in water. Preliminary studies demonstrated that the sulfonate terminated dendrimers were able to solubilize lipophilic alkyl-substituted benzene derivatives in aqueous solution in a micelle-like fashion. However, since aggregation was observed for the ammonium-terminated dendrimers, the formation of aggregates is also likely for the sulfonate-terminated dendrimers, leading to a solubility enhancement of the benzene derivatives. Detailed studies of our group revealed that aggregation was partly responsible for the solubilization of guest molecules by carbosilane dendrimers with modified surfaces [125]. Furthermore it was found that modified hyperbranched polytrialkylsilanes (Sect. 6.1) behaved very similar with respect to their solubilization behavior.

Crystalline dendritic arylalkylsilane/tetrahydrofuran inclusion complexes have been reported by Friedmann and co-workers [126, 127]. They obtained dendrimers with 12 and 36 phenyl groups at the periphery by means of the hydrosilylation/vinylation approach. The structure of the dendrimer carrying 36 phenyl group is sketched in Fig. 16.

The first generation (12 phenyl groups) gave rise to an inclusion compound when recrystallized in suitable solvents such as THF. Comparative X-ray structural analysis showed that the host dendrimer's conformation is nearly identical



in the pure dendrimer and in the inclusion complex. Furthermore it revealed that the guest molecules are located in cavities created by paired host molecules. The authors conclude that the tetrahydrofuran molecules are deeply buried and probably firmly locked in these cavities. Inclusion complexes have also been found for organosilicon dendrimers composed of 16 thiophene rings [47].

Polymer Architectures Based on Carbosilane Dendrimers

Star Polymers

Because of their precisely defined topology and large number of end groups, dendrimers have been used as core molecules for star polymers with unusually large numbers of arms ("multiarm star polymers"). Particularly carbosilane dendrimers are suitable cores, owing to their chemical stability which allows a variety of reactions without degradation of the dendrimer scaffold. Two different approaches to star-shaped polymers based on carbosilane dendrimers have been reported so far: the first approach, relying on the *arm-first* strategy, involves the attachment of living polymer chains to a carbosilane dendrimer possessing reactive end groups. In pioneering work, Roovers et al. obtained star polymers with 32, 64, and 128 arms, respectively, by coupling silyl chloride

terminated dendrimers (G3 to G5) with living polybutadienyllithium chains [22, 128, 129]. The arm molecular weight was varied between 6400 and 72,000 g/mol. The obtained star polymers were investigated in detail with respect to their dilute-solution properties, employing osmometry, viscosimetry, and light scattering. It was found that the isolated stars behave like hard spheres. Investigations on semi-dilute solutions of star polymers in good solvents and beyond the overlap concentration revealed a gel-like characteristic [130]. The formation of a macrocrystalline ordered phase with spacings of the order of 100–500 Å (SANS) was also observed. In this respect, such materials may be considered to resemble colloidal crystals. Allgaier et al. published an investigation on the structural perfection of such unusual multichain polymers, concerning arm number and polydispersity [17]. For this study, polybutadiene shortarm star polymers structurally very similar to those obtained by Roovers et al. [129] were studied by MALDI-TOF mass spectrometry. The mass spectra revealed that up to a functionality of 16, the quality of the linking agent as well as the star polymer itself is almost ideal with respect to functionality and polydispersity. If higher generations are employed as linker for the chains, the structures appear to be less perfect, which is both due to imperfections of the dendritic linking agent and the incomplete coupling reaction of the living polymer chains as well as silyl chloride groups of the dendrimers. This incomplete reaction is explained by increasing surface congestion with increasing generation number.

A very interesting structure has been obtained by Möller and co-workers [131]. They prepared a star-shaped 12-arm poly(styrene-*block*-isoprene) block copolymer by the reaction of polystyryllithium and polyisopropenyllithium with a carbosilane dendrimer possessing silyl chloride end groups. The carbosilane dendrimer used was synthesized from triallylphenylsilane, employing repeated hydrosilylations with dichloromethylsilane and alkenylation with allylmagnesium bromide. Subsequently, the allyl groups of the second generation were converted to chlorodimethylsilylpropyl groups via hydrosilylation with dimethylchlorosilane prior to subsequent coupling with the different living polymer chains. SEC evidenced a narrow molecular weight distribution. As to be expected, the block copolymer exhibits two glass transition temperatures. TEM and AFM studies of the resulting block copolymers showed that these molecules form regularly organized micelles in solution.

The second approach, relying on the *core-first* strategy, involves the polymerization of monomers, such as styrene or ethylene oxide, from a carbosilane dendrimer serving as multifunctional initiator. Roovers et al. used a dendritic polyol [89] as initiator for the anionic polymerization of ethylene oxide [132, 133]. The resulting star polymers with 4, 8, and 16 arms, respectively, exhibit narrow molecular weight distributions. Characterization of the star polymers and comparison of the properties with those of linear poly(ethylene oxide) indicated that the core material has a minimal effect on the conformation of the stars in methanol.

An elegant work, using the second approach has been reported by Muzafarov and co-workers [134–136]. They synthesized polyolithium derivatives of carbosilane dendrimers, which they used as initiators for the anionic polymerization

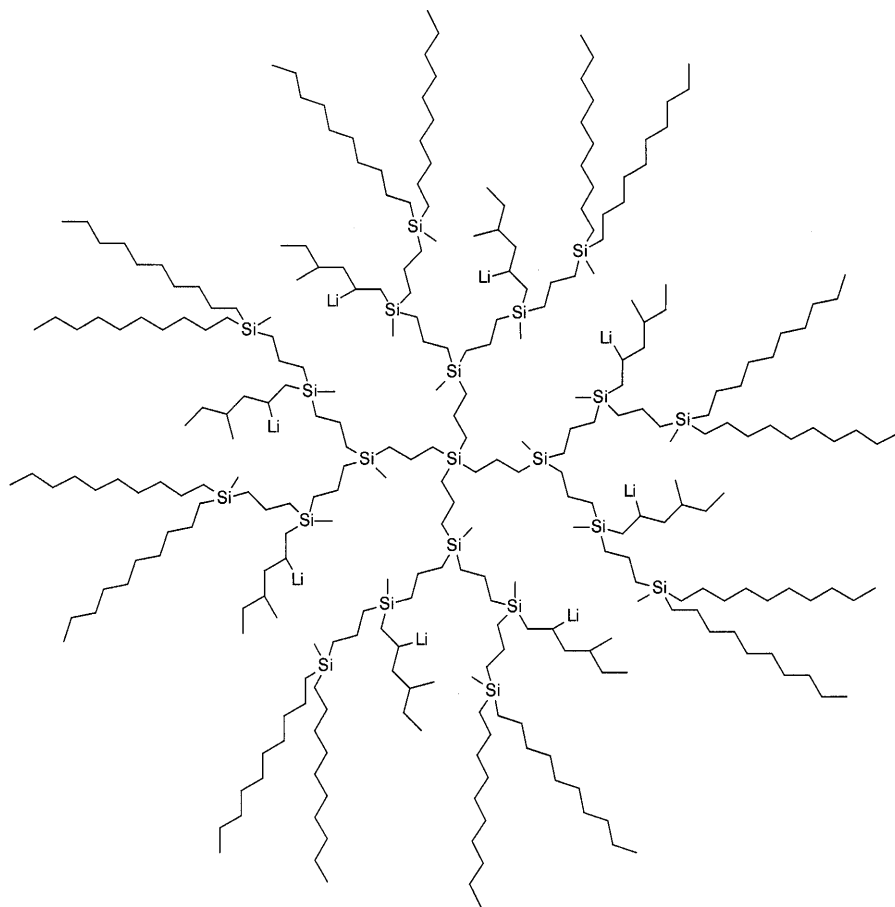


Fig. 17. Polyolithium derivative of a carbosilane dendrimer, obtained by reaction of inner allyl groups with *sec*-BuLi. Such dendrimers can be employed as polyfunctional initiators for the anionic polymerization of cyclic siloxanes, ethylene oxide, and styrene (Möller, Muzafarov et al.)

of different monomers, such as styrene, hexamethylcyclotrisiloxane, and ethylene oxide. The polyolithium derivatives were obtained by hydrosilylation of allyl-terminated dendrimers with the sterically demanding bisdecylmethylsilane. This led to the reaction of only one-half of the end groups, leaving allyl groups unreacted in the interior of the dendrimer. The reaction of these allyl groups with *sec*-butyllithium afforded the desired polyolithium derivative of the carbosilane dendrimer. One of the obtained polyanions is shown in Fig. 17. The important feature of this approach lies in the fact that, due to the location of the lithium atoms in the inner area of the dendrimers, a main problem of polyolithium compounds, i.e., their high tendency of aggregation, was avoided. The polyolithium compounds prepared were employed as polyfunctional initiators for the anionic polymerization of hexamethylcyclotrisiloxane, ethylene oxide,

and styrene. In all cases the polymerization afforded star polymers with a monomodal, narrow molecular weight distribution.

2.2.5.2

Dendronized Polymers

In recent years there has been a surge of interest in “dendronized polymers,” i.e., linear chain polymers with sterically demanding, “wedge-shaped” dendron side chains [137, 138]. This leads to strong stiffening and stretching of the chains, controlled by the shape of the dendritic substituents. The first example of a “dendronized” Si-based polymer was reported by Kim et al. [139]. Kim and co-workers treated poly(diphenylsilylenepropylene) $(\text{Ph}_2\text{SiCH}_2\text{CH}_2\text{CH}_2)_n$ with triflic acid, leading to the corresponding silyltriflate derivative of the polymer after cleavage of the Ph-Si bonds. The reaction with allylmagnesium bromide gave $(\text{allyl}_2\text{SiCH}_2\text{CH}_2\text{CH}_2)_n$, which was used as core molecule for the synthesis of dendritic carbosilane wedges attached to a carbosilane polymer backbone. According to the authors dendrimeric wedges up to the third generation are accessible.

Dendronized polymers with polysiloxane backbone and carbosilane dendritic wedges (G1 and G2, branching multiplicity 3) have been mentioned by Skoulios and co-workers recently. Small angle neutron scattering was employed to characterize these macromolecules. A pronounced increase of the persistence length as well as the Mark-Houwink parameter α from 0.53 (G0) to 0.94 (G2) indicated strong stretching of the chains to a rodlike conformation [140]. However, according to the authors preparation of G3-dendronized polymers failed and formation of insoluble products was observed, which is most probably due to the extremely high functional group density in the dendrons with a branching multiplicity of 3.

2.2.5.3

Applications

Due to their high functionality, dendrimers are considered to be interesting precursors for the preparation of nano-structured polymer networks, which are of interest in various fields. Having said this, one should remark critically that only very special properties will justify the use of such tediously prepared, discrete molecules in a crosslinking reaction, particularly if higher generations are considered. For instance, one may envisage peculiar template effects permitting an extremely precise control of the nanoporosity of novel hybrid materials.

In the first approach developed in this area by Michalczyk and Sharp, inorganic/organic hybrid networks were obtained via sol-gel chemistry, using dendritic alkoxyxilanes as precursors [141, 142]. Coupling trialkoxysilyl groups to small carbosilane dendrimers afforded the desired precursors. Incorporation of organic branching points into the glassy network markedly reduces brittleness and enhances toughness, which is explained by the high flexibility of the carbosilane precursor. Furthermore, gelation rates of star gel precursors were found to be considerably higher than those of conventional tetraalkoxyxilanes. A comprehen-

sive review concerning the perspectives of this approach for specialty glasses was published recently [143].

Carbosilane dendrimers have also been used as precursors for xerogels. Corriu and co-workers prepared carbosilane dendrimers up to the second generation by standard procedures [144], using triallylphenylsilane or triallyloctadecylsilane to introduce bulky units. Reactive functionalization for the gelation process was achieved by transformation of the trichlorosilyl end groups into trimethoxysilyl groups by methanolysis. Polycondensation of these molecules in a sol-gel procedure yielded the targeted xerogels. Porosity measurements revealed that the symmetrical dendrimers gave porous material while the unsymmetrical dendrimers formed porous and nonporous material depending on structure and gelation conditions. However, removal of the organic fraction by thermal oxidation was found to be critical and the porosity of the resulting silica network could not be controlled by varying the size of the precursors.

Recently Kriesel and Tilley also used carbosilane dendrimers as building blocks for xerogels [145]. Dendrimers with end groups suitable for the sol-gel process were obtained by hydrosilylation of the triallylsilyl terminated dendrimers (G2 and G3) with triethoxysilane. Hydrolysis of these compounds was carried out under acidic conditions. Solvent processing afforded xerogels, which were characterized using IR spectroscopy and nitrogen adsorption porosimetry, showing that there was an increase in the total surface area and pore volume with generation number. This unexpected result was tentatively explained by the authors with the compressibility of the dendritic precursors and the assumption that G2 might be more deformable than G3 because of the less congested surface.

The use of allyl-substituted dendrimers of the first generation in hardenable substances for dental use was patented by Zech and Lechner [146]. Carbosilane dendrimers containing no reactive groups have been patented by Mager et al. for the use as calibration materials in analytical processes and as fillers in plastics [147]. Oligoethyleneoxide-terminated carbosilane dendrimers have been used in a study comparing the hematotoxicity and in vitro cytotoxicity of various dendrimers [148]. The dendrimers used in this study were obtained by radical addition of mercapto-substituted derivatives of hydroxy terminated oligoethylene oxide. These dendrimers showed no toxicity towards various cell lines when incubated. However, the lowest generation was cytotoxic towards B16F10 cell lines at higher concentrations. With increasing branching, the toxicity diminished.

3

Siloxane and Carbosiloxane Dendrimers

3.1

Siloxane Dendrimers

Silicones (IUPAC: polysiloxanes) are by far the most important class of Si-based polymers, finding use as oils, elastomers, and silicone resins. Considering the widespread use of this class of polymers in specialty applications, e.g., in

medicine and highly water repellent coatings, the literature on dendritic siloxane structures is surprisingly scarce. In a recent review, the state of the art of branched polysiloxane architectures has been summarized by Bischoff and Cray [149]. Only very few dendrimers exclusively based on siloxane groups are known at present. The first work describing the synthesis of dendritic silsesquioxane molecules was reported by Muzaferov et al. in 1989 [150]. Muzaferov et al. obtained the dendrimers up to the third generation by repeated treatment of trichloromethylsilane or the intermediate product with sodium diethoxymethylsilanolate and subsequently with thionyl chloride. The ideal structure of the molecules prepared contains 48 ethoxy or chloride functionalities in the case of the third generation. However, a detailed characterization of the structural perfection was not given.

In 1990 Uchida and co-workers introduced silicone dendrimers with terminal silicon hydrides, which could be used for further modification [151–153]. Figure 18 shows one of the obtained dendrimers. The dendrimers were constructed by the coupling of $(^{\text{H}}\text{OMD}_3)_3\text{T}$ [154] and $(^{\text{H}}\text{MD}_3)_2\text{D}^{\text{Cl}}$. Repeated conversion of the hydrides into hydroxy groups followed by further treatment with $(^{\text{H}}\text{MD}_3)_2\text{D}^{\text{Cl}}$ led to higher generations. The dendrimers were characterized by NMR spectroscopy, SEC, as well as mass spectrometry. The presence of functional groups on the periphery renders these dendrimers suitable for further modification. Shortly after Uchida et al., Kakimoto and his co-workers presented a polysiloxane dendrimer bearing functionalizable groups at the periphery [155]. As core tris[(dimethylphenylsiloxy)dimethylsiloxy] methylsilane was used, as building block [bis(dimethylphenylsiloxy)methylsiloxy]dimethylsilanol. Treatment of the core molecule with bromine followed by diethylamine afforded the (*N,N*-diethylamino)silyl substituted siloxane, which was reacted with the building block to obtain G1. Repeating twice the series of bromination, amination, and reaction with the building block resulted in the synthesis of G2 and G3. After purification by preparative SEC the polysiloxane dendrimers were characterized by NMR spectroscopy. Furthermore, intrinsic viscosities were measured. The Mark-Houwink coefficient was found to be 0.21, indicating a spherical structure of the obtained dendrimers.

Cholesterol groups have been attached to siloxane dendrimers in the work of Shibaev and co-workers [156]. In this approach towards dendritic liquid crystalline polymers the authors first prepared a G1 dendrimer containing six Si-Cl groups according to the above-mentioned work of the same group [150]. The cholesterol containing mesogenic groups, whose synthesis is described below, were grafted to the chlorosiloxane dendrimer by heterofunctional condensation. Acetylation of cholesterol with the acyl chloride of 10-undecenoic acid followed by hydrosilylation of the terminal double bond with chlorodimethylsilane and hydrolysis in the presence of ammonia led to the mesogenic groups mentioned above. Due to this route the cholesterol groups are separated from the siloxane scaffold by a spacer consisting of ten methylene groups, which enhances the flexibility of the system. Polarizing optical microscopy revealed birefringence and formation of a fan texture typical for smectic liquid crystals.

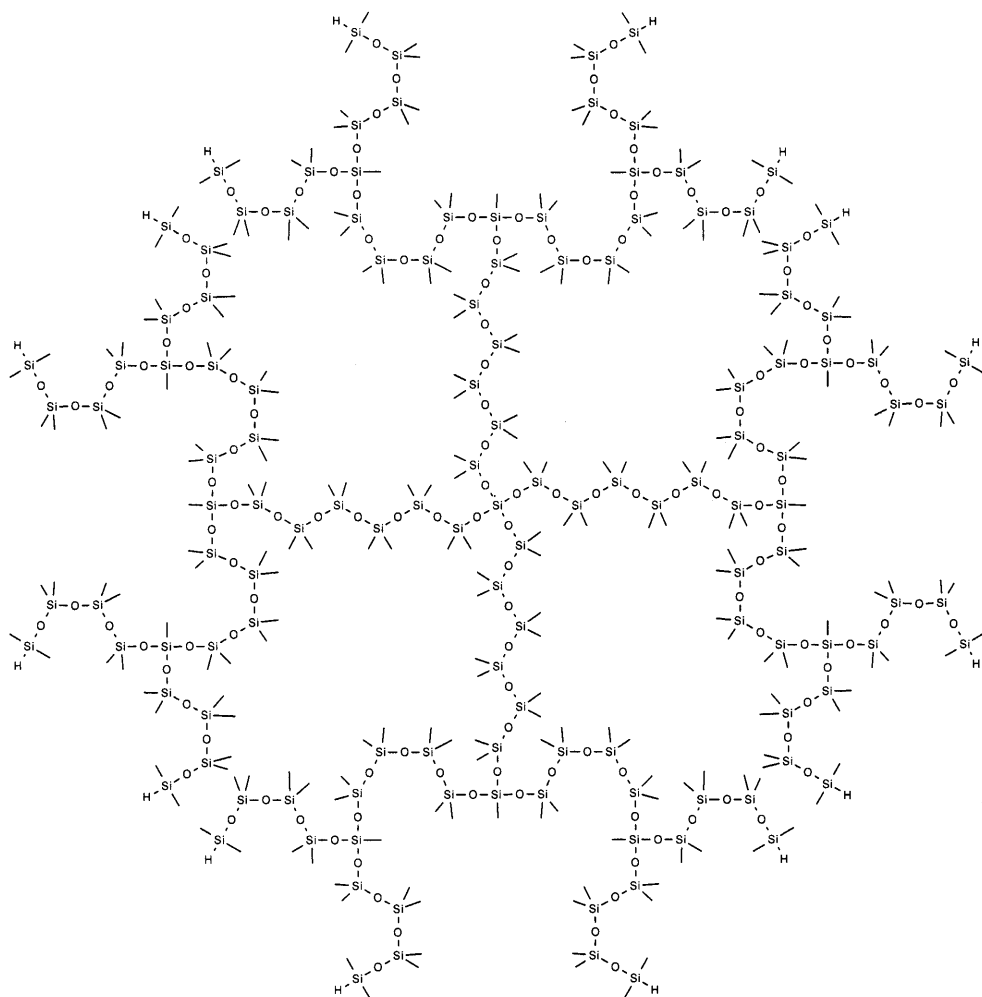


Fig. 18. G2 polysiloxane dendrimer (Masamune et al.)

3.2

Carbosiloxane Dendrimers

In general, carbosiloxane dendrimers are prepared by hydrosilylation of a terminal double bond with a chlorosilane to form an electrophilic silicon species, which is then reacted with a silanol. Thus, carbosiloxane dendrimers contain Si-O-Si groups as well as Si-(CH₂)_n-Si units. An interesting structure has been reported by Kakimoto et al. [157]. Applying the convergent strategy, Kakimoto and co-workers started with the hydrosilylation of allyl cyanide with chlorodimethylsilane. Subsequent amination with diethylamine followed by reaction

with the building block, allylbis[4-(hydroxydimethylsilyl)phenyl]methylsilane, afforded the first generation dendron. By repeating the procedure of hydrosilylation of the allyl group with chlorodimethylsilane, amination, and reaction with the building block, the dendrons G2, G3, and G4 possessing 4, 8, and 16 cyano groups, respectively, were obtained. By coupling the G3 dendrons to tris [4-(hydroxydimethylsilyl)phenyl]methylsilane, a dendrimer with 24 cyano end groups could be prepared. The molecules were characterized by NMR spectroscopy and SEC. The glass transition temperatures were around -50°C , reflecting the high flexibility of these compounds. It has been found that the glass transition temperatures increase with increasing generation number, which is in agreement with the theoretical work of Stutz [158].

Based on their previous work [24, 159], Muzafarov and co-workers introduced a scheme for the synthesis of large organosilicon dendrimers in 1997 [160]. This strategy, called “universal scheme” by the authors, combines the divergent and the convergent synthetic approach. First the authors prepared a carbosilane dendrimer of the first generation possessing eight allyl groups in the common divergent approach. Via a convergent approach Muzafarov et al. synthesized a G2 carbosiloxane monodendron possessing one Si-H group at the focal point. After coupling of core and monodendrons, the resulting carbosiloxane dendrimer (cf. Fig. 19) contains 93 silicon atoms and has a molecular weight of 7513 g mol^{-1} .

MALDI-TOF mass spectra, showing good agreement with the calculated molecular weight, have been published in a work of Sheiko et al. [161] concerning the solid-like states of the obtained dendrimer. Sheiko et al. studied the aggregation and film formation behavior of these molecules (Fig. 20) by SFM on samples which were prepared by casting dilute solutions on flat substrates, i.e., mica, pyrolytic graphite, and glass plates. The slow aggregation process of the dendrimers starts from single molecules, which coagulate to clusters and the latter to fluid droplets, eventually followed by the formation of a complete layer on the solid substrate. From dilute solutions cast on glass plates the authors were able to obtain images of single molecules or couples of them. The size of the molecules was found to be around 2.5 nm, which is consistent with the size estimated from the structure. Although being liquid at room temperature, the dendrimers exhibited rather low compliance when probed by the oscillating tip of the microscope and retained their mechanical integrity. In order to obtain corresponding macroscopic information, the dynamic shear compliance was measured. The resulting master curve showed a low plateau for the storage compliance in the range of the tapping frequency, which explains why the liquid dendrimer droplets could be observed by tapping force microscopy. In another study of Sheiko and co-workers the spreading of the carbosiloxane dendrimer discussed above on the air/water interface was dealt with [85, 86]. In contrast to the carbosilane dendrimer also studied (described in the carbosilane section of this review), the carbosiloxane dendrimer, obtained using the “universal scheme,” did not spread to form a monolayer, but retracted into a thicker film which did not affect the surface pressure until a molecular area considerably lower than the hard-disk area of a hypothetical sphere with the molecular mass and density of the investigated dendrimer was reached. This behavior is attributed to lower surface tension of the carbosiloxane dendrimer possessing

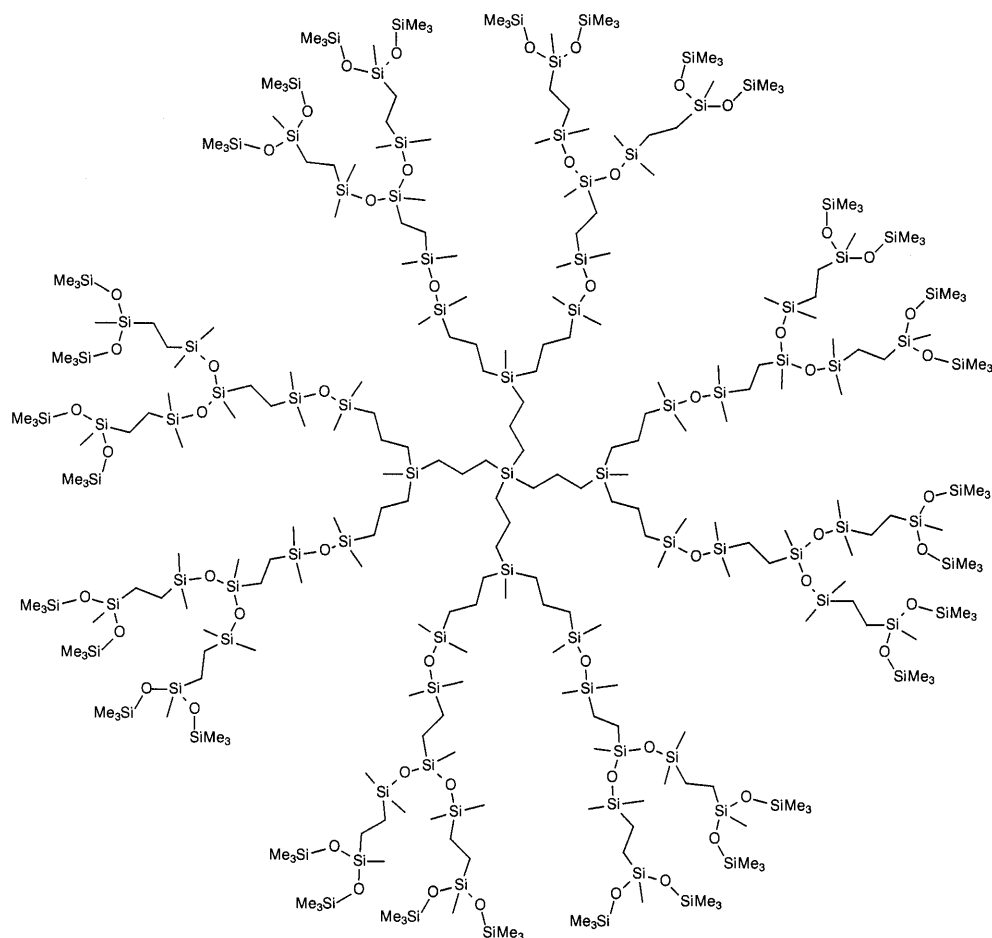


Fig. 19. G2 carbosiloxane dendrimer containing 93 silicon atoms (Muzafarov et al.)

trimethylsilyl end groups compared to the carbosilane dendrimer with hydroxyl end groups.

Fluorescently labeled carbosiloxane dendrimers have been reported by Muzafarov et al. [162]. Using similar reactions as in their previous work introducing the “universal scheme” [160] but starting from 1-(trialkylsilyl)-3-(dimethylpyrenylsilyl)propane as core, the authors obtained a carbosiloxane dendrimer carrying a pyrenyl group attached to the central silicon atom. An interesting result was obtained in a study of the concentration dependence of the spectra. Analysis evidenced excimer formation in concentrated solutions of both compounds indicating mutual accessibility of the pyrenyl groups in the core molecule and in the dendrimer. This result is especially remarkable, since no excimers were found in a solution of a pyrenyl group containing carbosilane

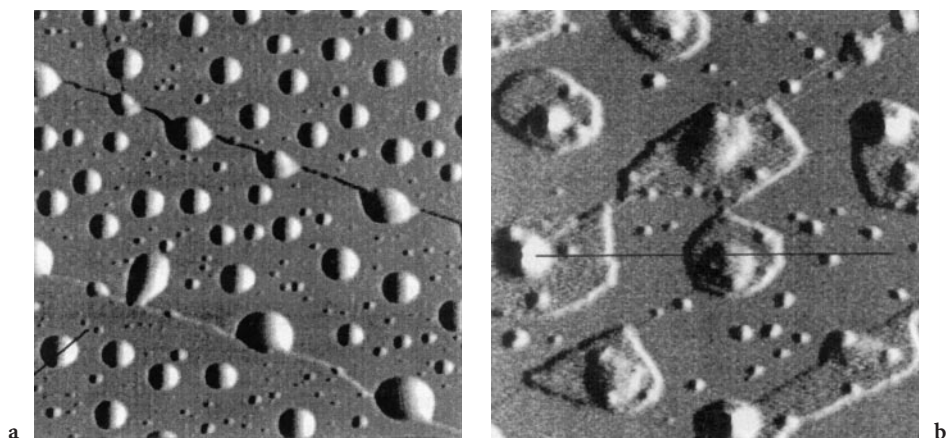


Fig. 20a, b. Ordering of G2 carbosiloxane dendrimers on mica surface: **a** directly after deposition on the mica-substrate (fluid nanodroplets); **b** after 1 month under ambient conditions; an ordered crystal-like state of the droplets is observed (Sheiko et al.)

dendrimer [121]. This behavior is attributed by the authors to a higher mobility of the trimethylsiloxy end groups of the carbosiloxane dendrimer producing a lower shielding effect in the course of excimer formation compared to the mobility of the allyl end groups of the carbosilane dendrimer. Excimer formation of the carbosiloxane dendrimer reviewed above and of a similar, somewhat larger, dendrimer has been examined in more detail in [123]. The fluorescence anisotropy decay of a pyrenyl group attached to the dendrimers has also been measured. It was found that the decay for the pyrenyl group attached to a small dendrimer deviates from that for a large dendrimer only at early times but both differ entirely from pure pyrene.

Transport properties of siloxane dendrimers at ambient and low temperatures have been studied by Bakeev et al. [163]. Bakeev and co-workers used carbosiloxane and carbosilane dendrimers with triethylsiloxy end groups, which were synthesized by Muzafarov et al. [159]. The gas permeability of supported liquid membranes filled with the dendrimers as well as with a linear oligodimethylsiloxane has been measured. It was found that the permeability of the dendritic fillers was five to ten times lower than that of the linear siloxane.

3.3

Alkoxy silane Dendrimers

Although alkoxy silane dendrimers contain no Si-O-Si groups, these materials are reviewed in this section since they are based on T-siloxane units [154] as branch points. Kim and co-workers reported alkoxy silane dendrimers with either 2,4,6,8-tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane or 1,2-bis(triallyloxysilyl)ethane as core and branching multiplicities varying from 2 to 3 [164, 165]. The molecules were built up using the reaction sequence of alternating hydrosilylations with chlorosilanes and alcoholysis with allyl-alcohol. Hydro-

silylations were carried out with dichloromethylsilane or trichlorosilane, depending on the desired branching multiplicity. The alcoholysis was carried out in a mixture of TMEDA and toluene. Starting from cyclotetrasiloxane and using trichlorosilane as hydrosilylation reagent, (branching multiplicity 3), dendrimers up to G2 were accessible only, whereas in the case of dichloromethylsilane (branching multiplicity 2), dendrimers up to G5 could be obtained. Dendrimers with 1,2-bis(triallyloxysilyl)ethane as core and a branching multiplicity of 2 were reported up to the third generation. A dendrimer with a branching multiplicity of 3 could not be obtained using this core, most probably because of surface congestion.

Only recently Brüning and Lang reported the synthesis of similar allyloxy-silane dendrimers with different branching patterns, prepared under slightly different reaction conditions [166]. The use of tetraallyloxysilane as core, dichloromethylsilane as hydrosilylation reagent, and allyl alcohol for the alcoholysis afforded dendrimers of the first and second generation. Elemental analysis and NMR spectroscopy were used for structure determination. To show the suitability of these dendrimers for further functionalization with organometallic building blocks via hydrosilylation reactions, the conversion of the obtained second generation with the metallocene ($\eta^5\text{-C}_5\text{H}_4\text{SiMe}_2\text{H}$)($\eta^5\text{-C}_5\text{H}_5$)TiCl₂ is mentioned. However, no experimental data or characterization have been given. Lang and co-workers used this approach to obtain alkoxysilane dendrimers with propargyloxy end groups [77]. These end groups were reacted with Co₂(CO)₈ to give the acetylenedicobalt hexacarbonyl terminated dendrimer. In addition to IR and NMR spectroscopy, SEC was used to characterize the compounds prepared.

4

Silane Dendrimers

Polysilanes are unusual polymers due to their photo- and semiconductivity, thermochromism as well as nonlinear optical properties caused by the catena Si-structure [167]. However, potential applications are limited by the relatively low stability of the Si-Si bond (dissociation energy 207 kJ mol⁻¹). Dendrimers based on oligosilane segments are extremely compact molecules, because each Si atom has to be completely saturated by methyl groups, since Si-H groups are highly reactive. The consideration that a dendritic structure might increase the inertness of such molecules by restricting or prohibiting the access of reagents to the inner bonds led to the synthesis of the first polysilane dendrimer by Lambert et al. in 1995 [168], who reported a G1 polysilane dendrimer. The synthesis is based on the commercially available tris(trimethylsilyl)silane, which is converted into methyltris(trimethylsilyl)silane via successive reaction with CHCl₃ and methyllithium. The reaction of methyltris(trimethylsilyl)silane with chlorotrimethylsilane and aluminum chloride gave methyl[tris(chlorodimethylsilyl)]silane. The conversion of this trichlorinated silane with tris(trimethylsilyl)silyllithium led to 2,2,6,6-tetrakis(trimethylsilyl)-[2',2'-bis(trimethylsilyl)-1',1',3',3',3'-pentamethyltrisilyl]undecamethylheptasilane, the desired polysilane dendrimer of the first generation (cf. Fig. 21).

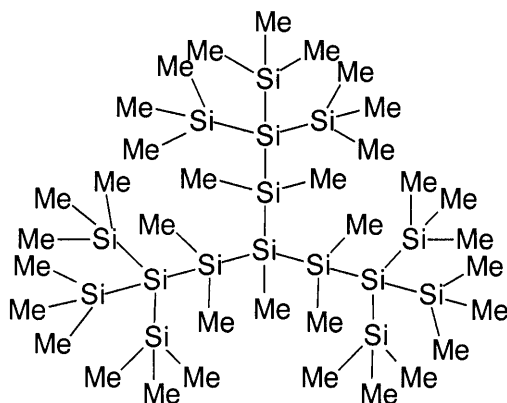


Fig. 21. Polysilane dendrimer of the first generation (Lambert et al.)

The structure of the obtained dendrimer was characterized by mass spectrometry, ^{29}Si NMR spectroscopy and further supported by X-ray diffraction. UV measurements revealed an absorption maximum of 272 nm, which lies in the range of linear silanes with similar chain length due to the longest polysilane chain of the dendrimer. However, the extinction coefficient was found to be one order of magnitude higher than that of corresponding linear silanes. The explanation given by Lambert and co-workers for this enormous increase is the high redundancy of the branched structure: in contrast to linear polysilanes, the longest polysilane chain can be found several times in the dendritic structure. The same type of dendrimer also has been obtained by Suzuki et al. [169] and Sekiguchi et al. [170]. Starting from trichlorosilane, Suzuki and co-workers obtained methyl[tris(dimethylsilyl)]silane in a Wurtz-type reaction with chlorodimethylsilane and lithium. This silane was chlorinated with CCl_4 to afford methyl[tris(chlorodimethylsilyl)]silane, which was converted into the targeted dendrimer by reaction with tris(trimethylsilyl)silyllithium. The UV spectrum was found to be almost identical to that of the linear heptasilane, which was explained with the similar length of the longest chain of the dendrimer. However, the fluorescence spectrum was strikingly different from that of linear polysilanes, exhibiting two very weak and broad emission maxima at 320 nm and 400 nm, respectively. The strong emission usually observed for linear polysilanes was not present. This behavior may be due to the high dimensionality of the silicon backbone structure in the dendrimer. Sekiguchi and co-workers employed a different, very elegant route to polysilane dendrimers. Using 2-lithio-1,3-diphenylpentamethyltrisilane as a key intermediate, they obtained dendrimers up to G2. The key intermediate was prepared by reaction of bis(1,3-diphenylpentamethyltrisilanyl)mercury with lithium. In the first step it was reacted with chlorodimethylphenylsilane to yield methyl[tris(dimethylphenylsilyl)]silane. By treatment with trifluoromethanesulfonic acid the phenyl groups were replaced by the better leaving group trifluoromethanesulfonate. The resulting precursor was reacted either with 2-lithioheptamethyltrisilane to give the permethyl-substituted first generation or with the key intermediate to

yield G1 with phenylsilyl groups. By repeating the treatment with trifluoromethanesulfonic acid followed by reaction with 2-lithioheptamethyltrisilane, the permethyl-substituted second generation was obtained. The dendrimers were characterized by NMR spectroscopy, mass spectrometry, as well as UV spectroscopy, showing a considerably larger extinction coefficient for the G2 compared to G1. Crystal structures have been obtained both for G1 of the phenyl-substituted and the permethyl-substituted polysilane dendrimers recently [171].

In 1996 Lambert et al. reported on the synthesis and characterization of a variety of polysilane dendrimers (G1) [172]. Structures varying in core multiplicity, number of spacer atoms between branch points, and branching multiplicity have been obtained. Synthetic strategies were analogous to the previous work [168]. Polysilane dendrimers with a tetrafunctional core and without spacers could not be isolated because of steric constraints. In another case, steric congestion was relieved by fragmentation into a smaller dendrimer or by angle distortion as seen from the crystal structures. X-ray diffraction confirmed the importance of orthogonal arrangements in polysilanes. Despite the absence of all-anti pathways, the dendrimers show UV absorption maxima at long wavelengths. As for linear polysilanes an increase is seen in $\lambda_{\max}$ with increasing length of the longest polysilane chain in the dendrimers. The extinction coefficients were found to range from slightly to significantly higher than in the linear counterparts, presumably as a result of the numerous pathways. Unexpectedly, absorption maxima and intensities are insensitive to the conformations of the dendrimers.

As mentioned above, one dendrimer, 2,6-bis(trimethylsilyl)-4-[2'-(trimethylsilyl)-1',1',2',3',3',3'-hexamethyltrisilyl]tridecamethylheptasilane, failed to crystallize. The structure of this dendrimer was determined by a new NMR technique, the 2D $\text{Si}^{29}\text{-Si}^{29}$ INADEQUATE experiment [173]. This experiment provided the connectivity for each of the three Si-Si bonds in the molecule and therefore allowed, in combination with the 1D ^{29}Si NMR spectra, the determination of the molecular structure. Since this 2D INADEQUATE method does not require crystalline or solid materials, it is a useful addition to X-ray diffraction. Another ^{29}Si NMR study was carried out by Thomas and co-workers [174]. Polysilane dendrimers (G1) with various substitution patterns were prepared and characterized by ^{29}Si NMR spectroscopy.

The polysilane dendrimer with the longest polysilane chain reported so far has been described by Lambert and Wu in 1998 [175]. The dendrimer, tris[2,2,5,5-tetrakis(trimethylsilyl)hexasilyl]methylsilane, with 13 silicons in the longest chain, was obtained by reaction of tris(chlorodimethylsilyl)methylsilane with 1,1,4,4-tetrakis(trimethylsilyl)-2,2,3,3,5,5,5-heptamethylpentasylolithium. The structure was confirmed by NMR, mass spectrometry, UV spectroscopy, and X-ray diffraction. The molecule exhibits two UV maxima comparable to that known for linear polysilanes of similar length. Yet the extinction coefficients of the dendrimer are an order of magnitude higher. This is again attributed to the presence of multiple linear pathways in the structure. The authors state that polysilane dendrimers with their expected more robust properties should be superior to linear systems in the field of conductive and nonlinear optical applications.

based on dendrimers as templates, e. g., to create nanoporous materials. The first polycarbosilazane dendrimers have been reported by Hu and Son in 1998 [177, 178]. Starting from tris(dimethylvinylsilyl)amine as core molecule they obtained carbosilazane dendrimers up to G2 by repeated hydrosilylation with chloro-dimethylsilane and nucleophilic substitution with lithiumbis(dimethylvinylsilyl)amide (cf. Fig. 23).

G3 could not be realized because the reaction of the chlorosilyl-terminated intermediate with the lithium amide failed to be complete. Steric congestion mentioned by the authors does not seem to be a likely reason for this problem due to the fact that the spacers between the branch points are long and only a branching multiplicity of 2 was employed. The dendrimers have been characterized by IR and NMR spectroscopy, elemental analysis, as well as vapor pressure osmometry. Preliminary MALDI-TOF-MS data confirming the perfect structures were mentioned. Although carbosilazane dendrimers are stable to air,

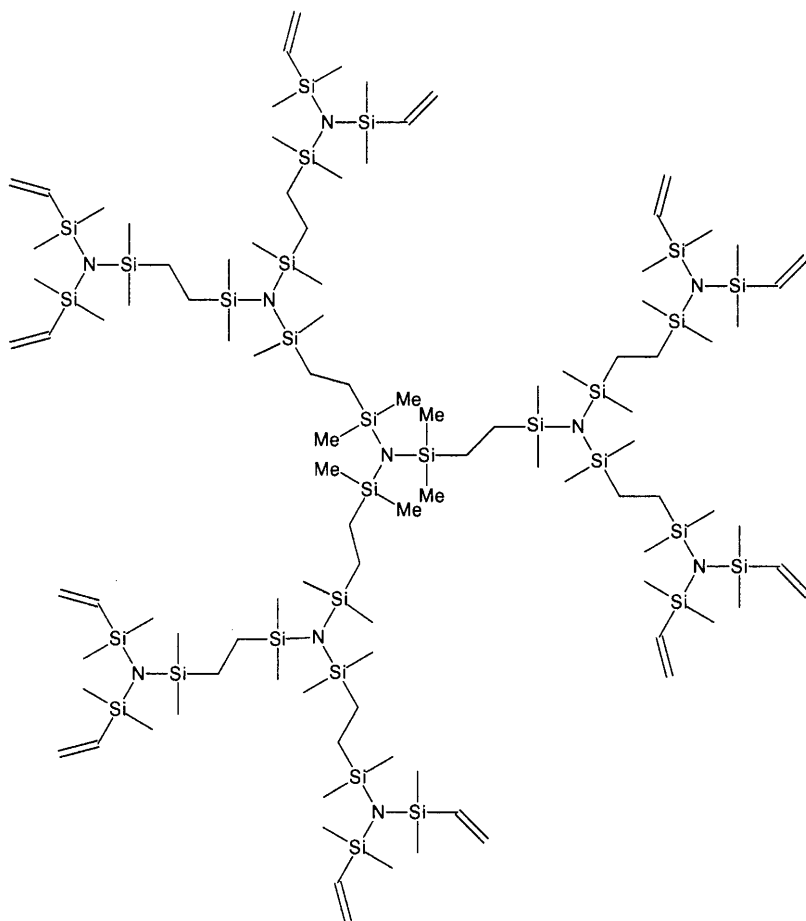


Fig. 23. Polycarbosilazane G1 dendrimer structure (Hu and Son)

water, and anhydrous hydrogen chloride solutions, they degrade rapidly and exothermically in aqueous hydrochloric acid solutions. A notable result is the observed interaction of anhydrous HCl with these dendrimers. IR spectroscopy suggests that H-N interactions exist.

Only recently, similar polycarbosilazane dendrimers have been reported by Veith et al. [179]. Using an analogous, although considerably improved, synthetic protocol [177, 178], dendrimers up to G4 have been obtained. Showing that the limiting generation lies beyond G2, this result is in contrast to the work of Hu and Son. Veith and co-workers characterized the dendritic molecules by elemental analysis, NMR spectroscopy and MALDI-TOF mass spectrometry, in which the protonated molecular ions of all compounds but the dendrimer of the fourth generation were observed. According to the authors the spectra show no impurities and no signals due to imperfectly branched dendrimers, originating from incomplete reactions in the course of the divergent synthesis. Surprisingly, single crystals of the methyl-substituted derivatives of the dendrimers of the first and second generation could be grown, but X-ray diffraction structure determination has failed so far.

5.2

Silatrane Dendrimers

An unusual class of Si-based dendrimers are the silatranes. Silatranes, in this case derivatives of 2,8,9-trioxa-5-aza-1-silabicyclo[3.3.3]undecane, are of interest because of their biological activity. Applications in agricultural chemistry have shown significant potential, e.g., for insecticides and crop yield enhancement. To provide novel biological properties, silatrane dendrons have been developed as an entirely new class of silatrane-containing materials by Kemmitt and Henderson in 1997 [180]. The structure of one of the obtained dendritic silatrane wedges is illustrated in Fig. 24. This structure has been prepared in a convergent approach. Reaction of trimethoxy(glycidoxypentyl)silane with triisopropanolamine led to 1-glycidoxypentyl-3,7,10-trimethylsilatrane. The pendant glycidoxypentyl groups of two such molecules have been reacted with ethanolamine to give a tri-alkanolamine, which can form a silatrane upon reaction with a trimethoxysilane. Thus, sequential addition of trimethoxy(glycidoxypentyl)silane and ethanolamine, respectively, allowed the construction of the desired dendritic silatrane wedges. By use of ammonia or diethanolamine instead of ethanolamine, the branching multiplicity could be controlled conveniently. Characterization was achieved by means of NMR spectroscopy. Electrospray mass spectrometry was used to confirm the structures. Mass spectra supported the purity of the obtained compounds.

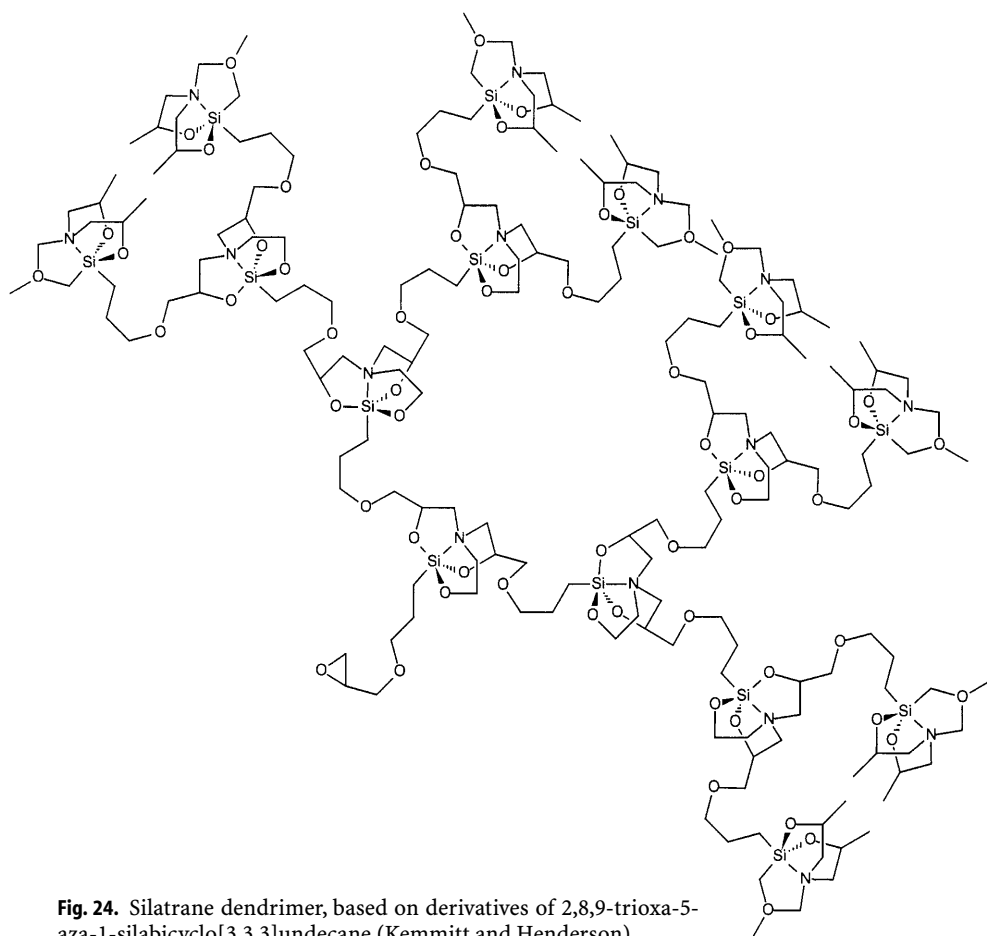


Fig. 24. Silatrane dendrimer, based on derivatives of 2,8,9-trioxa-5-aza-1-silabicyclo[3.3.3]undecane (Kemmitt and Henderson)

6 Silicon-Based Hyperbranched Polymers

Although silicon-based dendrimers are the central topic of this review, this would not be a comprehensive summary without a discussion of recent advances in the field of silicon-based hyperbranched polymers. As already discussed in the introduction, hyperbranched polymers are the randomly branched analogues of dendrimers, obtained in a one step synthesis by polycondensation or polyaddition of AB_m monomers, m being ≥ 2 . Due to the dendrimer hype in recent years, it has sometimes been overlooked that the branch-on-branch structure principle typical for cascade-type macromolecules has in fact been known for almost 50 years. In the early 1950s, Flory published theoretical and experimental evidence for the existence of branched “three-dimensional” macromolecules obtained via polycondensation of AB_m -type monomers

[181, 182]. Flory designated these polymers “AB_m-random polycondensates”. Although such polymers show no entanglements like conventional linear chain polymers, they are not very tough materials and were thus considered to be of little interest as polymeric materials. The field remained dormant until Kim and Webster coined the term “hyperbranched” for this class of materials in 1987 [183]. In recent years, in the tailwind of dendrimers, hyperbranched polymers have also seen a surge of interest [184]. As already shown by Flory almost 50 years ago, the fundamental dilemma of hyperbranched polymers lies in the fact that the high conversions required to achieve reasonable molecular weights in a random polycondensation reaction of AB_m monomers inevitably lead to extremely broad molecular weight distributions, often exceeding $M_w/M_n = 5$, and in many cases polydispersities exceeding 10 are obtained. A second dilemma, which was mentioned (but intentionally neglected) by Flory, lies in the reaction of the one focal A group of the macromolecules with one of the B-endgroups (“intramolecular cyclization”), which severely limits molecular weights achievable [185]. Furthermore, in contrast to the perfectly branched dendrimers, hyperbranched polymers are characterized by a randomly branched structure that is described by the “degree of branching” (DB). Theoretical foundations for the description and control of the DB as well as its relationship with the number of end groups and degree of polymerization have only been laid in recent years [186–188]. Commonly, the DB is determined by NMR-spectroscopy on the basis of low molecular weight model compounds possessing structures analogous to the perfectly branched (i.e., dendritic) and imperfectly branched units and end groups (i.e., terminal units) in the respective hyperbranched polymer.

At present, hyperbranched polymers are often regarded as the “poor cousins” of dendrimers, being considerably less defined; however, in the long run they are likely to present a cheap alternative to dendrimers for applications that necessitate high functionality, but do not require the high structural precision of a dendrimer. In recent years, theoretical concepts for the control of the key parameters molecular weight and polydispersity of hyperbranched polymers have also been developed. For instance, it has been shown that copolymerization of a core molecule B_f can be employed to reduce polydispersities [189]; slow monomer addition techniques in combination with a polyfunctional initiator can lower the polydispersity further [190]. The improved theoretical understanding is likely to permit the preparation of hyperbranched polymers that may eventually rival dendrimers [191].

Although hyperbranched analogs have been prepared for various Si-based dendrimers, the corresponding hyperbranched polymers have not been reported for all of them; for instance hyperbranched polysilazanes have not yet been prepared. In the next section we will briefly summarize the works on hyperbranched polycarbosilanes, polycarbosiloxanes, and polyalkoxysilanes published so far. It should be emphasized that the characterization of hyperbranched polymers is difficult and molecular weights determined by SEC based on linear polystyrene standards may in some cases be overestimated by an order of magnitude. Thus, unless molecular weights given were determined by absolute methods, they can only be taken as an indication of the actual degree of polymerization.

6.1

Hyperbranched Polycarbosilanes

A number of suitable AB_m -monomers for the preparation of hyperbranched polycarbosilanes have been reported in recent years. Some typical monomer structures are shown in Fig. 25.

The first hyperbranched carbosilane polymer was prepared by Interrante and co-workers in 1991 [192, 193]. Their approach to hyperbranched polymers involved the condensation of (chloromethyl)trichlorosilane via a Grignard reaction, in which the Grignard-reagent formed in situ after addition of Mg represents the AB_3 monomer. In order to obtain hydrolytically stable polymers, the intermediate hyperbranched polychlorocarbosilane was reduced with $LiAlH_4$ to obtain a carbosilane polymer possessing the formal structure $(SiCH_4)_n$. The structure of this material is schematically shown in Fig. 26.

The molecular weight was found to be in the range of 600 g mol^{-1} , corresponding to a degree of polymerization DP_n of 13. Taking advantage of the chemical stability of the backbone Si-C bonds and the high reactivity of the Si-X ($X=H, Br$) bond, Interrante and co-workers modified the end groups of the obtained hyperbranched polycarbosilane via bromination followed by alkylation using Li or Mg organometallic compounds [194]. Carrying out the alkylation

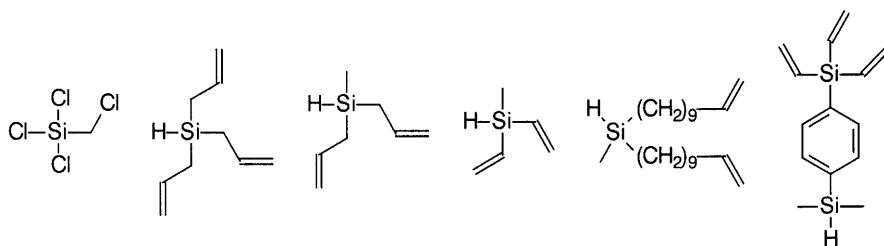


Fig. 25. Typical AB_2 and AB_3 monomers for the preparation of hyperbranched polycarbosilanes

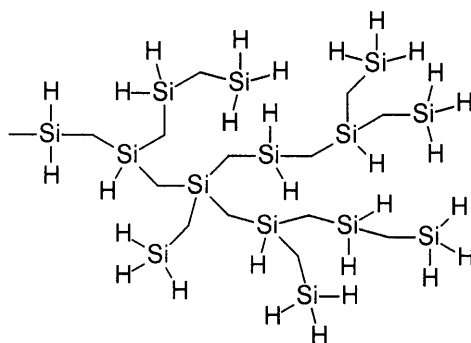


Fig. 26. Hyperbranched polycarbosilane prepared by condensation of (chloromethyl)trichlorosilane via a Grignard reaction. The intermediate hyperbranched polychlorocarbosilane was reduced with $LiAlH_4$ (Whitmarsh and Interrante)

tion with allylmagnesium bromide afforded an allyl-substituted hyperbranched polycarbosilane, which could be functionalized further by applying hydrosilylation with various silanes, e.g., dimethylphenylsilane or chlorodimethylsilane. Characterization by NMR and IR spectroscopy and SEC revealed that a high degree of substitution was achieved in the modification and that in most cases no decomposition respectively cross-linking reactions occurred during functionalization. The native hyperbranched polycarbosilane and the partially allyl-substituted derivative have proven useful as SiC matrix sources for SiC fibers and particulate-reinforced composites [195]. In further work, hyperbranched alkoxy-substituted polycarbosilanes based on the system described above were used to synthesize cross-linked polycarbosilanes/siloxane hybrid polymers by sol-gel processing [196]. The silicon oxycarbide ceramics formed by the pyrolysis of the obtained gels in high yields ($\sim 85\%$) have been found to exhibit relatively high surface areas and a microporous structure, which renders them interesting as catalyst supports or ceramic membranes for gas separation.

In 1998 Yao and Son reported on hyperbranched carbosilane oligomers also prepared by a "Grignard polymerization" [197]. Using (chloropropenyl)dichloromethylsilane as monomer they obtained a polymer possessing C-C double bonds. The product was characterized by NMR spectroscopy. An average DP_n of 8 was obtained [198]. Also based on a Grignard-coupling reaction, the same authors recently reported the preparation of hyperbranched poly(2,5-silylthiophenes) using the Grignard reagent derived from 2-bromo-5-(trimethoxysilyl)thiophene as AB_3 monomer. The polymers contain alternating silylene and thiophene groups along the branches, and are interesting in view of their σ - π -conjugation properties [199].

However, most hyperbranched polycarbosilanes prepared to date have been obtained by hydrosilylation of monomers containing C-C double bonds as well as Si-H groups. In 1993 Muzafarov et al. [24] reported on the synthesis of poly(methylvinylsilane). However, polymerization of the gaseous monomer proved to be difficult. For that reason the authors also considered the AB_m monomers diallylsilane, divinylsilane, and triallylsilane. An unexpected result was obtained upon addition of monomer to the hyperbranched polymer, which did not result in a significant effect on the molecular weight of the polymer. Since accessibility of all functional groups of the hyperbranched polymer could be proven by quantitative conversion with dichloromethylsilane, using analogous reaction conditions as for the polymerization, steric hindrance could be ruled out as the cause of this behavior. The authors explain the limited growth by kinetic factors; however, as shown below and in agreement with more recent studies, it is most likely due to cyclization. However, no detailed experimental data were presented in this work.

A detailed investigation of the degree of branching of hyperbranched polycarbosilanes obtained from the Pt-catalyzed polymerization of triallylsilane, based on ^{29}Si -NMR spectroscopy was reported by our group. The study showed that the polymerization of this AB_3 -monomer takes a random course, with all allyl groups possessing the same reactivity, manifested by the degree of branching of 0.42, which was in good agreement with the value of 0.44 expected for random polymerization of AB_3 monomers [186]. Copolymerizing

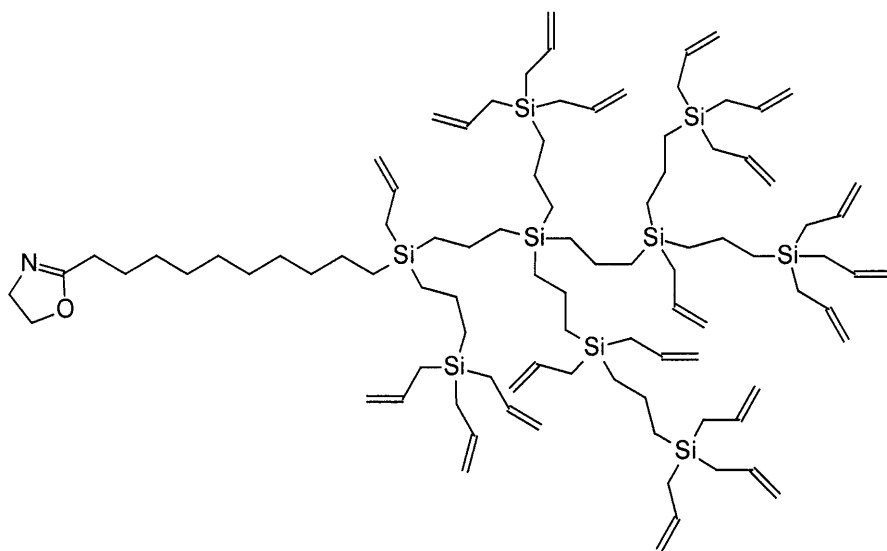


Fig. 27. Hyperbranched poly(triallylsilane) macromonomers possessing a focal oxazoline group (Frey et al.)

2-(10-decen-1-yl)-1,3-oxazoline as a B_1 -core molecule with triallylsilane prior to hydrosilylation, control over the degree of polymerization was achieved and poly(triallylsilane) possessing one oxazoline group was obtained (cf. Fig. 27) [200].

Since the oxazoline group can be polymerized, the obtained carbosilane represents the first example of a “hyperbranched macromonomer.” As expected, SEC measurements on several reactions employing different amounts of 2-(10-decen-1-yl)-1,3-oxazoline revealed a decrease of molecular weight and polydispersity with increasing amounts of the latter. In further work we reported polymerization of the oxazoline groups as well as attachment of the oxazoline-based hyperbranched macromonomers to a trifunctional core affording trimers of the hyperbranched fragments [201, 202]. Unexpectedly, the core-linked trimer was obtained as a transparent, rubber-like solid and strong, directed aggregation in solution was observed by various techniques. The results support formation of columnar structures by interaction of the polar cores of the trimers with their amide-ester bonds capable of forming hydrogen bonds. These polar centers of the stacks are surrounded by an apolar, disordered exterior [203].

In further work Getmanova and co-workers synthesized a hydroxyl end group-containing derivative of poly(diallylmethylsilane) [83]. 1-(3-Dimethylsilyl)propyloxy-2-trimethylsilyloxyethane was coupled with the hyperbranched polymer via hydrosilylation. Hydrolysis of the trimethylsiloxy group afforded the desired hydroxy derivative. IR spectroscopy provided evidence for the formation of a complicated hydrogen-bonded network in this compound. The structure of a hyperbranched polycarbosilane in solution has been investigated by Ozerin et al. [204]. Poly(diallylmethylsilane) was studied by small-angle X-ray scattering and molecular modeling.

Hybrid concepts, combining hyperbranched polymers with strategies from dendrimer chemistry, may also play a role in the future to improve structural control over hyperbranched polymers. Combining a reaction sequence well-known from carbosilane dendrimer synthesis, namely the hydrosilylation of terminal double bonds with trichlorosilane and subsequent displacement of the chloride groups by allylmagnesium bromide, with the synthesis of hyperbranched poly(triallylsilane) [24, 200] allows enhancement of the degree of branching postsynthetically [205]. An almost completely branched structure with a degree of branching close to 1 (“pseudodendrimer”) was generated in this manner. The introduced concept is universal and applicable not only to hyperbranched polycarbosilanes. However, it should be noted that the resulting polymers contain numerous short branches and do not possess the symmetry of a dendrimer despite the high degree of branching.

Investigations concerning the effect of a variation of the monomer structure on the kinetics of the addition reaction, the branching structure, and the occurrence of side reactions have been reported by Möller and co-workers [206]. It was confirmed that, in the case of diallylmethylsilane and methyldivinylsilane, subsequent addition of further monomer did not lead to an increase of the molecular weight. This was explained by a “self-regulation” process due to structural density. However, according to recent work by Fréchet et al. [219] as well as our group [207], this is probably due to cyclization consuming Si-H functionalities, thereby limiting the growth of polymer molecules. In the case of bis(undecenyl)methylsilane, the successive addition of new monomer yielded polymers with gradually increasing molecular weights. According to the authors this might be explained by the formation of sterically less crowded polymers in the case of monomers with long alkenyl groups. However, kinetically disfavored cyclization due to the large monomers appears to be a more likely explanation in this case.

Only recently Son and Yoon used 1-dimethylsilyl-4-trivinylsilylbenzene in an innovative approach as AB₃-monomer to obtain the first aromatic hyperbranched polycarbosilane by hydrosilylation [208]. Despite the presence of rigid aromatic moieties within the branching points, the glass transition temperature of the polymer is still relatively low ($T_g = 12^\circ\text{C}$) and general solubility is high. The hyperbranched poly(carbosilarylene)s based on AB₃-monomers were investigated in detail with respect to the formation of linear, semidendritic, and perfectly branched dendritic units [209]. The degree of branching was determined to be 0.42, close to the expected value of 0.44 for a random AB₃ polycondensation, indicating that all B-groups possessed the same reactivity. The authors suggest that such polymers could be used as components for advanced elastomers.

6.2

Hyperbranched Polycarbosiloxanes

Typical monomer structures employed for the preparation of hyperbranched polycarbosiloxanes are depicted in Fig. 28.

As early as 1991, Mathias and co-workers described the use of hydrosilylation to obtain highly branched carbosiloxane polymers [210, 211]. Hydrosilylation of

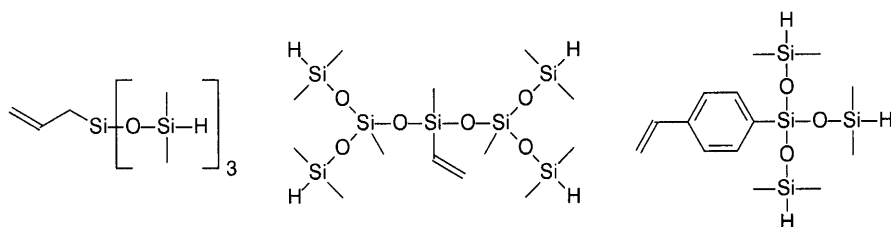


Fig. 28. Typical monomers (AB_3 , AB_4) for the preparation of hyperbranched polycarbosiloxanes

allyltris(dimethylsiloxy)silane afforded a hyperbranched polycarbosiloxane with a molecular weight of $19,000 \text{ g mol}^{-1}$ and an unexpectedly narrow molecular weight distribution. The structure of the obtained polymer is schematically shown in Fig. 29.

In order to convert the material into a less reactive derivative, the terminal Si-H groups containing hyperbranched polycarbosiloxane has been hydrosilylated with allyl phenyl ether. In further work, not only the reaction of the non-substituted hyperbranched polycarbosiloxane with allyl phenyl ether, but also with other allyl and vinyl groups containing molecules, e. g., acrylic acid and allyl terminated oligo(ethylene oxide), have been reported [212]. Reaction with oligo(ethylene oxide) remained incomplete. In subsequent work, the authors showed that intramolecular reaction of the monomer, allyltris(dimethylsiloxy)-

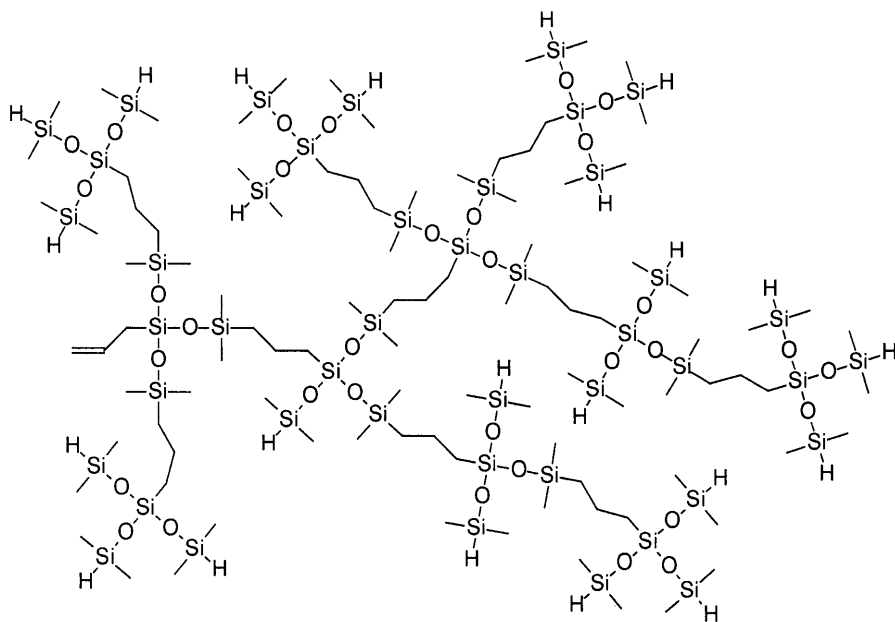


Fig. 29. Hyperbranched carbosiloxane polymer obtained by hydrosilylation of allyltris(dimethylsiloxy)silane (Mathias and Carothers)

silane, leading to a six-membered cycle, was prevalent in the system [213]. The cycle acts as a bifunctional (B_2) core during the polymerization, broadening the molecular weight distribution. To disfavor this undesired cyclization reaction entropically, Carothers and Mathias employed longer alkene-containing monomers such as 6-hex-1-enyltris(dimethylsiloxy)silane. However, the obtained polymers showed broad, multi-modal SEC traces with polystyrene equivalent molecular weights ranging from 12,000 to 21,000 g mol⁻¹.

Rubinsztajn also reported the synthesis of related polycarbosiloxanes [214]. He confirmed the formation of a significant amount of a six-membered cyclic product in the polymerization of allyltris(dimethylsiloxy)silane. To favor the intermolecular reaction leading to hyperbranched polymers, Rubinsztajn used vinyltris(dimethylsiloxy)silane and tris(dimethylvinylsiloxy)silane as monomers. The products of the intramolecular reaction of these monomers are five-membered cycles with high ring strain, which should diminish the yield of cyclic products. Polymerization of the novel monomers afforded the corresponding polymers in yields significantly higher compared to the monomer allyltris(dimethylsiloxy)silane. As expected, SEC analysis showed broad molecular weight distributions.

Vinyltris(dimethylsiloxy)silane has also been used as a monomer [215]. Herzig and Deubzer prepared hyperbranched polycarbosiloxanes by feeding the monomer to a multi(Si-H) functionalized core, e.g., propyltris(dimethylsiloxy)silane. Using this approach, the authors were able to control the viscosity of the products. However, cyclization of the monomers could also not be avoided. Up to 10 mol-% of the monomer cyclized during the polymerization. The authors also showed that the polymers obtained can be used as crosslinkers in addition cure formulations.

An interesting study of the effect of the branching multiplicity on the resulting polymers has been reported by Miravet and Fréchet [216, 217] using monomers with branching multiplicities of 2 (methylvinylbis(dimethylsiloxy)silane), 4 (methylvinylbis[methylbis(dimethylsiloxy)siloxy]silane) and 6 (vinyltris[methylbis(dimethylsiloxy)siloxy]silane), respectively. The polymerization of these monomers afforded hyperbranched polymers with terminal silicon hydride groups. In all cases, SEC traces showed the presence of multiple resolved peaks with elution volumes corresponding to low molecular weight compounds that were assigned to oligomers. Also a large peak with a retention volume essentially identical to that of the monomer was detected. Since spectroscopic analysis of the materials revealed no vinyl groups, this peak is most probably due to the product obtained by intramolecular cyclization of the monomers. Depending on the monomer employed, molecular weights up to 8900 g mol⁻¹ have been obtained after removal of the oligomers, the highest molecular weight being obtained from the monomer with a branching multiplicity of 4. Addition of extra monomer resulted in all cases in a very moderate increase of the molecular weight and afforded materials that, like the initial polymer, contained low molecular weight oligomers. All of the hyperbranched polycarbosiloxanes possess fully accessible terminal Si-H groups that have been modified with allyl or vinyl groups containing reagents such as allyl phenyl ether or allyl methyl triethylene glycol.

In order to overcome the molecular weight limitations and to obtain hyperbranched polycarbosiloxanes with higher molecular weights, Fréchet and co-workers applied the slow monomer addition method developed by our group as well as Müller et al. independently [189, 190] to the system discussed above [218, 219].

In this case, the resulting polymers were obtained in higher yields (72–79%) with higher molecular weights than in the analogous random polycondensation (8700–61,000 g mol⁻¹ after removal of the low molecular weight fractions). According to the authors, both the rate of addition of the monomer and the amount of monomer feed showed a predictable effect on molecular weight and polydispersity of the final polymer, affecting the cyclization probability.

An interesting structure was obtained by Muzafarov and co-workers polymerizing poly(dimethylsiloxane) macromonomers [220]. The macromonomers employed possess degrees of polymerization of 10, 50, and 100, respectively and contain one vinyl and two silicon-hydride end groups. Polymerization by hydrosilylation afforded long-chain hyperbranched polycarbosiloxanes bearing Si-H functionalities with molecular weights ranging from 15,000 g mol⁻¹ to 800,000 g mol⁻¹ depending on the macromonomer employed.

Another intriguing monomer was reported by Rubinsztajn and Stein [221]. They synthesized (4-vinylphenyl)tris(dimethylsiloxy)silane, which can be polymerized to give either hyperbranched polycarbosiloxanes or linear tris(dimethylsiloxy)silyl substituted polystyrenes. The hyperbranched polymer was prepared by hydrosilylation, and its molecular weight was found to be 9800 g mol⁻¹ (SEC). The polymer can easily be functionalized, as demonstrated by the authors by reaction with trimethylvinylsilane. Compared to the corresponding hyperbranched polymers based on the aliphatic monomer tris(dimethylsiloxy)vinylsilane, the new polymer showed a higher decomposition temperature.

6.3

Hyperbranched Polyalkoxysilanes

Hyperbranched poly(bis(undecenylloxy)methylsilane) was obtained by Möller and co-workers in 1995 [222]. The monomer structure used is shown in Fig. 30.

Choosing bis(undecenylloxy)methylsilane as monomer it was the authors' intention to synthesize a degradable polymer with a molecular surface defined by the topological arrangement of the end groups. This structure can be used as a template to create nanometer-size cavities in the matrix of another material. The authors showed that agglomerates of the hyperbranched molecules in a methacrylate resin could be removed from the latter by hydrolysis [223] leading to cavities in the matrix. This result clearly shows the feasibility of this approach.

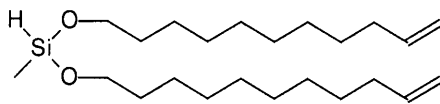


Fig. 30. Hyperbranched poly(bis(undecenylloxy)methylsilane) as an example for a hyperbranched poly(alkoxysilane) (Möller et al.)

An entirely inorganic hyperbranched structure has been reported by Muzafarov et al. in 1996 [224, 225]. Two different monomers, i.e., triethoxysilanol and triethoxysilyltri fluoroacetate, have been prepared starting from tetraethoxysilane. The heterofunctional condensation of each monomer led to hyperbranched ethyl silicates. The ethoxy end groups of these materials were converted into trimethylsilyl end groups rendering the polymer stable for the characterization. The obtained polymers were characterized by means of NMR spectroscopy and SEC. SEC revealed molecular weights up to hundreds of thousands depending on the reaction conditions during synthesis.

7

Summary and Outlook

Less than ten years after the first reports on Si-based dendrimer structures, a large variety of dendrimers based on a relatively small set of construction reactions has been developed, demonstrating the versatility silicon chemistry has to offer for both dendrimers and hyperbranched polymers. The basic synthetic routes towards branched Si-C-, Si-O-, Si-N-, and Si-Si based macromolecules are well-established by now. Despite this synthetic progress our knowledge concerning materials properties or effects that would systematically exploit the peculiar nature of the branched structures is still surprisingly limited.

With respect to the construction of unusual dendrimer topologies, combination of the different building principles known at present can easily be used to construct intriguing molecules in the future. One might envisage hybrid structures consisting of siloxanes and carbosilanes, radially layered dendrimer structures as well as novel macromolecular architectures, such as dendronized Si-based polymers.

With respect to macroscopic properties, the variability of the branching multiplicity of Si-based dendritic polymers represents a major advantage, which is valuable for the elucidation of fundamental structure-property relationships valid for dendrimers in general. This has for instance been demonstrated in the section on dendritic liquid crystalline structures that strongly depend on the branching multiplicity and consequently, the end group density. For instance, the high endgroup density attainable in relatively low generations of carbosilane dendrimers in the case of a branching multiplicity of 3 is an important peculiarity in order to get further insight into dendrimer-specific properties.

Turning to larger scale materials applications and considering the crucially important role silicone-based materials play in medicine, pharmaceutical applications, as well as specialty coatings and in many other areas, globular highly branched Si-based polymers hold great promise for the future. In addition, the combination of dendritic topologies with sol-gel chemistry as well as the exploitation of the peculiar rheological properties of this class of polymers offers attractive potential for the future. However, it is likely that for these types of applications, hyperbranched Si-based polymers will be the materials of choice, rather than the structurally perfect dendrimers. These, however, serve as valuable model compounds for the hyperbranched materials. In the long run, the combi-

nation of a branching monomer with conventional linear structures may reduce cost and still permit one to retain the peculiar properties of dendritic polymers [226]. Progress in this area may eventually lead to novel materials, particularly tough coatings, lubricants, adhesives, as well as fluids with unusual rheological properties. However, all of these applications will have to be based on improved understanding of structure formation and structure-property relationships [227].

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Host-Guest Chemistry of Dendritic Molecules

Maurice W.P.L. Baars · E. W. Meijer

Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology,
PO Box 513, 5600 MB Eindhoven, The Netherlands

E-mail: E.W.Meijer@tue.nl

In this chapter we will discuss the contribution of dendritic macromolecules to the field of supramolecular host-guest chemistry. Since the first publications on dendrimers more than two decades ago, their properties as molecular recognition compounds have been discussed many times. A brief introduction to the common host-guest interactions in the traditional supramolecular field is accompanied by a short overview of specific properties of these highly branched, three-dimensional macromolecules. Emphasis will be placed on the existence of internal voids in the dendritic interior. Subsequently, an overview will be given of the reported host-guest systems based on dendritic molecules. The host-guest systems discussed are arranged by type of interactions: from topological encapsulation to electrostatic, hydrophobic or hydrogen-bonding interactions. This review will emphasize contributions in which the pre-organized three-dimensional dendritic structure and the high local concentrations of sites display cooperative effects and which could be of interest towards future applications.

Keywords: Dendrimers, Host-guest chemistry, Conformation, Cavities, Molecular recognition.

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1

Introduction

Based on the first reports on cascade molecules [1], Maciejewski [2] presented a theoretical discussion of highly branched molecules as ideal molecular containers, showing the challenges in host-guest interactions of dendritic molecules. Experimentally, dendrimers were introduced by Newkome [3] and Tomalia [4, 5] and their initial publications suggested a plethora of applications including those related to controlled release of pharmaceuticals [6]. Now, almost 20 years later, this field of host-guest properties of dendritic molecules has grown into a special area of supramolecular chemistry [7–10]. Supramolecular chemistry is generally described as the chemistry beyond the covalent bond and takes into account specific molecular interactions and the relationship between geometrical structure and binding sites.

With a combination of theoretical and experimental studies, we discuss these new types of dendritic macromolecules and try to increase the understanding of their conformational behavior, an issue of vital importance in supramolecular host-guest chemistry. Of particular interest is the discovery of specific functions and properties that are a direct consequence of the dendritic architecture. A specific property of dendrimers is that their structures can produce localized microenvironments or internal voids (cavities), analogous to those found at the active sites of enzymes. With this in mind, the concept of topological trapping of guests is introduced and refers to the binding of guests in internal and confined cavities of a host system [2]. In addition, dendrimers contain three topologically different regions (core, branches and surface), each of which can exhibit functional properties modulated by the dendrimer as a whole [11]. Moreover, this review will show the main contributions of these structures in the field of host-guest chemistry. The many examples presented in this review indicate that dendrimers can indeed mimic the functions of natural proteins. The dendritic host-guest systems discussed are classified according to type of host-guest interactions, for instance, electrostatic, hydrogen bonding or hydrophobic interactions, and, in addition, these results are subdivided according to site of molecular recognition, either in the core, at the branching points or at the periphery of dendrimers.

With all the examples of dendritic host-guest systems presented, and with an increased understanding of molecular recognition in dendrimers, further optimization of future host-guest systems towards applications is an obvious next step.

2

Supramolecular Host-Guest Chemistry

Host-guest chemistry involves the binding of a substrate molecule (guest) in a receptor molecule (host). The design and construction of hosts that are capable of selectively binding guest molecules requires precise control over geometrical features and interactional complementarity. This can be achieved by using versatile building blocks that allow the introduction of binding sites with directional binding interactions at well-defined positions. Several types of interactions can be involved, such as electrostatic, hydrophobic and hydrogen-bond interactions. A combination of these will enhance the selectivity and strength of binding and will be the determining factor in the development of more efficient host-guest systems. Several highlights in the supramolecular field will be briefly addressed.

A translation of the constraints and rules of the traditional supramolecular field to dendritic host-guest systems will help us in the understanding and characterization of these systems and give us the possibility to highlight systems with clear-cut cooperative and/or dendritic effects.

2.1 Molecular Recognition

2.1.1

Complexation of Cations

The discovery of crown ethers by Pedersen [12, 13] approximately 30 years ago signaled the start of a new era in the chemistry of complexes with neutral ligands [14]. This led to the construction of families of crown compounds [15], coronands (hetero-crowns) [16], cryptands [17], podands [18] and spherands [15] by Cram, Lehn, and others (Fig. 1). These cyclic ligands are capable of chelating metal or ammonium ions in a selective way, based on geometrical features such as chirality. Therefore precise control is warranted over supramolecular systems with interesting properties in, among others, transport technology [8].

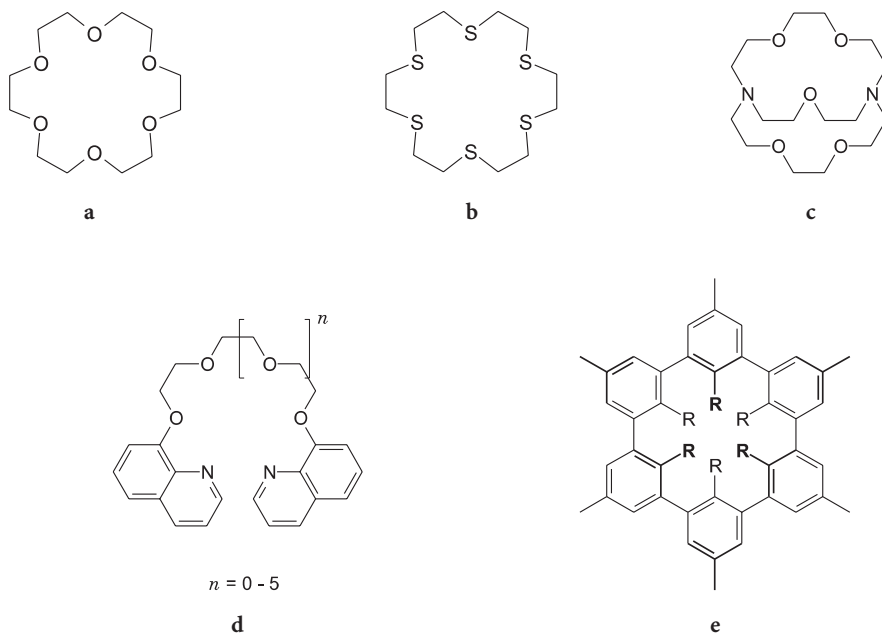


Fig. 1. Classification of neutral organic ligands. Typical examples are depicted: a crown ethers, b coronands, c cryptands, d podands, and e spherands

2.1.2

Organic Acids and Anions

Despite the role of anions in biological systems, e.g. amino acids, peptides and nucleotides, the coordination chemistry of anions has only recently received attention [19–22], in sharp contrast to the more advanced development of cations. The first attempts to develop receptor models for anionic guests

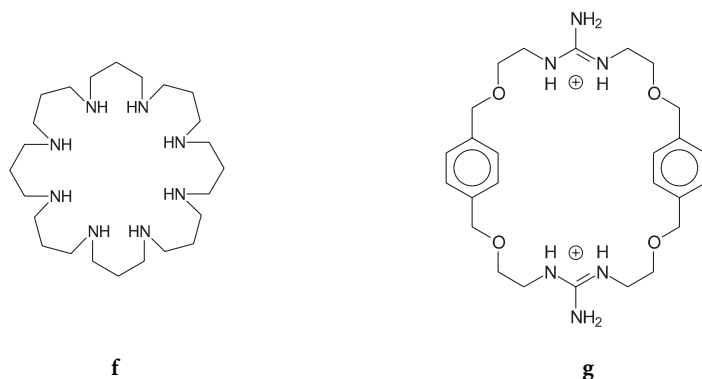


Fig. 2. Ligands with anion-complexing properties: **f** oligoammonium macrocycle [32]aneN₈ and **g** guanidinium-containing macrocycle

containing carboxylate groups concentrated on protonated macrocyclic oligoamines (Fig. 2) [23, 24].

These compounds effectively bind their anionic guests via electrostatic interactions. Binding constants become higher as the number of protonated host nitrogen atoms increases. A major limitation of oligoamine receptors is the use of strongly acidic media to achieve their full protonation, a problem which can be avoided by the use of more basic groups, like guanidines [25]. Examples in which biorelevant species like zwitterionic amino acid residues or the structurally diverse nucleotides can be complexed have also been published [24]. However, due to the complex nature of these species, a simultaneous recognition of several sites is often required for effective molecular recognition.

2.1.3

Hydrophobic Interactions

The tendency of relatively apolar molecules to assemble in aqueous solutions is explained by hydrophobic interactions [26]. These interactions play a vital role in surfactant aggregation, the assembly of lipids in biomembranes, and enzyme-substrate interactions. Although the role of hydrophobic interactions in host-guest chemistry and molecular recognition is still ambiguous, it is generally accepted that complexation of neutral apolar molecules with macrocyclic hosts is governed by hydrophobic interactions [27, 28]. Among the building blocks frequently used are the cyclophanes [29] and cyclodextrins (Fig. 3) [30].

Depending on the size of the cyclophane ring, hydrophobic guests like arenes or steroids can be complexed. Cyclodextrin is capable of complexing hydrophobic guest molecules within the cavity in aqueous media; the principal binding interactions are most likely a summation of van der Waals interactions, hydrophobic interactions and the release of 'high energy water' from the cavity. The contribution from each effect depends on the type of cyclodextrin, solvent, and guest. For instance, β -cyclodextrin can host bulky benzene derivatives, naphthalene, ferrocenyl or adamantyl derivatives [31]. In general, the guest mole-

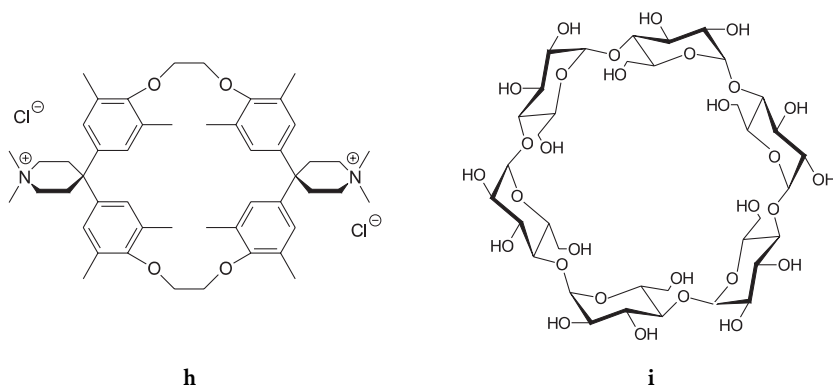


Fig. 3. Receptor molecules using hydrophobic interactions: **h** cyclophane and **i** α -cyclodextrin

cule prefers the apolar cavity of the host, where it is, to some extent, shielded from the solvent.

2.1.4

Hydrogen-Bonding Interactions

The highly selective and directional nature of the hydrogen bond makes it an ideal building block for use in the construction and stabilization of large non-covalently linked molecular and supramolecular architectures [32]. As a consequence hydrogen-bonding interactions can be used to complex guest molecules. The Jorgensen model [33] has shown that cooperativity of the hydrogen bonds, e.g. by using an array of hydrogen bonds, increases the strength, specificity and directionality of the interaction. Illustrative is the synthesis of an artificial

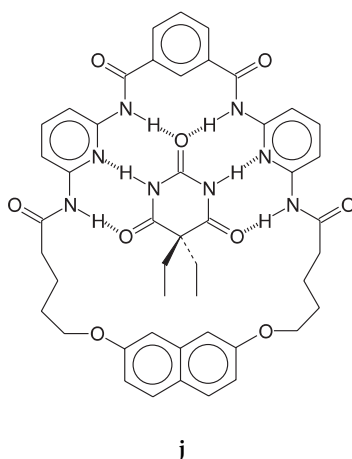


Fig. 4. Hamilton receptor (**j**) using hydrogen-bonding interactions

receptor (Fig. 4), developed by Hamilton et al. [34], in which a combination of complementarity, directionality and geometry generates an efficient host-guest complex.

2.2

Clathrate Inclusion Compounds

In the previous discussion many examples of inclusion were given. A cavity-containing host component incorporates, on a molecular level, one or several guest components, without any covalent bonding. The term clathrate [35] is usually introduced when guest molecules are incorporated into existing extra-molecular cavities, like, for example, in a crystal lattice. Most clathrates have been discovered purely by chance, by recrystallizing a compound for example [36]. This type of reversible physical imprisonment of guests even without directional forces makes clathrates interesting for applications in (chiral) separation processes, organic conductors or to perform reactions in geometrically confined surroundings [8].

2.3

A First Step Towards Dendritic (Host) Molecules

By a precise programming of the molecular recognition process, practical exploitation of the non-covalent interactions described in Sect. 2.1 yielded significant progress in the development of nanoscopic assemblies. In the quest for large, substrate-selective ligands, many efforts have been focused on the synthesis of “octopus” [37–39] and “tentacle” [40] molecules. In 1978, it was stated by Vögtle et al. [1] that, for the construction of such ligands with large molecular cavities, it would be advantageous to devise synthetic pathways with an iterative reaction sequence. Experimentally, the hypothesis was tested by the design of a series of cascade molecules (Fig. 5). Although the synthetic scheme used was still

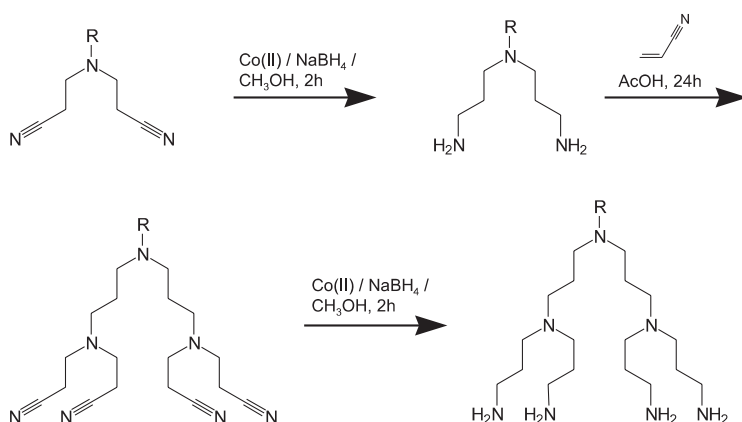


Fig. 5. First example of an iterative reaction sequence, as developed by Vögtle

elaborate and troublesome, the construction of a new type of (oxygen-free) hexaaza-cryptands, capable of host-guest interactions, was realized.

3

Dendrimers: a New Type of Supramolecular Hosts

3.1

Dendritic Macromolecules

Tomalia [4, 5] and Newkome [3] established their names as early pioneers in the field of highly branched macromolecules with the synthesis of poly(amido-amine) dendrimers and arborols, respectively. Newkome and Vögtle [41] have published an excellent monograph covering historical accounts [42], synthetic methodologies and the terminology of the dendrimer field. Ideally, these structures are perfect monodisperse macromolecules with a regular and highly branched three-dimensional structure which are produced in an iterative sequence of reaction steps, each additional iteration leading to a higher generation material. These structures are established as a new class of well-defined macromolecules, with dimensions and molecular weights in between the traditional synthetic molecules and classical polymers. Two methodologies have been developed to construct dendrimers, i.e. either the divergent 'from-core-to-periphery' route [4, 43, 44] or the convergent 'from-periphery-to-core' strategy [45–49]. The latter approach was first targeted by Fréchet. Currently, only the divergent approach is attractive for the production of kilogram quantities and only two classes of dendrimers are commercially available: poly(amidoamine) dendrimers and poly(propylene imine) dendrimers [43, 50]. The divergent methodology has specific characteristics and the purity of the final dendritic product is related to the synthetic approach used.

Since a dendrimer is grown in a stepwise manner from a central core, and numerous reactions have to be performed on a single molecule without the possibility of purification, every reaction has to be highly selective to ensure the integrity of the final product. In the case of the poly(propylene imine) dendrimers, all generations with amine or nitrile end groups have been analyzed by electrospray ionization mass spectrometry (ESI-MS) to quantitatively determine the degree of various side reactions [51]. The synthetic scheme and the possible side reactions are depicted in Fig. 6. The significance of the side reactions has been calculated using an iterative computing process. These simulations have indicated a polydispersity (M_w/M_n) of 1.002 and a dendritic purity, i.e. the percentage of dendritic material that is defect free, of ca. 23% for a fifth generation amine-functionalized poly(propylene imine) dendrimer. This can be related to an average selectivity of 99.4% per reaction step, since 248 reactions are required to obtain a fifth generation with 64 end groups ($0.994^{248} = 0.23$). The reality of statistically defect structures is also recognized in the iterative synthesis of polypeptides or polynucleotides on a solid support, known as the Merrifield synthesis [52]. In contrast, the difficulties associated with many reactions are overcome by the convergent approach and a constant and low number of reaction

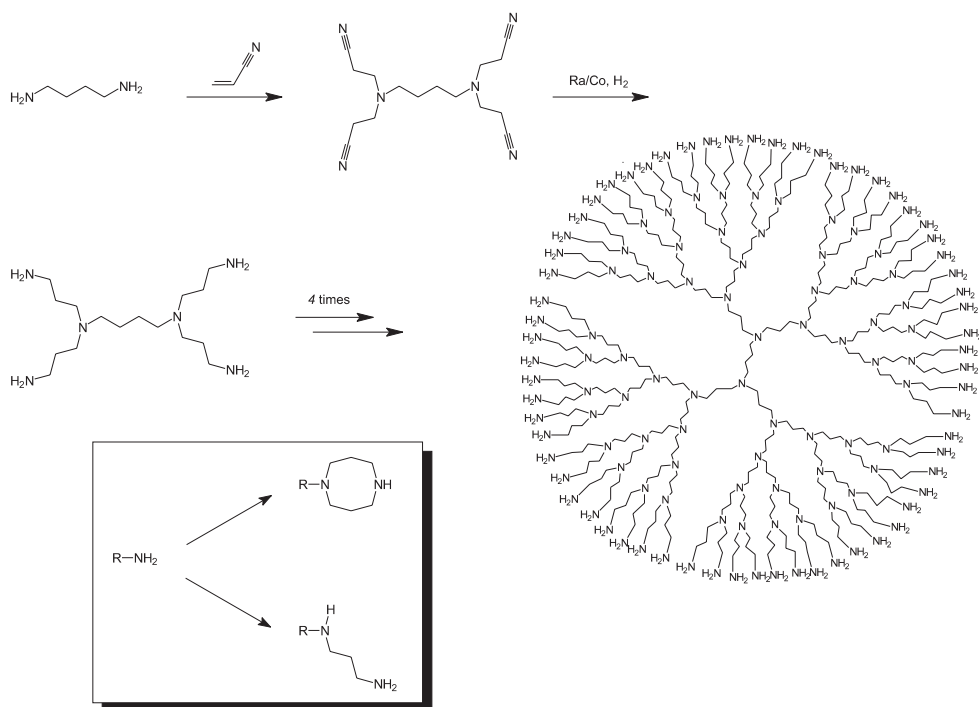


Fig. 6. Synthesis of the poly(propylene imine) dendrimers and unwanted side reactions

sites is warranted in every reaction step throughout the synthesis. As a consequence this ‘organic chemistry approach’, with only a small number of side products and the ability of purification, yields dendrimers which are relatively defect-free [53]. If the iterative multistep reaction sequence is replaced by a one-step procedure, branched macromolecules are obtained with a high degree of branching and a large molecular weight distribution, which are coined hyper-branched polymers [54–56].

The unique branched architecture, as well as the multifunctional number of end groups that become available with these dendritic structures, can be used as a tool to display desired functions, such as well-defined shape, internal voids or a variable surface functionalization. Many of the intriguing properties of dendrimers – from design and synthesis and towards applications – have been reviewed by various experts in the field [6, 57–70]. Moreover, many applications have been claimed in the field of host-guest chemistry and pharmaceuticals, such as their use as molecular carriers, enzyme mimics [71] or potential drug-delivery vehicles [72–75]. Before discussing the most impressive dendritic host-guest systems (Sect. 4), the physical properties of dendrimers have to be understood in detail. What is the shape of dendrimers? Do dendrimers contain cavities? Is there a change in physical properties as a function of generation and the molecular dimensions? How special are the dendritic properties in comparison with linear analogues? In other words: what is the conformational be-

havior of dendrimers? Finally, are we able to understand these properties in a general way, even with the many different sets of dendrimers available today, and is it possible to tailor the properties of dendritic host-guest systems towards nanoscopic devices or selective drug-delivery vehicles?

3.2

Conformational Characteristics

One of the most interesting topological aspects of dendrimers is the exponential increase in end groups as a function of generation, while the sphere that is conformationally available only increases with the cube of generation. The increase in branch density is believed to have striking effects on the conformational shape of dendrimers. The localization of the end groups or the presence of internal voids or cavities is still an issue of current debate. With an overview of the theoretical calculations and experimental studies, an attempt is made to clarify this issue.

3.2.1

Theoretical Calculations

So far, many theoretical studies have discussed the shape of dendrimers, their density distribution as a function of the radius, and their dependence as a function of solvent polarity and ionic strength. The resulting properties can depend strongly on the type of dendrimer that is used in the calculation, i.e. an ideal theoretical dendritic structure or an existing compound. This complicates a general conclusion on some of the intriguing questions.

De Gennes and Hervet [76], however, presented a model with growth up to a certain – predictable – limiting generation and a low density region at the core, and suggested the presence of cavities. The model of Lescanec and Muthukumar, on the other hand, predicts a monotonic decrease in density on going from the center of the dendrimer to its periphery [77]. Mansfield and Klushin have obtained similar results with Monte Carlo simulations [78], except that in the latter case the results correspond to an equilibrium situation. Other studies in this field are from Murat and Grest [79], who show an increase of backfolding with generation and a strong effect of solvent polarity on the mean radius of generation, and from Boris and Rubinstein [80], who also predict that density decreases monotonically from the center using a self-consistent mean field model. So far these studies deal with non-existent molecules.

Studies on specific dendrimers have been reported by Naylor et al. [81], who discussed poly(amidoamine) dendrimers, and Scherrenberg et al. [82], who report on poly(propylene imine) dendrimers. The conformational changes as a function of solvent quality (Fig. 7) were nicely demonstrated and, in the latter case, a relatively homogeneous radial density distribution was observed. Welch and Muthukumar [83] demonstrated the dramatic change in dendrimer conformation relative to the ionic strength of the solvent. Since the examined polyelectrolytes are topological analogues of the poly(propylene imine) dendrimers and also to some extent of the PAMAM dendrimers, the two main (commercially) available dendrimers are covered.

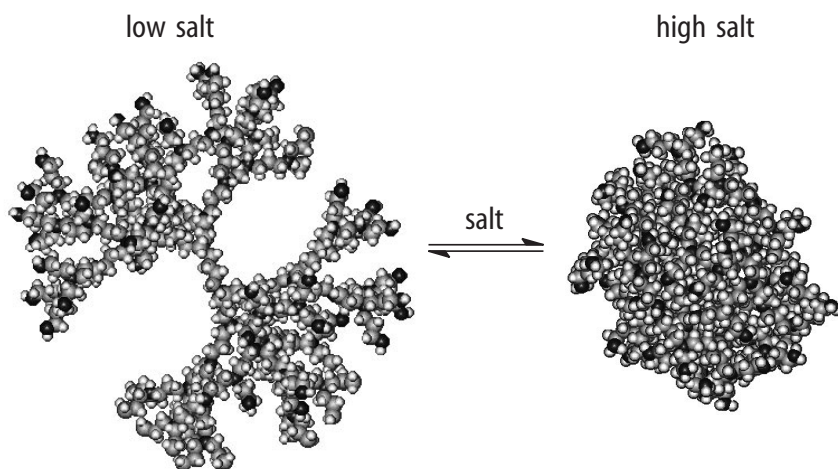


Fig. 7. Dense shell and dense core conformations of the amine-functionalized poly(propylene imine) dendrimers at different ionic strength (picture kindly provided by B. Coussens, DSM Research, The Netherlands)

Goddard et al. [84] and Cavallo and Fraternali [85] discussed the properties of the dendritic box, a fifth generation poly(propylene imine) dendrimer functionalized with bulky amino acid residues. This is one of the few publications in which an existing dendritic system is studied at a molecular level, in contrast to the many simulations on ideal theoretical molecules discussed above. The investigations found a low-density region inside the higher generation dendrimers and an increasing inter-end-group interaction when going from the first to the fifth generation. These data show that the molecular conformation is strongly influenced by the type of end groups and specific non-covalent interactions that can take place between them. None of the theoretical studies presented so far discriminates between dendrimers with or without specific secondary interactions within the structure. Therefore, even though detailed computer modeling studies and theoretical calculations on dendrimers have been performed and a great deal of insight can be obtained from these studies, the results must be interpreted with care.

3.2.2

Experimental Studies

The polyether dendrimers synthesized by Fréchet et al. [45] have been studied using many techniques to understand their conformational properties. Size exclusion measurements performed by Mourey et al. [86], rotational-echo double resonance (REDOR) NMR studies by Wooley et al. [87], and spin lattice relaxation measurements by Gorman et al. [88] reveal that backfolding takes place and the end groups can be found throughout the molecule. The observed trends are in qualitative agreement with the model of Lescanec and Muthukumar [77]. Scherrenberg et al. [82] studied poly(propylene imine) dendrimers using

viscometry and small angle neutron scattering (SANS) measurements and observed a linear relationship between the radius of gyration of the dendrimer and its generation number. These results agree well with the molecular dynamics studies of Murat and Grest [79]. From another SANS study it was concluded that the same type of dendrimers tend to stretch upon protonation [89]. All these data are indicative of the flexibility of poly(propylene imine) dendrimers when no specific interactions between the end groups have to be taken into account.

However, it is evident from many studies [90–95] that upon end-group modification of the dendrimer, phase segregation between the dendritic core and the end groups can take place. Reviewing the cited reports, the chemical structure of the dendrimer in question determines the conformational behavior of the macromolecule. This is in sharp contrast to the flexible nature [96] of most known (unmodified) dendrimers for which a homogeneous density distribution is encountered; thus, the voids inside the dendrimer are filled up to a certain extent by the peripheral end groups. The presence of secondary interactions, such as π - π interactions, electrostatic interactions, hydrophobic effects or hydrogen-bonding interactions, makes it possible to assemble the end groups at the periphery of the dendrimer. Backfolding is thereby precluded, yielding an inhomogeneous density distribution over the dendritic macromolecule and a decrease in flexibility.

3.3

Do Cavities Exist in Dendrimers?

The issue of internal cavities in dendritic molecules is still under debate. Many of the theoretical discussions lack the influence of solvents and suggest the presence of voids. The three-dimensional motif of dendrimers impart to them unique structural features, unlike linear polymers which possess random coil structures with a high degree of conformational freedom. On the other hand, pre-organized supramolecular receptor molecules might contain internal cavities, but they lack the presence of a distinct microenvironment suitable for complexation of multiple molecules. The concept of trapping guest molecule(s), i.e. topological trapping, by a (dendritic) host molecule with a spherical structure was suggested for the first time by Maciejewski in 1982 [2]. Compared to the relatively open structures of lower generation dendrimers, the higher generations tend to adopt an extended conformation with a spherical surface containing pockets of spaces in the interior, which are capable of guest inclusion. In a more collapsed state, due to an increase in backfolding, the size of these voids might be significantly diminished.

The conformational behavior of PAMAM dendrimers has been examined using various techniques [97, 98] based on size-exclusion chromatography (SEC) in combination with intrinsic viscometry measurements. The authors concluded that these dendrimers have a hollow core and a densely packed outer layer, in agreement with the de Gennes model. However, these inhomogeneous distributions are in contrast to findings for most known, unmodified, dendrimers. The hydrogen-bond interactions at the branching segments might account for these findings. Jansen and Meijer [99] reacted a fifth-generation

amine-functionalized poly(propylene imine) dendrimer with a (*t*-Boc)-protected L-phenylalanine residue resulting in a dendrimer with a flexible core/rigid shell structure, coined “dendritic box”, with a molecular weight of almost 23 kD (Fig. 8). The dendritic structure was characterized by a variety of techniques, like IR, UV, ^1H - and ^{13}C -NMR spectroscopy, and all data were in full agreement with the structure assigned. However, a significant line broadening of the resonances in the ^{13}C -NMR spectra for the higher generations prompted measurements of spin-lattice (T_1) and spin-spin (T_2) relaxation times. The observed increase in T_1 relaxation times after the third generation is indicative of a decrease in molecular motion for the higher generations; an almost solid-phase behavior of the shell in solution is proposed. Further evidence for this close packing of the shell is obtained from chiroptical studies [100]. Presumably, intramolecular hydrogen bonding between several L-Phe residues in the shell contributes to this solid-phase character. The dimensions of the amino acid derivative proved critical for the construction of a dense shell structure. According to NMR and modeling studies, the modification with L-Phe residues provided ideal dense shell characteristics in contrast to the bulkier L-Trp, in which incomplete reaction took place, or L-Ala, which is too small to yield a dense shell packing.

Molecular mechanics calculations of the dendritic box were performed to obtain insight into the three-dimensional structure. The interior is (almost) completely shielded by the bulky end groups and a globular architecture is found with an estimated radius of 2.3 ± 0.3 nm, similar to dimensions obtained from dynamic light scattering studies and small-angle X-ray scattering (SAXS) measurements [101]. It is suggested that the dendritic structure possesses a flexible core and a dense shell, that will have internal cavities available for guest molecules.

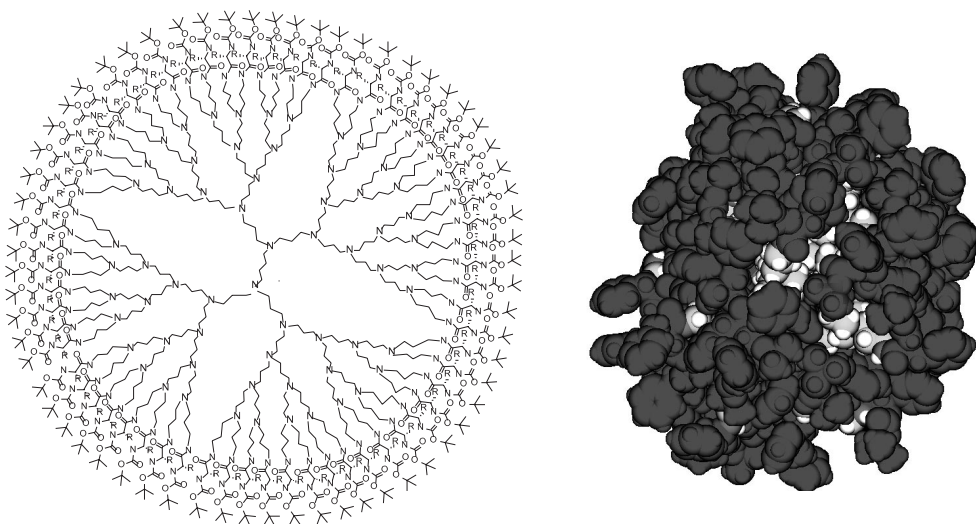


Fig. 8. Chemical and molecular modeling structures of the dendritic box

In conclusion, shallow cavities or voids in the dendritic interior depend strongly on the actual dendritic structure. In particular, secondary interactions between end groups, in combination with a critical end group modification, seem to be very important to create a soft core-dense shell motif. In all cases, dependent on the conditions used, the cavities can be filled up by end groups, solvents or guests.

4

Dendritic Host-Guest Systems

4.1

Solvent Encapsulation

Solvent molecules are the simplest examples of guests imaginable. Seebach et al. [102] observed the formation of very stable clathrates with several chiral dendrimers. Physical encapsulation of carbon tetrachloride, 1,4-dioxane, ethyl acetate or water was observed and removal of solvents proved to be elaborate. Although the term “clathrate” might be questionable (see Sect. 2.4), these observations clearly indicate that dendritic structures can host solvent molecules. It has been commonly observed that with increasing generation it becomes more difficult to remove solvents. The flexible dendritic molecules try to retain their conformation as much as possible by a physical inclusion of solvent molecules. Once solvents have been removed, the conformation of the dendrimers is likely to change to a collapsed state as it usually requires a long time to redissolve dried dendrimer samples.

4.2

Topological Entrapment: The Dendritic Box [103]

4.2.1

Encapsulation of Guest Molecules

The experimental and modeling results of the dendritic box, as shown by Jansen and Meijer [99–101], suggested a solid shell/flexible core structure with internal cavities available for guest molecules. As the shell is constructed in the final step, it is possible to perform this coupling reaction in the presence of guest molecules (Fig. 9). In fact, guest molecules with some affinity for tertiary amines could be encapsulated within the dendritic box. Excess of guest and/or traces of guests adhering to the surface are removed by extensive washing and/or dialysis. Successful encapsulation when using a dendrimer of lower generation proved impossible since the shell is not dense enough to capture the guests and removal by extraction is possible. A large variety of guest molecules have been encapsulated and this opens a plethora of interesting chemical and biochemical applications. We will discuss some of these nanometer-sized guest-host systems here as well as the properties of the guest molecules that are critically influenced by the dendritic box. Three different guests are discussed: 3-carboxy-PROXYL, Rose Bengal and Eriochrome Black.

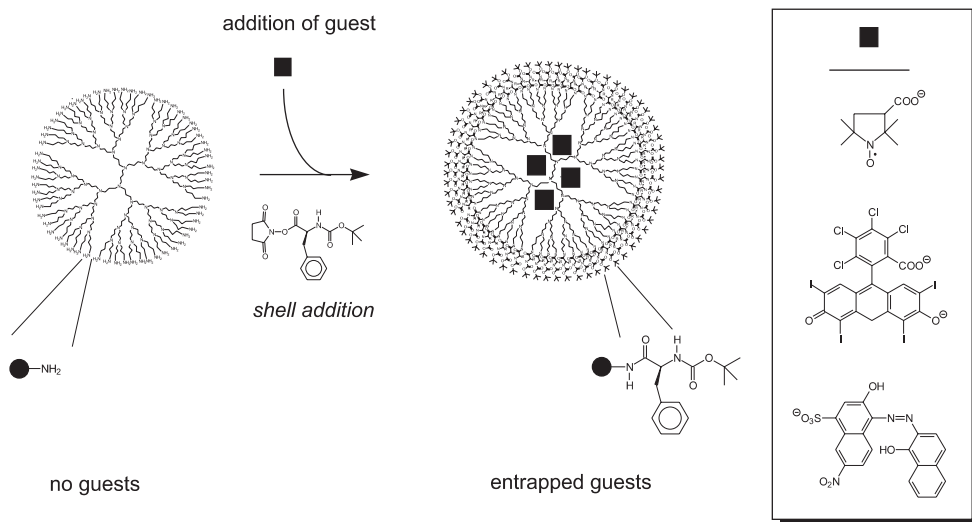


Fig. 9. Topological entrapment of guests in the dendritic box

When using 3-carboxy-PROXYL as the guest, the number of entrapped radicals varied from 0.3 to 6 molecules per dendritic box as determined by electron spin resonance (ESR) spectroscopy [104]. The number of 3-carboxy-PROXYL radicals in the dendritic box does not increase above 6, clearly demonstrating that the maximum attainable number of radicals is restricted by the shape of the cavities in the box. The ESR spectra of the host-guest complexes dissolved in 2-methyltetrahydrofuran are strongly temperature dependent. At 305 K, a rapid rotational diffusion of the radical spin probes is observed; however, the decreasing intensity of the isotropic spectrum and the appearance of an anisotropic ESR spectrum at lower temperature are consistent with a more restricted motion of the spin probe.

UV spectroscopy was used in the case of Rose Bengal, an anionic xanthene dye, to estimate the number of encapsulated guest molecules. The maximum number of guest molecules attainable is limited, in this case to four. Although the absorption spectra of 'free' Rose Bengal and the Rose Bengal complex are identical, there is a large difference in the fluorescence spectra as recorded in CHCl₃. The fluorescence is only present if the dye is encapsulated and effectively quenched in the case of the 'free dye'. The emission of the guest-host system is relatively insensitive to solvent effects, indicative of a host-guest complex with an environment-independent emission profile of the guest. Circular dichroism (CD) spectra of a variety of dyes encapsulated in the dendritic box have been determined. In case of Rose Bengal, two samples have been investigated with, on average, one and four molecules of Rose Bengal encapsulated per dendritic box. Although both samples show identical UV spectra, a significant difference is observed in their induced CD spectra. The dendritic box with one molecule of Rose Bengal encapsulated exhibits an induced CD spectrum related to the UV spectrum, in which all bands possess a negative Cotton effect. However, an exciton-

coupled spectrum is observed in the case with four guests per box, indicative of the close proximity of chromophores with a certain fixed orientation [105].

Finally, Eriochrome Black T [106] was used to study the diffusion of the dye out of the box in acetonitrile, a solvent for the dye but not for the host-guest complex. Even after prolonged heating, dialysis or sonification, the aqueous phase of the dispersion did not become colored due to diffusion, and it was concluded that the diffusion of dye out of the box is immeasurably slow.

By comparing the encapsulation results of a large variety of dye molecules, it became apparent that many coplanar dye molecules with an anionic functionality can be encapsulated into the dendritic box, and the affinity seems to be related to acid-base interactions between guest and dendritic host.

4.2.2

Shape-Selective Release of Encapsulated Guests

The rigid, densely packed shell of the dendritic box limits the diffusion out of the box of almost all guest molecules studied. However, the size of the amino acid residues can be used as a tool to tune the permeability of the dendritic shell. For instance, a semipermeable box can be obtained when the dendrimer is functionalized with *t*-Boc-protected glycine units [93, 107] or by using L-Phe derivatives without the protective *t*-Boc group. The latter compound is used to allow a shape-selective liberation of guests (Fig. 10) [108].

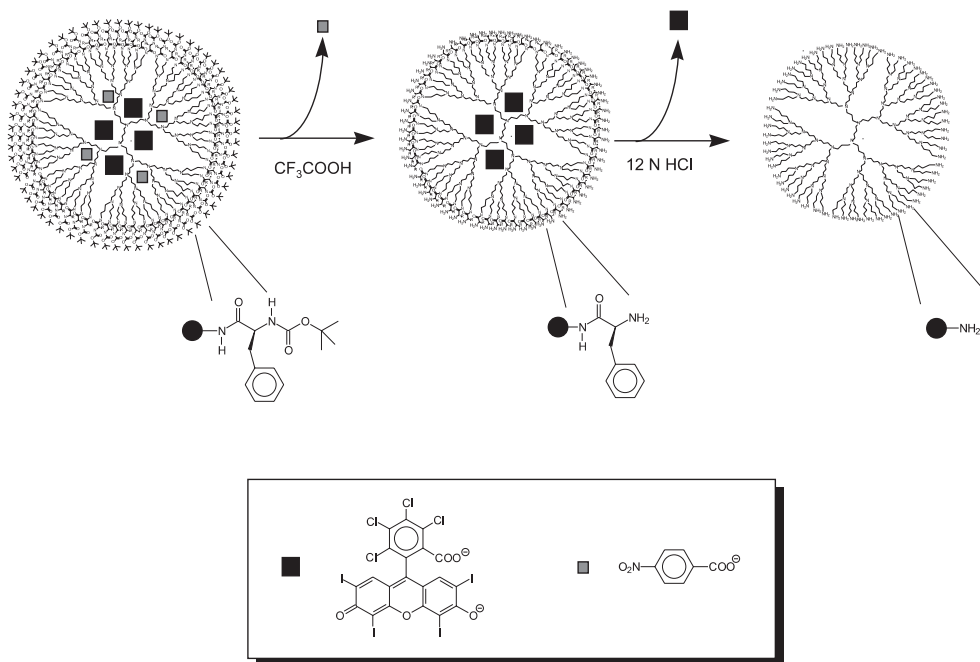


Fig. 10. Procedure for the (selective) liberation of guests from the dendritic box

After encapsulation of four molecules of Rose Bengal and eight to ten molecules of *p*-nitrobenzoic acid in the dendritic box, hydrolysis of the *t*-Boc groups with formic acid (95 % HCOOH, 16 h) was performed. Subsequent dialysis of the reaction mixture (5 % water in acetone) yielded a perforated dendritic box in which all four molecules of Rose Bengal remained entrapped; however, all the *p*-nitrobenzoic acid molecules were released into the acetone/water mixture. Rose Bengal was not liberated from the perforated box, even after the addition of acid. However, after hydrolysis of the outer shell using 12 N HCl, Rose Bengal was liberated, as proven by dialysis (100 % water). The unmodified poly(propylene imine) dendrimer was recovered in 50–70 % yield. This two-step hydrolysis procedure could be applied to a variety of (mixtures of) guest molecules, indicating that this shape-selective liberation is a general principle. Moreover, by changing the amino acids in the shell and the protecting group of the amino acid, a fine-tuning of the liberation principle was possible [107].

4.3

Dendrimers as Unimolecular Amphiphiles

With the development of dendritic structures, it was recognized that these structures were new promising candidates for the construction of unimolecular micellar systems. Dependent on the distribution of polar and apolar regions one can distinguish between unimolecular micelles (hydrophobic core/hydrophilic periphery) or unimolecular inverted micelles (hydrophilic core/hydrophobic periphery). These substances have proven to be interesting substances for the complexation of guests molecules in the dendritic interior.

4.3.1

Unimolecular Micelles

Micellanoate Dendrimers. In pioneering studies, Newkome et al. [109] showed that water-soluble hydrophobic dendrimers, i.e. Micellanoic acids (Fig. 11), act analogously to micelles and that these dendrimers, with a unimolecular micellar structure, can encapsulate hydrophobic guests within their branches. These dendrimers are monomeric in aqueous media over a broad range of concentrations, as indicated by dynamic light scattering studies.

The specific host-guest characteristics of these poly(ammonium carboxylate)s were demonstrated by UV/Vis analysis of guest molecules, such as pinacyanol chloride (PC), Phenol Blue (PB) and naphthalene, and fluorescence lifetime decay experiments employing diphenylhexatriene as a molecular probe. Additional evidence for inclusion (solubilization) was provided by using naphthalene as a probe, which changes in absorption intensity upon solubilization in the Micellanoate. All probe molecules are solubilized in the dendrimer interior. Using PC as a probe, and comparing these results with micellar systems like sodium dodecyl sulfate (SDS), it could be proven that if there is any critical micelle concentration present, it must be smaller than 0.39 μM .

The Micellanoate dendrimers have been examined as micellar substitutes for the separation of a homologous series of alkyl parabens via electrokinetic

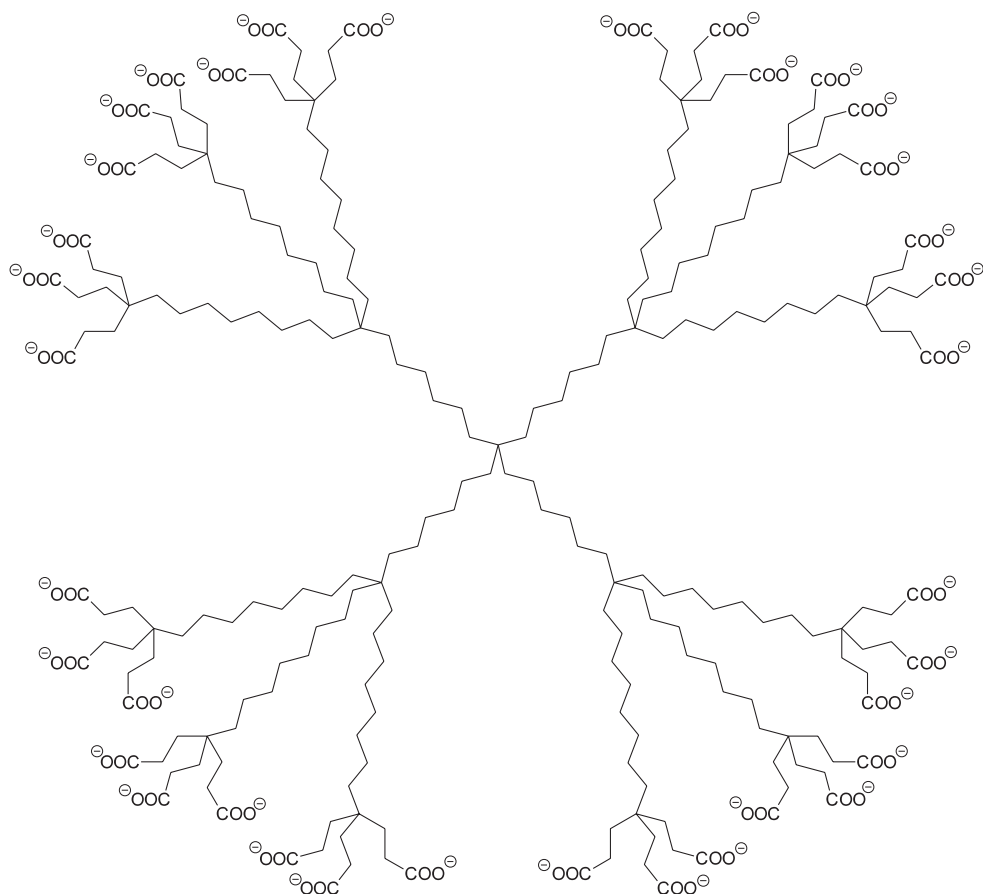


Fig. 11. Unimolecular all-hydrocarbon micelle, coined Micellanoic acid

capillary chromatography [110] employing aqueous mobile phase conditions in order to eliminate or effectively reduce the effect of micellar concentration, solvent strength, pH and temperature. Addition of the dendritic micellar substitutes to the analysis buffer separated the parabens as a function of their affinity for the hydrophobic microenvironment of the dendrimer. Separations using dendrimers yield excellent efficiency and resolution. Higher generation dendrimers demonstrate enhanced affinity for the parabens relative to lower generation dendrimers. The observed results are superior to reports of polymerized surfactant aggregates in which the presence of a critical aggregation concentration and the use of organic cosolvents in the mobile phase decreases the efficiency of micellar inclusion.

Water-Soluble Polyether Dendrimers. Fréchet et al. [111] reported the convergent synthesis of a polyether dendrimer with 32 carboxylic acid moieties on the periphery (Fig. 12). The corresponding potassium salt resembles a unimole-

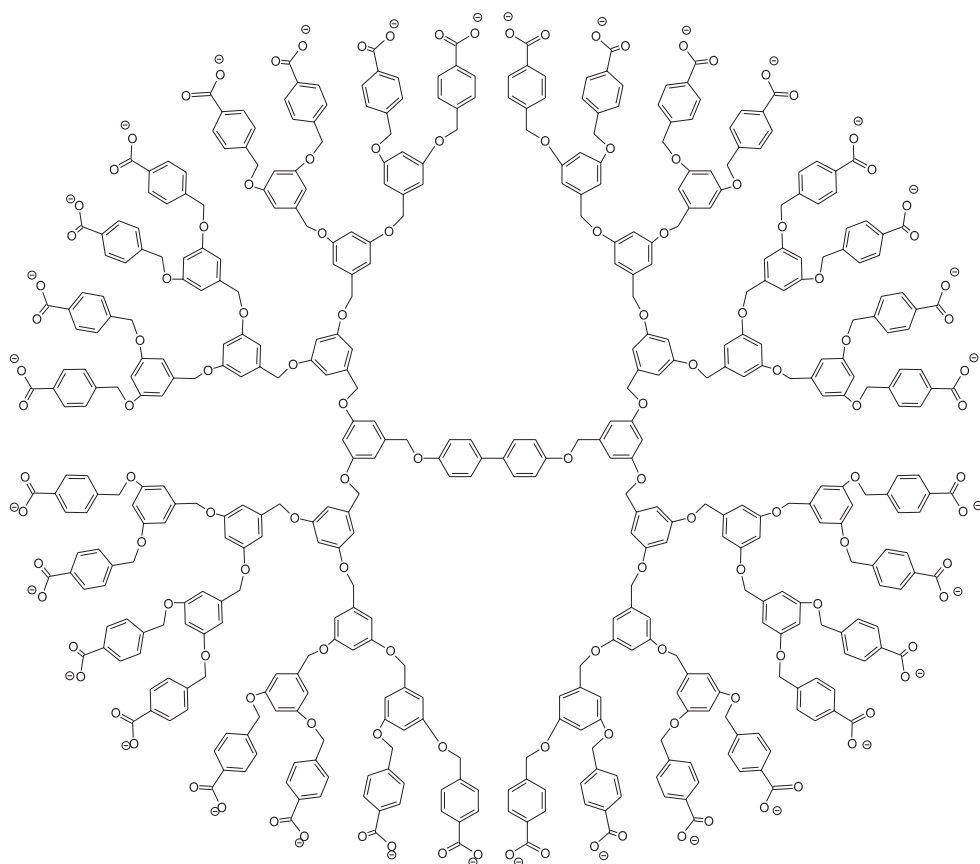


Fig. 12. Water-soluble acid-functionalized polyether dendrimer

cular micelle, with a hydrophobic core and a hydrophilic periphery, and consequently was tested for micellar characteristics.

In the presence of the unimolecular micelle a 120-fold increase was observed in the solubilization of apolar organic molecules like pyrene, resulting in the solubilization of 0.45 pyrene molecules per dendrimer. A comparable number has been found for well-known micelles, like sodium dodecyl sulfate (SDS), in which roughly 0.9 pyrene molecules are solubilized per micelle and of which the molecular weight is roughly twice that of the polyether dendrimer. Moreover, dendrimers show a linear relationship between the solubilized pyrene concentration and the concentration of polyether dendrimer, due to the absence of a critical micelle concentration. This is in marked contrast to traditional micelles where essentially zero solubility is found below the critical micelle concentration (ca. 8 mM for SDS). Pyrene solubilization can be further increased to 1.9 pyrene molecules per dendrimer upon addition of NaCl, since the increase in ionic strength decreases the concentration of water within the interior of the dendrimer and increases the hydrophobic nature of the local microenvironment within the dendrimer. The

very high solubilizing power of the polyether dendrimers can be related to the formation of stabilizing π - π interactions with aromatic guests. The saturation concentration of anthracene is increased 58 times, 1,4-diaminoanthraquinone 56 times and 2,3,6,7-tetranitrofluorenone 258 times relative to pure water.

The whole system can be used as a novel and recyclable solubilization and extraction system. After solubilization of pyrene inside the dendrimer interior, the dendrimer can be precipitated by a decrease in pH of the aqueous medium. Collection of the precipitate results in an almost complete recovery of the original amount of dendrimer. The collected precipitate can be dissolved in an organic medium and UV/Vis spectroscopy can be used to indicate that all solubilized pyrene has precipitated with the dendrimer. Upon extraction of the organic medium with aqueous KOH, the polyether dendrimer migrates to the aqueous medium, whereas pyrene remains in the organic medium. This solubilization and extraction procedure, with no decrease in efficiency, shows potential for a cyclic procedure.

Fréchet et al. [112] further extended this solubilization approach by covalent attachment of poly(ethylene oxide) (PEO) oligomers (MW ca. 2000) to the same dendrimers yielding non-ionic macromolecules. This provides an interesting host-guest system because it is non-immunogenic and exhibits low toxicity. Studies with pyrene indicate that the guest resides in the dendrimer core and not in the polar chains. It has also been shown that the polarity inside the dendrimer is similar to that of chloroform and that the dissolved guest has a low conformational mobility.

Water-Soluble Hyperbranched Poly(phenylene)s. Kim and Webster [113] synthesized fully aromatic water-soluble hyperbranched poly(phenylene)s with carboxylic end groups (Fig. 13). These structures showed solubilities in aqueous media exceeding 1 mg/ml. Complexation studies were performed with ^1H -NMR spectroscopy using *p*-toluidine as the guest molecule. Upon addition of the hyperbranched structure (pH ca. 10) a shift in the methyl signal of *p*-toluidine

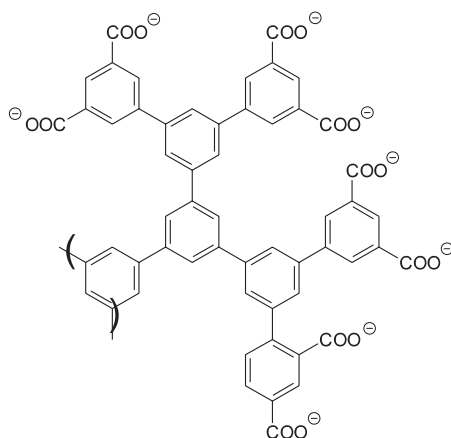


Fig. 13. Carboxylate-terminated hyperbranched poly(phenylene)s

was observed reaching a limiting value at ratios higher than 2.5. The poorly defined hyperbranched structure and the possibility of multiple complexes with *p*-toluidine (when the ratio of host to guest is low) hampers an accurate determination of the equilibrium constant, which is estimated at $510 \pm 150 \text{ M}^{-1}$. The hyperbranched structure is furthermore capable of dissolving naphthalene in high concentration in aqueous media, and enhances solubility of Methyl Red (30 times) and Methyl Orange (twice) in 0.1 M K_2HPO_4 solution.

4.3.2

Unimolecular Inverted Micelles Based on Poly(propylene imine) Dendrimers

Modification of polar poly(propylene imine) dendrimers with apolar end groups like palmitoyl and adamantyl units yields dendrimers with an unimolecular inverted micellar structure, i.e. a polar core and an apolar periphery (Fig. 14), as demonstrated by Meijer et al. [94, 114, 115].

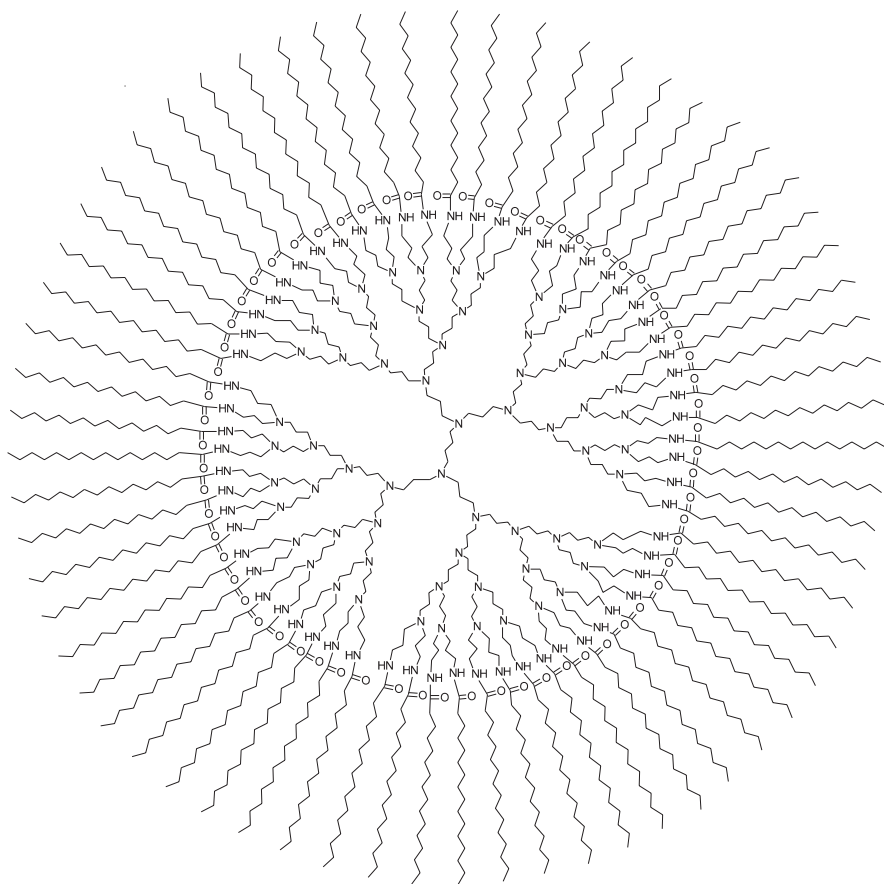


Fig. 14. Palmitoyl-modified poly(propylene imine) dendrimers

The palmitoyl dendrimers show single particle behavior with a hydrodynamic radius of 2–3 nm in dichloromethane and absence of clustering, as determined from dynamic light scattering. These compounds are able to encapsulate guest molecules like Rose Bengal in organic media [114]. Recently, Baars and Meijer have extended the research in this field and have shown that these dendrimers produce a new family of tertiary amine extractants [116] resembling the structures of low molecular weight tri-*n*-octylamine extractants [117–120]. The dendritic extractants are very effective and selective in the transfer of anionic solutes from an aqueous medium into an organic phase, typically dichloromethane or toluene. Typical solutes used are anionic xanthene and azobenzene dyes, which are depicted in Fig. 15.

The interaction between dendrimer (host) and solute (guest) is based on acid-base interactions and depends strongly on the acidity of the solute and the basicity of extractant and consists of a combination of electrostatic interactions, hydrogen bonding, ion-exchange interactions or solubility effects. The host-guest interactions are therefore reversible and depend strongly on pH, resulting in an extraction efficiency which is strongly modulated by the pH of the aqueous medium. At low pH complete extraction takes place, whereas no solutes are extracted at higher pH. Moreover a sharp inflection point, i.e. the pH at which

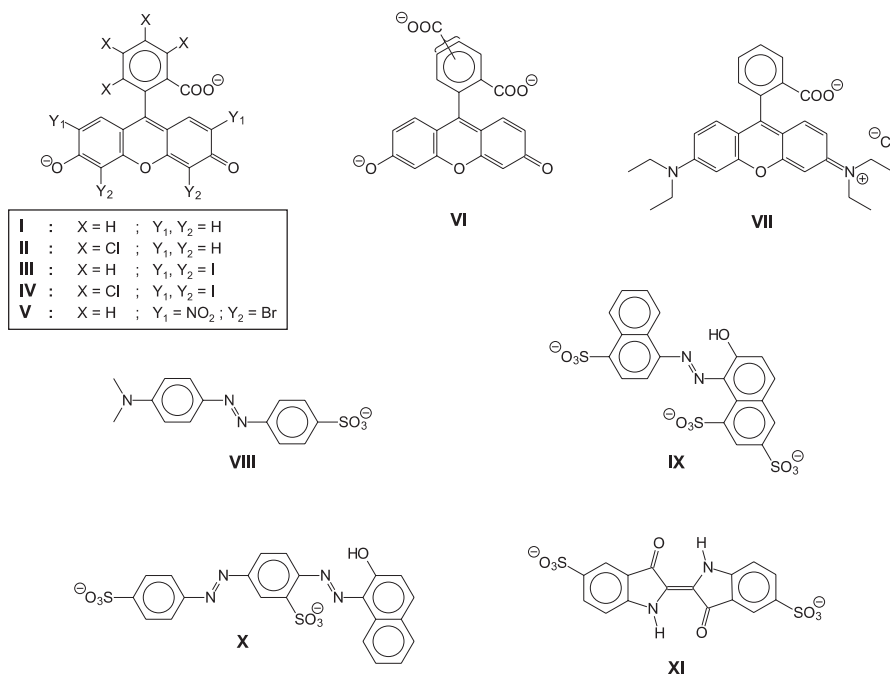


Fig. 15. Typical solute molecules used: *I* fluorescein; *II* 4,5,6,7-tetrachlorofluorescein; *III* Erythrosin B; *IV* Bengal Rose; *V* Eosin; *VI* carboxyfluorescein; *VII* Rhodamine B; *VIII* Methyl Orange; *IX* New Coccine; *X* Biebrich Scarlet; and *XI* Indigocarmin. All solutes are depicted in the anion conformation

50% of the solute is extracted, can be observed. The position of the inflection point depends strongly on the type of dye, and shifts to higher pH values when the acidity of the solute increases. This can be rationalized by more efficient (electrostatic) interactions between the protonated tertiary amine sites and the anionic guests. The difference in extraction yield of Rose Bengal and fluorescein enabled a highly selective extraction. At pH 10, even in a 10,000:1 ratio of fluorescein to Rose Bengal, complete and selective extraction of Rose Bengal was possible [116]. The selectivities observed for the complexation of anionic guests by dendritic extractants even exceed selectivities observed in complexation of (a mixture of) alkali metals by crown ether derivatives [8].

The dendrimer generation determines the number of tertiary amine sites and, as a consequence, the amount of solute molecules that can be extracted per dendrimer. Although for fluorescein (Fig. 15, I) only 1–2 dye molecules per dendrimer can be extracted with a fifth generation dendrimer, it is possible to extract up to 50 Rose Bengal molecules, yielding an assembly with a molecular weight of 70 kDa, ca. 2.5 times the molecular weight of the dendrimer. The results suggest that a maximum of 1:1 complexation of the tertiary amine with the solute should be possible. The end groups determine the solubility characteristics of the dendritic molecule but have no major effect on the extraction characteristics. A large difference in extraction is observed between a fifth generation dendrimer (containing 62 tertiary amine sites) and a first generation dendrimer (containing two tertiary amine sites) or tri-*n*-octylamine (TOA) (containing one site). Moreover, a fifth generation extractant shows a solvent-independent behavior in contrast to the solvent-dependent properties of a first generation extractant; such solvent-dependent properties are commonly observed for other low molecular weight extractants [118, 120]. The absence of the solvent dependence in the case of a fifth generation dendrimer can be explained by a local microenvironment consisting of a high concentration of the tertiary amine sites. Finally, these dendritic extractants can be used as a shuttle for the transport of (mixtures of) solutes from one aqueous phase (with a low pH) to another aqueous medium with a higher pH [121].

Modification of the poly(propylene imine) dendrimers with fluorinated chains enables the extraction of water-soluble solutes into supercritical carbon dioxide, and this has been investigated by de Simone et al. (Fig. 16) [122] and Keurentjes et al. [123]. The mechanism of extraction of both systems is similar to that of the poly(propylene imine) dendrimers with apolar end groups; however, this technology uses an environmentally friendly process design with green solvents and has the potential to replace hazardous organic solvents [124].

The efficiency and selectivity of the dendritic extractants has prompted us to apply these dendrimers in a commercial purification technology that consists of macroporous polymer particles containing an extraction fluid [125]. Solubilization of the dendritic extractants in the extraction fluid now enables the removal of anionic compounds with the same process setup. In addition, regeneration (desorption) can be achieved with steam, similar to the conventional process. The application of dendrimers enables the extraction of a broader range of solutes and demonstrates the efficiency of dendritic extractants in purification technology.

The extraction of dyes with hydrophobic PAMAM dendrimers is discussed later, but similar results are found [126, 127].

aromatic guests, like steroids [27, 129–131] or arenes, using π - π stacking and C-H $\cdots \pi$ interactions. As a consequence, dendritic cyclophanes (Fig. 17) mimic apolar binding sites buried within globular protein superstructures. Enlargement of the cyclophane core is used as a tool to complex larger steroid molecules [27, 130].

The substrates are located exclusively in the cyclophane cavities and non-specific incorporation into voids in the dendritic shell is negligible. ^1H -NMR binding titrations and fluorescence relaxation measurements in basic aqueous buffer solutions indicate fast host-guest kinetics. The dendrimers form inclusion complexes with association constants of 10^3 M^{-1} , which is of similar stability to those of the initiator core cyclophanes. This suggests a relatively open structure of the dendrimer for all generations. Studies with fluorescent probes like 6-(*p*-toluidino)naphthalene-2-sulfonate (TNS) have demonstrated that the micropolarity around the binding cavity is significantly reduced with increasing dendritic size and comparable with ethanol for the higher generations. This suggests that these water-soluble dendrophanes are attractive targets for catalytically active mimics of globular enzymes, since the exchange rate and the polarity around the binding cavity are only slightly reduced for

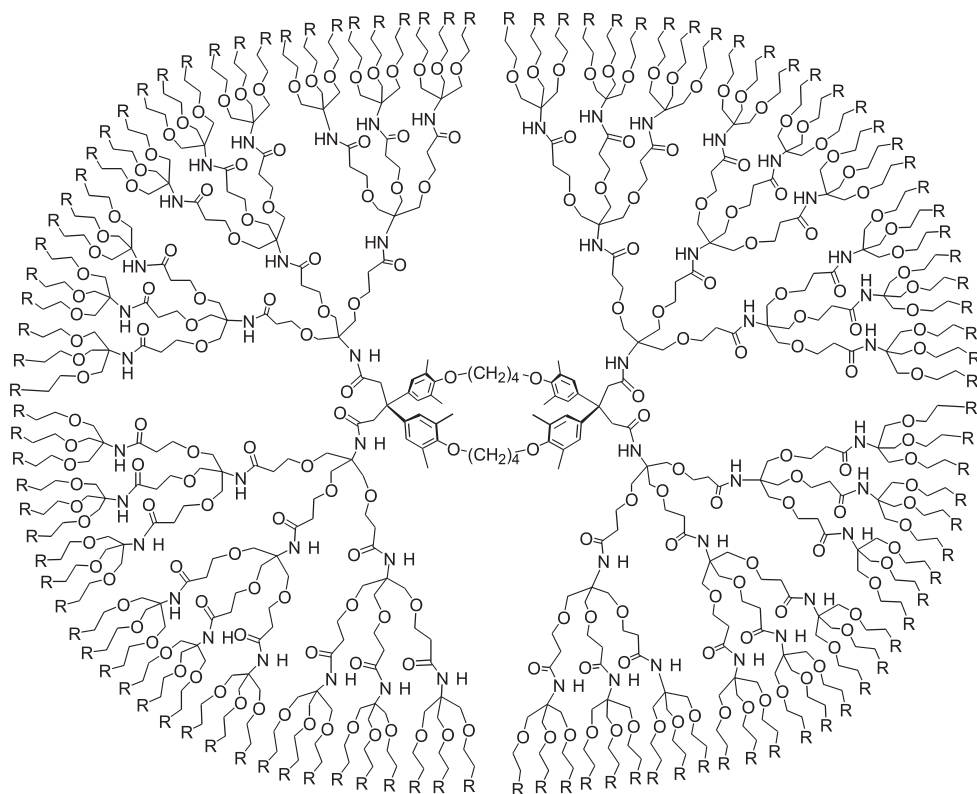


Fig. 17. Dendritic cyclophanes as receptors of hydrophobic compounds

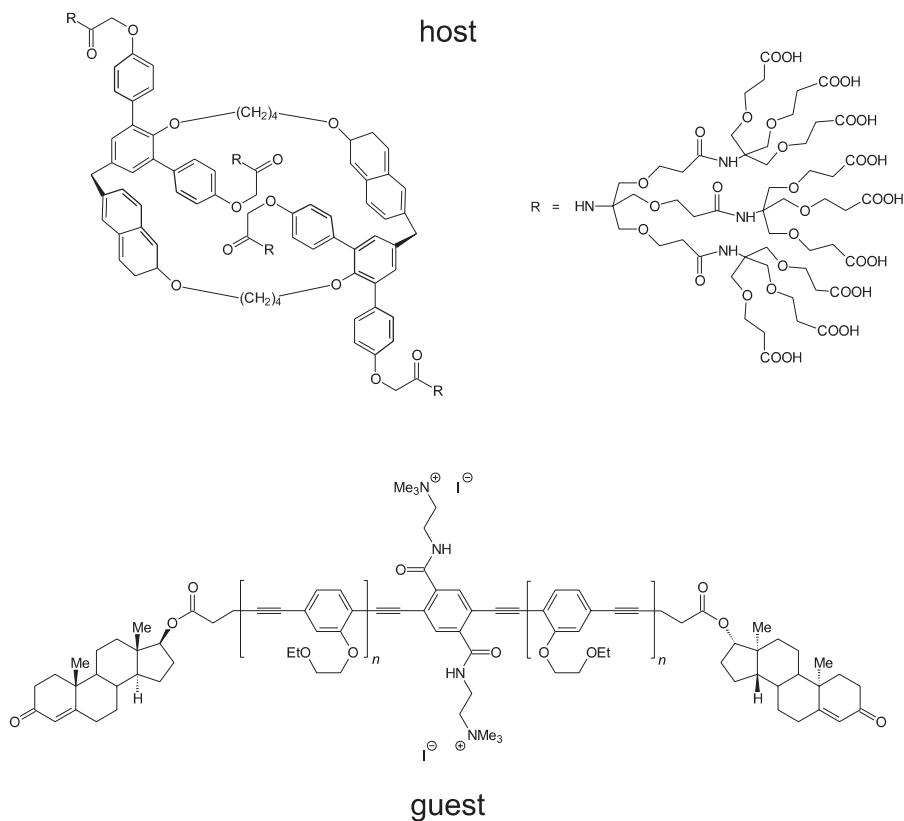


Fig. 18. The use of dendritic cyclophanes in a modular approach ($n = 1-3$)

the higher generation dendrimers in comparison with non-dendritic cyclophanes.

Recently, Diederich et al. [132] described the threading of dendritic cyclophanes on molecular rods functionalized with steroid termini (Fig. 18). The threading of the dendrophanes onto the testosterone termini is hydrophobically driven (apolar interactions, hydrophobic desolvation) and yields well-defined structures with molecular weights exceeding 14 kDa. Ion-pair interactions are also likely to play a role, due to the anionic nature of the dendritic end groups and the cationic nature of the rods. Information about optimal threading, like K_a and ΔH_b , has been obtained from NMR and fluorescence spectroscopy techniques. The threading is highly dependent on the generation number of the dendrophanes and the dimensions of the bifunctional steroid rod. For larger dendrophanes a larger distance between the testosterone termini is required to obtain a 2:1 complex, whereas a 1:1 complex is formed for smaller rods. The procedure of hydrophobic threading promises to provide a rapid, efficient way to construct higher molecular architectures based on dendritic modules [133–135].

4.4.2

Recognition Using β -Cyclodextrins

Kaifer et al. described the synthesis of different generations of ferrocenyl-functionalized poly(propylene) imine dendrimers [136–139]. Since ferrocene [140] is an excellent substrate for inclusion complexation by β -CD (K_a ca. 1230 M^{-1}), the host-guest properties of these dendrimers towards β -CD have been investigated using ^1H -NMR spectroscopy (Fig. 19) [141].

Although the solubility of the dendrimers in aqueous media decreases with generation, a significant enhancement is observed in the presence of β -CD. This is rationalized by the formation of β -CD/ferrocene inclusion complexes on the surface of the dendritic structures. The maximum solubility of ferrocene dendrimers in the presence of β -CD decreases with generation. It is also indicated that a minimum number of ferrocene units needs to be complexed to dissolve the dendrimer. Together with the rather low K_a values and enhanced steric con-

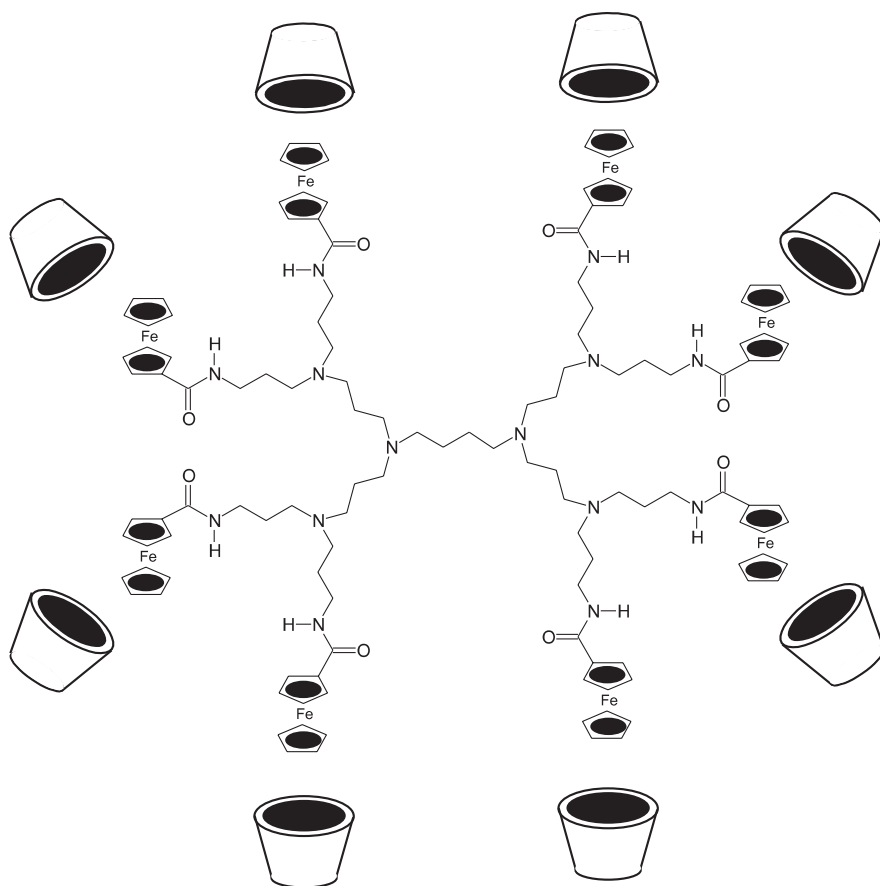


Fig. 19. Complexation of ferrocenyl dendrimers with β -cyclodextrin

gestion for the higher generations, it is therefore not possible to dissolve beyond generation three. Interestingly, the availability of redox-active ferrocene end groups makes it possible to break up these supramolecular species electrochemically, as the binding affinity constant of the β -CD/ferrocene complex is strongly diminished by ferrocene oxidation. The dendrimer serves to organize the β -CD receptors in the periphery of the dendrimer structure.

The same concept of using dendrimers as a three-dimensional, electrochemically switchable, template for the organization of β -CD has also been shown for a series of poly(propylene imine) dendrimers functionalized with 4, 8, 16, 32 and 64 peripheral cobaltocenium units [142]. Dendrimers of generation 1 to 3 constitute a type of host-guest system in which the formation of multisite β -CD/dendrimer complexes is driven by the reduction of the cobaltocene sub-units of the dendrimers. Upon reduction, the charged end groups are transformed into very hydrophobic species that efficiently complex in the β -CD cavity. Higher generations were not described in this publication; steric reasons and low K_a values are also likely reasons in this case.

Newkome et al. [143] have described the synthesis of water-soluble β -cyclodextrin-based dendrimers, i.e. dendritic wedges of different generations attached to a β -cyclodextrin receptor. Binding studies with phenolphthalein, adaman-

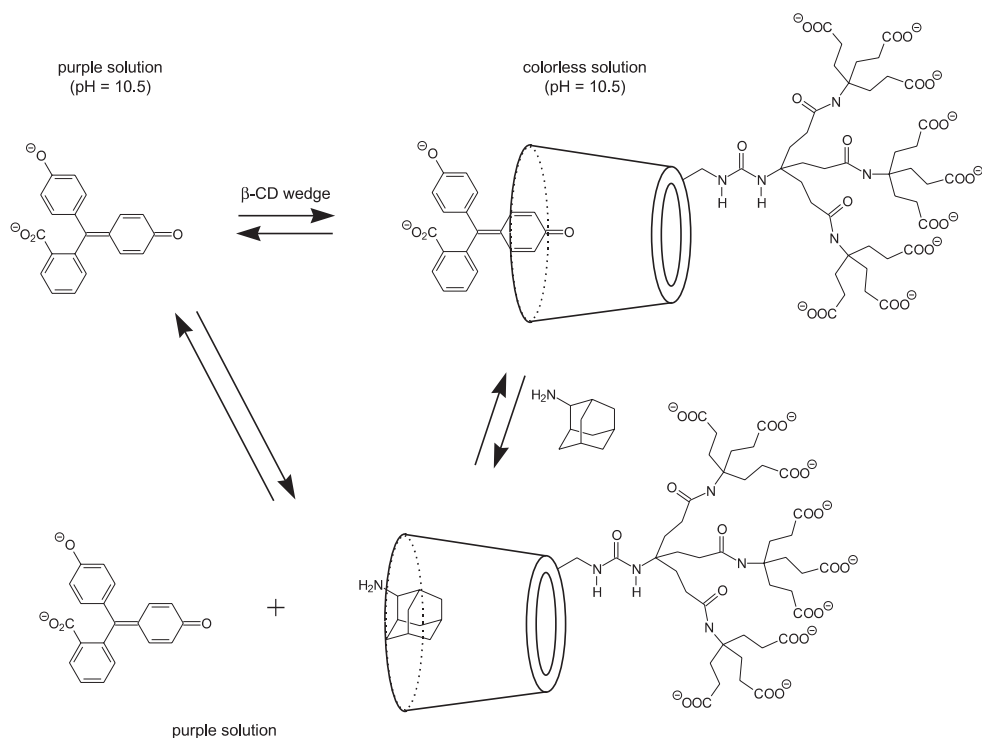


Fig. 20. Recognition of adamantyl derivatives and phenolphthalein by a dendrimer-functionalized β -cyclodextrin receptor

tane-amine, or a bis(adamantane) unit have shown that the binding cavities of the modified receptors retain their molecular recognition properties (Fig. 20). Using the bifunctional adamantyl compound, a first step towards recognition-based assembly of dendrimers has been established, similar to Diederich's threading process [132].

4.4.3

Recognition of Saccharides

Shinkai et al. [144] described the synthesis of dendritic saccharide sensors. A PAMAM dendrimer was labeled with eight boronic acid residues. The dendritic compound shows enhanced binding ability of saccharides D-galactose or D-glucose (which contain two binding sites) or D-fructose when compared with a mono-functional boronic acid moiety (Fig. 21). This can be primarily ascribed to the co-operative action of two boronic acids to form an intramolecular 2:1 complex. The efficient recognition of saccharides is explained by an increased number of binding sites: when one boronic acid binds a saccharide, any one of seven remaining boronic acids can complex the second binding site of the (bound) saccharide.

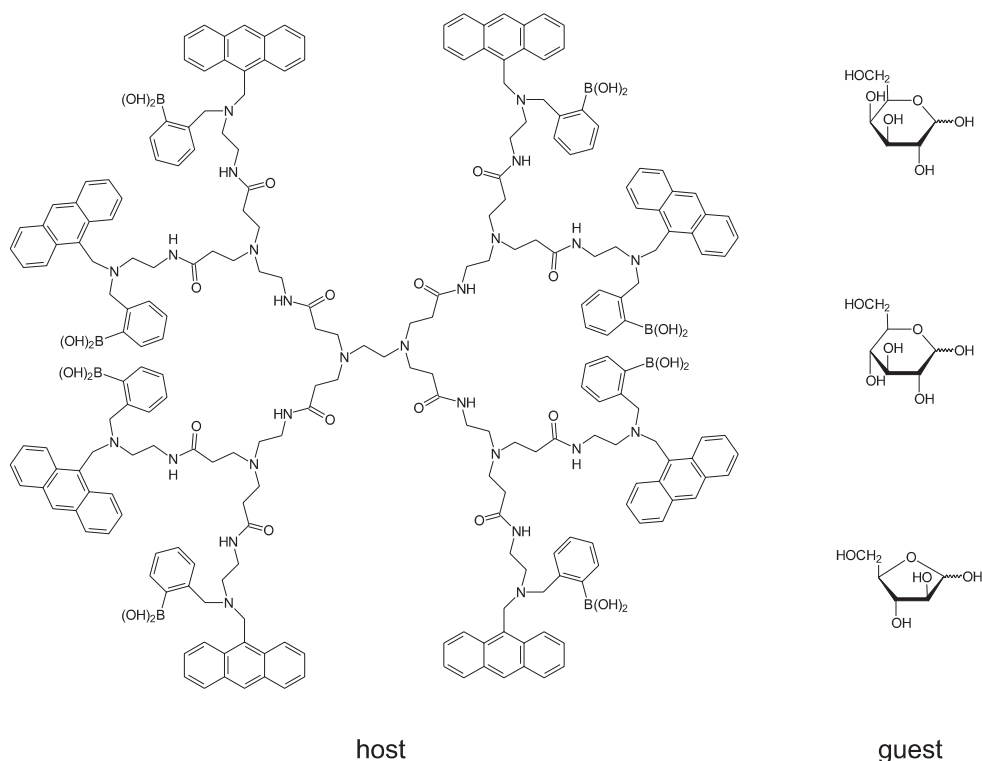
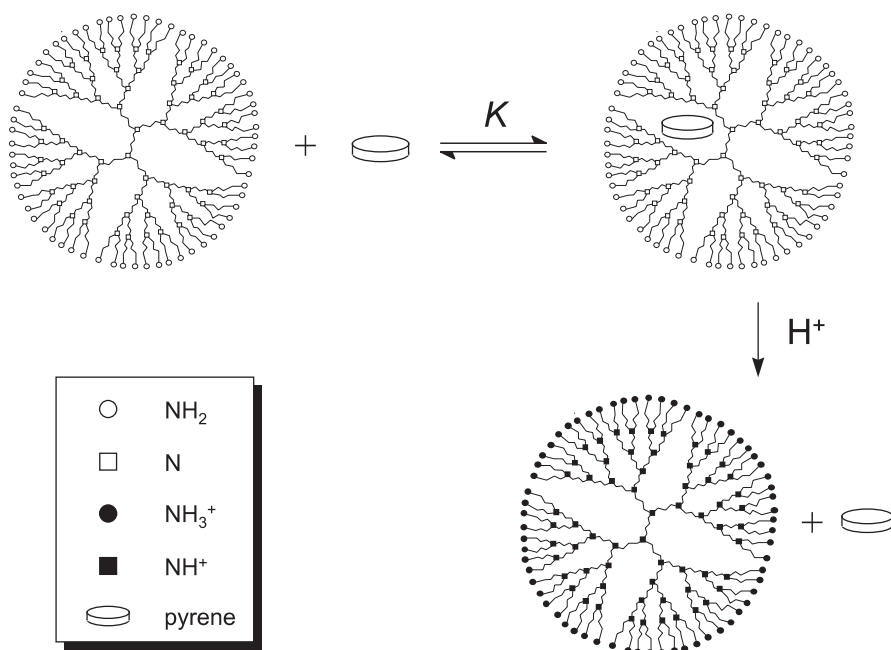


Fig. 21. A dendritic saccharide sensor and the recognition of D-galactose, D-glucose and D-fructose (from top to bottom)



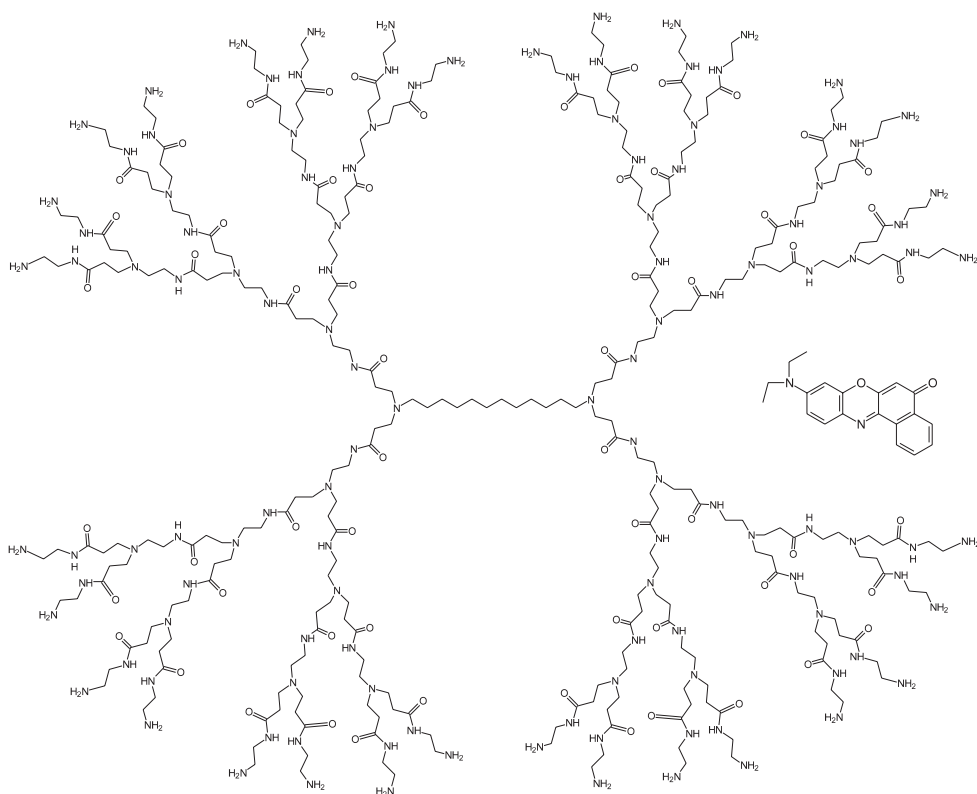


Fig. 23. Interactions of poly(amidoamine) dendrimers with a hydrophobic core and Nile Red

rescence studies. However, the hydrophobicity of the dendrimer is not only dependent on the length of the diaminoalkyl core but also on the dendrimer generation. Nile Red is prevented from gaining access to the hydrophobic core at a certain generation (higher than generation 4), presumably due to an increase in the overall polarity of the molecule with generation.

4.5

Recognition Based on Hydrogen-Bonding Interactions

Hydrogen-bonding interactions between dendrimers and guests have been achieved by incorporation of coordinating sites that are complementary to the guest at the focal point or in the core of the dendrimer. However, Fox et al. [148] studied the intrinsic hydrogen-bonding interactions of low generation amine- and ester-functionalized poly(amidoamine) dendrimers with several biologically important guests, like pyridine, quinoline, quinazoline, nicotine and trimethadione. Weak interactions were determined for the complexation of pyridine with both types of dendrimers (K_a of ca. 1 M^{-1}). Whereas pyridine complexes to external and internal sites for the amine-functionalized dendrimers, in

the case of the ester-terminated dendrimers no complexation to the periphery takes place. Interaction of quinazoline and quinoline with the ester-terminated dendrimers proved to be highly dependent on the chain length of the methyl ester, which surprisingly was explained by a tight local packing of these relatively small dendrimers. Trimethadione and nicotine showed no significant interactions with any of the dendrimers.

4.5.1

Dendrimers with Interior Hydrogen-Bonding Units

Newkome et al. [149] have reported the construction of dendrimers in which four 2,6-diamidopyridine units are incorporated in the interior (Fig. 24).

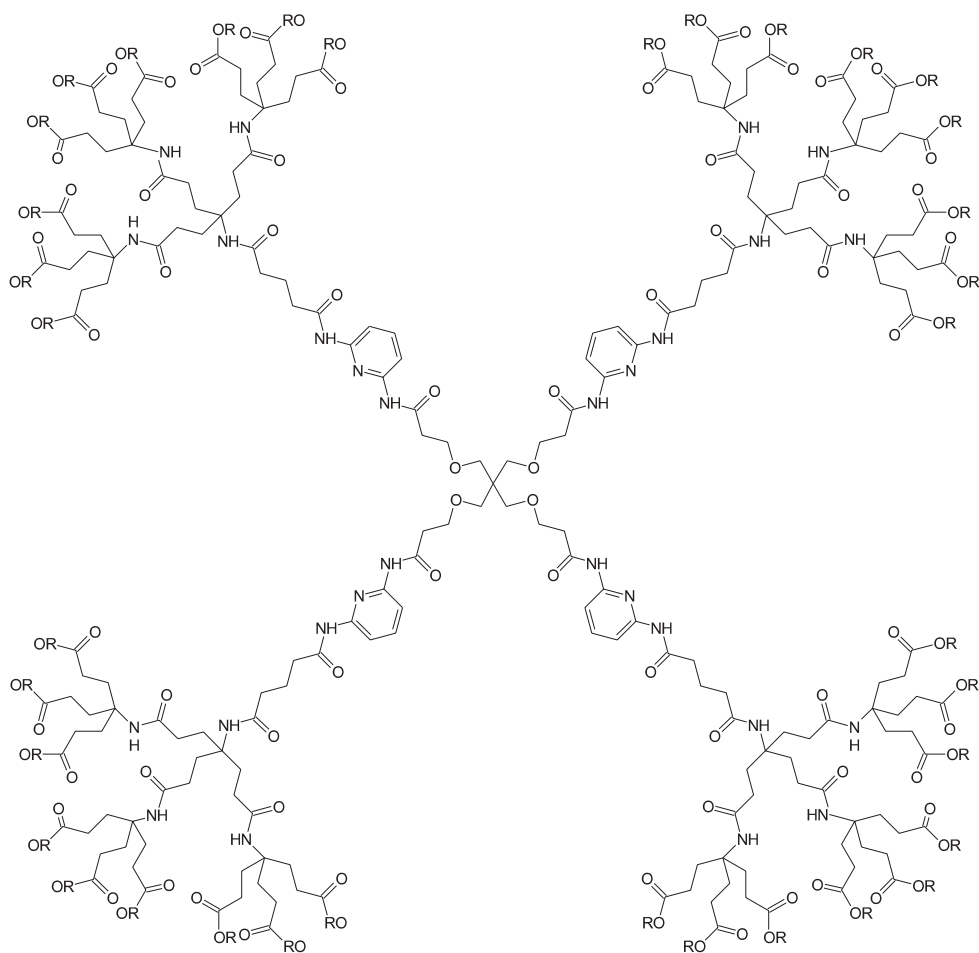


Fig. 24. Dendrimers with 2,6-diamidopyridine as hydrogen-bonding unit incorporated in the interior (R = *t*-Bu)

Several generations were synthesized up to 36 end groups. The association behavior with complementary guests such as glutarimide, barbituric acid and 3'-azido-3'-deoxythymidine (AZT) [150] has been investigated by ^1H -NMR spectroscopy in CDCl_3 , yielding apparent association constants of ca. 70 M^{-1} . These constants are comparable with reported values for similar host-guest complexes [151]. Unfortunately, the system suffers from some drawbacks, like self-association between the different tiers of the dendritic host, especially for the higher generations, and inefficient donor-acceptor alignment. Also, the guest molecules can bind at alternate hydrogen-bonding sites within the host's infrastructure. These disadvantages make it crucial to evaluate the host-guest interactions and hamper studies of the effect of dendrimer generation on strength and kinetics of complexation.

4.5.2

Dendritic Wedges with a Hydrogen-Bonding Unit at the Focal Point

The effect of dendrimer generation on hydrogen-bonding complexation has been satisfactorily investigated by Zimmerman and Moore [152] who reported the suitability of dendrimers to site-specifically complex molecules within their interiors (Fig. 25). Two classes of dendritic hosts have been synthesized with

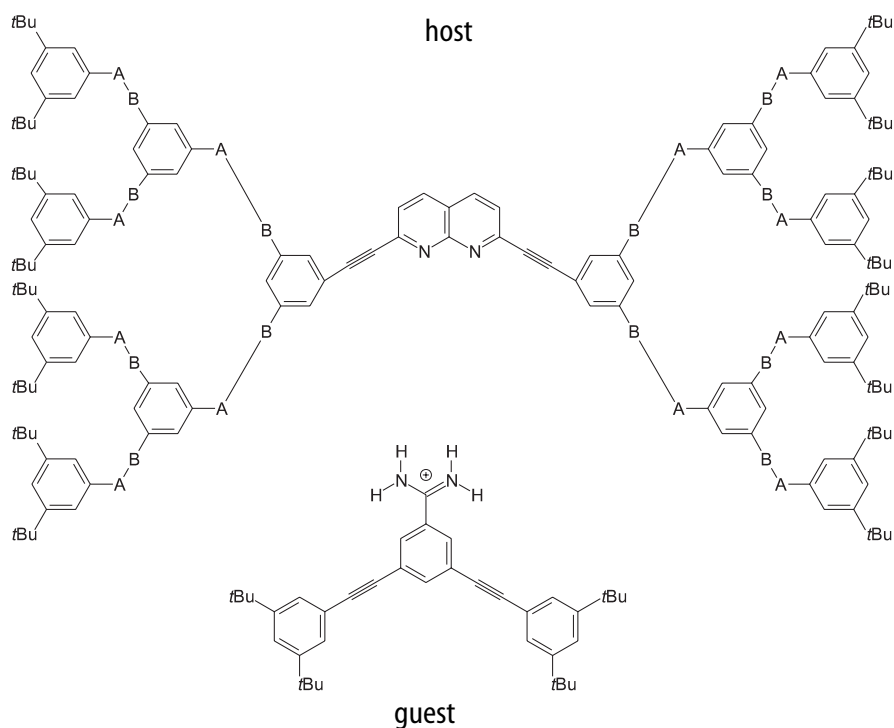


Fig. 25. Dendritic wedges functionalized with anthipyridine units at the focal point (A-B=CH₂-O or C≡C) and a study of the hydrogen-bond interactions with benzamidinium guests

naphthyridine units at the focal points capable of hydrogen bonding two types of benzamidine derivatives. Different (dendritic) guests were used as a probe of the dendrimer's internal accessibility and polarity.

Two hosts, differing only in polarity, were studied and their association constants determined by ^1H -NMR spectroscopy in mixtures of $\text{CD}_3\text{CN}/\text{CDCl}_3$. An accurate determination of the (larger) association constants in pure CDCl_3 proved impossible. The observed results suggest that the environment at the naphthyridine core of both hosts is either apolar or controlled by the solvent, indicating that no distinct dendritic environment is obtained even when using the highest generation. These data are in contrast to the observations of Hawker and Fréchet [153] who reported a change in the local polarizability parameter at the core as a function of the generation. In the case of Zimmerman and Moore,

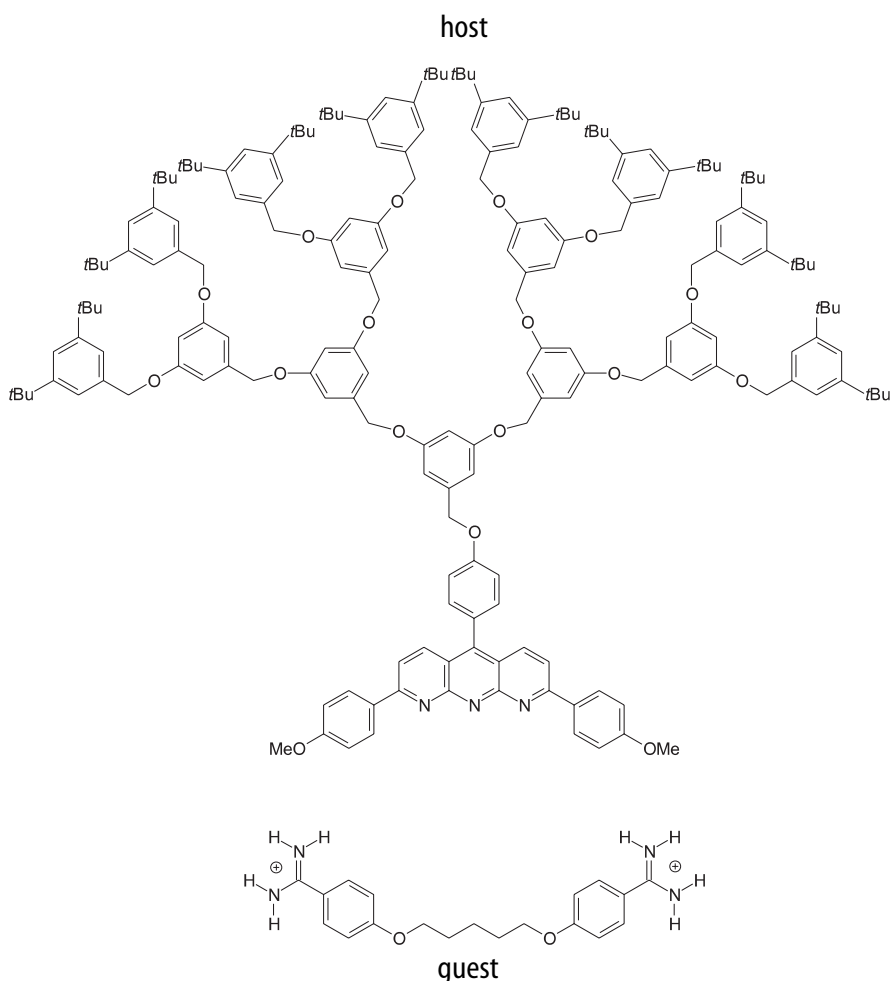


Fig. 26. The use of hydrogen-bonding interactions in a modular approach

a negligible influence from the dendrimer is observed, and the hosts are highly porous for small complementary guests even for the highest generation. Only for the bulkier dendritic guests is the binding weaker with increasing generation, reflecting the increased steric constraints for complexation.

Zimmerman et al. [154] have also studied the complexation of anthypyridine-based dendrimers (AAA-motif) via hydrogen-bond interactions with benzamidine and pentamidine derivatives (DD-motif). The association constants, as determined in $\text{CD}_3\text{CN}/\text{CDCl}_3$ by ^1H -NMR spectroscopy, gives K_a values of ca. $3 \times 10^4 \text{ M}^{-1}$ for a benzamidine guest. Using the bifunctional pentamidine derivative (Fig. 26), it was possible to construct a didendron with molecular weight larger than 10,000 amu from smaller, accessible sub-units. Unfortunately, complexation of the dendritic host with a fully complementary DDD-motif using 2,6-diamino-1,4-dihydropyridine proved impossible due to the instability of the latter compound.

4.6

Electrostatic Interactions: Recognition of Anions

The unimolecular inverted micelles discussed in Sect. 4.3.2 constitute an example of molecular recognition of anionic molecules. In this section we discuss the specific recognition of inorganic and organic anions by (non-amphiphilic) dendritic hosts.

4.6.1

Inorganic Anions

Astruc et al. have designed neutral [155] and cationic [156] polyamidoferrocene dendrimers. In the case of the neutral dendrimer (Fig. 27), ^1H -NMR spectroscopy and cyclic voltammetry were used to study interactions between dendrimers and small inorganic anions like H_2PO_4^- , HSO_4^- , Cl^- and NO_3^- . It was found that all redox centers behave independently and that strong interactions are observed in the case of the higher generation dendrimers.

These interactions can be rationalized by an electrostatic interaction (involving ferricinium cation and anion) and hydrogen bonding of the amide hydrogen atom with the anion. In the case of hydrogen bonding alone, the interaction is usually weak. The sensing of anions (especially H_2PO_4^- and HSO_4^-) by cyclic voltammetry increases with generation ($3 \rightarrow 9 \rightarrow 18$ end groups). The authors explain this by a shape selectivity originating from the dendrimer. For the polyamidoferrocene dendrimers presented above, recognition in the neutral state is by far weaker (and only present for H_2PO_4^-) than in the cationic state, since the neutral diamagnetic 18-electron form does not usually interact efficiently with anions.

A polycationic ferrocene-functionalized dendrimer [156] was synthesized in an attempt to create recognition of anions with ferrocene in its 18-electron form, without the need for cyclic voltammetry. These dendrimers show a large dendritic effect, i.e. better association with increasing generation, for the recognition of Cl^- and Br^- . Chelating anions like H_2PO_4^- are not recognized, in contrast

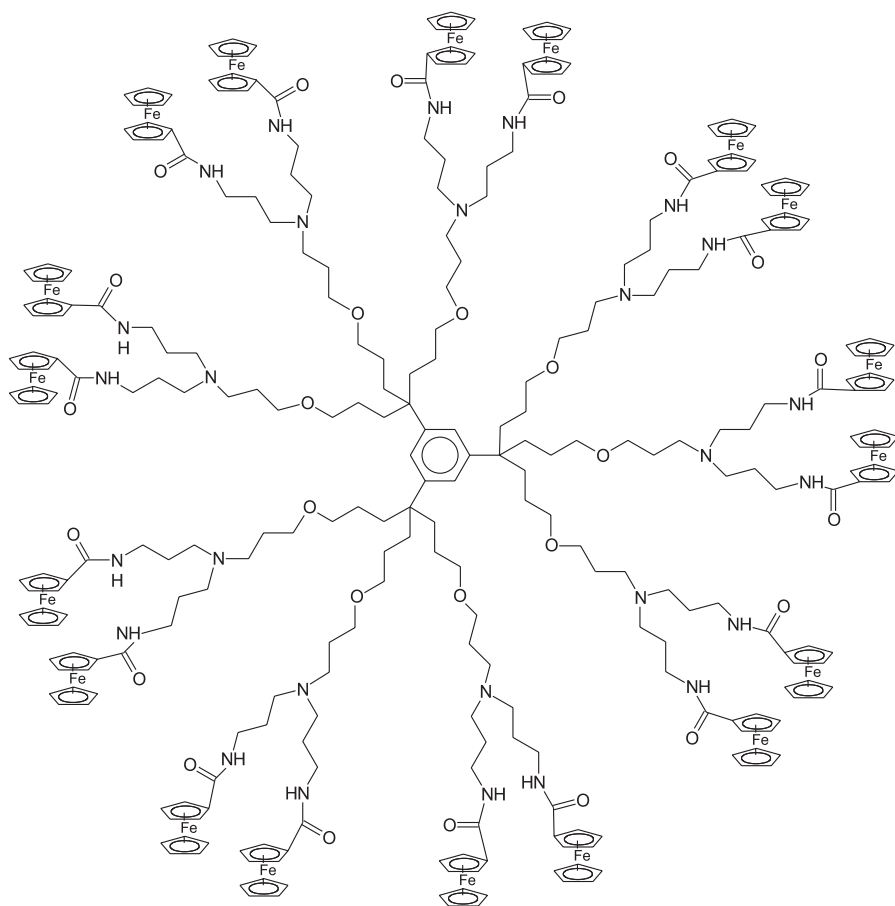


Fig. 27. Ferrocenyl-functionalized dendrimers

to the neutral species, probably due a difference in molecular structure. Whereas the neutral species contains amide linkages, the cationic dendrimers contain secondary amines that preferentially interact with single-atom halogen anions, like Cl^- and Br^- . Synergistic effects between the single $\text{X} \cdots \text{HN}$ hydrogen bond, the electrostatic attraction, and the shape selectivity of the dendritic structure (peripheral cavities, dendrimer branches) account for the recognition of the halogens Cl^- and Br^- .

4.6.2

Interaction of Organic Acids with PAMAM Dendrimers

Tomalia et al. [81] reported the random complexation of host molecules in dendritic structures by monitoring the change in guest ^{13}C spin-lattice relaxation times (T_1). PAMAM dendrimers with methyl ester termini were used as the den-

dritic host with aspirin and 2,4-dichlorophenoxyacetic acid as guest molecules (Fig. 28). T_1 values of the guests in CDCl_3 change in the presence of a dendrimer and a distinct dependence on the generation is observed. The values for T_1 decreased, as the generation number increased from 0.5 to 3.5, but remained constant for higher generations. The maximum concentration of the guests is roughly 3:1 based on a molar comparison of the carboxylic guest and the interior tertiary amines, suggesting an acid-base interaction between host and guest.

Similar results have been obtained by Twyman and Mitchell [157], who developed a convenient route to highly water-soluble dendrimers starting from PAMAM dendrimers. These dendrimers are capable of binding and solubilizing small acidic, water-insoluble, hydrophobic molecules, like benzoic acid, salicylic acid and 2,6-dibromonitrophenol. However, tioconazole and other small non-ionic molecules could not be retained within the dendrimer. Again an interaction between the acidic functionality of the guests and the basic tertiary nitrogens of the dendritic hosts is suggested. In the case of a second generation dendrimer up to 46 benzoic acids can be dissolved, i.e. an average of 3 guests per tertiary amine site, in good agreement with the results of Tomalia et al. [81]. Unfortunately, the exact mode and mechanism of binding has not yet been elucidated.

Crooks et al. [126] recently reported the transfer of amine-functionalized poly(amidoamine) dendrimers into toluene containing dodecanoic acid. The

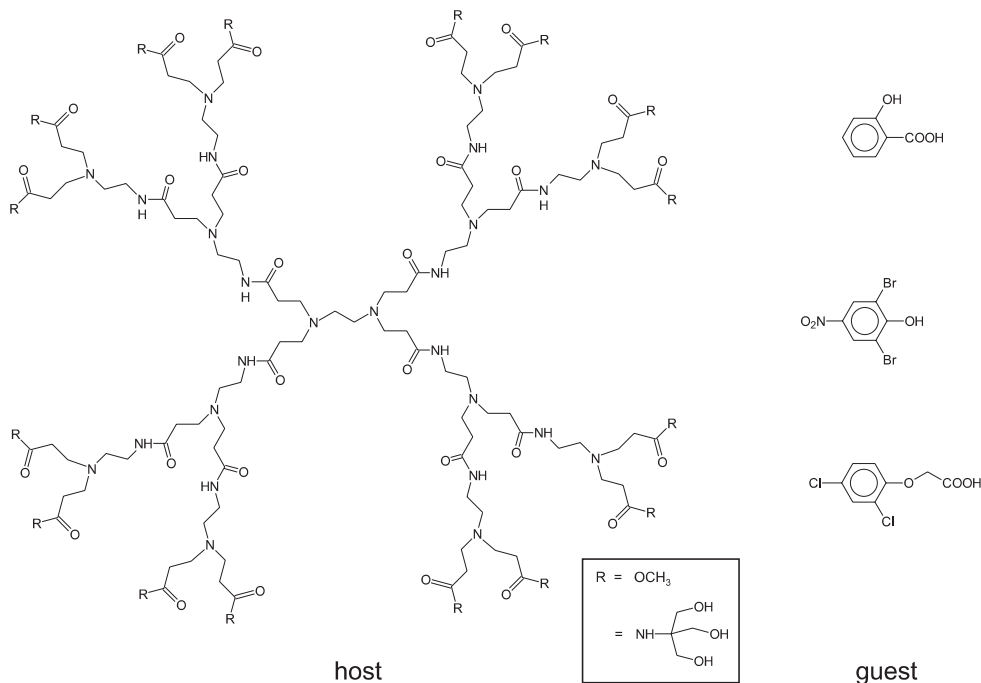


Fig. 28. Interaction of organic acids, like salicylic acid, 2,6-dibromophenol or 2,4-dichlorophenoxyacetic acid (from top to bottom), with poly(amidoamine) dendrimers

method is based on the formation of ion pairs between the fatty acids and the terminal amine end groups. The amount of dendrimer that can be dissolved roughly corresponds to a stoichiometry of one fatty acid per amine end group, as evidenced by transmission Fourier transform infrared spectroscopy (FTIR). In the presence of a large excess of dodecanoic acid, proton transfer extends to the tertiary amine groups within the dendrimer interior, similar to the interactions of functionalized poly(propylene imine) dendrimers with anionic guests [116]. Finally, the dendrimer/fatty acid complexes can be used as phase-transfer vehicles for the transport of Methyl Orange, an anionic dye molecule, into an organic medium, similar to previous publications [116, 122].

4.6.3

Complexation of Organic Acids with Poly(propylene imine) Dendrimers

Baars and Meijer [158] have recently investigated the host-guest properties of poly(propylene imine) dendrimers functionalized with tris-3,4,5-tri(tetraethyleneoxy)benzoyl units (Fig. 29). These hosts are characterized as monodisperse compounds and are highly soluble in a broad range of solvents, from

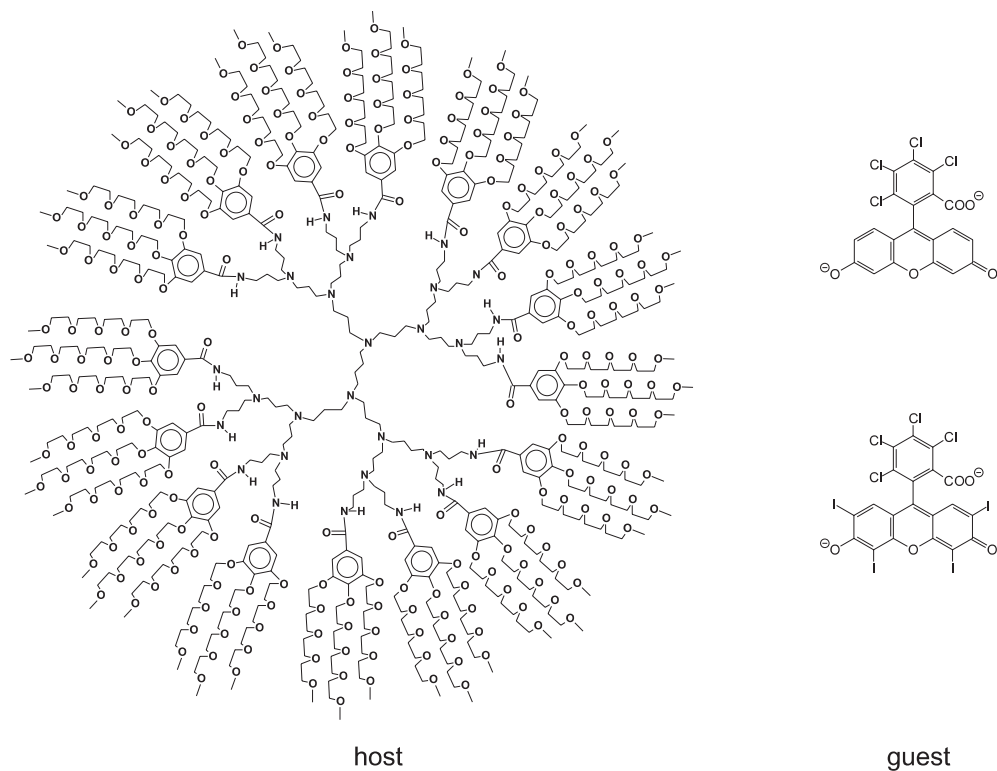


Fig. 29. Ethylene glycol functionalized poly(propylene imine) dendrimers as water-soluble hosts of TCF (*top*) or RB (*bottom*)

apolar solvents like toluene to polar aqueous media. In all solvents, the hosts behave as uncorrelated macromolecules and show no tendency for aggregation. In the case of a fifth generation host, dimensions reach over 6 nm and molecular weights exceed 50 kDa.

The host-guest properties were studied in buffered aqueous media using two water-soluble anionic xanthene dyes, i.e. 4,5,6,7-tetrachlorofluorescein (TCF) and Rose Bengal (RB) as guest molecules. The measured association constants are $3.0 \pm 0.4 \times 10^4$ and $5.0 \pm 0.04 \times 10^5 \text{ M}^{-1}$ for TCF and RB, respectively. This indicates that the association of RB with the dendritic host is much more efficient than that of TCF. For TCF, the average host-guest ratio is less than *one*. In the case of RB, a strong complexation takes place and an average load of 40 (!) can be calculated, yielding a host-guest complex with almost twice the molecular weight of the host. Interactions can be rationalized by acid-base interactions between the acidic functionality of the guest and the tertiary amines of the dendritic host, similar to other presented host-guest systems. This is supported by the strong pH-dependent association behavior of TCF. However, the pH-independent behavior of RB suggests that as well as electrostatic interactions (acid-base), properties like the high polarizability and hydrophobicity of RB play an important role in the association process.

Kleppinger used SAXS measurements to study the location of RB in the presented complexes (Fig. 30). The halogenated guests are ideally suited for these type of measurements, because the halogens Cl and I yield an enormous scattering contrast. The dimensions (radius of gyration, R_g) of the complexes were determined as a function of the host-guest ratio and show an unexpected decrease with loading that can only be explained by a preferential organization of the guests in the center regions of the dendritic hosts (Fig. 30A). However, if more guests are complexed to the dendritic hosts, the dendritic interior becomes saturated and consequently the outer regions are filled up (Fig. 30B), as is evidenced by an increase in the radius of gyration. These results yield new insights into the localization of the guests obtained from experimental studies, and stress the importance of the SAXS technique for structural elucidation.

Finally, efficiency and selectivity of dendritic hosts can be studied using the ultrafiltration technique. As the size of the host-guest complexes is modulated by the dendrimer generations, by application of a membrane with a molecular

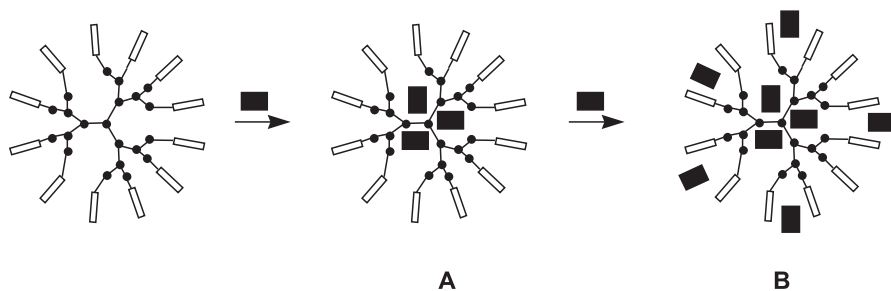


Fig. 30. Cartoon of the location of the guest in the ethylene glycol dendrimer as the concentration of the dye is increased (from left to right)

weight cut-off of approximately 10 kDa, we were able to distinguish between host-guest complexes of a first generation dendrimer (3 kDa) and a fifth generation dendrimer (53 kDa). In the latter case, all guest molecules are retained in the filtration cell, indicative of the high molecular weight of the host and the strong association between host and guest. This is in sharp contrast to a host-guest system of a first generation dendrimer which passes the membrane, as evidenced by UV/Vis spectroscopy. Temperature and pH can be used as a method to release guests. The selectivity of the host-guest interactions is shown when mixtures of different guests are filtered. For instance, a mixture of fluorescein and Bengal Rose shows a complete and selective filtration of the first compound only. We believe that the dendritic interior with a high local concentration of tertiary amines creates a certain selective microenvironment, that is to some extent shielded from the solvent. These properties are unique for dendrimers and can be directly related to their branched structure.

Recently, Balzani, de Cola and Vögtle [159] reported the first attempts to develop a dynamic host-guest system in which the interactions could be tuned by an external stimulus, for instance light (Fig. 31). The interaction of a fourth generation azobenzene-functionalized poly(propylene imine) dendrimer with Eosin Y was studied in dimethylformamide (DMF) (Fig. 31). It was also shown that light absorbed by Eosin is effective to promote the photoisomerization of azobenzene moieties from the *E*-form to the *Z*-form. Fluorescence quenching experiments showed that Eosin is hosted inside the dendrimer, as a consequence of acid-base interactions between host and guest [116], and suggest that the *Z*-form of the dendrimer is a better host than the *E*-form.

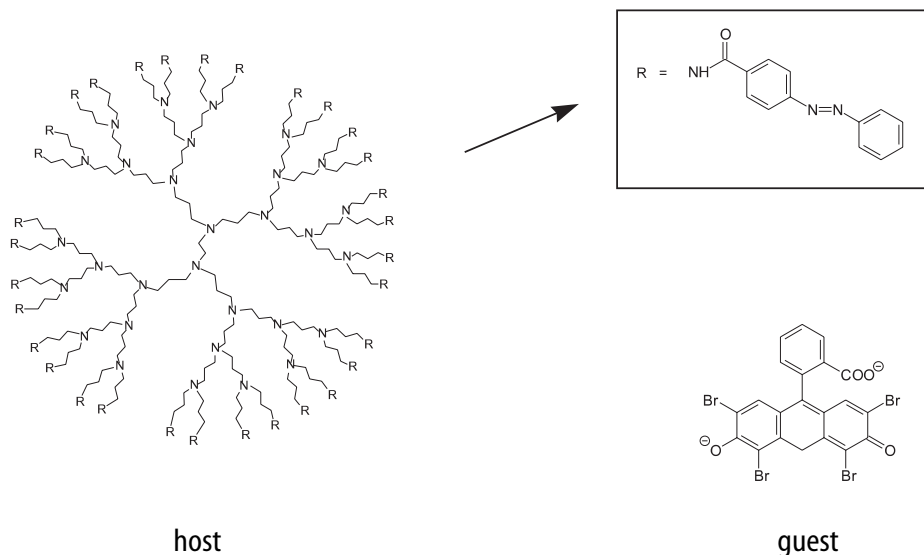


Fig. 31. Interaction of azobenzene-functionalized poly(propylene imine) dendrimers with Eosin Y

4.7

Electrostatic Interactions: Recognition of Cations

Many examples are known in the field of metal complexation. With a suitable periphery a dendrimer serves as an ideal polyfunctional ligand, i.e. host, for the complexation of metals, either at the periphery or with complexation at the interior. This has been of interest in the field of catalysis [160, 161]. Challenging possibilities for ultrafiltration are foreseen. Recently, a highly sensitive sensor was based on dendrimer-based ligands [162]. We will briefly illustrate the main contributions in the field of dendrimers and metal complexation. Dendrimers that use metal ions as building blocks will not be discussed, since these topics have only a slight interaction with the framework of host-guest complexation, but the reader is referred to more extensive reviews on metal-containing dendrimers [64, 163, 164].

4.7.1

Ligand Binding in the Dendritic Core

Aida et al. [165, 166] reported the coordination of different generation dendritic imidazoles to a dendritic porphyrin (Fig. 32). With a 1:1 stoichiometry of host and guest, binding constants decreased significantly as the generation number of the porphyrin increased from 4 to 5, indicative of a decreased possibility for

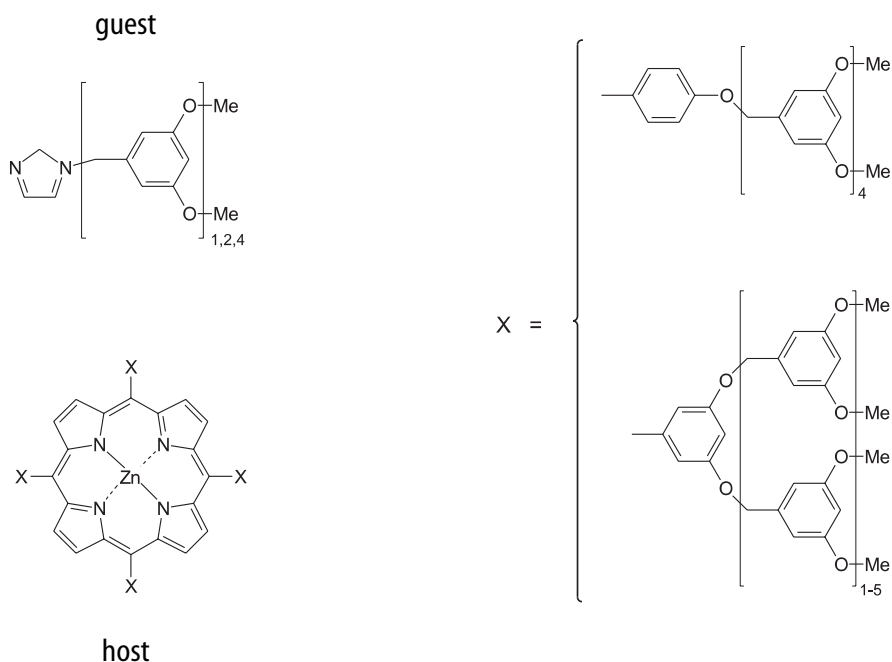


Fig. 32. Complexation of porphyrin dendrimers with imidazole-containing dendritic wedges

interpenetration of host and guest. Size-selective guest complexation was observed as the dendritic porphyrin bound preferentially a small vitamin K₃ molecule (2-methyl-1,4-naphthoquinone) in the presence of a larger porphyrin guest. The dendritic substituents serve as a steric barrier preventing the larger molecule from binding close to the core of the metalloporphyrin [166].

4.7.2

Dendrimers with Metal Binding Sites in the Dendritic Interior

Newkome et al. [167] synthesized a series of dendrimers possessing multiple, internally incorporated, piperazine moieties, which readily form Pd(II) and Cu(II) complexes (Fig. 33). It is postulated that the piperazine ring adopts the

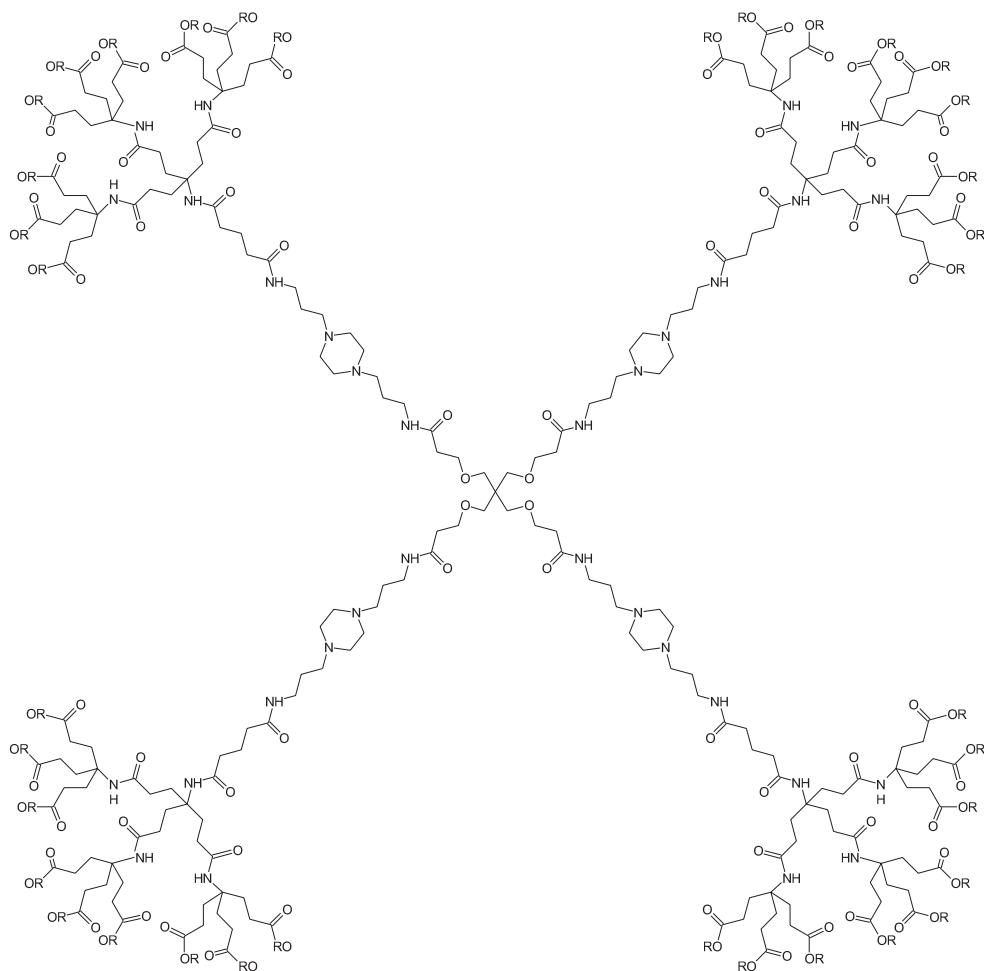


Fig. 33. Dendrimers with piperidine-based units in the interior (R = *t*-Bu)

boat conformation in order to chelate the metal ion. Complexation was followed via ^1H -NMR titration and became evident from a broadening and shifting of the moieties adjacent to the metal coordination center.

Similarly, Ming and Newkome [168] utilized Co(II) as a paramagnetic ^1H -NMR probe to complex to dendrimers containing internal diaminopyridinyl units. Recently, dendrimers with four bipyridine subunits at precise locations within the dendritic substructure have also been reported and their transformation into $[\text{Ru}(\text{bpy}')(\text{bpy})_2]^{2+}$ complexes has been described by Newkome et al. [169].

4.7.3

Metal Binding Sites Throughout Dendrimers

Shinkai and coworkers [170, 171] reported the synthesis and metal-complexation chemistry of a novel series of crown-ether-based cascade molecules (Fig. 34). The amide linkage was reduced to increase the ion-binding affinity of the crown ether moieties. The dendrimer was able to extract metal ions in a generation-independent manner and form a 1:1 complex with Cs^+ unlike the sandwich complexes that Cs^+ forms with polymeric crown ethers. The above results indi-

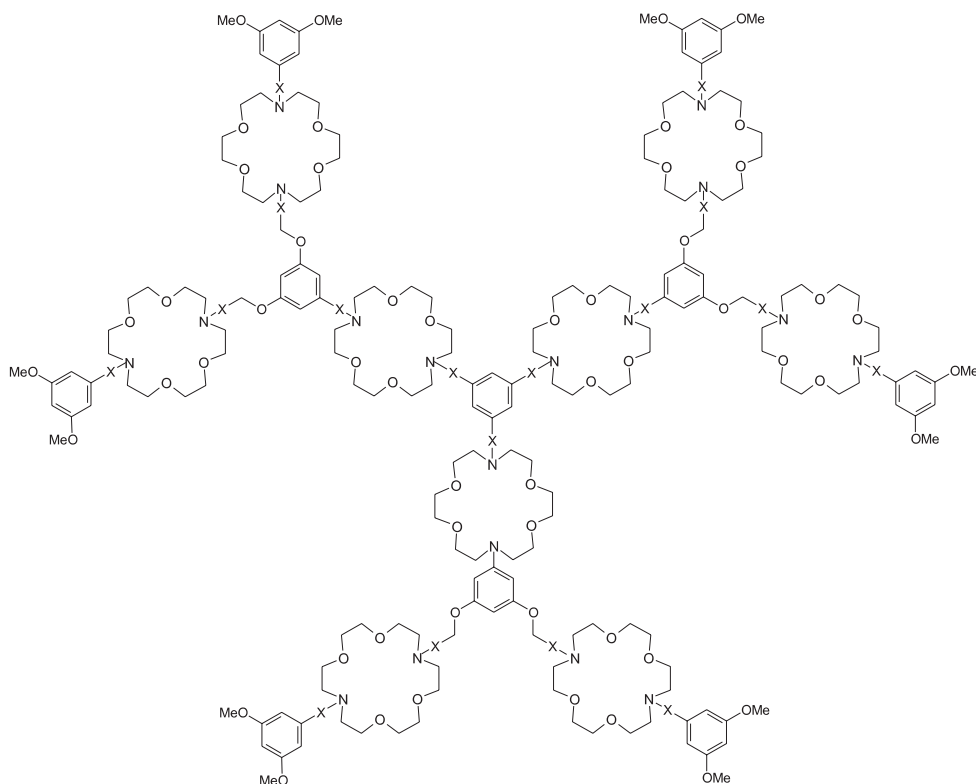


Fig. 34. Dendritic crown ethers

cate that the crown ether moieties in the dendrimer do not necessarily function in a cooperative manner. Solubilization of myoglobin in organic solvents like DMF through interactions of multiple azacrown ethers with ammonium or carboxylate functions on the peptide is only possible for the lowest generation azacrown. Apparently, many dendrimers are required to solubilize one myoglobin molecule, and, presumably, the higher generations are closed structures that do not allow adequate interactions with the protein.

Tomalia et al. [127] have reported on hydrophobically modified PAMAM dendrimers, to obtain an unimolecular inverted micellar structure, and discussed their ability to function as nanoscopically sized container molecules. This was evidenced by the transport of copper(II) salts into various hydrocarbon solvents, like toluene and chloroform. The authors concluded from the blue shift of the absorption maximum that a coordination of the copper to the tertiary amines took place. Incorporation of copper ions into the interior of amine-functionalized poly(amidoamine) dendrimers has previously been shown by ESR and UV/Vis studies [172, 173].

4.7.4

Dendrimers with Peripheral Ligands

Bosman et al. [174] reported the use of amine-functionalized poly(propylene imine) dendrimers as polyvalent ligands (Fig. 35) for various transition metals,

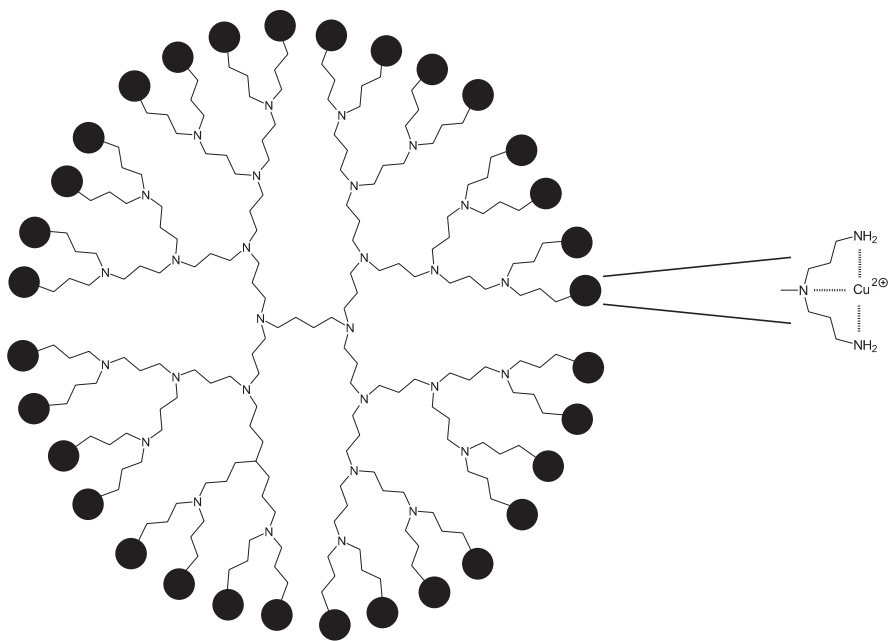


Fig. 35. Amine-functionalized poly(propylene imine) dendrimers as tridentate ligands for the complexation of Cu(II)

like Cu(II), Zn(II) or Ni(II). The bis(propylamine)amine pincer, already present in the periphery of the parent poly(propylene amine) dendrimers, acts as a tridentate ligand for these metals, as evidenced by UV/Vis, ESR and NMR measurements.

A first generation amine-functionalized poly(propylene imine) dendrimer has also been used as a template for the assembly of two rigid Tröger base dizinc(II) bis-porphyrin receptor molecules yielding a self-assembled spherical superstructure encapsulating the dendrimer (Fig. 36) [175]. This concept was also extrapolated to higher generation poly(propylene imine) dendrimers, although steric interactions hampered complete loading of the dendrimer [107].

The amine-functionalized poly(propylene imine) dendrimers represent one of the few examples of dendritic polyfunctional ligands, without the need for modification [59, 176]. Many of the systems known today require an extra modification step to link the coordination site to the dendrimer [149, 177–185].

The use of dendrimers as polyfunctional skeletons has been particularly useful for diagnostic purposes and is based on the possibility of multiplying certain functionalities and hence achieving higher sensitivities. Dendritic substances have been the subject of crucial advances and have already been tested in pre-clinical studies, particularly in the field of contrast media for magnetic resonance. Attachment of Gd(III) chelates to poly(amidoamine) or poly(lysine) dendrimers [186–192] increases ion relaxivity of the contrast agent, which enhances the efficiency (Fig. 37). The dendritic contrast agents are more effective contrast agents than other macromolecular chelates attached to albumin, polylysine or dextran. For instance, animal tests showed quantitative renal elimination and high intravascular retention time.

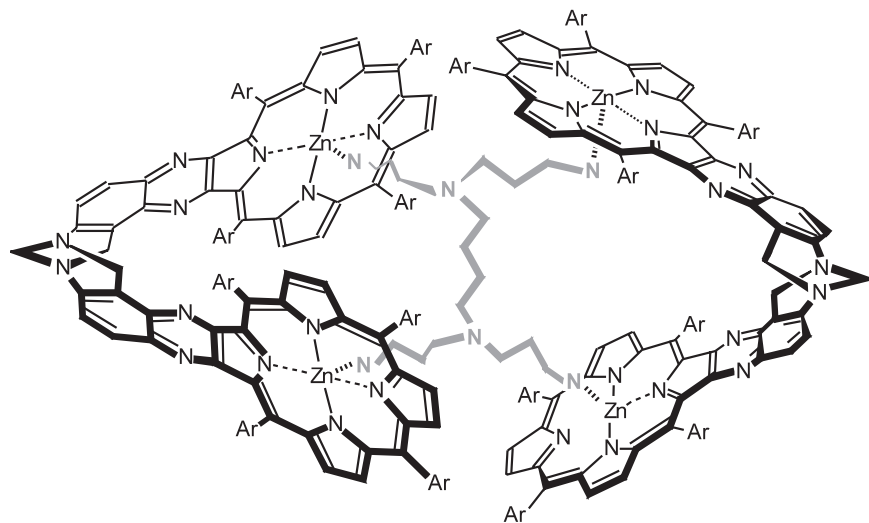


Fig. 36. Templated assembly of two Tröger base dizinc(II) bis-porphyrin receptor molecules around a first generation poly(propylene imine) dendrimer (Ar = 3,5-di-*t*-Bu-benzene)

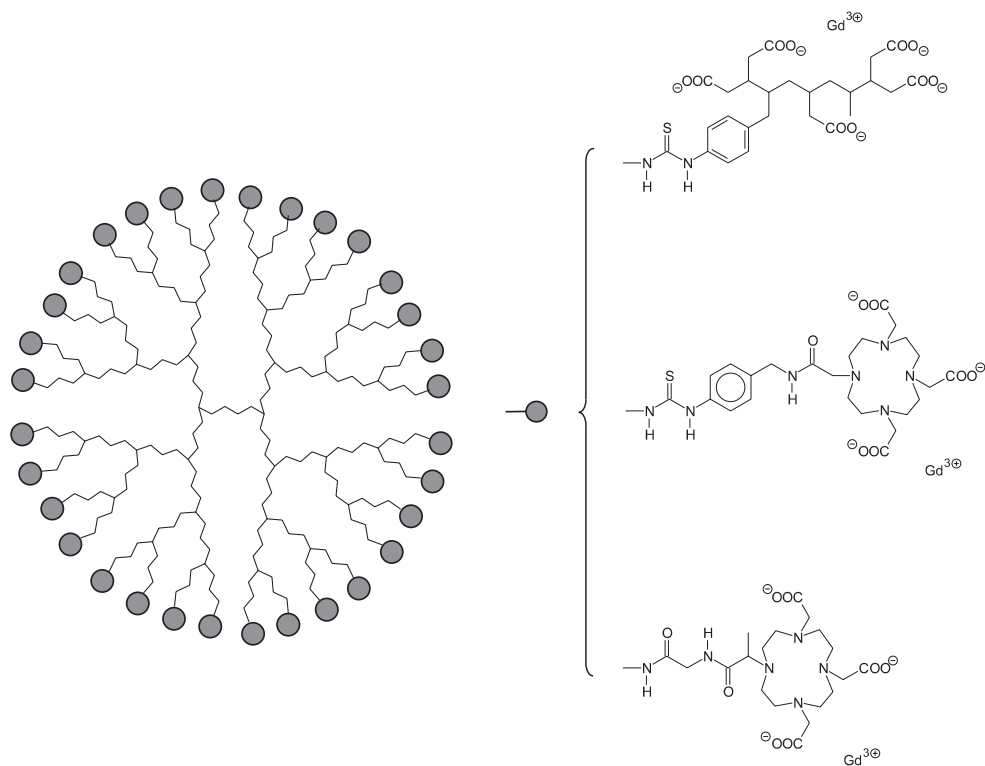


Fig. 37. Dendritic MRI contrast agents consisting of a poly(amidoamine) or poly(lysine) skeleton

4.7.5

Recognition of Other Cationic Guests

Smith [193] recently reported the solubilization of a hydrophilic cationic dye with a carboxylic acid functionalized dendritic wedge (Fig. 38). Solid-liquid extraction experiments were performed using proflavine hydrochloride in the presence of the acid-functionalized dendritic branches. A small, yet significant, amount of the dye could be dissolved. Unfortunately, the complex has low solubility, which prevented an accurate analysis of the stoichiometry. However, the methyl ester functionalized dendrimer showed no uptake. Acetic or stearic acid could not solubilize the dye either, indicating that a simple carboxylic acid or a long unbranched hydrophobic chain is not effective. It is, therefore, suggested that carboxylic acid and dendritic branching act cooperatively, presumably via the formation of supramolecular interactions between the acid and the amine groups within the dendritic environment. The observed change in optical properties, e.g. λ_{max} shifts with increasing generations, are consistent with a model in which the hydrophilic dye becomes encapsulated within a branched environment, shielding it from bulk solvent and enhancing its solubility in the hydrophobic solvent phase.

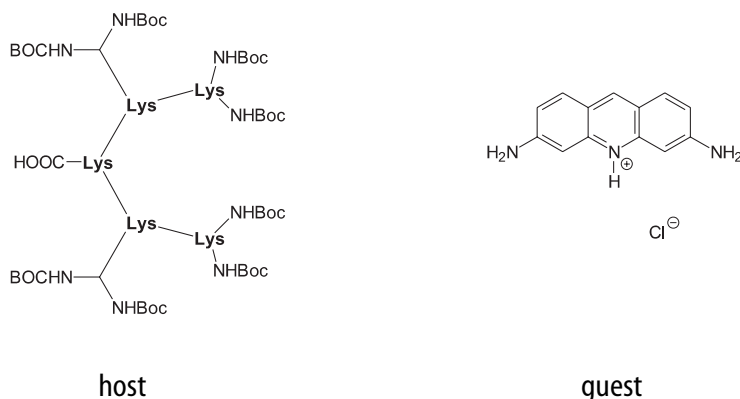


Fig. 38. Complexation of cationic guests using a dendritic poly(lysine)-functionalized carboxylic acid

5 Conclusions and Perspectives

After the initial reports of Tomalia and Newkome, the field of dendrimers has emerged as a new field in macromolecular chemistry. The combination of a discrete number of functionalities, high local densities of functions in one molecule, together with the nanometer dimensions, have explained the broad interest. Due to the large body of research that has been performed on the synthesis of these structures, in principle almost all properties can be tailored. Many methodologies have been established to give the chemist ideal control over architecture, functionality and microenvironment. Moreover, the incorporation of special functions, at the core, in the branches or at the periphery, should enable supramolecular dendrimer chemists to construct the 'ideal host-guest system'. It is the aim of this review to present a personal overview of the field of dendritic host-guest chemistry and show the possibilities and limitations of the dendritic host-guest systems that are available today.

The unimolecular nature of dendrimers yields a new type of amphiphiles, with properties that are superior to those of conventional low molecular weight species. The high local concentration of sites and/or the presence of a microenvironment account for unique (dendritic) features with cooperative effects. The well-defined dimensions and number of functionalities of dendritic molecules also explain the interest from the field of process technology; dendrimers can be used in membrane reactors for purification or workup procedures. The cooperative nature of a multifunctional structure can play an important role in the development of sensors or in medicinal applications. In the area of biomedical engineering, the interest in dendrimers can be understood from the point of multivalency, known as the cluster effect [194]. The studies of Stoddart [195], Roy [196] and Lindhorst [197] on carbohydrate dendrimers are characteristic of this field. Roy and Magnusson [198] reported increased bioactivities of dendritic saccharides relative to their monofunctional derivatives.

With this in mind, the dendritic host-guest systems known today could be applicable in tomorrow's nano- and biotechnology. Thus, with thorough rationalization of the features of dendritic host-guest systems, it should be possible to broaden the potential of dendrimers in supramolecular chemistry even further.

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6

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Supramolecular Dendrimer Chemistry: A Journey Through the Branched Architecture

David K. Smith¹ · François Diederich²

¹ Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK
E-mail: dks3@york.ac.uk

² Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, 8092 Zürich, Switzerland
E-mail: diderich@org.chem.ethz.ch

The three-dimensional branched architecture of a dendrimer consists of three topologically distinct regions: multivalent surface, branching repeat and encapsulated core. This paper discusses the use of dendritic architectures for supramolecular chemistry and, in particular, focuses on the unique ability of the branched shell to affect molecular recognition processes in these three regions. The multivalent nature of the fractal dendrimer surface allows the recognition of multiple guests with maximum efficiency and accessibility. Such multivalent recognition has been used both to enhance binding strengths for weak molecular recognition processes, and also to endow the receptor with much improved guest sensing properties.

With the site of recognition in the branched repeat unit, dendritic hosts can exhibit not only high guest uptake, but also interesting cooperative binding effects. Meanwhile, recognition sites buried at the core experience the unique microenvironment generated by the dendritic branching. This microenvironment can generate new modes of binding and hence novel guest selectivities. As a consequence, such host molecules can mimic aspects of biological behaviour, particularly that of enzymes. Well-defined molecular recognition events with dendritic molecules also provide an entry into more highly organised supramolecular constructions and assemblies. This paper provides a survey of dendritic molecular recognition processes and, in particular, highlights the different ways in which the branched shell can actively control the binding event.

Keywords: Dendrimer, Supramolecular chemistry, Molecular recognition, Self-assembly, Micro-environment.

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1

Introduction

The link between the structure and the function of a molecule is perhaps the most fundamental issue currently addressed by chemists. To what extent can we generate and control molecular properties by tuning the molecular structure through synthetic manipulations? Dendrimer chemistry [1] has constituted such an exciting recent advance precisely because it addresses this type of question. In what ways can the three-dimensional branched architecture control the behaviour of the molecule as a whole, at both a microscopic and a macroscopic level?

Molecular recognition [2] is one of the most sensitive and tunable events studied in modern chemistry and, hence, it is of little surprise that chemists have become fascinated with the interplay between supramolecular chemistry and dendritic architectures [3]. Furthermore, molecular recognition is perhaps the most important biological event and, given that dendrimers are molecules designed to operate on the biological scale, the potential for modelling enzyme behaviour and intervening in biological processes is vast [4]. Potential applications of supramolecular dendrimer chemistry lie in a wide array of areas, ranging from recyclable catalyst design through sensor technology to remediation of industrial pollution. Currently, however, these applications (which will surely come) lie in the future. The goal of the supramolecular dendrimer chemist is to fully understand and characterise the behaviour of these structurally novel receptors. Only when we truly understand the crucial relationship between dendritic structure and function can we design systems to fully maximise the unique properties to which dendrimers provide access.

For the purposes of this article, and for deeper conceptual reasons, we have sub-divided supramolecular dendritic processes into three distinct types dependent on the topological region of the branched architecture (Fig. 1) in

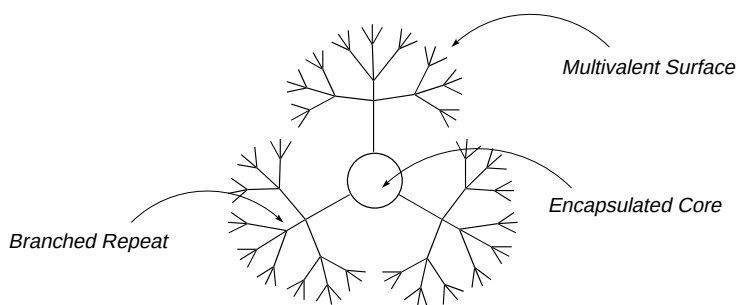


Fig. 1. A generalised dendritic structure with its three unique topological regions

which they take place: (1) the multivalent surface, (2) the branching repeat, and (3) the encapsulated core. In each case, the branched shell plays a different role in controlling the molecular recognition event. In this article we shall journey down through the branched architecture from surface to core, providing a critical overview of dendritic supramolecular processes as we do so. Along the way, we will focus on the unique active roles which the dendritic branching can play. It is hoped this journey will prove thought-provoking to those already in the field, whilst stimulating newcomers to become involved in unveiling more of the fundamental behaviour of these fascinating molecules.

2 Recognition on the Surface

2.1 Introduction

Our starting point is the fractal surface of the dendritic superstructure: perhaps one of its most distinctive features. Like the leaves on a tree, it is the dendritic surface which is presented to the outside world and, consequently, structural control of the surface plays a major role in controlling the physical properties (e.g. solubility) of the molecule as a whole [5]. The multiplicity of surface groups suggests a number of special features which molecular recognition at the dendritic surface could exhibit. These include (1) the formation of complexes with high guest/dendrimer stoichiometries, (2) the enhancement of weak binding processes through the capacity to form multiple host-guest interactions, and (3) enhanced sensory effects as a consequence of the multiple molecular recognition processes causing a greater perturbation of the dendritic host. Examples of these and other effects of the branched shell will be highlighted in the following sections.

2.2 Metal Complex Formation

One of the best understood recognition processes is metal ion binding, and there has been considerable interest in the formation of multiple metal ion com-

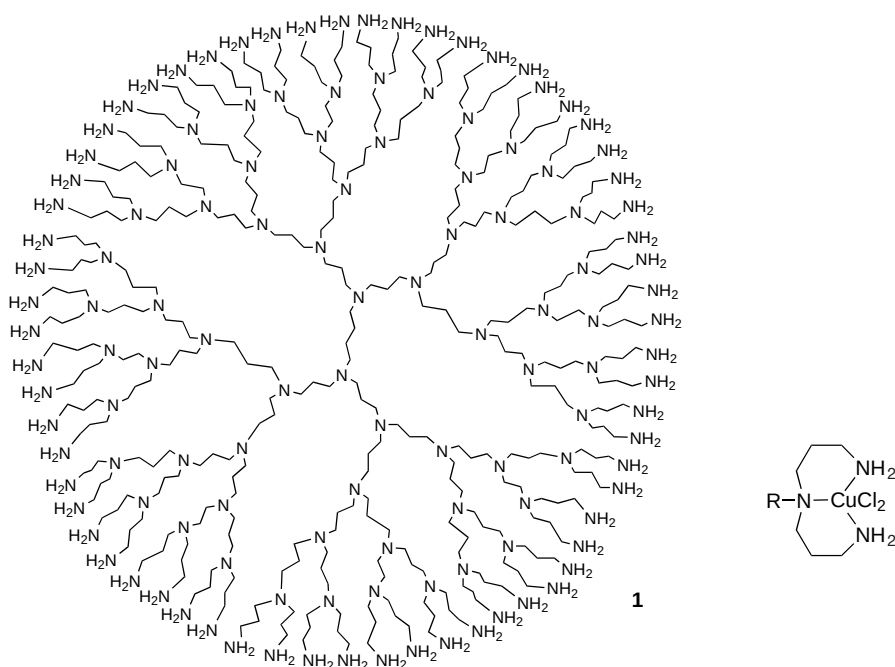
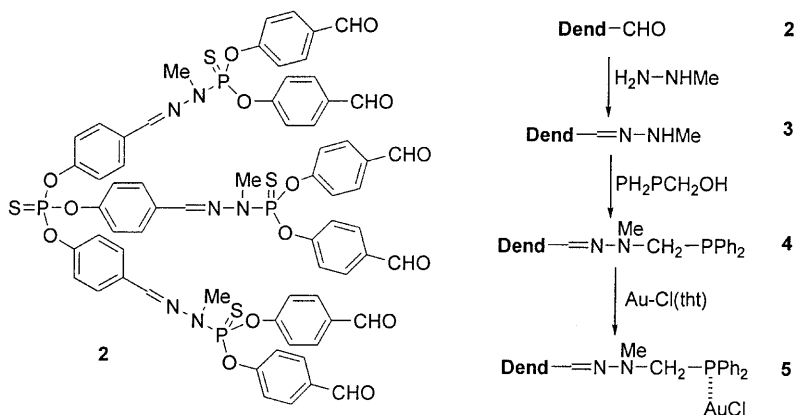


Fig. 2. Dendrimer 1 binds up to 32 metal ions across the surface of the branched molecule

plexes covering a dendritic surface. An illustrative example of dendritic surface metallation (1) is shown in Fig. 2 [6]. Each bis(3-aminopropyl)amine unit can complex one copper(II) ion. The degree of metal ion uptake was indeed shown to be controlled by the dendritic generation, being proportional to the number of surface group ligands available. The Cu(II) complex of the [G-5] dendrimer was visualised using electron microscopy as spherical particles with a radius of 30 ± 10 Å. These metallodendrimer complexes were investigated electrochemically, exhibiting a single irreversible reduction wave. Interestingly, the reduction of Cu(II) to Cu(I) became more favoured at higher dendritic generation, presumably as a consequence of destabilisation of the more highly charged Cu(II) ion as its density on the surface increases. There is particular interest in surface-metallated dendrimers as a consequence of the ability of metal ions to catalyse a range of interesting synthetic transformations [7]. It is hoped that the increased molecular weight of dendritic catalysts will render the catalyst more amenable to recycling, for example, via ultrafiltration technology. Furthermore, it should be possible to constrain such catalysts (like enzymes) within membrane reactors without any leakage.

Majoral and co-workers have prepared phosphorus-based dendrimers up to the 10th generation and subsequently grafted phosphino groups onto their surfaces (sequence 2–5 in Scheme 1) [8]. These surface-located phosphino groups are ideal for binding Au(I). The [G-10] dendrimer (theoretical molecular weight 1,715,385), when complexed to gold, was visualised as spheres of 150 Å



Scheme 1. Phosphorus-based dendrimers such as **2** can, after appropriate functionalisation, bind multiple numbers of gold atoms across their surface allowing visualisation by electron microscopy (tht = tetrahydrothiophene)

diameter using high resolution electron microscopy. In addition to these isolated spheres, aggregates were also detected. Unfortunately, the complexation process was only followed by ^{31}P NMR methods, and no quantitative estimate of surface coverage was given. There was, however, no marked difference in reactivity or complexation on going from [G-1] to [G-10] and, although there must be some doubts about the monodispersity of these molecules, the architectures remain, nevertheless, spectacular.

There are a number of metal ions which are useful in medicine. For example, lanthanide chelates are used as contrast agents for the magnetic resonance imaging of soft tissues [9]. Unfortunately, these low molecular weight chelates flow very quickly out of blood vessels and are consequently not useful for the visualisation of flowing blood (angiography). Macromolecular contrast agents should remain in the blood vessels due to their size. Furthermore, the increased mass of the complex should increase the tumbling rate of the complex and yield increased relaxivities (and better imaging sensitivity). There has therefore been considerable interest in the use of dendritic lanthanide complexes [10]. For example, Margerum and co-workers compared surface-modified dendritic lanthanide receptor **6** (Fig. 3) with similarly modified polylysine derivatives [11]. Loading of the dendritic surface with gadolinium complexes, although high, was not complete. Nevertheless, the authors did measure two clear dendritic effects on the activity of these gadolinium complex contrast agents. The first was that as the dendritic generation increased, so did the relaxivity: from 14.8 ([G-3]) to 18.8 ([G-5]) mM s^{-1} . Secondly, the half-life for elimination from the blood of rats was increased from 11 min ([G-3]) to 115 min ([G-5]). Meanwhile, modified polylysine only showed a relaxivity of 10.4 mM s^{-1} and the half-life for elimination from blood was just 65 min. This indicates the way in which both the size and structure of the branched macromolecule can favourably affect the properties of such metal complexes.

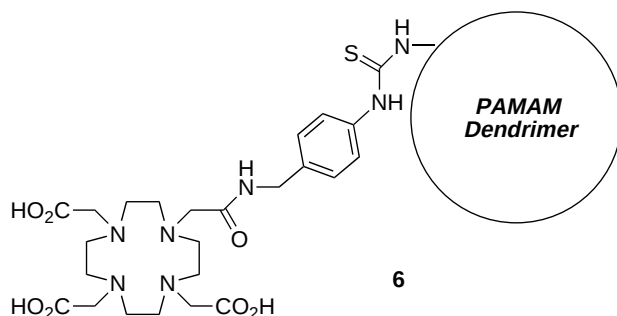


Fig. 3. Multiple lanthanide receptor **6**, suitable for use as a magnetic resonance imaging contrast agent. PAMAM = poly(amido amine)

2.3

Anion Recognition

The design of selective receptors for anionic guests is an area of great current interest to supramolecular chemists, and of considerable biological and environmental relevance [12]. Astruc and co-workers have taken an interesting approach to the synthesis of dendritic anion receptors, such as **7**, in which the periphery of a branched molecule is functionalised with amido-ferrocene units (Fig. 4) [13]. Such subunits interact with anions through the formation of hydrogen bonds from the amide N-H group and, on oxidation of the ferrocene groups, an electrostatic interaction with the bound guest can also occur. This means that such receptors can electrochemically sense the presence of bound anions in CH_2Cl_2 solution via a cathodic shift of their redox wave. The electrochemical interaction with a variety of anions (e.g. H_2PO_4^- , HSO_4^-) was investigated and the anion-induced redox shift increased in magnitude with increasing dendritic generation. The authors argued that this dendritic effect was a consequence of the greater surface packing of the sensor groups at higher dendritic generation.

As an extension to this work, Astruc and co-workers produced dendrimers in which the amido-ferrocene groups on the surface were replaced by a positively charged amino-functionalised Fe-based organometallic in which one of the ferrocenyl cyclopentadienyl rings was replaced by a benzene ring [14]. The interaction of these receptors with anions in d_6 -DMSO could be easily monitored by ^1H NMR titration methods: the interaction is strong as a consequence of the permanent positive charge on the dendritic receptors. For halide anion complexation there was an increase in the apparent association constant with dendritic generation, as would be expected on the basis of the increased surface charge. For HSO_4^- anion recognition, however, the apparent association constant was lower for the dendritic system as compared with smaller individual dendritic branches. It was argued that the cavities at the dendritic surface could not open sufficiently to accommodate this larger anion.

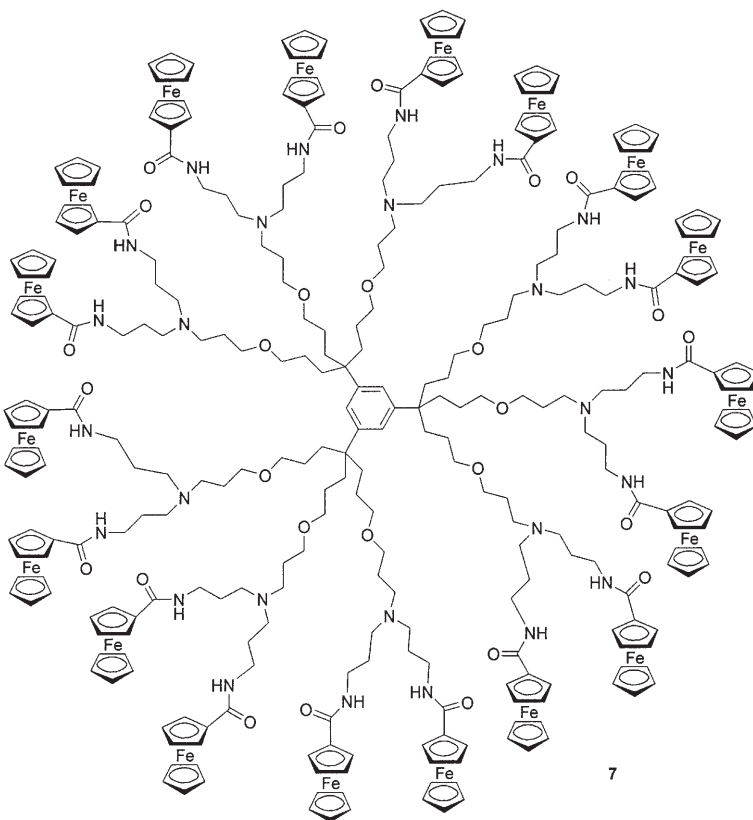


Fig. 4. Dendritic receptor 7 binds and electrochemically senses the presence of inorganic anions in CH_2Cl_2 solution. Smaller, less-branched analogues exhibit a smaller redox response to negatively charged guests

2.4

Neutral Molecule Recognition

Neutral molecule recognition is one of the more challenging areas of supramolecular chemistry and, in particular, there is a need for sensors for biologically and environmentally relevant substrates [15].

In 1996, Shinkai and co-workers reported a small branched poly(amido-amine) (PAMAM) dendrimer terminated with boronic acid residues (Fig. 5) [16]. It is well known that such boronic acids form cyclic boronate esters with vicinal diols and, consequently, act as efficient sugar receptors in aqueous solution [17]. The dendritic receptor 8 bound D-galactose and D-fructose 100 times more strongly than a simple monomeric analogue. The enhanced binding strength was ascribed to the ability of the two boronic acids located on the dendritic surface to act cooperatively in binding one saccharide guest. Furthermore, each boronic acid had a nearby amino-anthracenyl unit, capable of detect-

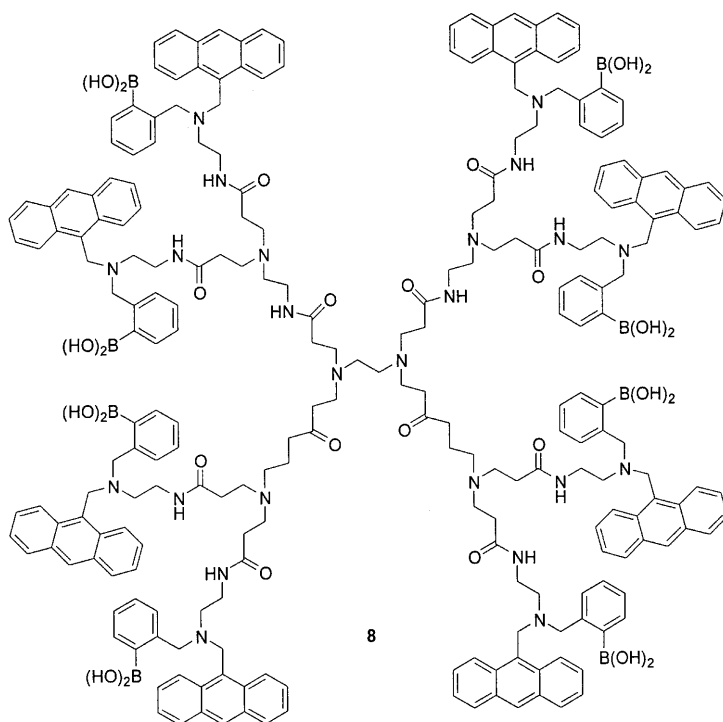


Fig. 5. Dendritic receptor **8** for saccharide guests senses their presence in methanolic solution through a fluorescent response

ing the presence of the bound guest via a perturbation of its fluorescent output. In the absence of sugar, the (aminomethyl)anthracenyl N-atoms quench the emission of the aromatic chromophores by photoinduced electron transfer. Upon boronate ester formation, these N-atoms coordinate to the B-atoms with their lone pair and anthracene fluorescence appears. The magnitude of sensory response was considerably higher for the branched receptor compared with a simple monomeric boronic acid. This indicates an advantage of the increased degree of functionalisation available for molecular recognition on a dendritic surface.

Metallodendrimer **9**, reported by van Koten and co-workers, has been used for the detection of sulfur dioxide gas, an important pollutant (Fig. 6) [18]. Sulfur dioxide binds strongly and reversibly to this receptor into one of the vacant axial coordination sites on each square planar platinum centre and, in doing so, induces a change in the UV-vis spectrum of the dendrimer (colourless to bright orange), even at very low concentrations. Repetitive adsorption-desorption cycles were performed without significant loss of material or activity. The authors proposed that the principal dendritic advantage in this case was that the large, rigid, disc-like branched molecule would be more amenable to recovery via ultrafiltration technology. Research in pursuit of larger, more sensitive, recyclable dendritic SO_2 sensors is ongoing.

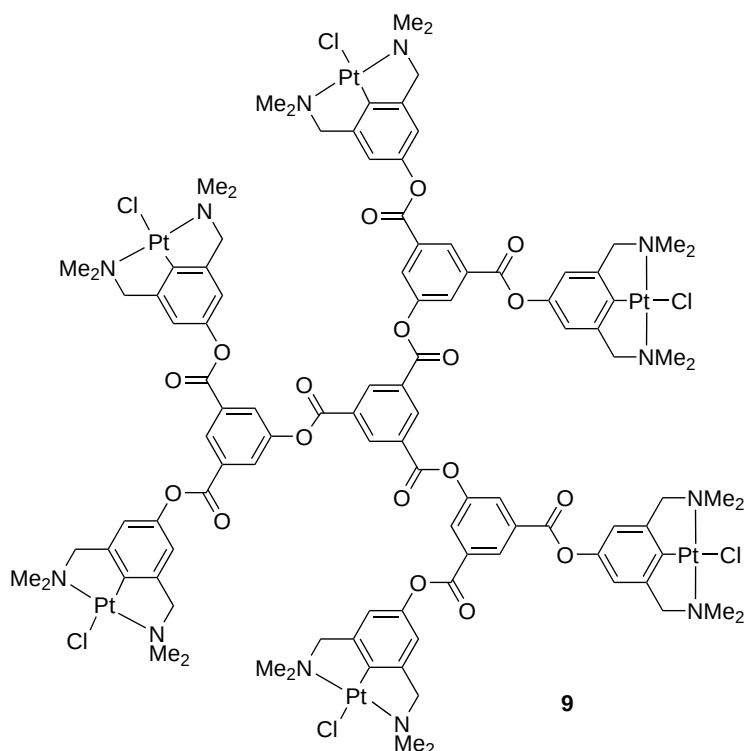


Fig. 6. Dendritic platinum complex **9** acts as both a receptor and a sensor for sulfur dioxide gas in CH_2Cl_2 solution

2.5

Dendritic Surfaces Designed for Biological Intervention

Perhaps the most exciting area of dendritic surface chemistry has been the development of dendrimers designed to specifically intervene in different biological processes. Such dendrimers frequently have surfaces modified with biologically relevant building blocks. In an excellent review, Stoddart and co-workers described the synthetic progress made by themselves and others towards the incorporation of carbohydrate building blocks into dendritic macromolecules [19]. The importance of saccharides in biological systems, in particular their ability to interact with a range of biologically important proteins [20], has established them as a major focus of current research [21]. Sugar-protein interactions are dependent on both multiple hydrogen bonds and hydrophobic interactions and are relatively weak due to competition from the O-H groups of the aqueous solvent medium itself. It is well established that one way of enhancing these host-guest interactions is by using saccharide clusters rather than individual sugars [22].

Since 1993, Roy and co-workers have published a series of excellent papers, extending this principle of carbohydrate multivalency to dendritic systems [23].

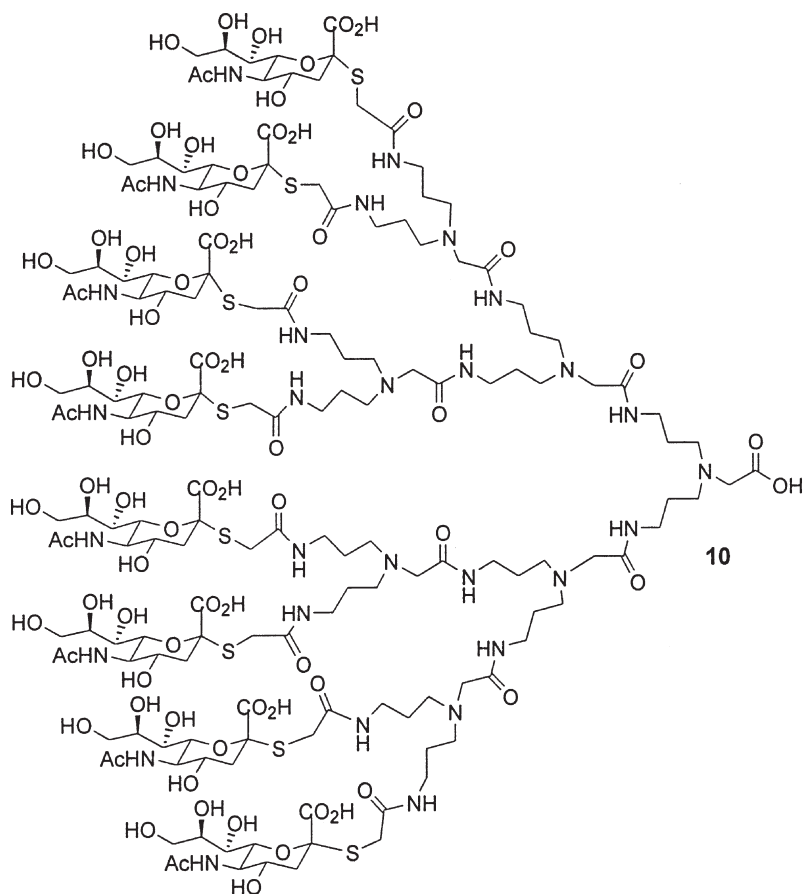


Fig. 7. Branch-like multidentate dendritic saccharide **10** designed for intervention in biological systems

In one of these [23c], they compared the supramolecular properties of α -sialodendrimers with different geometries: branch-only (**10**) and spherical (**11**) (Figs. 7 and 8) [24]. In particular, they monitored the ability of these novel glycodendrimers to preferentially interact with human α_1 -acid glycoprotein and inhibit the binding of horseradish peroxidase labelled *Limax flavus* lectin. For the branch-only type dendrimer, interaction with the protein was strongest for the tetrameric system, with the relative potency decreasing for the octamer and hexadecamer (Table 1). For the spherical system, however, the relative potency increased up to a dendrimer valency of 6, and then maintained this high level of inhibition (IC_{50} around 100 nM per sugar; Table 1). It seems clear that the conformational and geometric organisation of the sialoside is of considerable importance in controlling the interaction of the branched molecule with the protein. Such studies with carefully designed branched structures promise to yield considerable insight into the sugar-binding properties of proteins. Inter-

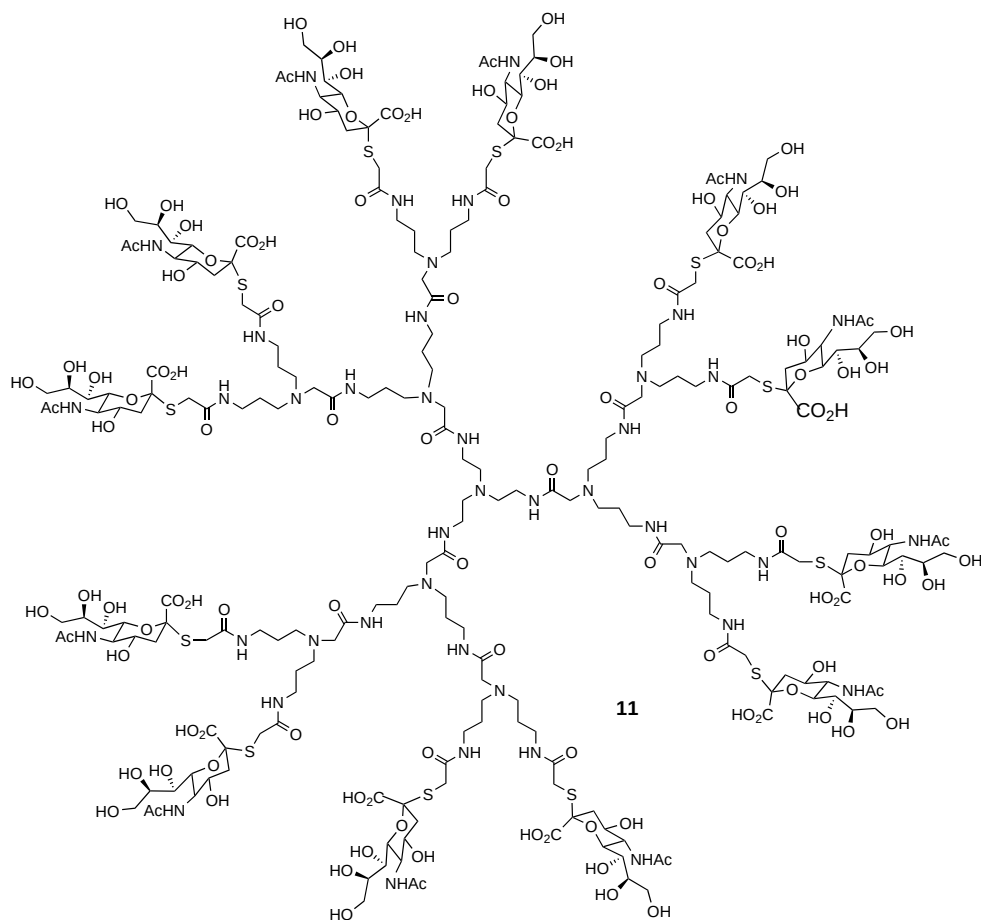


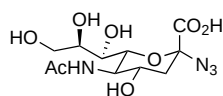
Fig. 8. Spherical multidentate dendritic saccharide **11** designed for intervention in biological systems

vention in biological saccharide-protein recognition events is of considerable practical interest and importance because it could give rise to anti-adhesive drugs [25] and carbohydrate-based vaccines [26].

Other biologically important building blocks have also been used for the construction of branched architectures. Of particular relevance to supramolecular chemists are the branched nucleic acids of Damha and co-workers [27], the interaction of which with RNA has been investigated, and also the peptidic dendrimers of Tam and co-workers [28], of particular interest for the development of peptidic vaccines. It has also been illustrated that folate-functionalised dendrimers accumulate efficiently in tumour cells – indicating the way in which surface-modified branched molecules may be applied to the problem of targeting specific sites of disease [29].

Table 1. Inhibition of binding of human α_1 -acid glycoprotein (orosomucoid) to horseradish peroxidase labelled *L. flavus* by sialodendrimers. The standard used for calibration was 2-acet-amido-5-deoxy-D-glycero- α -D-galacto-2-nonulopyranosyl azide

Structure	No. of sialoside residues	Relative potency	Potency per sialoside	IC ₅₀ (nM)	IC ₅₀ (nM) per sialoside
Standard	Monomer (1)	1	1	1500	–
Branch-only	Dimer (2)	8.5	4.2	176	352
Branch-only	Tetramer (4)	127	32	11.8	47.2
Branch-only	Octamer (8)	7.3	0.91	206	1650
Branch-only	Hexadecamer (16)	3.5	0.22	425	6800
Spherical	Tetramer (4)	26	6.4	58.7	235
Spherical	Hexamer (6)	89	15	16.9	101
Spherical	Octamer (8)	86	11	17.5	140
Spherical	Dodecamer (12)	182	15	8.2	99

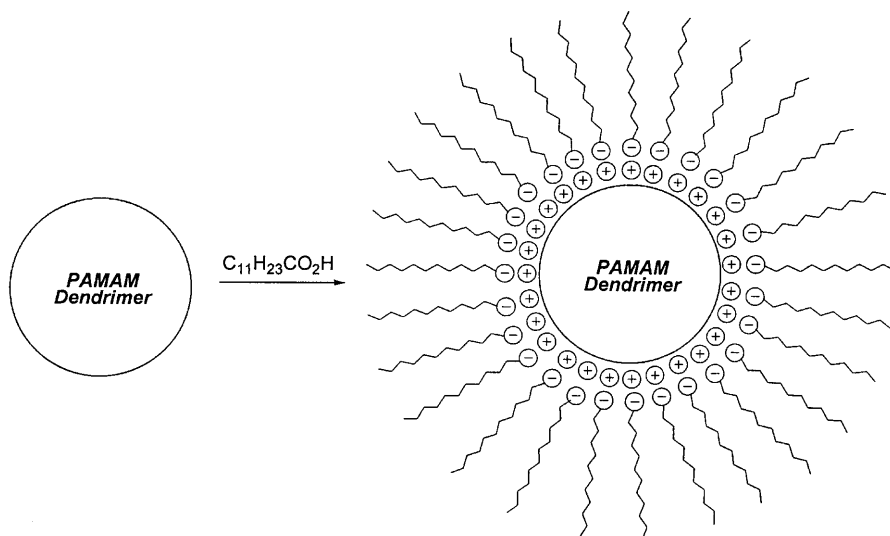
**Standard**

2.6

Surface Ion-Pairing Chemistry

Another interesting approach which uses supramolecular dendrimer chemistry to intervene in biological processes has been reported by Tomalia and co-workers. Their PAMAM dendrimers can, when protonated in aqueous solution, interact with polyanionic guests such as polyphosphate nucleic acids (DNA, RNA) [30] via ion-pairing, with the associated formation of a large number of intermolecular coulombic and hydrogen-bonding interactions [31]. Furthermore, such complexation assists the transfer of genetic material into mammalian cells. The [G-9] PAMAM dendrimer was considerably more effective than commercially available cationic lipid preparations in a majority of cell lines. It is also noteworthy that the dendritic delivery systems are more efficient than simple polylysine, a linear chain analogue of the branched system. There is, however, some debate surrounding these results. Szoka and co-workers reported that the transfection ability of monodisperse PAMAM dendrimers was actually relatively poor, and that the dendrimers were considerably more active when somewhat degraded [32]. This was illustrated by deliberately degrading PAMAM dendrimers and then measuring their enhanced transfection abilities. They argued the importance of the structure on processes such as dendritic collapse, swelling and aggregation accounts for this phenomenon. Obviously, the accurate characterisation and structural analysis of these dendrimer-nucleic acid aggregates poses considerable problems, although a recent report indicates an interesting use of EPR spectroscopy to this end [33]. The medicinal relevance of this general approach to gene transfer, however, is obvious (e.g. antisense technology [34]).

Crooks and co-workers have used supramolecular ion-pairing on a dendritic surface to completely modify the properties of the branched molecule as a whole



Scheme 2. Ammonium carboxylate ion-pairing can be used to modify surface properties, and hence the physical behaviour, of a PAMAM dendrimer

[35]. Hydrophilic PAMAM dendrimers possessing an amine-functionalised surface can be solubilised into toluene by the addition of dodecanoic acid. Transmission Fourier transform infrared (FTIR) spectrometry indicated that the solubilisation was accompanied by proton transfer from the carboxylic acid to the amine groups on the dendrimer. This process therefore resulted in multiple ammonium carboxylate ion-pair interactions with supramolecular assembly of a hydrophobic shell around the hydrophilic branched molecule (Scheme 2). This approach also allowed the extraction of dendrimer-encapsulated metal nanoparticles into organic solvents, where they remained catalytically active. The assembly process is reversible and the hydrophobic shell can be simply removed from the dendritic exterior by extraction into a low pH aqueous phase, which ensures the protonation of dodecanoic acid. This is an elegant way of using supramolecular chemistry to moderate macroscopic dendrimer properties.

3

Recognition in the Branches

3.1

Introduction

Underpinning the dendritic surface is the dendritic branching itself. As a consequence of extensive and elegant synthetic development [36], there is now a huge range of dendritic motifs available to the molecular architect. Whilst it is the surface that controls many of the macromolecular properties of the dendrimer, such as solubility, it is the branched repeat unit which mediates the properties of the dendritic interior.

3.2

Non-Specific Recognition

The dendritic branches are spread through most of the architecture and, as a consequence of this, much of the work on complexation within the branches of a dendrimer has been devoted to the investigation of relatively non-specific recognition events, which will only be briefly discussed here. The concept is simple: a spherical branched molecule, if suitably functionalised, can act like a unimolecular micelle. Newkome et al. [37] and Fréchet and co-workers [38] reported systems in which the surface of the dendrimer consisted of negatively charged carboxylate groups, whilst the interior branching was primarily hydrophobic in nature. The dendritic surface therefore provides aqueous solubility, whilst the dendritic interior provides the ideal refuge for hydrophobic molecules. Easily traced molecules, such as hydrophobic dyes, provided an ideal method for measuring the degree of solubilisation inside such dendritic micelles. One great advantage of these unimolecular micelles is that, unlike traditional micelles, they are stable even at low concentration (i.e. there is no critical micelle concentration). Therefore guest solubilisation can occur across a much wider range of conditions.

Recently, the approach has been reversed, with the synthesis of dendrimers containing apolar peripheries but polar interiors. These reverse unimolecular micelles have been used for the extraction of hydrophilic dyes from the aqueous phase into organic solution [39], and for a dendrimer functionalised with fluororous chains, into liquid and supercritical CO₂ [40].

Meijer's 'dendritic box' [41] permanently incorporates dye molecules into the interior of the branched molecule by the process of trapping [42]. The guest molecules become trapped when a sterically congested, hydrogen-bonding surface is synthetically grafted onto the dendrimer. Selective release of smaller trapped guests was achieved by partial deprotection of the surface groups – a good example of the way in which the dendritic surface can still control the recognition process occurring inside the branched molecule.

3.3

Specific Recognition

Examples in which specific recognition sites are incorporated in the dendritic branches are, however, severely limited. This is presumably partly for synthetic reasons, and partly as a consequence of the difficulty of accurately characterising multiple recognition events in the dendritic interior.

Shinkai and co-workers have reported branched receptor **12** containing multiple crown ether sites (Fig. 9) [43]. As expected, this receptor exhibited good metal ion binding and extraction ability, in particular for K⁺. The efficiency of metal ion extraction was not affected by the dendritic generation. Interestingly, however, the complexation process appeared to have 1:1 crown/cation stoichiometry, and no cooperative complexation effects, in which two crowns become involved in binding one guest, were observed, even with the larger alkali metal cations. The interaction of these dendritic receptors with the surface of myo-

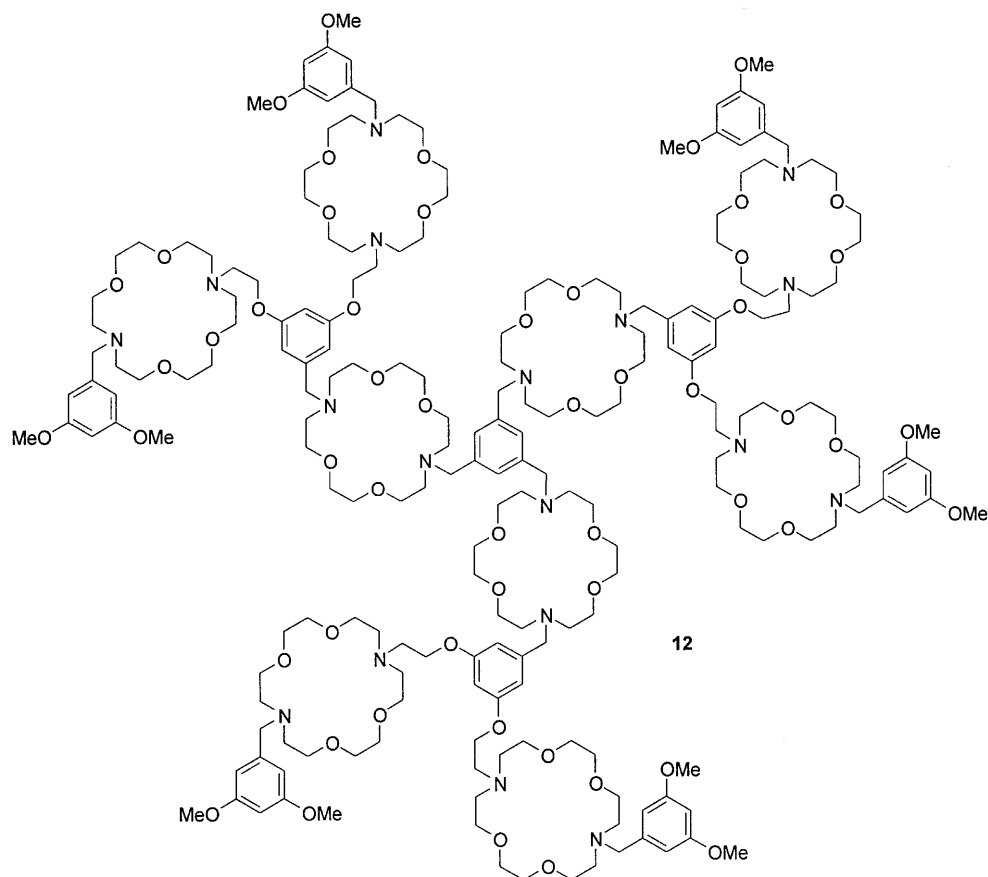


Fig. 9. Dendritic crown ether **12** binds multiple alkali metal cations in its branches

globin was also investigated. This protein has a number of protonated amines on its surface. The [G-1] dendrimer interacted most strongly with myoglobin, solubilising it into organic solvents. More than one equivalent of the branched molecule per protein was required for this solubilisation process to occur. Surprisingly, however, [G-2] (**12**) and [G-3] receptors did not exhibit this solubilisation effect, an observation the authors ascribed to the increased steric hindrance of these molecules, which may inhibit their ability to interact with, and cover, the surface of myoglobin efficiently. Branched molecules with multiple recognition sites and a planar or slightly curved cross-section would be of considerable interest for their interaction with large surfaces having relevance to biological or materials chemistry.

Sanders and co-workers recently reported branched metalloporphyrin **13** containing nine porphyrin rings in its skeleton, connected via a combination of rigid and flexible linkers (Fig. 10) [44]. This elegant structure is designed in such a way that the arms can fold in a cooperative and predetermined manner in

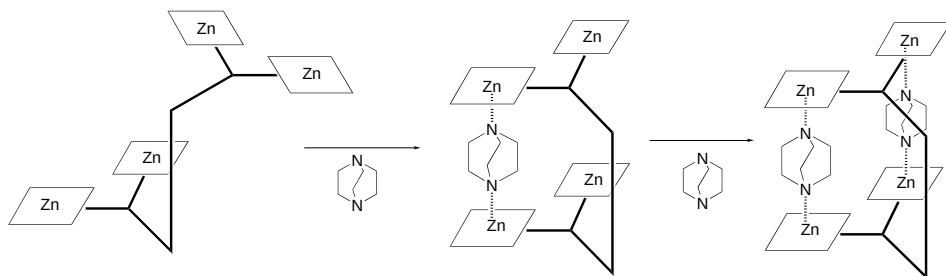
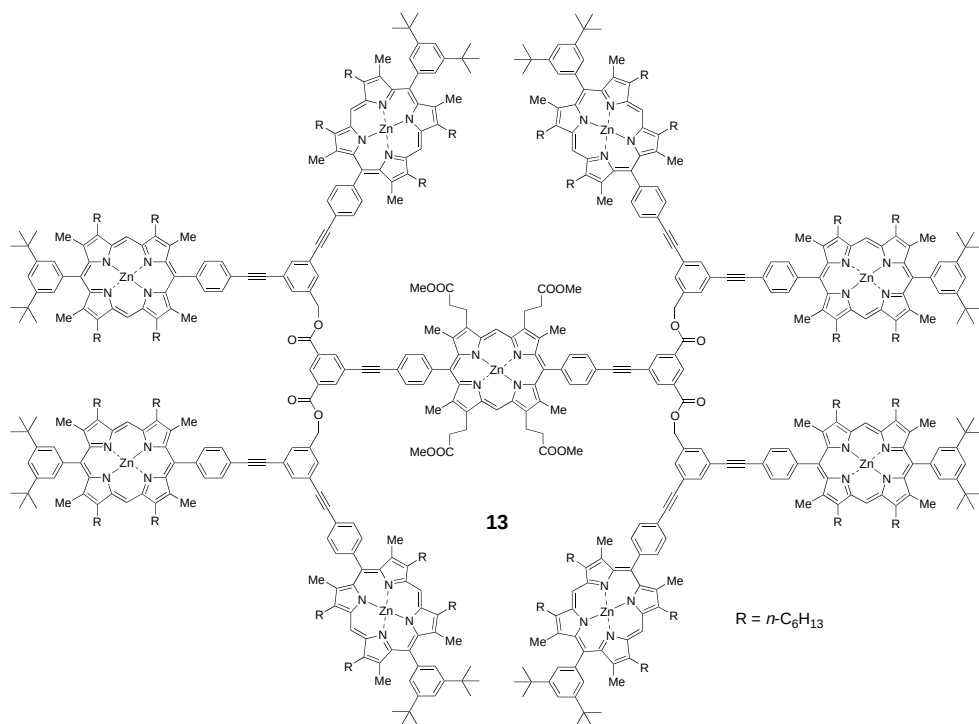


Fig. 10. Dendritic metalloporphyrin-based receptor **13** exhibits interesting cooperativity effects on binding rigid diamine guests such as DABCO

response to the bifunctional ligand 1,4-diazabicyclo[2.2.2]octane (DABCO). In particular, binding of the first equivalent of DABCO should encourage the binding of the second equivalent, leading to a strong cooperativity for the recognition event. Although it is difficult to extract precise binding constants from such complex systems (one of the problems of investigating recognition in the dendritic branches), UV-vis spectroscopy was used to analyse the properties of the dendrimer-DABCO complex. Control experiments showed that the Soret band of an uncomplexed zinc-porphyrin monomer appears at 412 nm, whilst that for the 1:1 complex with DABCO appears at 426 nm. By contrast, a complex with 2:1

porphyrin/DABCO stoichiometry absorbs at 420 nm. For dendrimer **13** in the presence of up to an almost 10^6 -fold excess of DABCO, the Soret band still occurs at 420 nm; the difficulty of converting these '2:1 complexes' to the '1:1 complexes' in this case was taken as evidence for the strength of the '2:1 complexes', bolstered by the cooperativity of the well-designed recognition event in the dendritic branches. As further evidence for this cooperativity, an analogue which cannot exhibit a cooperative effect on binding DABCO was studied. It required only a 7000-fold excess of DABCO to switch the porphyrin/DABCO stoichiometry from 2:1 to 1:1.

It is expected that, in the coming years, recognition in the dendritic branching will increasingly enable unique cooperative effects to be observed. Furthermore, as Sanders and co-workers point out, the effect of such cooperative recognition on the electrochemical, photophysical and conformational properties of dendritic molecules could be profound.

4

Recognition at the Core

4.1

Introduction

Our journey has now taken us downwards from the dendritic surface through the branches to the very centre of the dendrimer. It can easily be visualised that the encapsulated core experiences an environment which is generated principally by the branched shell surrounding it and, in 1993, Fréchet and co-workers reported that the centre of a dendritic structure experienced just such a unique microenvironment [45]. Since then, there has been considerable interest in modifying physical properties, such as optical [46] or electrochemical [47] behaviour, by dendritic encapsulation. In a previous article [4], we highlighted the way in which this type of dendritic microenvironment is analogous to the local environments generated within protein superstructures. Such microenvironments frequently play a crucial role in mediating molecular recognition and enzyme catalysis. Consequently, there has recently been intense interest in the development of dendritically buried recognition sites as mimics for biological systems.

4.2

Apolar Binding

Perhaps the most highly developed dendritic receptors are the dendrophanes (dendritically shielded cyclophanes) of Diederich and co-workers, which possess a hydrophobic recognition site encapsulated within the branched architecture [48]. These receptors were designed to mimic the behaviour of the large number of enzymes which contain deeply buried apolar binding sites within their globular superstructures [49]. The synthesis of dendrophanes such as **14** (Fig. 11) was first achieved via the divergent strategy, using the poly(ether amide)

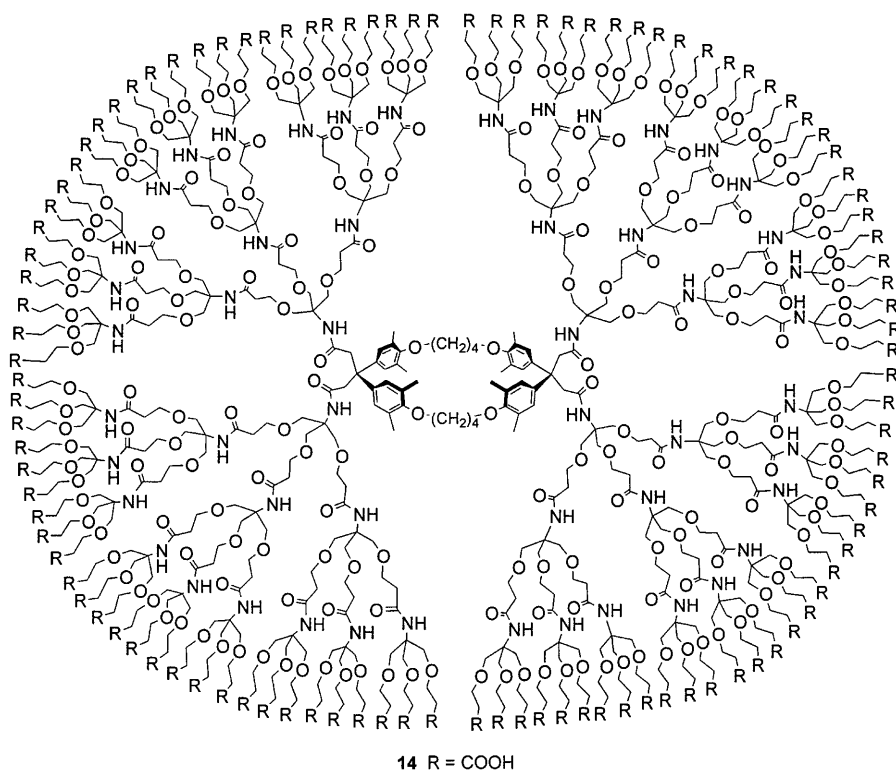


Fig. 11. Dendritic cyclophane (dendrophane) **14** possesses a hydrophobic recognition site deeply buried within the branched shell

dendritic branching popularised by Newkome and co-workers [50]. Such dendrophanes [51] are soluble in aqueous or mixed aqueous solvents at moderate to high pH values, when the exterior surface is negatively charged. This high electrostatic charge on the dendritic surface should yield an open structure, as a consequence of mutual surface group repulsion.

The recognition properties of **14** towards naphthalene-2,7-diol were investigated in aqueous phosphate buffer which contained small quantities of organic co-solvent. In all cases, the binding occurred with 1:1 host/guest stoichiometry and with specific perturbation of the nuclear magnetic resonances (NMR) of the cyclophane unit. This validated the concept of localised molecular recognition at the dendritic core, ruling out the possibility of non-specific recognition within fluctuating voids in the branched shell. ^1H NMR analysis indicated that the host-guest exchange kinetics became slower as the dendrimer became larger, and whilst titration studies with [G-1] and [G-2] were amenable to quantitative analysis, titrations with [G-3] no longer displayed resolved signals, a finding attributed to slow host-guest exchange. The binding constants for [G-1] and [G-2] were of a similar order of magnitude to those for the non-dendritic cyclophane [G-0].

Table 2. Emission maxima (λ_{max}) of TNS ($c = 10 \mu\text{M}$) in aqueous phosphate buffer (pH 8.0) bound in the cyclophane cavity of differently sized dendrophanes of type **14** ($c = 0.25 \text{ mM}$, $\lambda_{\text{exc}} = 360 \text{ nm}$, $T = 300 \text{ K}$). The emission maxima of TNS in selected protic solvents are given for comparison

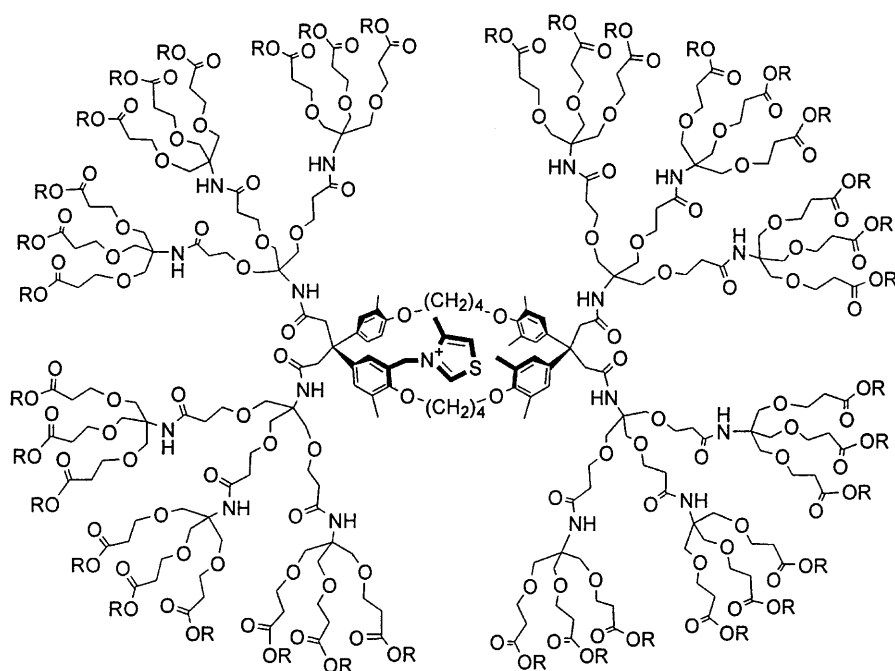
Environment	λ_{max} (nm)	Environment	λ_{max} (nm)
[G-0]	ca. 450	H ₂ O	ca. 500
[G-1]	443	MeOH	443
[G-2]	435	EtOH	429
[G-3]	432		

Perhaps, most interestingly, 6-(*p*-toluidino)naphthalene-2-sulfonate (TNS) was used as a fluorescent probe of the dendritic microenvironment generated at the core of these dendrophane receptors. TNS is bound by the cyclophane moiety, and its emission maximum reports on the microenvironmental polarity that it experiences. As the dendritic shell enlarged, the emission maximum shifted hypsochromically, indicative of a decrease in micropolarity (Table 2). The dendritic shell therefore does indeed have a marked effect on the environment in which molecular recognition takes place.

Interestingly, it is well known that certain reactions, such as the decarboxylation of pyruvate, are favoured in media of decreased polarity [52]. It was consequently postulated that a large contribution to catalysis of this process by thiamine diphosphate (ThDP) dependent enzymes is derived from the ability of the enzyme to generate a microenvironment of reduced polarity compared with the surrounding aqueous solution. It was already known that thiazolio-cyclophanes, containing both an apolar binding site and a thiazolium cofactor, mimic the behaviour of such enzymes [53]. Consequently, given the ability of the branched shell to lower the micropolarity at the binding site yet further, it was postulated that such branching could have a positive effect on the catalytic behaviour of such thiazolio-cyclophane receptors.

Catalytic dendrophanes **15** and **16**, with two different types of surface, were synthesised via the convergent strategy (Fig. 12) [54]. One contained methyl ester groups (**15**), whereas the other featured triethylene glycol monomethyl ether (TME) solubilising end groups (**16**). Dendritic receptor **16** bound 2-naphthaldehyde with a similar affinity to the non-dendritic thiazolio-cyclophane analogue. Microenvironmental investigations using the emission wavelength of TNS once again showed that the dendritic branches have a profound impact on the micropolarity of the cyclophane core. The emission data of TNS bound to the two receptors in H₂O/MeOH (1:1) clearly showed that the TME branches in **16** (λ_{max} (TNS) = 424 nm) are much more effective in reducing the polarity at the dendritic core than the methyl ester residues in **15** (λ_{max} (TNS) = 436 nm). This could be attributed to the larger dimensions of the TME-functionalised dendritic shell which should provide a better and, possibly, more densely packed coverage of the cyclophane core.

The ability of these dendrophanes to catalyse the oxidation of 2-naphthaldehyde to methyl 2-naphthoate in the presence of an added flavin cofactor was



15 R = Me

16 R = CH₂CH₂O(CH₂CH₂O)₂Me

Fig. 12. Dendrophanes **15** and **16**, modified with a thiazolium cofactor, have potential for catalytic activity within the well-defined binding site

investigated. Unfortunately, whilst the unfunctionalised cyclophane exhibited high catalytic activity, the dendrophanes displayed only a weak activity (**15** and **16** were 160 and 50 times less active than the non-dendritic cyclophane, respectively). It was argued that the intermolecular electron transfer from the 'active aldehyde' intermediate, which is formed by reaction of the substrate with the thiazolium ion in the cavity, to the externally added flavin derivative became rate determining due to the steric shielding of the dendritic branching, and hence any favourable contributions of the dendritic microenvironment were being masked. Thus, although providing greater insight into dendritic structure and behaviour, this study did not provide an enhanced enzyme mimic.

We believe that for enzyme mimicry, the disordered nature of dendritic branching, which possesses a distinct lack of secondary structure, is a severe disadvantage, as steric interference will generally hamper catalysis. In an enzyme, the protein shell, as well as providing the correct catalytic residues in the right orientation and at the perfect micropolarity, also maintains an open pocket to ensure the reaction can occur free from steric hindrance. This is achieved through peptide backbone hydrogen-bonding and hydrophobic folding effects –

the incorporation of such well-defined secondary structural motifs within dendritic branching is one of the major future challenges in the design of catalytic dendrophanes.

Dendrophanes with expanded cavities such as **17** have also been reported (Fig. 13) [55]. As a consequence of their increased diameter, such receptors are capable of binding larger, biologically relevant, hydrophobic guests. These water-soluble dendrophanes were able to bind steroids, for example testosterone, with binding affinities similar to that displayed by the non-dendritic analogue. Amazingly, the binding kinetics were fast on the ^1H NMR time scale at all generations. This is in contrast to [G-3] dendrophane **14** which exhibited slow host-guest exchange kinetics on the NMR time scale, and is a consequence of the larger cyclophane core of **17**, which leads to a less dense packing of the dendritic branches. As a consequence of its strong binding and fast host-guest exchange kinetics, dendrophane **17** and lower generation analogues have been used as building blocks for the assembly of new supramolecular architectures (Sect. 5.4).

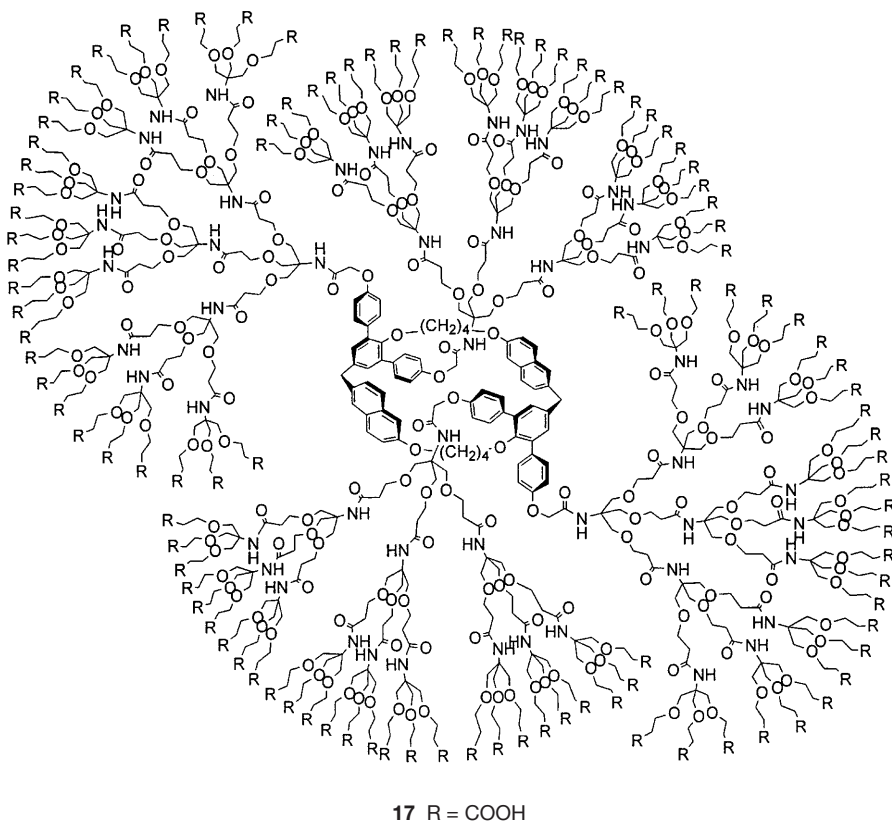


Fig. 13. Dendrophane **17** with its expanded cyclophane cavity recognises biologically important guests such as steroids with fast binding kinetics in aqueous solution

Cyclodextrins have been extensively studied as hosts for hydrophobic molecular recognition [56]. Newkome and co-workers reported dendritic β -cyclodextrins (β -CD) of first and second generation (**18**) (Fig. 14) [57]. The recognition properties of these dendritically modified receptors were investigated using phenolphthalein as guest. In moderately basic aqueous solution, the deep purple colour of this indicator disappeared on the addition of **18**, as a consequence of a specific host-guest interaction involving the hydrophobic effect, van der Waals forces and hydrogen bonding. In order to illustrate that the binding was taking place within the cyclodextrin cavity rather than in the dendritic branches, an adamantane derivative, known to bind very strongly to β -CD, was added to the solution. This guest displaced phenolphthalein from the binding site and regenerated the colour of the solution. The extensive branched shell therefore does not prevent recognition in the binding cavity. Unfortunately, as yet, no quantitative binding studies have been reported, and the effect of the dendritic shell on binding strength or host-guest exchange kinetics is not clear. These dendritic cyclodextrins have also been used to generate higher-order supramolecular assemblies (Sect. 5.4).

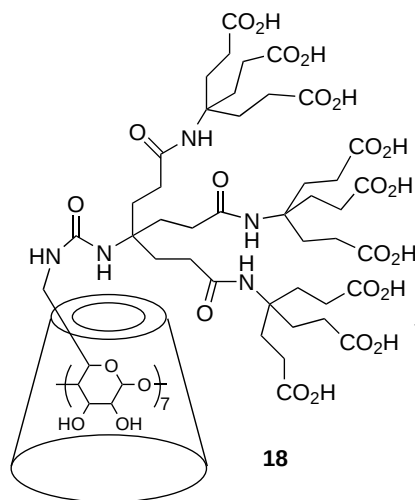


Fig. 14. Dendritic cyclodextrin binds guests within the recognition cavity in aqueous solution

Recently, Nierengarten and co-workers have reported dendritic cyclotri-*veratrylenes* (CTVs), such as **19**, in which the branching is provided by aromatic ether wedges (Fig. 15) [58]. They investigated the ability of these hosts to bind C_{60} fullerenes in CH_2Cl_2 solution [59], the interaction being followed using UV-vis spectroscopy. In each case a 1:1 complex was formed, with the fullerene bound in the CTV cavity and, interestingly, as the dendritic generation increased, so did the strength of binding, from $K_a = 85\text{ M}^{-1}$ for [G-0], to 120 M^{-1} for [G-1], 200 M^{-1} for [G-2], and 340 M^{-1} for [G-3] ($T = 298\text{ K}$). Binding strengths were similar in C_6H_6 solution. The authors postulated that additional π - π inter-

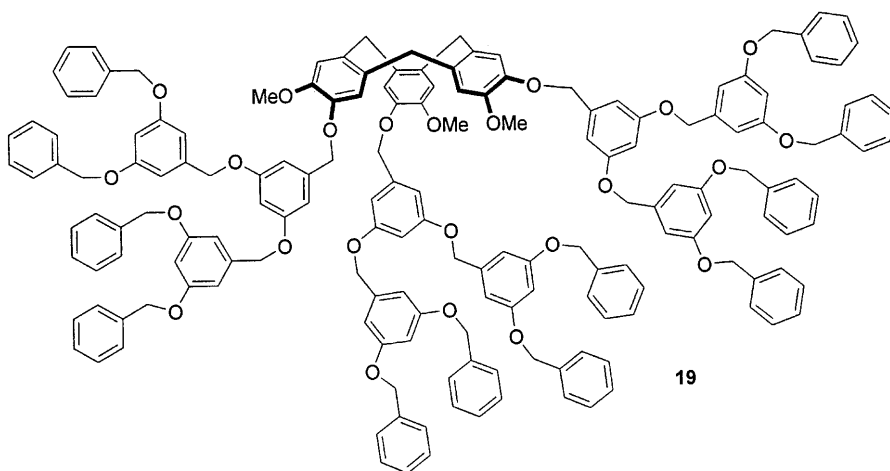


Fig. 15. Dendritic cyclotrimeratriylene **19** binds C_{60} in CH_2Cl_2 or toluene solution. The presence of aromatic ether dendritic branching enhances the binding strength

actions between the aromatic dendritic branches and the fullerene are responsible for this increase in binding strength. The existence of such interactions between aromatic ether dendritic branching and C_{60} fullerene has been confirmed by Shinkai and co-workers [60]. They reported that just a simple tris(hydroxy)benzene core functionalised with aromatic ether wedges would also bind C_{60} fullerene in toluene solution. The association constants were between 5 and 70 M^{-1} , smaller than those observed by Nierengarten and co-workers, presumably due to the lack of the CTV binding cavity.

4.3 Hydrogen-Bond Recognition

Hydrogen bonds are of key importance in biological systems, playing crucial structural, recognition and catalytic roles in enzymes. It is, therefore, perhaps surprising that so few dendritic superstructures with well-designed hydrogen-bonding recognition sites at their core have been reported.

In 1996, Newkome and co-workers reported a flexible dendritic hydrogen-bonding receptor (Fig. 16) [61]. Receptor **20** contains four 2,6-diamidopyridine hydrogen-bonding units. The interaction of this host with the complementary guest, barbituric acid, was investigated. Free barbituric acid was solubilised by these hosts into CD_3CN , in which it normally shows only sparing solubility, up to the limit of complementary complexation. A full quantitative analysis was, however, hindered as a consequence of dendrimer self-association and the possibility of guest interaction with other hydrogen-bonding sites in the dendritic branches themselves. It is clear that a more structured dendritic system would prove more amenable to analysis. Consequently, the hydrogen-bonding receptors reported in 1998 and described below have a much greater degree of rigidity and order built into their superstructures.

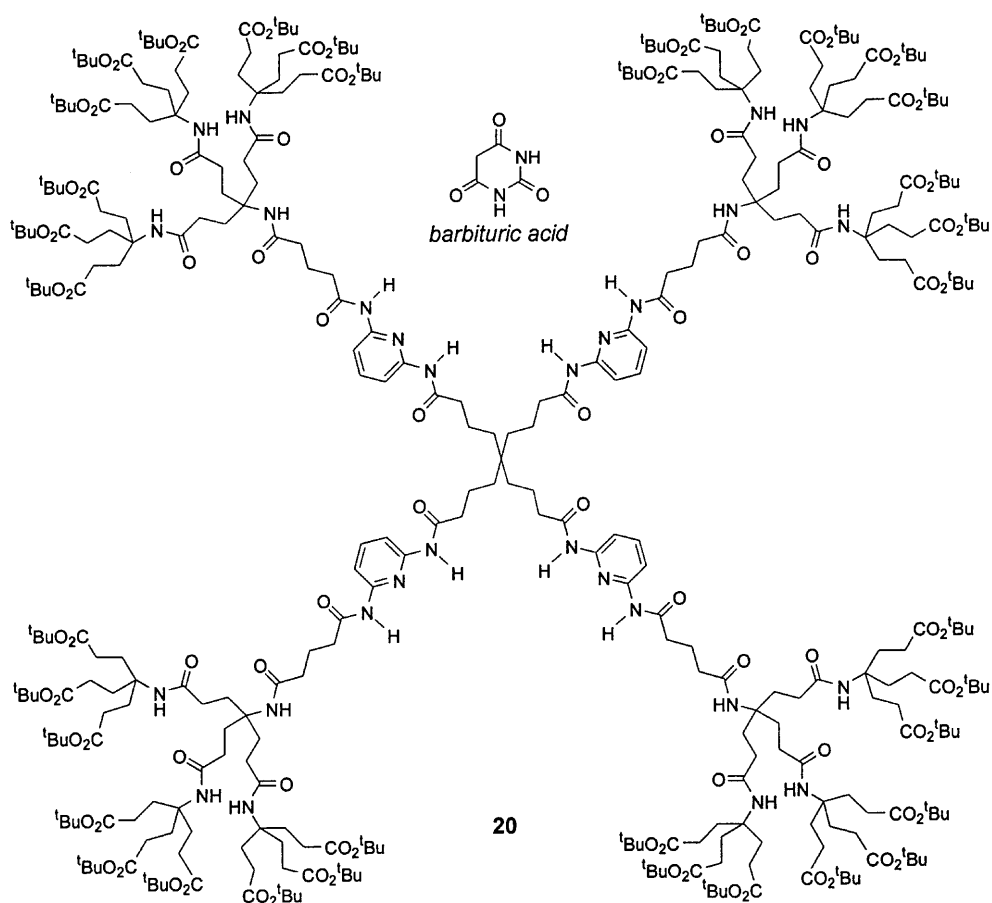


Fig. 16. Flexible dendritic hydrogen-bonding receptor **20** solubilises barbituric acid into CH_3CN

Zimmerman, Moore and co-workers reported two classes of dendritic hosts capable of hydrogen-bond-mediated recognition (Fig. 17) [62]. These dendrimers differed in the linker connecting the aryl groups of the dendritic shell, one containing benzyl ether linkages (**21**), the other being based on acetylenic linkages (**22**). Both types of dendrimer possess encapsulated naphthyridine units. This recognition fragment is capable of accepting hydrogen bonds, and hence is suitable for binding benzamidinium guests **23** and **24**. Association studies were performed in dry $\text{CDCl}_3/\text{CD}_3\text{CN}$ (9:1), and binding constants determined by ^1H NMR titration techniques (Table 3). The stoichiometry of all host-guest complexes was 1:1. In a control experiment, a simple naphthalene-cored dendrimer was shown not to interact with these amidinium guests, and this proved that for dendrimers such as **21** and **22**, the binding is driven by specific hydrogen-bond pairing at the encapsulated core. In all cases, binding was fast on the NMR time scale, indicating that the guests have good access to the recognition site. Most striking was the observation that the size and nature of the den-

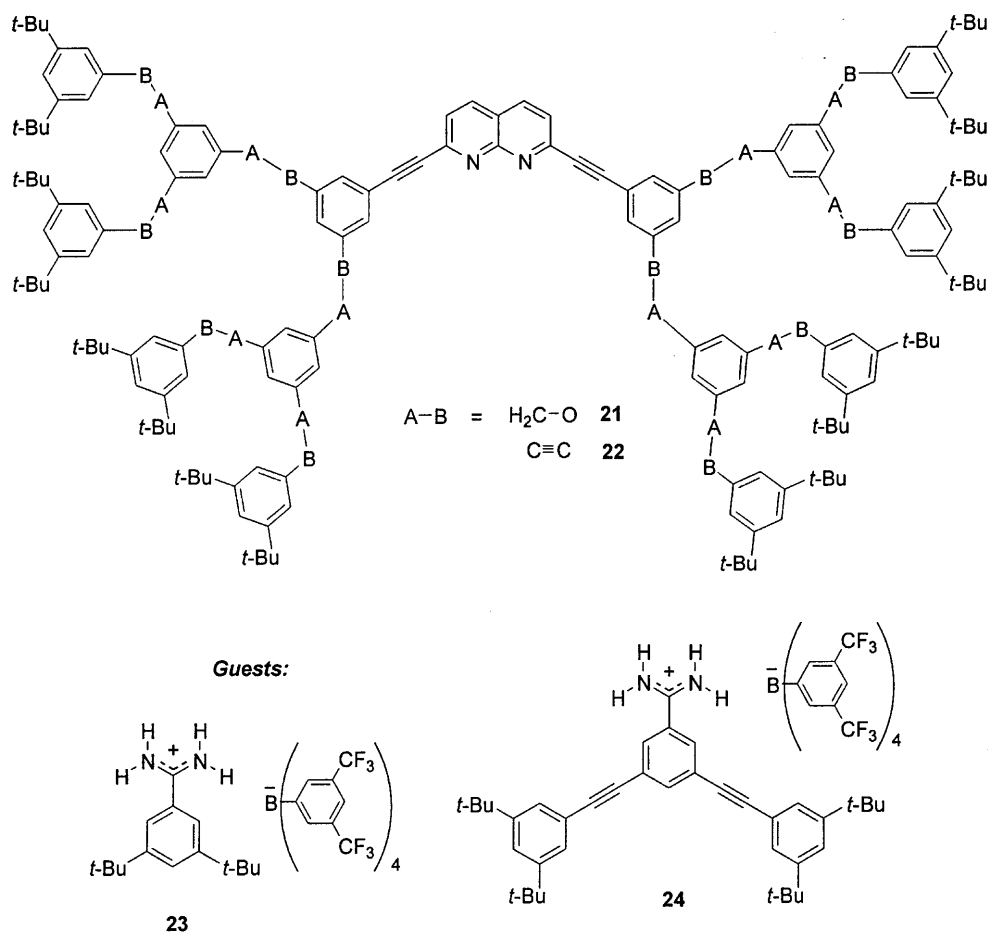


Fig. 17. Dendritic hydrogen-bonding receptors **21** and **22** bind amidinium guests **23** and **24** (in $\text{CDCl}_3/\text{CD}_3\text{CN}$ 9:1)

Table 3. Association constants (K_a) and binding free energies ($-\Delta G^\circ$, kJ mol^{-1}) between dendritic hosts and guests **23** and **24** in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (9:1) at 293 K

Dendrimer	Generation	K_a (M^{-1}) [23]	$-\Delta G^\circ$ (kJ/mol) [23]	K_a (M^{-1}) [24]	$-\Delta G^\circ$ (kJ/mol) [24]
21	[G-1]	940	16.7	1100	17.1
21	[G-2]	810	16.3	790	16.3
21	[G-3]	780	16.2	560	15.4
21	[G-4]	800	16.3	390	14.5
22	[G-1]	1400	17.6	2040	18.6
22	[G-2]	1290	17.4	1370	17.6
22	[G-3]	1030	16.9	1080	17.0
22	[G-4]	820	16.3	520	15.2

dritic branching hardly altered the stability of the complexes formed with **23** [$\Delta(\Delta G^\circ) < 1.5$ kJ/mol], whilst for the recognition of **24**, as the dendrimer increased in size, the binding strength diminished significantly [$\Delta(\Delta G^\circ) > 2.5$ kJ/mol], reflecting the increased steric demands for complexation. The effect of solvent composition on the strength of binding was also investigated – each dendrimer showed a very similar response to solvent polarity, indicating that the dendrimer itself does not alter the polarity experienced by the recognition event. It was therefore concluded that these dendritic hosts were highly porous and failed to generate a unique microenvironment at the recognition site.

Smith and Diederich reported receptors carefully designed for chiral hydrogen-bond recognition (Fig. 18) [63]. These dendritic cleft type receptors (dendroclefts) (**25**) contain as initiator core a rigid, optically active 9,9'-spirobi[9H-fluorene] moiety bearing 2,6-bis(carbonylamino)pyridine moieties in the 2,2'-positions. This pre-organised hydrogen-bonding cleft is suitable for the complexation of monosaccharide guests via hydrogen bonding in non-competitive solvents. The branches attached to this core are flexible, and lack hydrogen-bond donors, reducing their ability to compete efficiently for the bound saccharide. Such dendroclefts model, in a crude way, the active site of sugar-binding proteins, which frequently possess a hydrogen-bonding cleft deeply buried within a hydrophobic pocket of the enzyme superstructure [64].

Recognition studies were performed with octyl α - or β -glucopyranosides (**L** and **D**) **26–28** by ^1H NMR titration in dry CDCl_3 . All complexation processes were kinetically fast on the NMR time scale; 1:1 complexes were observed and association constants were evaluated (Table 4). It was noted that all complexes formed by [G-1] and [G-2] dendroclefts, as well as the [G-0] core, were of similar strength (K_a between 100 and 600 M^{-1}). Large complexation-induced downfield shifts of the diamidopyridine N-H resonances gave evidence for the importance of hydrogen-bond formation. Apparently the flexible dendritic shell does not prevent the sugar molecules from penetrating the receptor and interacting with the core hydrogen-bonding sites. Interestingly, the presence of dendritic branching subtly alters the selectivity of these novel receptors. The core receptor, which has no dendritic branching, exhibits a high enantioselectivity [$\Delta(\Delta G^\circ)$ 3.6 kJ/mol] for octyl α -D-glucoside (**27**) over octyl α -L-glucoside (**26**), whilst the dendritically functionalised receptors do not. Conversely, whilst [G-0] shows little diastereoselectivity for octyl β -D-glucoside (**28**) over octyl α -D-glucoside (**27**), [G-1] and [G-2] dendroclefts exhibit a marked diastereoselectivity which increases with dendritic generation [$\Delta(\Delta G^\circ)$ 2.3 kJ/mol for [G-2]]. Not only was this the first report of chiral recognition within a branched shell, but this use of dendritic branching to modulate the stereoselectivity of a recognition process was unprecedented. Analysis of the complexation-induced changes in chemical shift suggested that, with increasing dendritic generation, the $\text{N-H}\cdots\text{O}$ host-guest hydrogen bonds become weakened, and it was proposed that these interactions are increasingly replaced by $\text{O}\cdots\text{H-O}$ interactions between the ether O-atoms of the dendritic branches and the sugar OH groups. In other words, the dendritic branching plays an active role in modulating the mode and strength of substrate recognition.

In addition to binding monosaccharides, these dendrocleft receptors are able to sense the presence of the bound sugar through perturbations of their circular

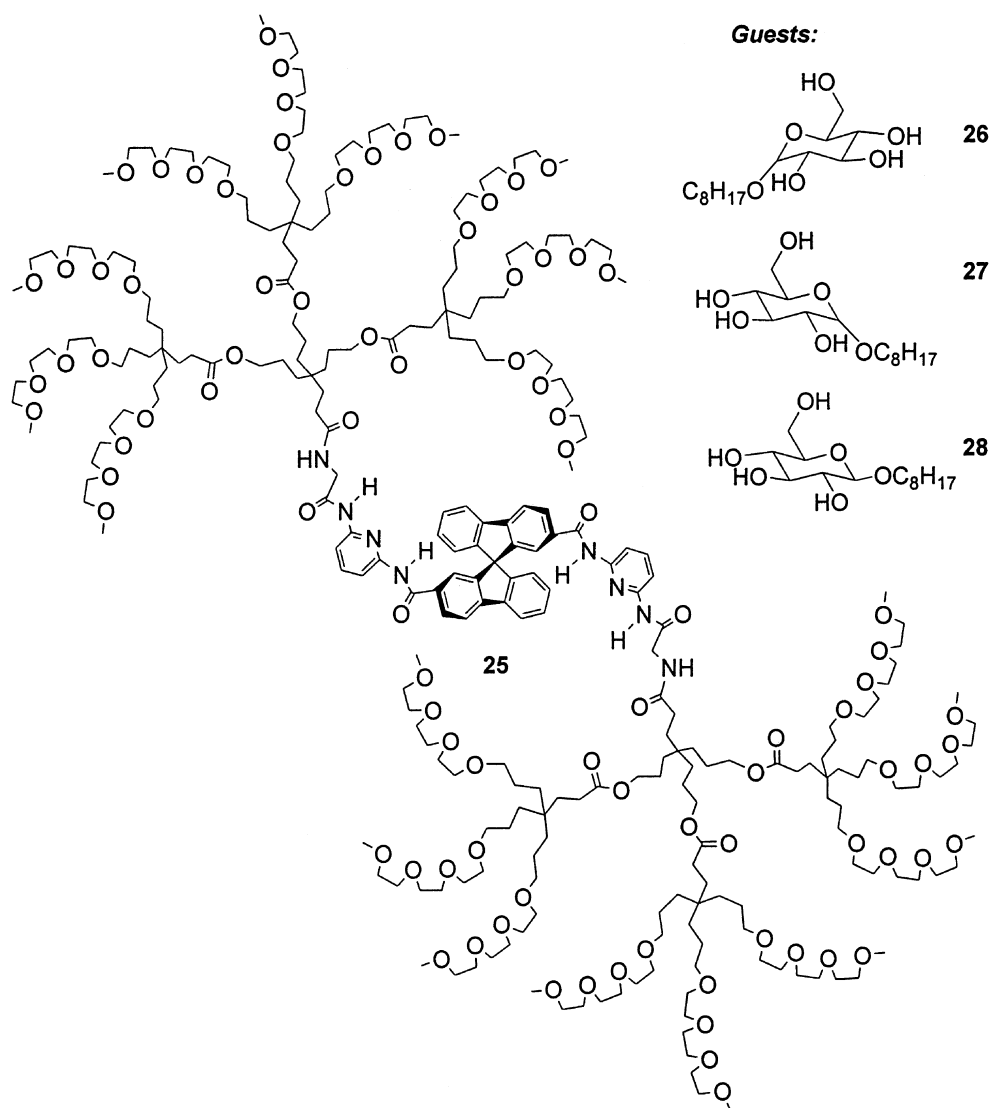


Fig. 18. Dendroleft receptor 25 binds monosaccharide guests 26–28 in non-competitive CDCl₃ solution. The enantio- and diastereoselectivities are modulated by the presence of the branched shell

dichroism (CD) spectra in an unambiguous and selective manner. The dendritic branching has a direct impact on the magnitude of the CD sensory response, reducing it markedly. This would suggest that the dendritic branching, by modulating the binding geometry, strength and selectivity, causes the sugar guest to bind, on time average, less closely to the spirobifluorene core, hence perturbing its optical properties less strongly. All dendritic receptors were

Table 4. Association constants (K_a) and binding free energies ($-\Delta G^\circ$) for 1:1 complexes of dendroclefts (e.g. **25**) with pyranosides (**26–28**). The enantioselectivity [$\Delta G^\circ(27) - \Delta G^\circ(26)$] and diastereoselectivity [$\Delta G^\circ(28) - \Delta G^\circ(27)$] of the binding processes are also given

Receptor	Pyranoside	K_a (M^{-1})	$-\Delta G^\circ$ (kJ/mol)	Enantioselectivity (kJ/mol)	Diastereoselectivity (kJ/mol)
[G-0]	26	100	11.4		
[G-0]	27	425	15.0	3.6	0.7
[G-0]	28	570	15.7		
[G-1]	26	160	12.6		
[G-1]	27	225	13.4	0.8	1.4
[G-1]	28	390	14.8		
[G-2]	26	170	12.7		
[G-2]	27	205	13.2	0.5	2.3
[G-2]	28	530	15.5		

readily recycled after sensing experiments by simple gel filtration and this clearly illustrates the potential application of this type of dendritic technology.

It is interesting to observe that for these dendroclefts, the dendritic shell modifies the recognition event, apparently by forming interactions with the bound substrate. This is possible because of the multiple hydrogen-bonding functional groups present on the sugar guest, not all of which can be satisfied by the recognition site alone. This type of additional interaction, however, would not be possible in Zimmerman's hydrogen-bond receptor, in which host and guest form a completely complementary pair, with all hydrogen-bonding possibilities of the bound substrate satisfied by the dendritic core alone. It is therefore perhaps not so surprising that the only dendritic effect observed by Zimmerman and co-workers was that of steric congestion on binding the sterically more demanding guest, whilst for the dendroclefts the branching appears to play a more active role.

In a recent report, the ability of a branched shell to generate just such a hydrogen-bonding microenvironment has been discussed [65]. The optical properties of dendritically modified tryptophan residues were shown to crucially depend on the extent of the dendritic shell. This branched shell contains a number of hydrogen-bonding functionalities that interact with the tryptophan subunit, perturbing its emission wavelength.

Surprisingly, these are currently isolated examples of dendrimers with hydrogen-bond recognition units at their core. With these interesting results, however, it seems inevitable that this area of research will experience dynamic growth.

4.4

Metalloporphyrin-Based Receptors

Metalloporphyrins are of special interest, firstly as a consequence of their biological relevance, and secondly because of the vast range of different functions they possess. In a series of fascinating papers, the ability of the branched

shell to generate a unique environment, which the porphyrin can sense through electrochemical perturbation, has been explored [47 a, 66]. The analogy between the behaviour of dendritic porphyrins and cytochrome proteins, which also exhibit dramatically shifted redox potentials, has been highlighted. One of the other features of many metalloporphyrins, however, is their vacant coordination site, allowing the metal ion to act as a receptor.

The first report of a dendritic metalloporphyrin interacting with a specific guest was made by Aida and co-workers [67]. Their dendritic tetraphenyl zinc-porphyrin (**29**) was functionalised with aromatic ether dendritic branches (Fig. 19). They were particularly interested in the interaction of a histidine residue with the metal centre, an important event in the biological chemistry of heme proteins. Consequently, they prepared a series of dendritically functionalised imidazoles and investigated their interaction with the dendritic metalloporphyrin. In all cases, a 1:1 binding stoichiometry was observed, but the binding constants decreased as both of the dendritic components increased in size, presumably as a consequence of the recognition event becoming sterically disfavoured. It is, nevertheless, remarkable that the [G-4] imidazole was still able to bind to the [G-5] dendritic zinc-porphyrin, indicating an unexpectedly high degree of dendritic interpenetration.

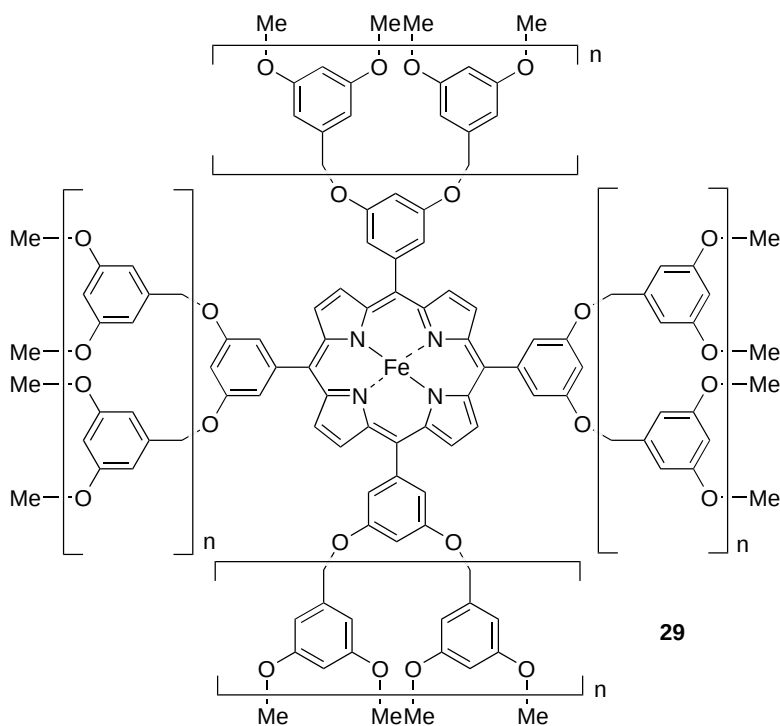


Fig. 19. Dendritic metalloporphyrin **29** acts as a receptor via guest binding in its vacant coordination site

Perhaps the most important recognition event performed by metalloporphyrins *in vivo* is reversible dioxygen binding, performed by hemoglobin and myoglobin. At a similar time, both Collman, Diederich and co-workers [68] and Jiang and Aida [69] proposed that dendritic iron(II)-porphyrins may act as effective heme protein mimics. Both groups reported that the dendritic shell acted as a steric shield for the porphyrin macrocycle, analogous to a 'picket-fence' [70], preventing the formation of μ -oxo dimers, and allowing reversible dioxygen binding.

Aida's dendritic heme protein mimic **29** (Fig. 19) was investigated in both anhydrous and water-saturated toluene solution [69]. Interestingly, in water-saturated toluene, the survival time of the dioxygen complex was dependent on the dendritic generation of the host. The rate of decay for the O_2 complex of the fifth generation receptor was $7.4 \times 10^{-13} \text{ s}^{-1}$ (>95% survival after two months), whereas for the fourth and third generation hosts the rates of decay were considerably faster (3.2×10^{-5} and $1.3 \times 10^{-4} \text{ s}^{-1}$, respectively). Another remarkable feature of these receptors was the low gas permeability of the dendritic shell. Complete oxygenation of the [G-5] derivative required 12 min and deoxygenation required 180 min of bubbling nitrogen. For the [G-3] derivative, however, these values were 2 and 30 min for complete oxygenation and deoxygenation, respectively. It was concluded that the dendritic shell acts as a steric and hydrophobic shield, protecting the active site and, in addition, giving rise to a decreased rate of gas permeation through the architecture.

Collman, Diederich and co-workers' dendritic porphyrin **30** was functionalised with a flexible poly(ether amide) cascade (Fig. 20) [68]. They investigated the gas-binding properties in toluene solution, in the presence of a large excess of 1,2-dimethylimidazole to ensure complete formation of the five-coordinate high-spin iron(II) complex. In this case, the branched shell had a dramatic effect on both the strength and selectivity of binding. The O_2 affinity of the dendritic systems was vastly enhanced when compared with a picket fence model system measured under the same conditions. The affinity for CO, on the other hand, was actually decreased. Consequently, the dendrimer strongly selects oxygen over carbon monoxide, a remarkable result. The extremely high binding strength and selectivity for O_2 resembles that observed for the heme protein of the blood worm *Ascaris*. It was proposed that the reason for this dendritic control could be the amide group in the branched shell which can form a hydrogen bond with the terminal oxygen atom of O_2 . It is therefore clear that, in these cases, the dendritic shell has a profound effect on the supramolecular event occurring at the dendritically encapsulated core.

Dendritic manganese(III)-porphyrins have been used by Moore, Suslick and co-workers for catalytic purposes [71]. The porphyrin was encapsulated in a branched shell based on phenyl ester linkages. In particular, the use of these receptors for the shape-selective epoxidation of alkenes was investigated, with the reactivity of substrates containing two double bonds being studied. As the degree of dendritic branching increased, the regioselectivity in favour of the less sterically hindered double bond increased. This is indicative of branching playing a steric role in controlling the catalysis, which occurs in the dendritic interior.

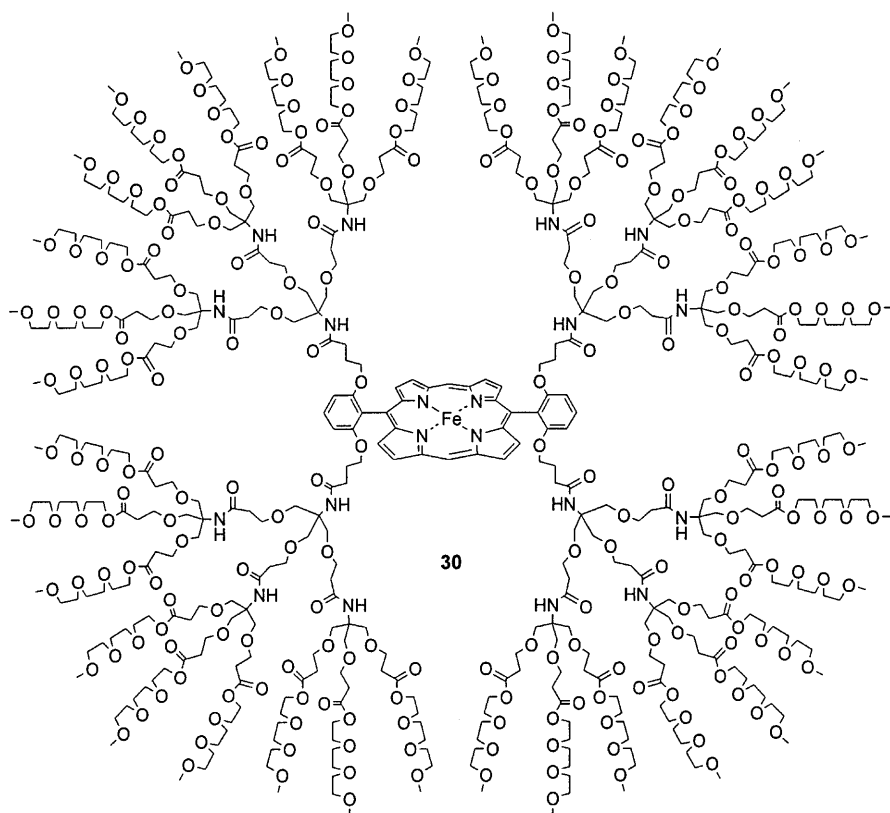


Fig. 20. Dendritic metalloporphyrin **30** acts as a heme protein mimic, showing a remarkable selectivity for O_2 over CO

It is clear that the encapsulated recognition sites discussed above only begin to scratch the surface of potential host-guest interactions which could be investigated within a dendritic superstructure. The described examples illustrate the great amount of information which sensitive recognition processes can provide about the properties inside macromolecules. Furthermore, this type of system has great potential to mimic the behaviour of biologically important systems and generate new functional materials. It therefore seems clear that this fascinating area of supramolecular dendrimer chemistry looks set for remarkable growth.

5 Supramolecular Assemblies

5.1 Introduction

We have journeyed down through the dendritic structure, examining molecular recognition in each distinct topological region. There is, however, another

approach to using supramolecular chemistry in the field of dendrimer science. That is, rather than looking at recognition in a specific region of the dendrimer, to use supramolecular chemistry to assemble the dendritic superstructure itself.

As a consequence of the time and effort required to achieve covalent synthesis and the requirements of industry for ever more economic and effective approaches to problem-solving, the concept of self-assembly has become a recurring theme in supramolecular chemistry [72]. Assembly processes can either be templated (for example around a metal cation or guest anion) or they can simply stem from the mutual interactions between a given molecular building block. Both approaches have been used by supramolecular chemists aiming to generate new assembled dendritic architectures. Furthermore, recent reports have linked complete spherical dendrimers together through a series of recognition events, taking us to the next level of supramolecular dendritic organisation.

5.2

Template-Directed Assembly

Perhaps the best understood templates for self-assembly are metal ions and these have seen considerable development as templates for the construction of dendritic supermolecules [73]. Newkome and co-workers first reported the assembly of novel dendrimers using ruthenium ion coordination (Fig. 21) [74]. The ruthenium ion can act as an electrochemical probe, providing evidence for the formation of complexes such as **31** [75]. As the dendritic generation increased, the reversibility of the electrochemical process decreased, indicating encapsulation of the metal ion, which limits its interaction with the electrode surface.

Fréchet and co-workers have reported an assembled lanthanide complex, in which three identical dendritic branches with a carboxylic acid residue at the focal point deprotonate and bind to a lanthanide cation (Er^{3+} , Tb^{3+} and Eu^{3+}) [76]. These complexes have particularly fascinating luminescent properties, which are dependent on the size of the branched shell, with the intensity of emission increasing with increasing dendritic generation. The dendritic branching can play two roles: firstly, it can act as an antenna, funneling energy absorbed by the branched shell down to the metal ion [77], secondly, it can site-isolate the metal ion from its neighbours, leading to a decrease in self-quenching. Such branched lanthanide complexes have potential application in components for advanced fibre optics.

Metal ions, however, are not the only potential templates for supramolecular assembly. Zimmerman and co-workers have reported well-defined assemblies with a molecular weight >10000 amu (e.g. **32**) based on anthryridine-benzamidine hydrogen-bond interactions (Fig. 22) [78]. There was little effect of the dendritic branching on the strength of association of these assemblies, but this was expected as the branches were attached to the focal point in a geometry which would tend to orient them away from the site of hydrogen bonding.

Smith reported the ability of individual peptidic branches with a carboxylic acid at the focal point (**33**) to solubilise proflavine hydrochloride (**34**), a hydrophilic dye containing multiple amine groups, into apolar dichloromethane solu-

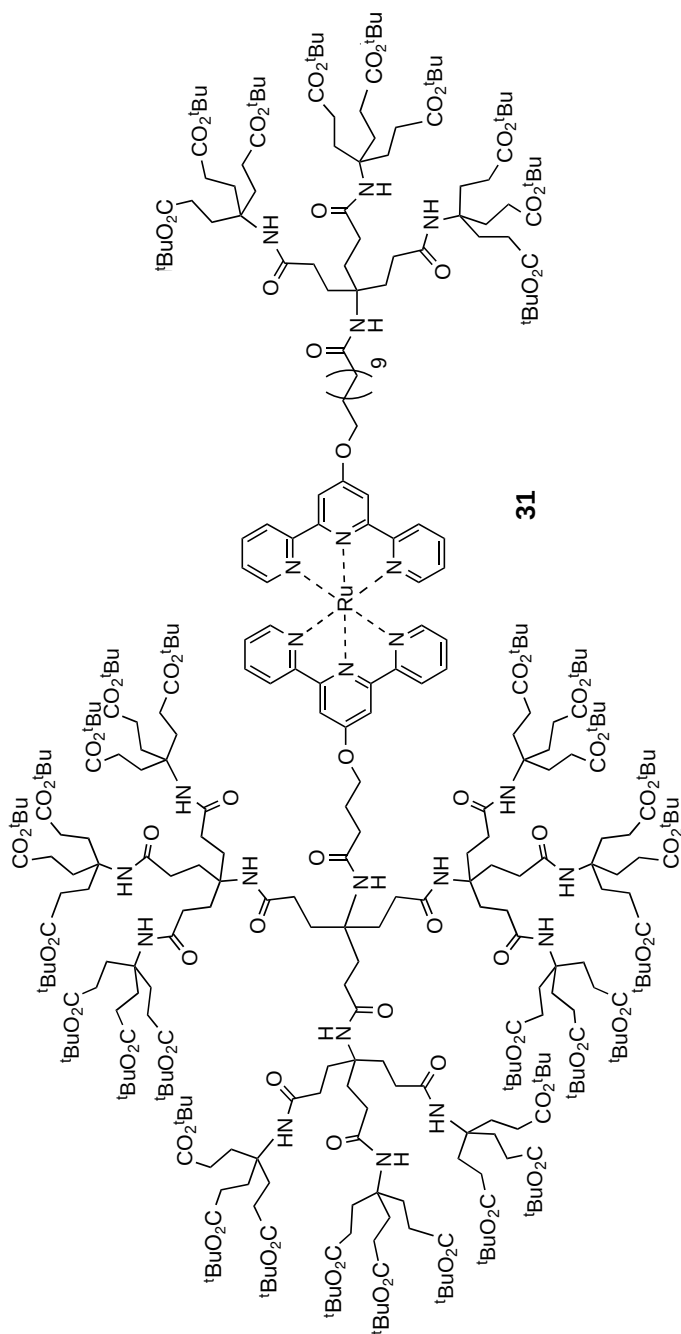


Fig. 21. Dendritic assembly **31** forms via ruthenium ion coordination



Fig. 22. Assembly of dendritic supermolecule **32** occurs via hydrogen-bonding interactions (in $\text{CDCl}_3/\text{CD}_3\text{CN}$ 9:1)

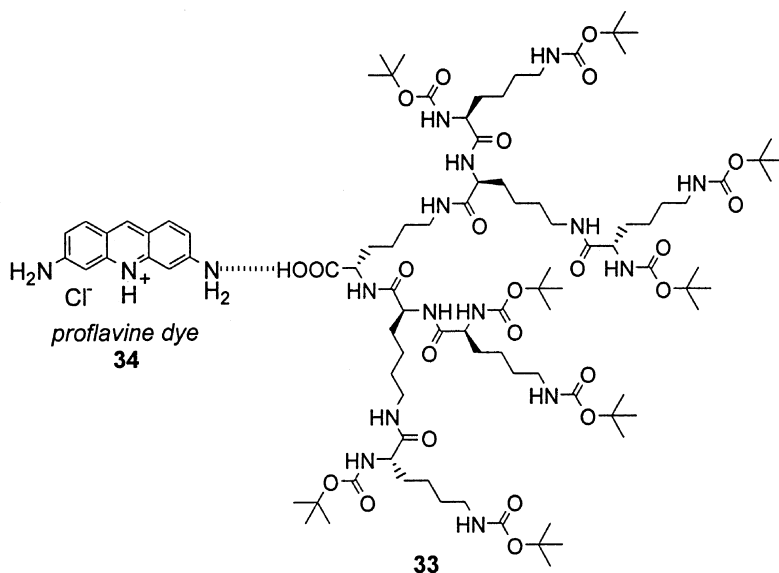


Fig. 23. Hydrophilic proflavine dye **34** is solubilised into apolar CH_2Cl_2 via interaction with **33**, a dendritic branch containing a carboxylic acid at its focal point. The dye experiences a distinct dendritic microenvironment

tion (Fig. 23) [79]. Control experiments indicated that both the carboxylic acid group and the dendritic branching were essential in order for dye uptake to be observed. It was proposed that hydrogen-bonding interactions formed between the dendritic branch and the dye, with the branched shell solubilising the complex as a whole. Interestingly, the optical properties of the solubilised dye were dependent on the generation of the dendritic branching employed for its solubilisation. The UV-vis absorption wavelength shifted progressively from 446 [G-1] to 450 nm [G-3], indicating that the solubilised dye experiences a unique microenvironment as the dendritic branching becomes more extensive. This example therefore illustrates how a supramolecular approach using individual dendritic branches can control molecular behaviour and properties.

In a recent paper Kraft and co-workers have thoroughly characterised the formation of assemblies such as **35**, which form via the interactions between the tris(imidazoline) branched core and tetrazoles (Fig. 24) [80]. The aggregates exhibit interesting stacking properties, both in the crystal and in solution – this approach should eventually lead to ordered columnar structures similar to those more fully investigated by Percec and co-workers (see below) (e.g. supramolecular liquid crystals).

Recently, in an excellent paper, a dendrimer was self-assembled in a novel way around a bis(μ -oxo)dicopper(III) core (Scheme 3) [81]. Firstly, complex **36** was synthesised via a convergent approach. When this complex was dissolved in CH_2Cl_2 at -78°C , and a stream of dioxygen bubbled through the solution, the colour gradually changed from pale purple to deep orange-brown, displaying growth of intense absorption bands at 302 and 411 nm in the UV-vis spectrum.

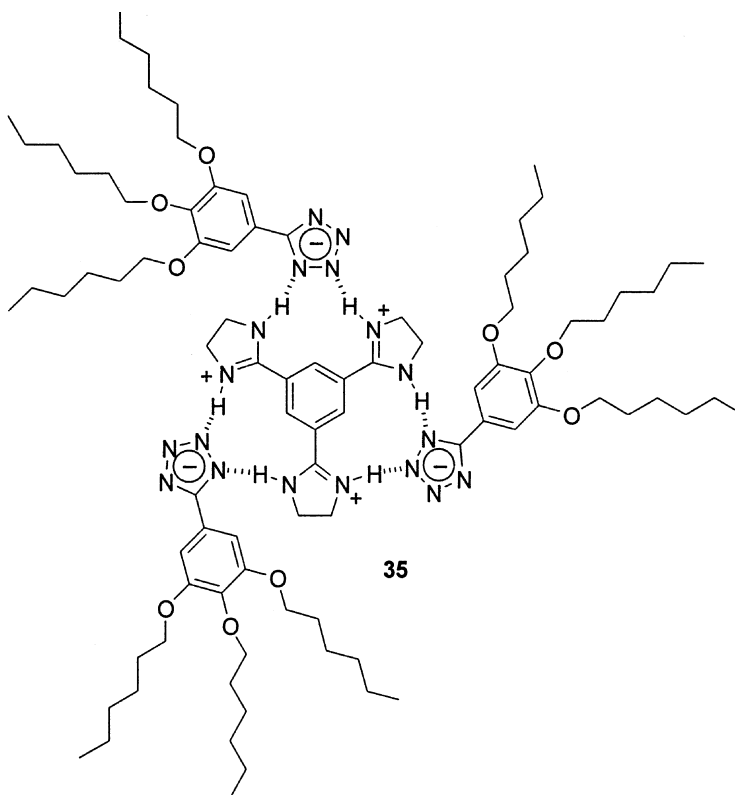
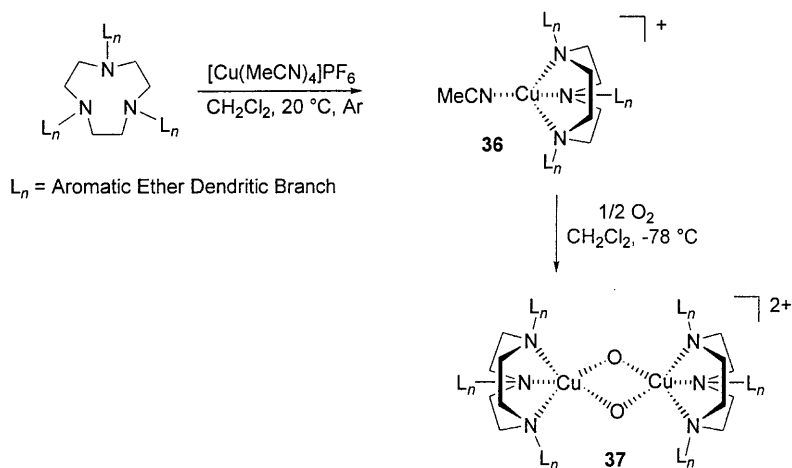


Fig. 24. Branched assembly **35** forms via interactions between the basic tris(imidazoline) template and three tetrazoles (which possess a similar acidity to carboxylic acids)



Scheme 3. Assembly of a novel dendritic bis(μ -oxo)dicopper(III) species **36**

Such a band is characteristic of a bis(μ -oxo)dicopper(III) species (37). Dioxygen therefore acts as a reactive template for this assembly process. The formation of this complex was strongly dependent on the dendritic generation, with the [G-2] system exhibiting a bimolecular rate constant of $1.39 \text{ M}^{-1} \text{ s}^{-1}$, whilst that for [G-3] was $0.0131 \text{ M}^{-1} \text{ s}^{-1}$ and that for [G-4] was effectively zero, with none of the assembled species being observed during a 16 h period. This indicates a steric role of the branched shell, hindering the assembly process. More interesting, however, was the effect of the branched shell on the stability of the resultant complex towards oxidative degradation. On warming, these complexes decompose by oxidative cleavage of the N-C(dendron) bonds. For [G-0] the half-life for decomposition was 7 s, for [G-2] this rises to 24 s, whilst, remarkably, for [G-3] it was 3075 s. This increased half-life was a consequence of a more unfavourable activation entropy for the reaction of the higher generation system. The authors speculated that in the more hindered larger dendrimers the N-C(dendron) bonds would be less open to access from the oxidising core, as a consequence of conformational locking. This example clearly illustrates the way in which a branched shell can stabilise a reactive subunit. Such bis(μ -oxo)-bridged bimetallic complexes are of great interest as synthetic models of the active sites of multinuclear metalloproteins such as methane monooxygenase and ribonucleotide reductase [82].

5.3

Untemplated Assembly

There are cases of dendrimer self-assembly in which the dendritic branches alone contain enough information to be able to self-assemble into a well-organised superstructure without the presence of any sort of template. Perhaps the clearest example of this type of assembly was provided by Zimmerman and co-workers (Fig. 25). In 1996, they reported the design, synthesis and hydrogen-bond-mediated self-assembly of a new dendritic branch (38) [83]. The structure of dendritic branch 38 was designed such that it could form a hydrogen-bonded six-membered-ring rosette motif. Fascinatingly, the formation of this discrete rosette, as examined by size exclusion chromatography, vapour pressure osmometry and laser light scattering, was dependent on the generation of dendritic branching attached. At low dendritic generation, the formation of a poorly defined aggregate was observed, whilst at higher dendritic generation, only the desired hexameric aggregate was present in solution. It was postulated that the larger dendritic branches cannot be accommodated in linear aggregates (which can occur for smaller dendritic substituents). In this way, the size of the dendritic branching controls and defines the assembly process, acting as a steric buttress.

A self-assembling hydrogen-bonded rosette motif has also been reported by Reinhoudt and co-workers [84], as well as Fréchet and co-workers [85]. In both of these cases, two complementary wedges were used in order to achieve assembly: one with a melamine hydrogen-bonding subunit at the focal point, the other possessing a barbituric or cyanuric acid derivative. These subunits have often been used by Whitesides and co-workers to achieve directed assembly of

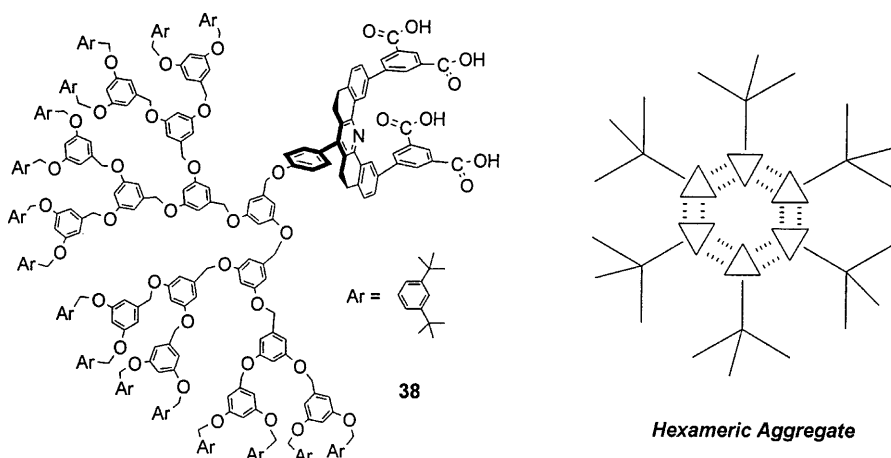


Fig. 25. Dendritic branch 38 spontaneously self-assembles to yield a discrete hexameric rosette motif in CH_2Cl_2 solution

non-dendritic systems [86]. For the dendritic system, Fréchet and co-workers observed that whilst [G-2] wedges gave rise to the expected hexameric rosette, [G-3] and [G-4] branches did not. It was argued that because the hydrogen-bonding interactions involved in this assembly are relatively weak, the effect of steric hindrance from the branching is marked.

Kraft and Osterod have also reported branched structures which self-assemble via the formation of hydrogen-bonding interactions. They comment on the interesting materials properties of the aggregates but, as yet, their structures do not appear to be clearly defined [87].

Percec and co-workers have built up an impressive body of research based on the assembly of dendritic branches mediated through supramolecular interactions [88]. Ideally, as chemists, we would like to be able to control the macroscopic structure of the supramolecular aggregate by controlling the structure of the dendritic branches at a microscopic level. This is, most eye-catchingly, what Percec and co-workers have achieved [88e]. Their general approach has used tapered monodendrons in which the periphery of the branched structure is functionalised with long aliphatic or fluororous chains. This provides one of the driving forces of the assembly process: hydrophobicity or fluorophobicity. They reported different generations of dendrons functionalised with C_{12} chains at the dendritic periphery and observed that the shape of the supramolecular assembly of these branches was determined by the dendritic generation (Fig. 26). Low-generation monodendrons, such as 39, had shapes that were fragments of a disc-like molecule and, consequently, they assembled into stacked cylindrical columns. Higher-generation branches (40), however, being sterically more demanding, had the shape of a spherical section and, as a consequence, the supramolecular assembly had a spherical structure. These supramolecular structures were characterised in the melt phase, and this type of assembly has direct relevance to the development of new liquid-crystalline materials.

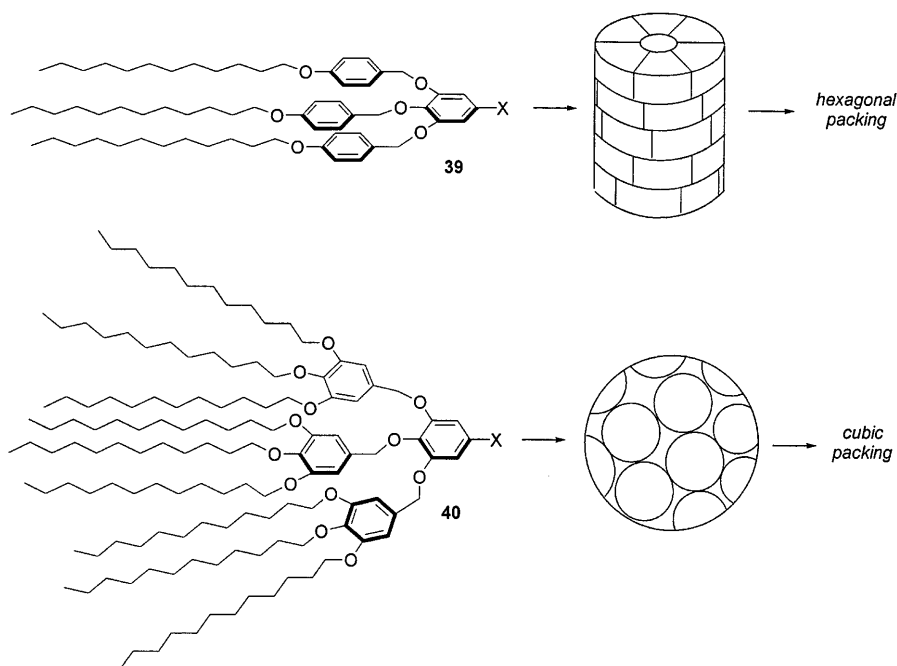


Fig. 26. Dendritic branch 39 self-assembles into hexagonal columnar arrays, whilst dendritic branch 40 self-assembles to generate a spherical superstructure

5.4

Assemblies of Dendrimers

Recently, a number of groups have begun to assemble a number of fully formed spherical dendrimers. This rapidly opens the possibility of synthesising assemblies with very high molecular masses and well-defined geometries.

Newkome and co-workers reported that their dendritic cyclodextrin (**18**) could be assembled to form a 2:1 complex (**41**) with a bis(adamantane ester) (Fig. 27) [57]. In this case, however, no effect of the dendritic branching on the assembly process was reported.

Diederich and Kenda used dendritic cyclophane (dendrophane) receptors for the generation of new assembled superstructures in aqueous solution (Fig. 28) [89]. The high binding strengths and fast binding kinetics observed with **17** make this dendrimer and lower-generation analogues ideal for the construction of nanoscale architectures and, consequently, two molecular rods, terminated with steroid nuclei, were synthesised. Such rods allow the formation of complexes with 2:1 dendrophane/rod stoichiometry. The steroid nuclei are ideal for binding in the cyclophane ring whilst the rigid rod should effectively bridge the two dendrophanes involved in complexation. It was expected that, with their different lengths, these rods would accommodate dendrophanes of different diameter. Solubility of these (largely hydrophobic) rods in water

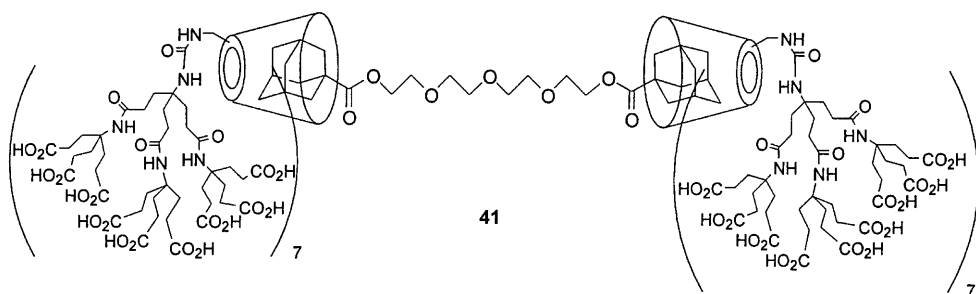


Fig. 27. Assembly of dendritic cyclodextrin **18** with a bis-adamantane derivative generates supermolecule **41**

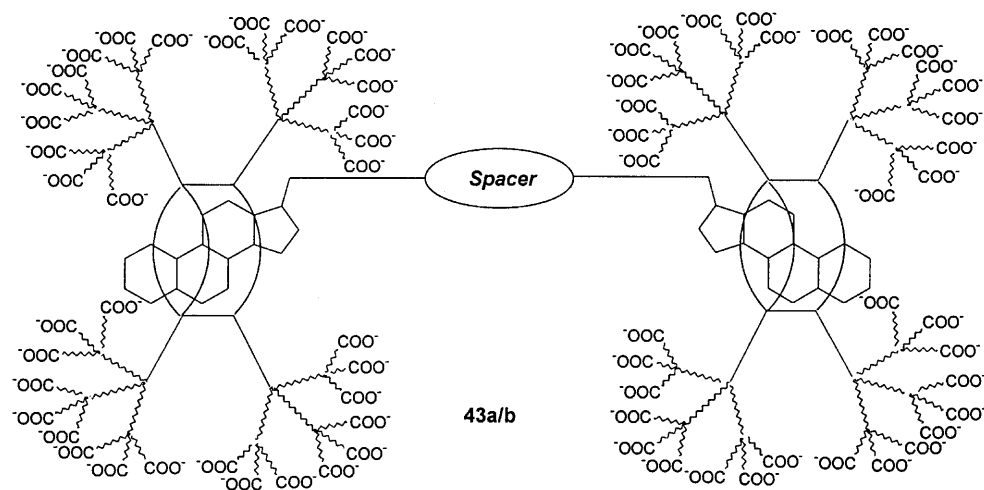
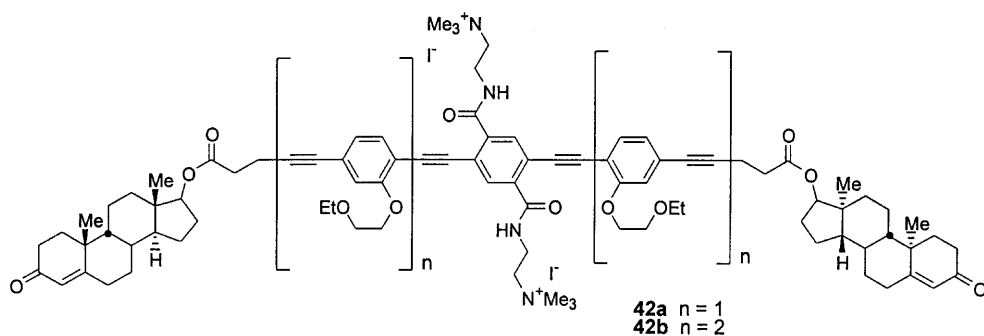


Fig. 28. Assembly of dendrophane **17** with designed rigid rods **42a** and **42b** in mixed aqueous solvent gives rise to well-defined supermolecules **43a** and **43b**, respectively. The stoichiometry of the aggregation process is dependent on both dendritic generation and the length of the rod

Table 5. Binding constants of 1:1 ($-\Delta G_{11}^{\circ}$) and 2:1 ($-\Delta G_{21}^{\circ}$) stoichiometric complexes assessed via fluorescence titration for the assembly of nanoscale architectures in water/methanol (1:1, 0.15 M phosphate buffer, pH = 8.7, 298 K) using dendrophanes such as **17** and steroid-functionalised rods **41 a** and **41 b**

Dendrophane	Rod	$-\Delta G_{11}^{\circ}$ (kJ/mol)	$-\Delta G_{21}^{\circ}$ (kJ/mol)
[G-0]	41 a	25.5	24.7
[G-1]	41 a	28.1	19.3
[G-2]	41 a	23.9	not observed
[G-1]	41 b	25.5	25.5
[G-2]	41 b	28.5	20.5

presented a considerable challenge, overcome by the attachment of glycol ether groups and quaternary ammonium ions. These ions were additionally expected to undergo ion-pairing with the negatively charged dendritic surface and thus reduce the electrostatic repulsion between two anionic dendrimers threaded on one rod.

As planned, complexes of both 2:1 and 1:1 stoichiometry were observed by NMR and fluorescence methods. Their relative stabilities were dependent both on the length of the rod and the generation of the dendrophane (Table 5). With the smaller rod, **42 a**, [G-0] threaded smoothly onto both terminal testosterone, for [G-1] the second threading was thermodynamically less favoured, whilst for [G-2] the 2:1 complex was not observed at all. This is presumably due to repulsion between the negatively charged and bulky dendritic shells. For the longer rod, **42 b**, however, [G-1] threaded smoothly onto both testosterone groups, whilst even with [G-2] a 2:1 complex could still be observed (although thermodynamically less favoured). This 2:1 complex has the remarkable molecular weight of 14714 amu. The formation of this complex with the longer rod is due to its greater ability to penetrate into the dendritic shell. Given that the two rods are rigid and possess steroid...steroid distances of 41 and 55 Å, the extensions of the dendrophane branched shells can be estimated. Thus molecular rods **42 a** and **42 b** act as rulers on the molecular scale.

As supramolecular and dendrimer chemists become increasingly adept, the boundaries of assembled superstructures will certainly be pushed ever further. It is expected that a wide range of novel functional assemblies will be reported. In particular, it is expected that assemblies of branched molecules in which the separate components possess complementary forms of functional behaviour, and the branching plays an active role in controlling the properties of the aggregate as a whole, will be of special interest.

6 Conclusions and Future Prospects

Writing this review has taken us, as authors, on a fascinating journey through the branched architecture, and allowed us to consider the unique influences which the different topological regions of dendrimers can have on supramole-

cular behaviour. We have reconsidered a wide range of recognition processes and believe this dynamic research area still possesses vast untapped potential. Hopefully, the coming years will bring an increasing number of examples in which molecular recognition events are investigated in the context of branched molecules. Not only do we expect this to yield an increased understanding of the connection between structure and function, but also a deeper insight into the behaviour of biological systems and, furthermore, a range of novel functional materials suitable for the application of dendritic supramolecular technology to real-world problems.

7

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The First Organometallic Dendrimers: Design and Redox Functions

Didier Astruc¹ · Jean-Claude Blais² · Eric Cloutet¹ · Laurent Djakovitch¹ ·
Stéphane Rigaut¹ · Jaime Ruiz¹ · Valérie Sartor¹ · Christine Valério¹

¹ Groupe de Chimie Supramoléculaire des Métaux de Transition, LCOO, UMR CNRS No. 5802,
Université Bordeaux I, 33405 Talence Cédex, France
E-mail: d.astruc@lcoo.u-bordeaux.fr

² Laboratoire de Chimie Structurale Organique et Biologique, EP CNRS No 103,
Université Paris VI, 4 Place Jussieu, 75252 Paris, France

This review summarizes our original organometallic route to stars, dendrimers, metallostars and metallodendrimers and the redox functions of these macromolecules in catalysis and anionic recognition. The synthesis of metal-sandwich stars and dendritic cores was achieved using the CpM⁺ induced polyallylation and polybenzylation of polymethylbenzenes (M = Fe or Ru) and pentamethylcyclopentadienyl ligands (M = Co or Rh). Subsequent functionalization of the polyallyl dendritic cores yielded polyols which are precursors of polyiodo, polymesylates, polynitriles, polyamines and polybenzaldehyde cores. The synthesis of dendrimers up to 144-nitrile and 243-allyl was subsequently achieved starting from mesitylene. Functionalization of the polybenzyl dendritic cores was achieved by regiospecific Friedel-Crafts reactions (acetylation, chlorocarbonylation) in the para position. Various metallodendrimers were synthesized with amidoferrocene, amidocobaltocenium and FeCp*(η^6 -*N*-alkylaniline)⁺ termini in which the redox centers show a reversible behavior and are all independent as observed by cyclic voltammetry. The 9-, 18- and 24-amidometallocene dendrimers were used for the recognition of the oxo anions H₂PO₄⁻ and HSO₄⁻ by cyclic voltammetry, whereas a 24-iron-alkylaniline dendrimer was efficient to recognize Cl⁻ and Br⁻ anions by ¹H NMR with sharp dendritic effects. Differences between the responses to the different anions were large and the largest effects were found for the 18-Fc dendrimer (dendritic effect). A water-soluble star-shaped hexa-iron redox catalyst was as efficient as the mononuclear species for the cathodic reduction of NO₃⁻ and NO₂⁻ in water. In conclusion, metallostars are suitable for catalysis, and metallodendrimers present optimal topologies for molecular recognition. These specific functions related to the topologies cannot be interchanged between the metallostars and the metallodendrimers with optimized efficiency in the present examples.

Keywords: Dendrimers, Supramolecular chemistry, Molecular recognition, Catalysis, Macromolecular, Organometallic

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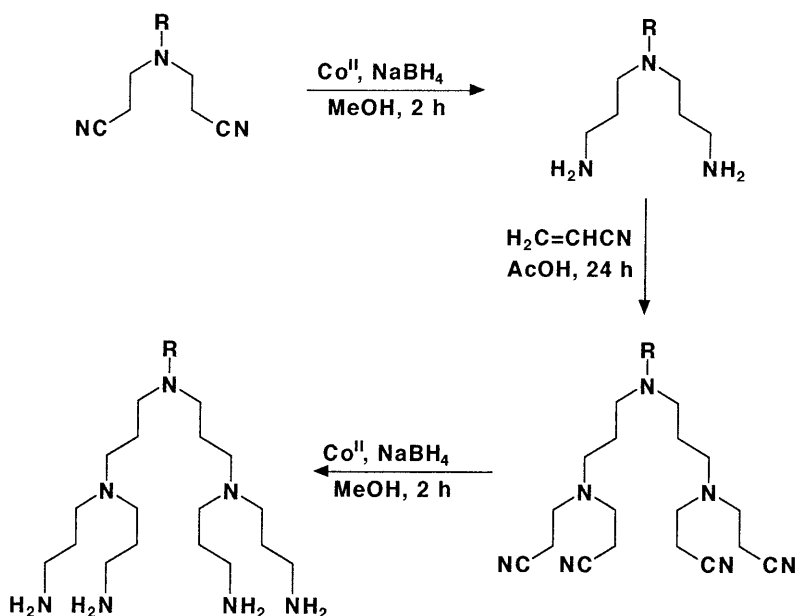
1

Introduction

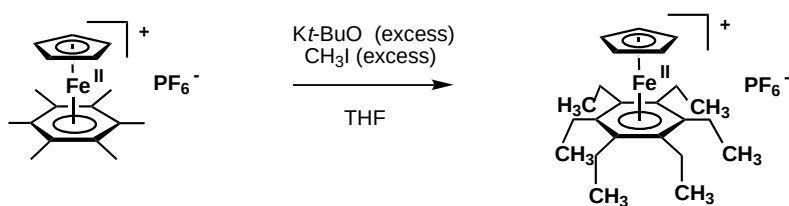
Redox processes are essential in Nature and technology [1], and are intimately connected to supramolecular chemistry [2, 3]. Thus, the redox properties of dendrimers, a now well-established field of supramolecular chemistry [4, 5], are likely to play an increasing role in the future. Recent reviews on dendrimers are numerous [6–28], and we shall concentrate here on metallodendrimers in which *reversible redox centers* have been attached in any way, allowing applications to processes which involve the use of the *redox functions*. Specifically, we will compare the redox properties of metallostars and metallodendrimers with respect to two functions: *catalysis* and *molecular recognition*.

In 1978, Vögtle published the first iteration of a reaction leading to the formation of a tetraamine from a monoamine after two sequences consisting of a Michael reaction followed by the reduction of the nitrile to the amine (Scheme 1) [29]. In 1979, we independently reported the CpFe^+ mediated one-pot hexamethylation of the hexamethylbenzene ligand to hexaethylbenzene (Scheme 2) [30]. This reaction comprises six deprotonation-alkylation sequences. In this case, the iteration of the sequence was achieved without compulsory isolation of the intermediate products. Although the reaction is not catalytic, the ligand is firmly held on the metal center while the reaction sequences are repeated several times until the steric limit is reached. This kind of reaction system represents a new type of process intermediate between stoichiometric reactions and catalysis. It is made possible by the enhancement of the acidity of the benzylic protons in the cationic complex. The $\text{p}K_{\text{a}}$ in dimethyl sulfoxide (DMSO) was indeed found to be about 14 units lower for the 18-electron complexes $[\text{MCp}(\eta^6\text{-C}_6\text{Me}_6)][\text{PF}_6]$ ($\text{M} = \text{Fe}$, 1; Ru , 2) ($\text{p}K_{\text{a}} = 29$) than for the free arene ($\text{p}K_{\text{a}} = 43$) [31–33]. Thus, the organometallic complex is a *reservoir of protons* in these reactions.

The use of this system with various polymethylbenzene ligands in the complexes $[\text{MCp}(\eta^6\text{-arene})][\text{PF}_6]$ ($\text{M} = \text{Fe}$ or Ru) and the pentamethylcyclopentadienyl ligand in the complexes $[\text{M}^*\text{Cp}(\eta^5\text{-C}_5\text{Me}_5)][\text{PF}_6]$ ($\text{M} = \text{Co}$ or Rh) led to a variety of non-chiral and chiral dendritic cores starting from functionalizable halides such as benzyl bromide and benzyl bromide. Subsequently, redox-active late-transition-metal sandwich units, ruthenium-polypyridine species and C_{60} fragments have been attached to the tethers of these stars and dendrimers. We will first describe these syntheses, then address the redox properties and their uses



Scheme 1. The first iterative cascade synthesis of tetraamines reported by Vögtle [29]



Scheme 2. One-pot hexamethylation of $[\text{MCp}(\text{C}_6\text{Me}_6)][\text{PF}_6]$ ($\text{M} = \text{Fe}$ or Ru) using excess *t*-BuOK and methyl iodide in THF. With Fe, the reaction occurs with a spontaneous smooth reflux for 1 min (5 mmol-scale) upon addition by cannula of a THF solution of MeI to the other solid reactants with stirring. With Ru, heating the reaction mixture for 1 d at 40 °C is needed

in molecular recognition and catalysis. Other metallocene dendrimers, in particular the polyferrocene dendrimers synthesized by the groups of Cuadrado, Jutzi and Togni, have appeared in the literature [34–39]. Ru-polypyridine dendrimers were introduced in the seminal work of Balzani's group [40–43], then by the groups of Newkome and Constable [44–47]. Other redox-active dendrimers are those decorated with tetrathiafulvalene (TTF) units reported by the groups of Bryce and Becher [48–51] and dendrimers centered on metalloporphyrins [52, 53], metal-polypyridine units [54–57], metal clusters [58–60], ferrocene derivatives [61, 62], C_{60} [63, 64] and naphthalene diimine [65, 66].

2

CpFe⁺ Mediated Synthesis of Stars and Dendritic Cores

2.1

Syntheses of Hexa-Arm Stars Starting from Hexamethylbenzene

The reaction of the PF₆⁻ salt of **1** or **2** [67–69] with excess KOH (or *t*-BuOK) in dimethyl ether (DME) and excess methyl iodide or benzyl bromide leads to a one-pot hexa-substitution (Scheme 3, Fig. 1) [30, 70]. With allyl bromide (or iodide) in DME, either the hexa-allylation [71] or the dodeca-allylation [72] product is obtained, depending on the reaction time. The prototypal hexafunctionalization is represented in Scheme 3. Both the hexa- and dodeca-reactions are well controlled. On the other hand, the reaction with excess benzyl bromide or *p*-alkoxybenzyl bromide only gives the hexabenzylated [70, 73] or hexaalkoxybenzylated [74, 75] complex as the ultimate reaction product. Similarly,

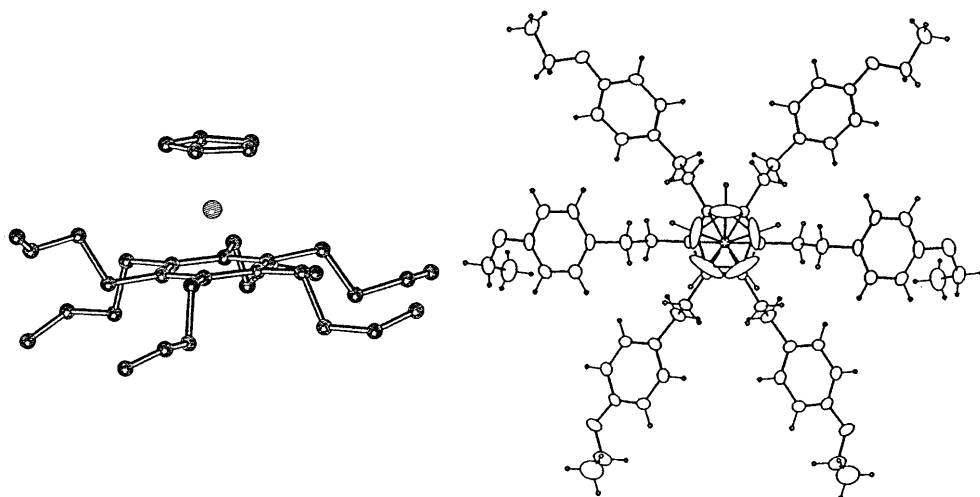
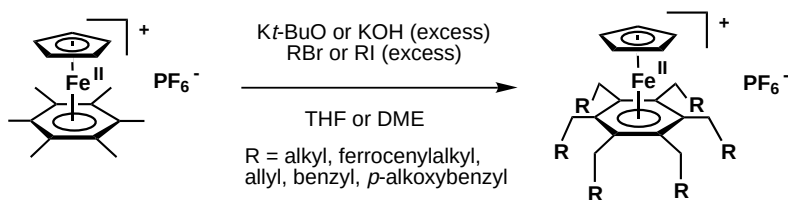
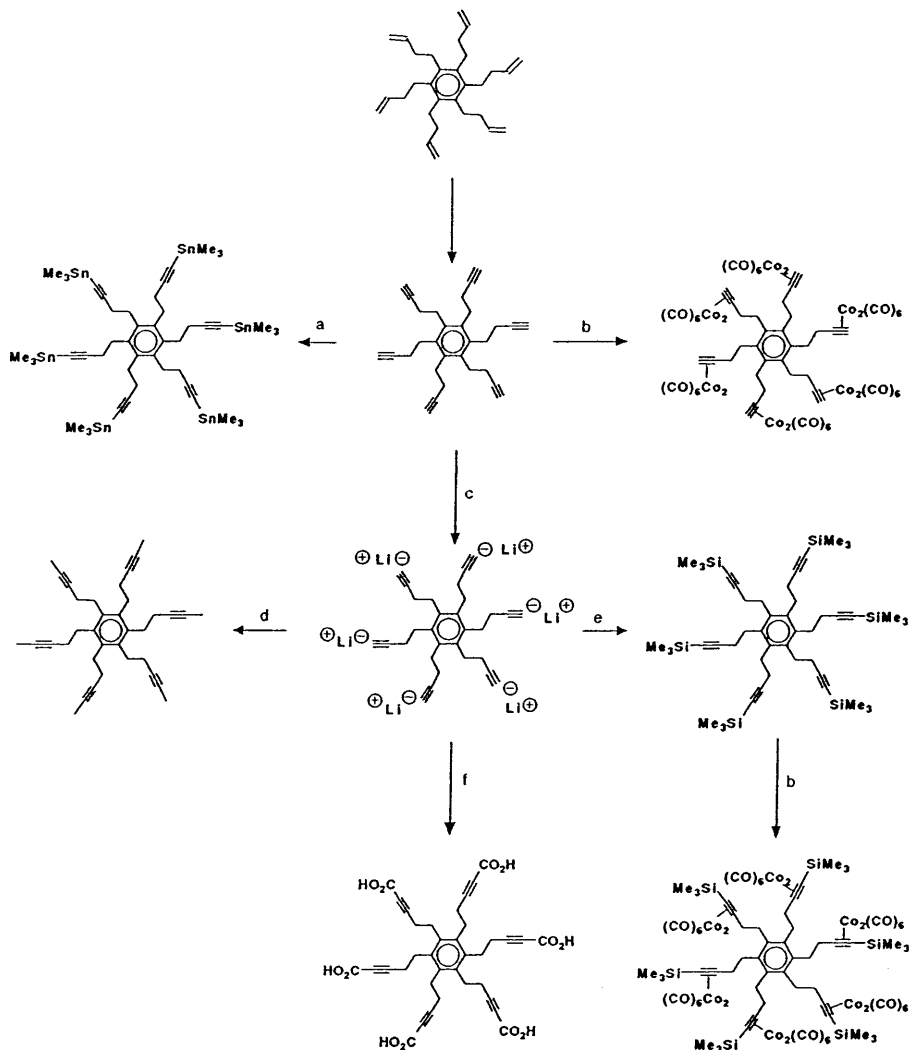


Fig. 1. X-ray crystal structures. Ortep views of [FeCp{ η^6 -C₆(CH₂CH₂-CH=CH₂)₆}][PF₆] (left side view) obtained by hexa-allylation of **1** and of [FeCp{ η^6 -C₆(CH₂-*p*C₆H₄OEt)₆}][PF₆] (right top view) obtained by hexaethoxybenzylation of **1**



Scheme 3. One-pot hexafunctionalization of [FeCp(C₆Me₆)](PF₆) using various electrophiles. Reaction temperatures vary between RT and 40 °C and reaction times are overnight or 1 d

with ferrocenylalkyl iodide, the hexaferrocenylalkylation product [74] is obtained from 1, free of any more highly branched product. This type of reaction can only work with halides which are compatible with the presence of the base in excess. For instance, alkyl halides only react if the base is KOH, not *t*-BuOK, since the latter leads to dehydrohalogenation [75]. For this reason also, alkynyl halides cannot be used, but alkynyl substituents can be introduced from the hexaalkene derivative by bromination followed by dehydrohalogenation of the dodecabromo compound (Scheme 4) [76]. The hexaalkene is also an excellent



Scheme 4. Synthesis (by reaction of the hexaalkene with Br_2 in CH_2Cl_2 at RT followed by NaNH_2 in NH_3 at -33°C) and reactions of the hexaalkyne. **a** $\text{Me}_2\text{NSnMe}_3$; **b** $[\text{Co}_2(\text{CO})_8]$, pentane, RT; **c** $n\text{BuLi}$, THF, RT; **d** MeI , THF, RT; **e** Me_3SiCl , THF, RT; **f** CO_2 , THF then aq. HCl, RT

starting point for further syntheses, especially using hydroelementation reactions. Hydrosilylation reactions catalyzed by Speir's reagent lead to long-chain hexasilanes [71] and hydrometallations can also be achieved using $[\text{ZrCp}_2(\text{H})(\text{Cl})]$ [77]. The hexazirconium compound obtained is an intermediate for the synthesis of the hexaiodo derivative [77].

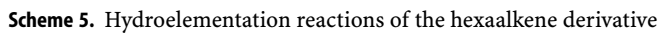
The most useful hydroelementation reaction, however, is hydroboration leading to the hexaborane which is oxidized to the hexol using H_2O_2 under basic conditions [71]. This chemistry can be carried out on the iron complex or, alternatively, on the free hexaalkene, which may be liberated from the metal by photolysis in CH_2Cl_2 or MeCN using visible light [71, 78]. Williamson coupling reactions between the hexol and 4-bromomethylpyridine or -polypyridine leads to hexapyridine and hexapolypyridine and their ruthenium complexes (Scheme 5) [79]. The hexol is indeed the best source of the hexaiodo derivative either using HI in acetic acid or even better by trimethylsilylation using SiMe_3Cl followed by iodation using NaI [80]. This hexaiodo star was condensed with *p*-hydroxybenzaldehyde to give a hexabenzaldehyde star which could further react with substrates bearing a primary amino group. Indeed, this reaction yielded a water-soluble hexametallallic redox catalyst which was active in the electroreduction of nitrate and nitrate to ammonia on an mercury (Hg) cathode in basic aqueous solution (*vide infra*) (Scheme 6).

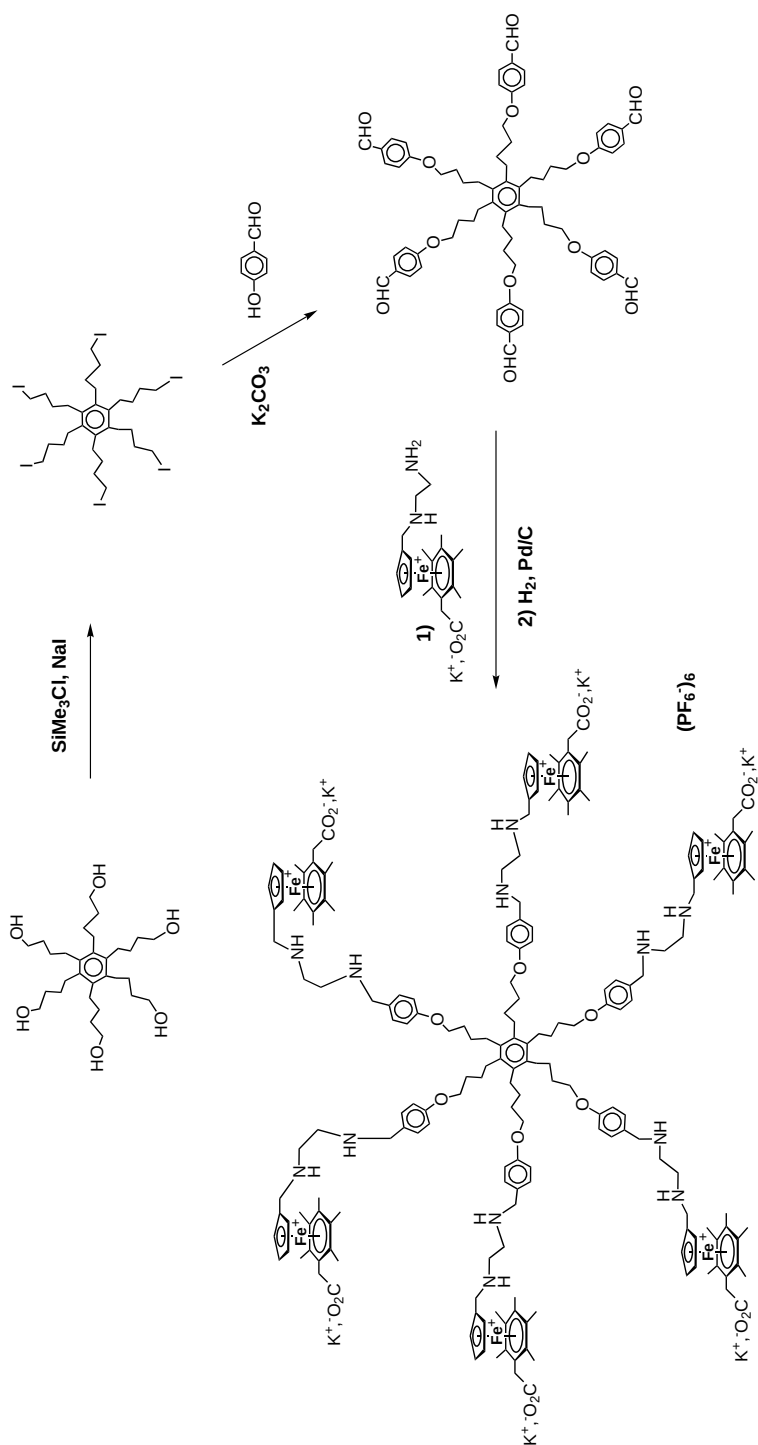
Hexa-arm polystyrene polymers with M_n up to 90,000 g/mol with polydispersities of 1.1 can be synthesized by regiospecific acetylation of the hexabenzylated arene, followed by reduction to the hexa-secondary alcohol, chlorination with SOCl_2 and living polymerization of styrene at -50°C using SnCl_4 as the Lewis acid, *n*- Bu_4NCl as the Cl source which quenches the living carbocation, and 2,6-di-*tert*-butylpyridine as the base. The hexa-arm polystyrene polymer of $M_n = 18,000$ g/mol (30 repeat styrene units per branch) bearing secondary chloro atoms at the termini of the branches can be transformed, using a 100-fold excess of Me_3SiN_3 , to its hexaazido analogue which cleanly reacts in refluxing PhCl with C_{60} in one day to give a tetrahydrofuran (THF)- and CH_2Cl_2 -soluble, hexa- C_{60} star, characterized *inter alia* by ^{13}C NMR, thermogravimetry, monomodal distribution in size-exclusion chromatography and cyclic voltammetry (Scheme 7) [81]. Before closing this section, it is important to note that various other symmetrically hexasubstituted benzene families are known [82].

2.2

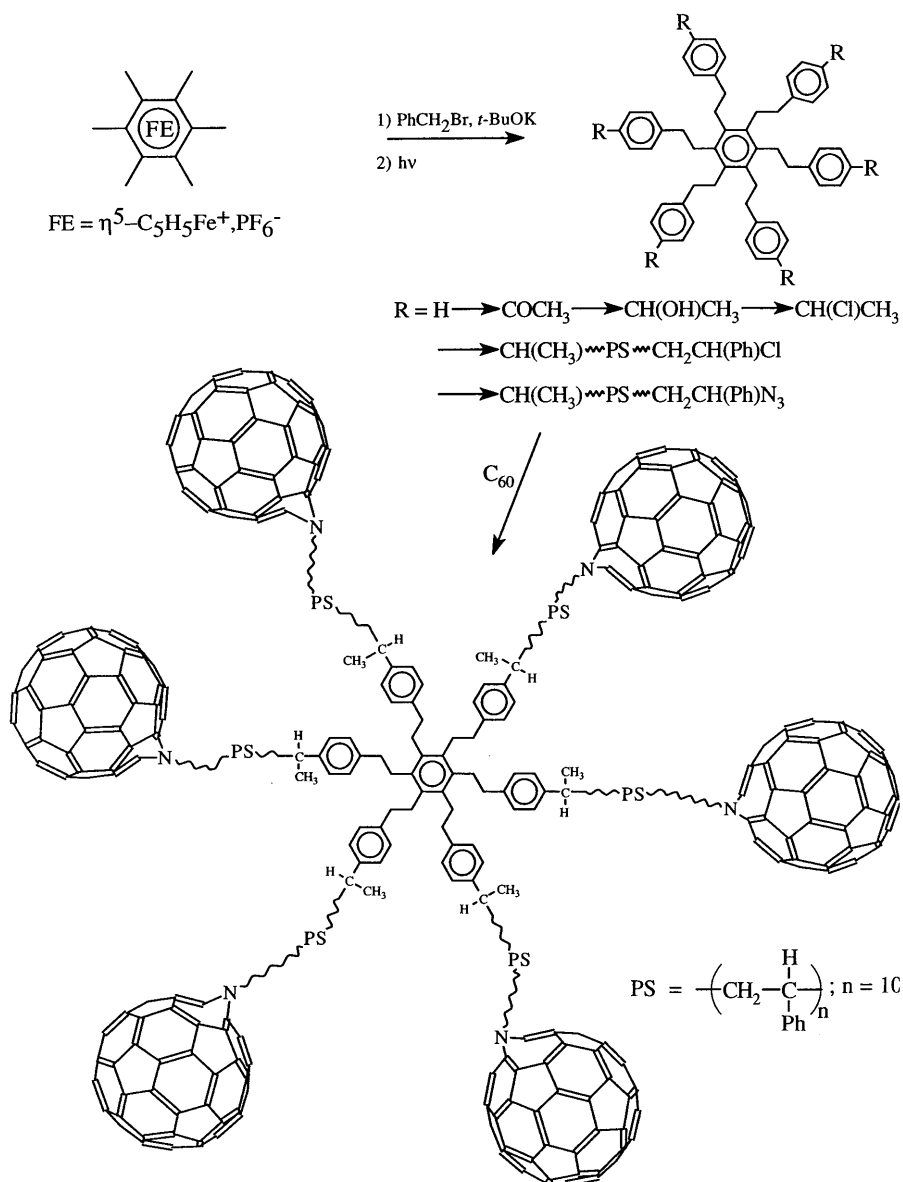
Syntheses of Octafunctional Dendritic Cores Starting from Durene

In compound **1**, the CpFe^+ induced perfunctionalization reaction is limited by the bulk of the six alkyl substituents around the benzene ring. Thus, the usual trend is that only one hydrogen per methyl substituent can be replaced by the branch introduced using the halide (the only exception being the prolonged reaction with allyl bromide which can be pushed to double substitution, Scheme 8). However, depending on the bulk around the methyl groups, the substitution pattern varies. Fortunately, reactions can always be made specific for the formation of a single product. In $[\text{FeCp}(\eta^6\text{-durene})][\text{PF}_6]$ (**3**) each methyl

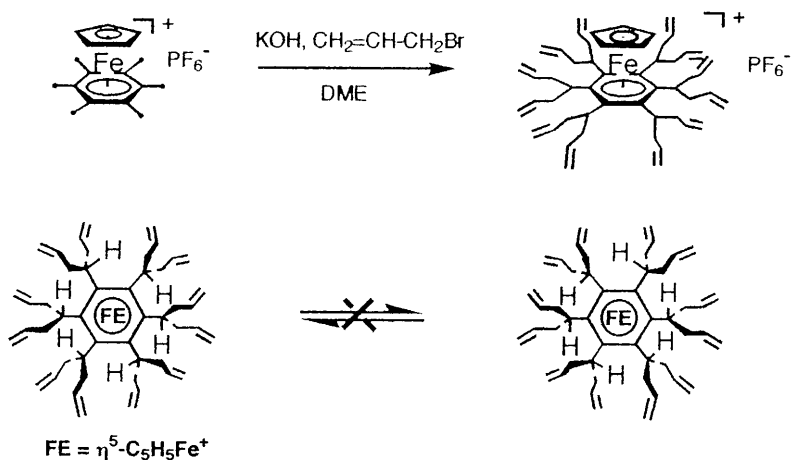




Scheme 6. Synthesis of a star-shaped hexanuclear water-soluble complex from the hexaalkene

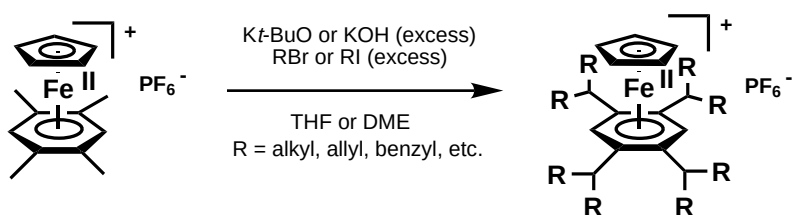


Scheme 7. Synthesis of a star-shaped hexa- C_{60} polymer derivative by CpFe^+ induced hexa-benzylation of C_6Me_6 followed by regiospecific acetylation, reduction to the hexol with NaBH_4 , chlorination in the benzylic positions using SOCl_2 , living polymerization by reaction with SnCl_4 and styrene, formation of the hexaazido by reaction with NaN_3 , and reaction of the hexaazido with C_{60}

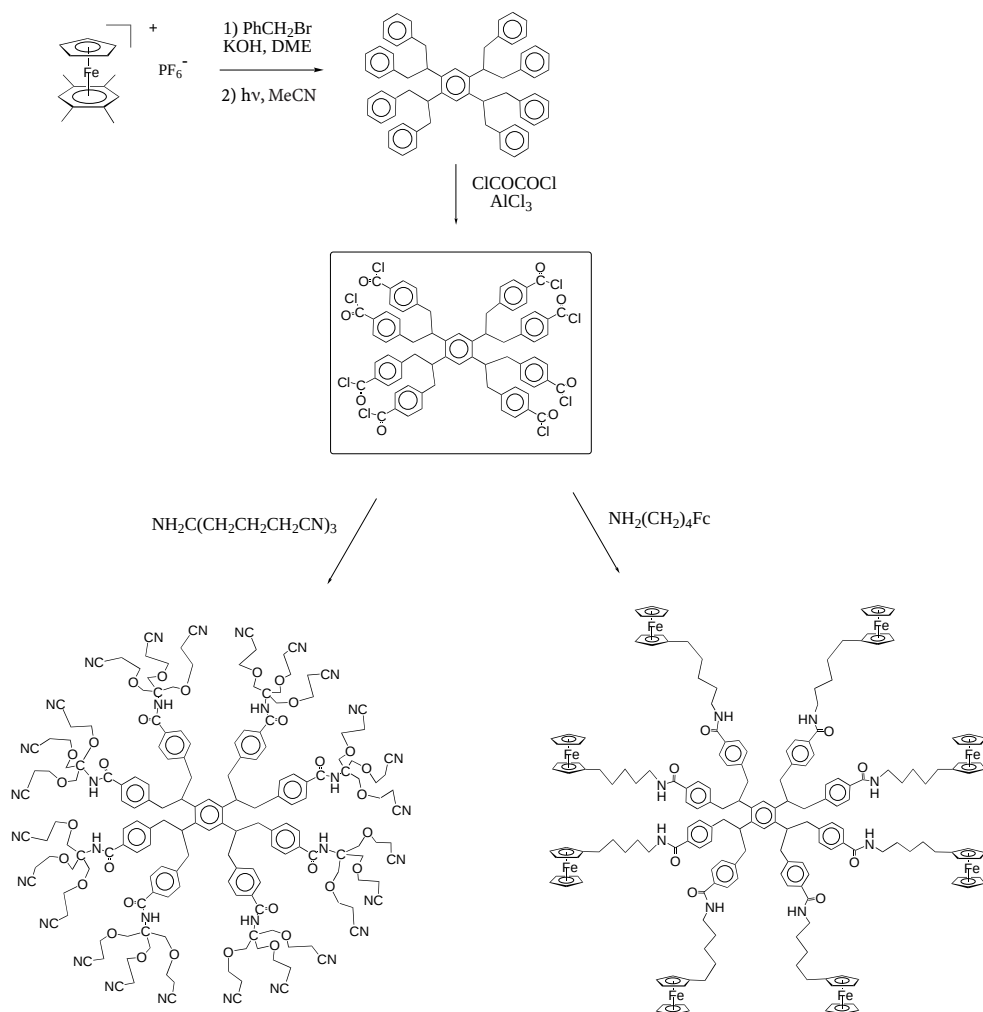


Scheme 8. Synthesis of the bulky dodecaallyl derivative and self-assembly of the two enantiomers with opposite directionality

group has only one methyl neighbor, so that double branching proceeds easily and selectively by reaction with excess methyl iodide, allyl bromide or benzyl bromide (Scheme 9) [72]. Regiospecific hydroboration of the octaallyl product followed by oxidation by $\text{H}_2\text{O}_2/\text{OH}^-$ gives the octol [72] whereas regiospecific chlorocarbonylation of the octabenzyl product selectively provides the octachlorocarbonyl derivatives in which chlorocarbonylation only occurs in the para position [83]. This compound is an excellent starting point for the synthesis of octamide derivatives by reaction with amines. This allows the branching of ferrocene and tripodal units such as Newkome's amino tripod (Scheme 10) which leads to a 24-nitrile dendrimer of generation 0 whose matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrum is shown in Fig. 2 [83].



Scheme 9. Syntheses of dendritic cores: Iron-cyclopentadienyl-mediated octa-alkylation of durene



Scheme 10. Regiospecific chlorocarbonylation of the octabenzyl derivative followed by reactions of the octachloro derivative with tripodal and organometallic amines

2.3

Syntheses of Nonfunctional Dendritic Cores Starting from Mesitylene

In $[\text{FeCp}(\text{mesitylene})][\text{PF}_6]$ (**4**) [83], each methyl group is free of a methyl neighbor on the adjacent arene positions. This is indeed the optimal situation for the maximum substitution, i.e. replacement of the nine H-atoms of the three methyl groups by nine branches. In the initial reaction of **4** with *t*-BuOK and MeI in THF, the tris-*tert*-butyl benzene complex was obtained [70]. However, the introduction of nine bulkier groups by reactions of other alkyl and benzyl halides failed, substitution being incomplete [85]. As for **1**, this limit has an exception with allyl

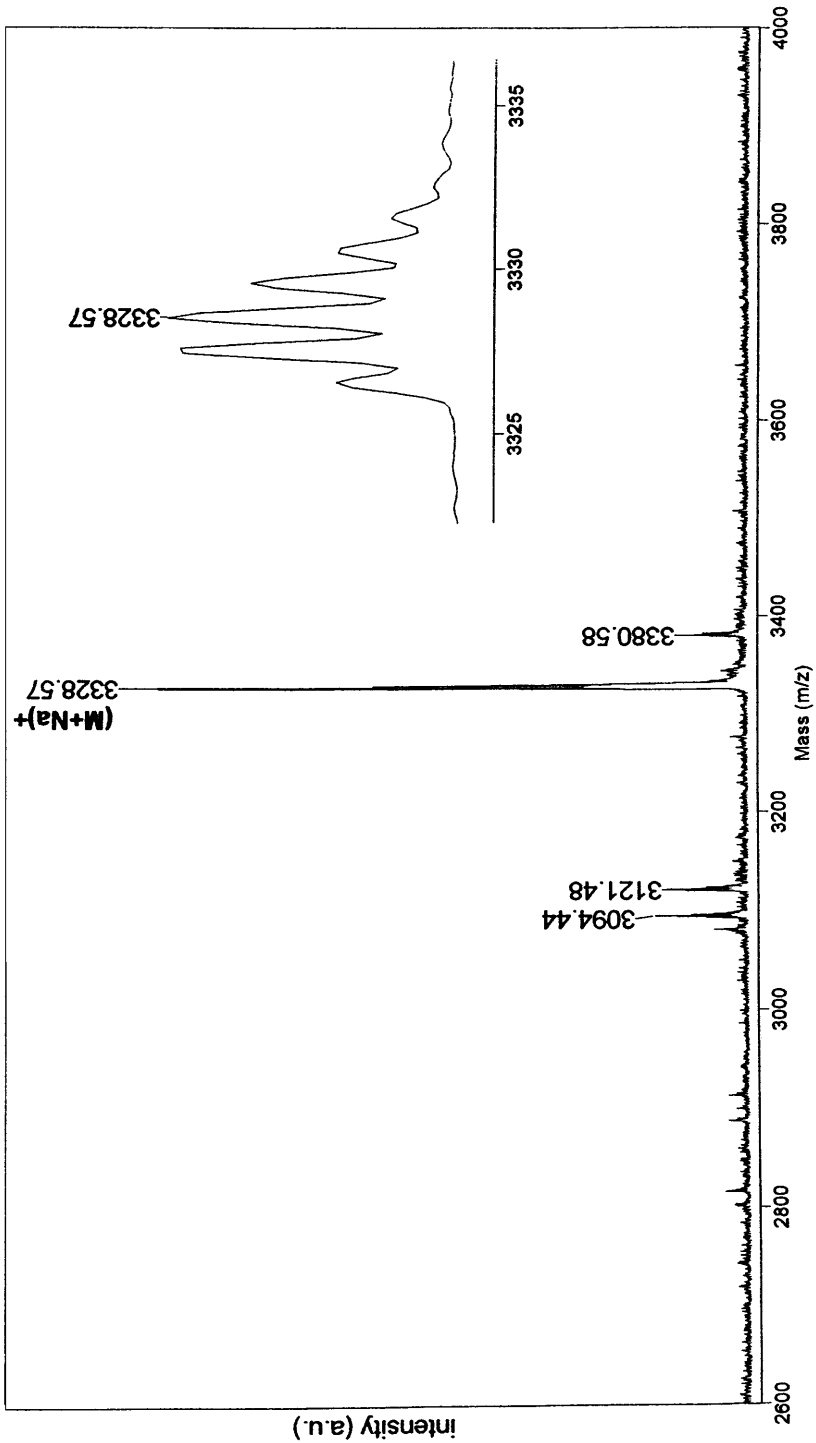


Fig. 2. MALDI-TOF mass spectrum of the 24-CN dendrimer. The molecular peak is $[M + Na]^+$ at 3328.57 (isotopic distribution on the right)

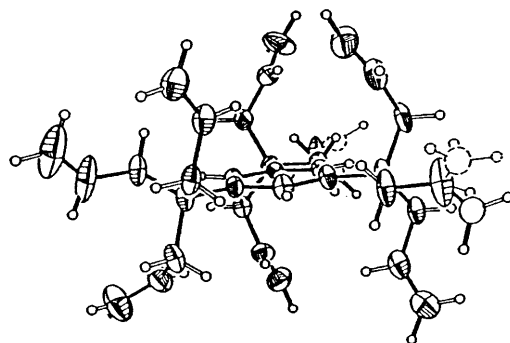
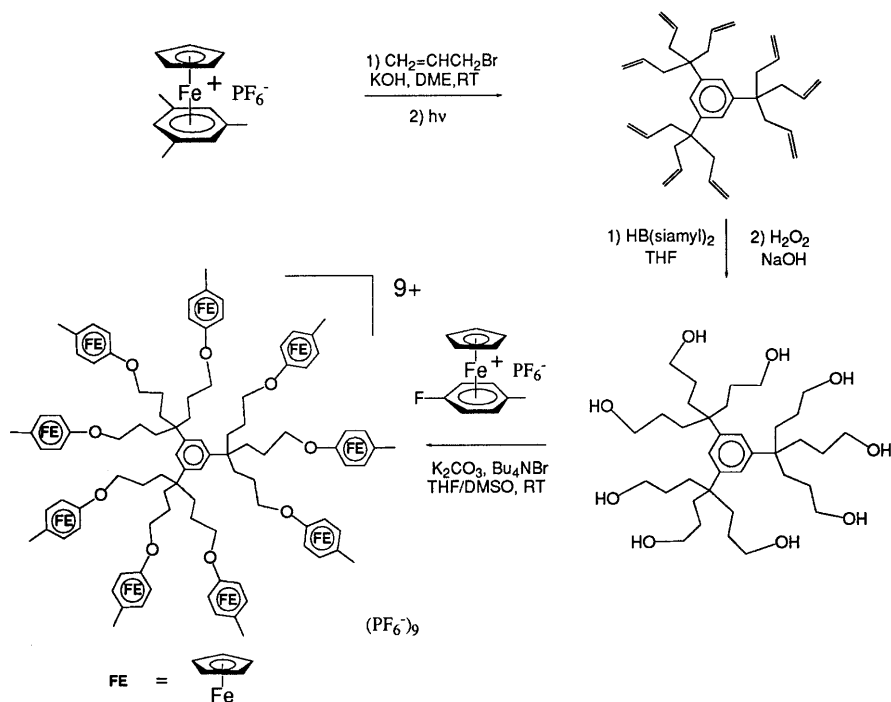


Fig. 3. X-ray crystal structure of $C_6H_3[C(CH_2CH=CH_2)_3]_3$ obtained by $CpFe^+$ induced nona-allylation of mesitylene. Ortep view along the plane of the benzene ring

bromide; in this case, the reaction leads to nona-allylation in high yield (Fig. 3) [85]. As for the hexa-allylation of **1** and **2**, the facile nona-allylation of **4** leads to subsequent synthetic developments, in particular via the quantitative hydroboration followed by oxidation to the nonol. At this point, it is already possible to introduce metallocene redox centers [84], but molecular engineering is necessary in order to match the required structure with the desired function (Scheme 11).



Scheme 11. $CpFe^+$ induced nona-allylation of mesitylene and regiospecific functionalization of the nonaallyl derivative

2.4

Syntheses of New Polyamine Dendrimers

The hexol and nonol can be easily transformed, via the nonaiodo and the nonanitrile, to hexa- and nonaamines in which the branches have the same length [85]. However, we forecast that the branches of such hexa- and nonaamines would be too short to provide soluble hexa- and nonametallocenes. Thus, we used the Michael-type condensation of acrylonitrile with the nonol to increase the length of the branches by three carbons and one nitrogen atom. This reaction has been used by Newkome to synthesize a trinitrile tripod from a triol tripod [86]. The nonanitrile was obtained in high yield, but its reduction to the nonaamine was a delicate task. The Raney nickel catalyzed hydrogenation was not as efficient in our hands as announced in the recent literature [87], as only up to 90% hydrogenation could be obtained after repeated attempts using the same mixture.

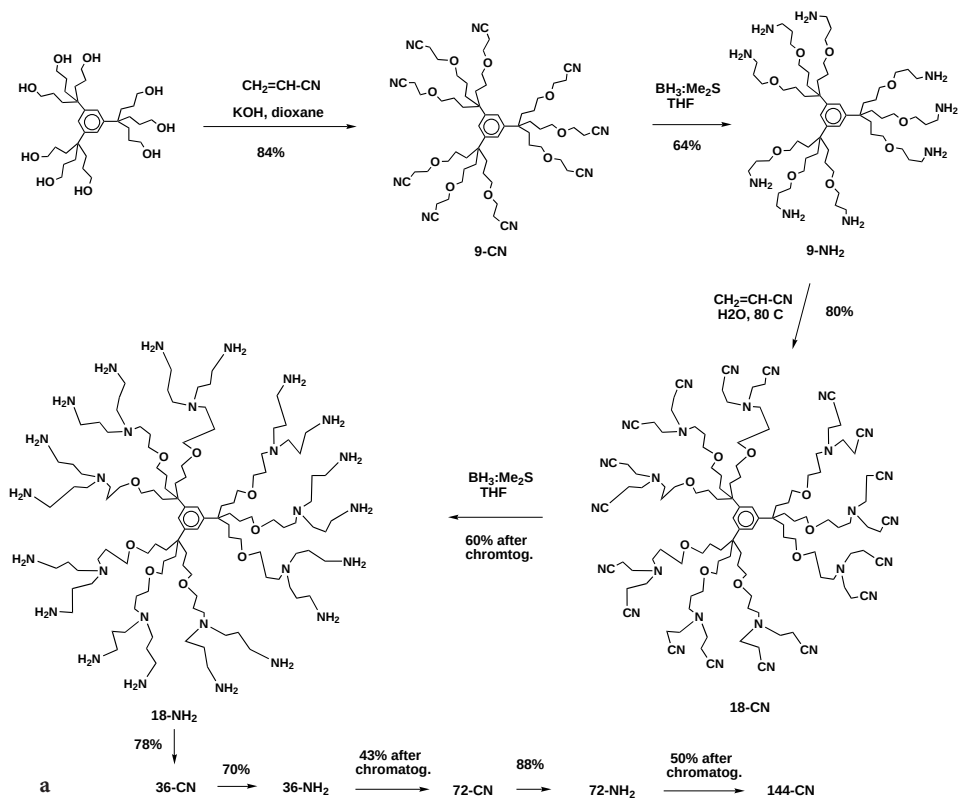
We turned our attention to the efficient reduction using the $\text{BH}_3/\text{Me}_2\text{S}$ reagent [88]. Reduction was quantitative and free of retro-Michael reaction using this reagent at 20 °C, as shown by the mass spectrum of the nonaamine from which boron educts had been removed by methanolysis in refluxing methanol. Using Vögtle's seminal iteration (Scheme 1) [29, 35], consisting of the Michael reaction of acrylonitrile with a diamine to form a tetranitrile, we performed the reaction of the nonaamine with acrylonitrile which gave a 18-nitrile. This dendritic strategy was pursued until the 72-amine and 144-nitrile [90, 91]. The ^{13}C NMR spectra showed the absence of significant amounts of products resulting from side reactions, and elemental analyses of the polynitriles were correct (Scheme 12).

2.5

A Fast Organoiron Route to Large Dendrimers

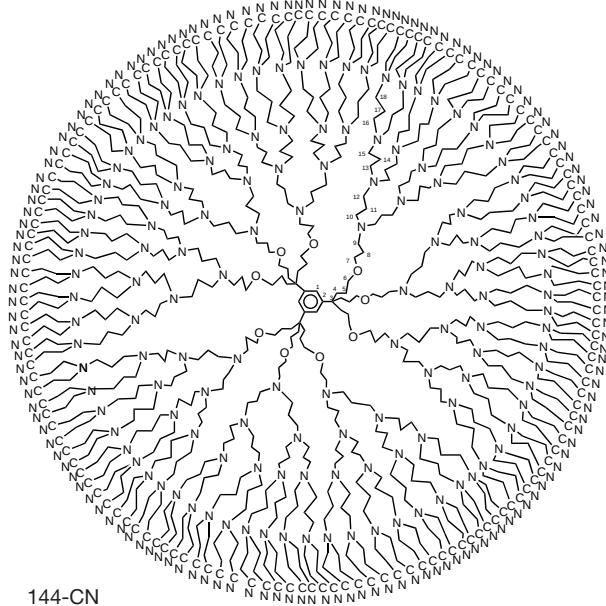
Polybranching using CpFe^+ activation of benzylic protons was extended to functional aromatics in order to open the route to dendrons. For instance, starting from $[\text{FeCp}(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{OEt})][\text{PF}_6]$, reaction with excess allyl bromide and KOH leads to the tripodal dendron $p\text{-OHC}_6\text{H}_4\text{C}(\text{CH}_2\text{-CH=CH}_2)_3$ in a one-pot reaction consisting of eight steps which must proceed in the right order: three deprotonation-allylation sequences, cleavage of the O-Et bond and decomplexation (Scheme 13). This dendron can be branched onto a nonaiodo-, or better, onto a nonamesylate core (obtained from the nonol core) to give the 27-allyl dendrimer which, in turn, can be transformed into the 27-alcohol dendrimer whose MALDI-TOF mass spectrum is shown in Fig. 4. Iteration of this process leads to the 81-allyl dendrimer whose molecular peak is still the major peak in the MALDI-TOF mass spectrum and to the 243-allyl dendrimers whose ^{13}C NMR spectrum shows complete substitution of the mesylate groups [78].

Scheme 12. a Synthesis of new polynitrile and polyamine dendrimers starting from the nonaallyl compound (Scheme 11) and using the seminal strategy of Vögtle shown in Scheme 1; b 144-CN, the ultimate dendrimer of Scheme 12 a

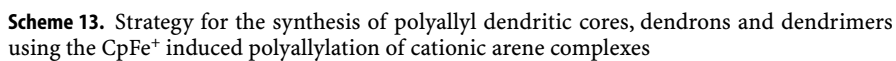


a

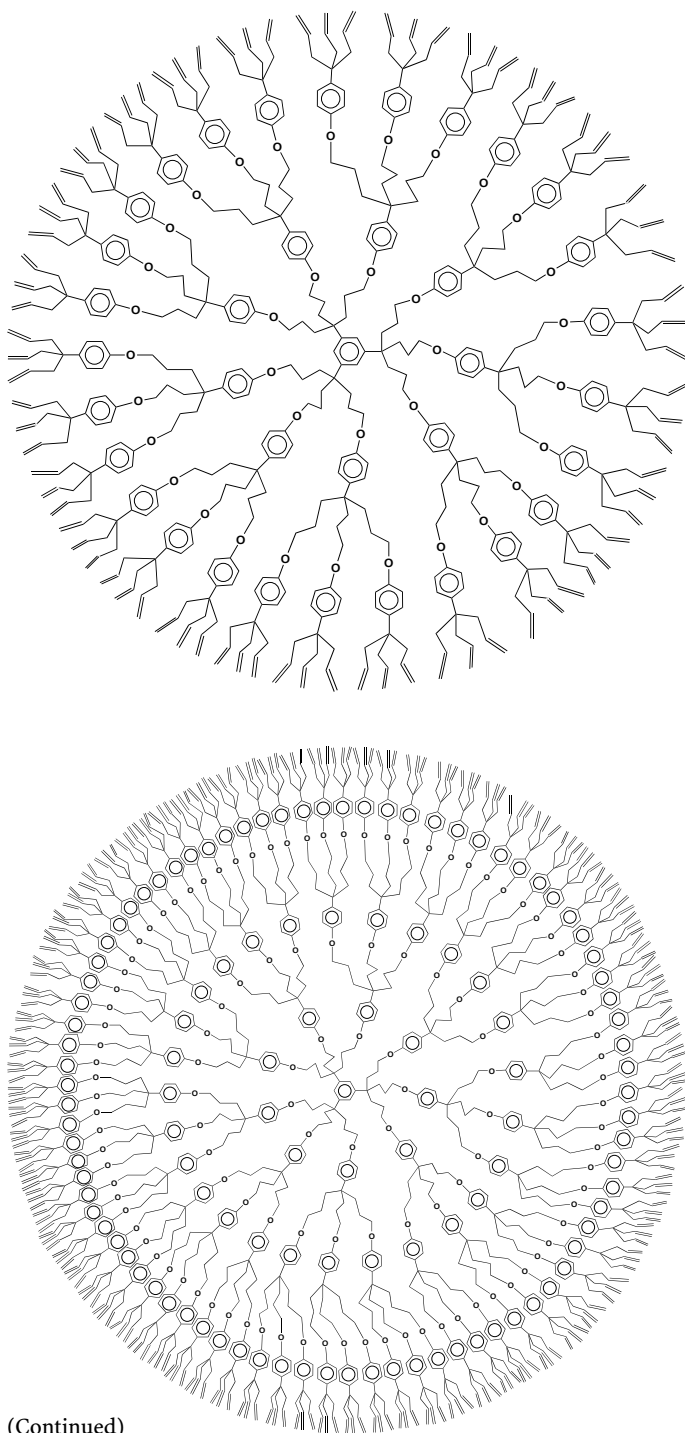
144-CN



b



Scheme 13. Strategy for the synthesis of polyallyl dendritic cores, dendrons and dendrimers using the CpFe^+ induced polyallylation of cationic arene complexes



Scheme 13 (Continued)

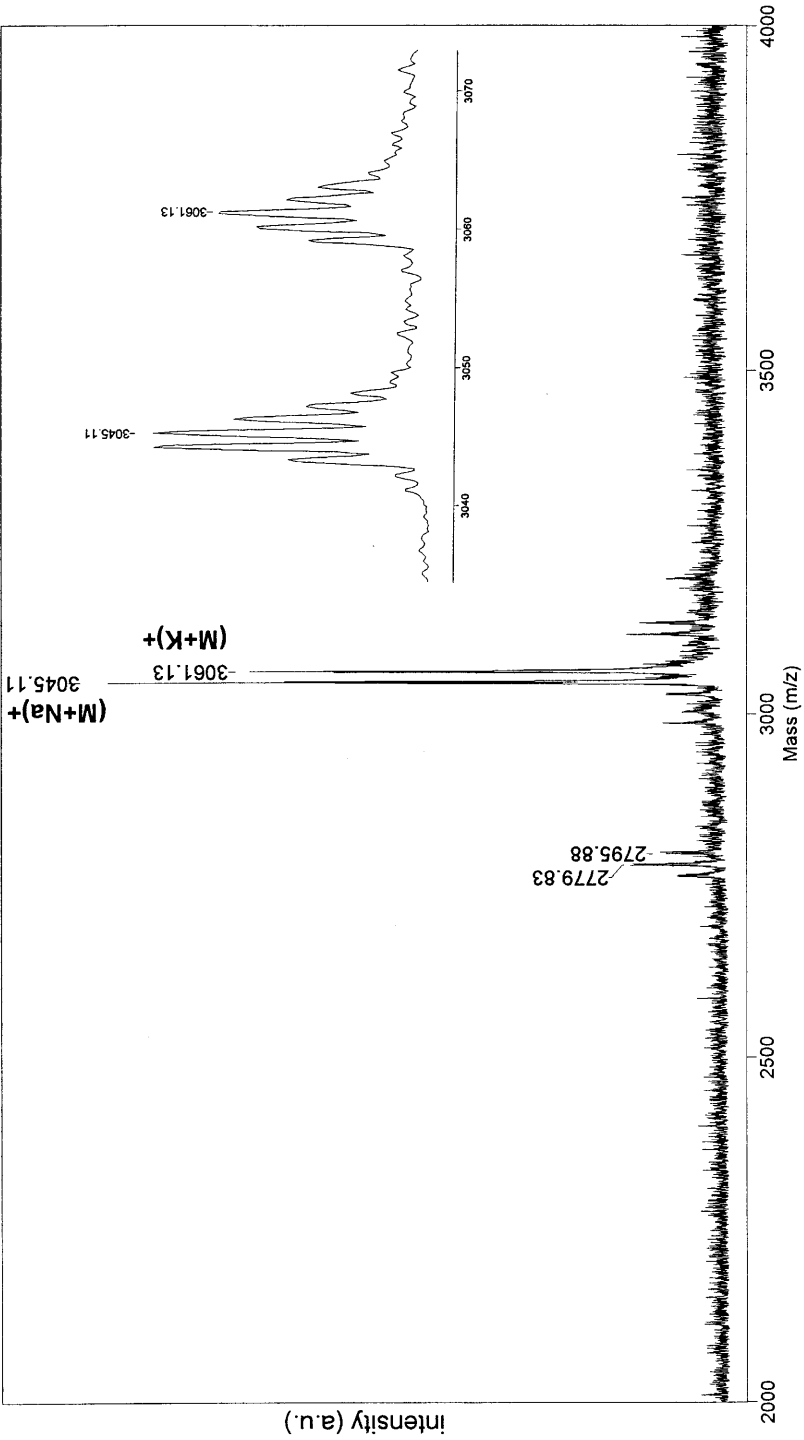


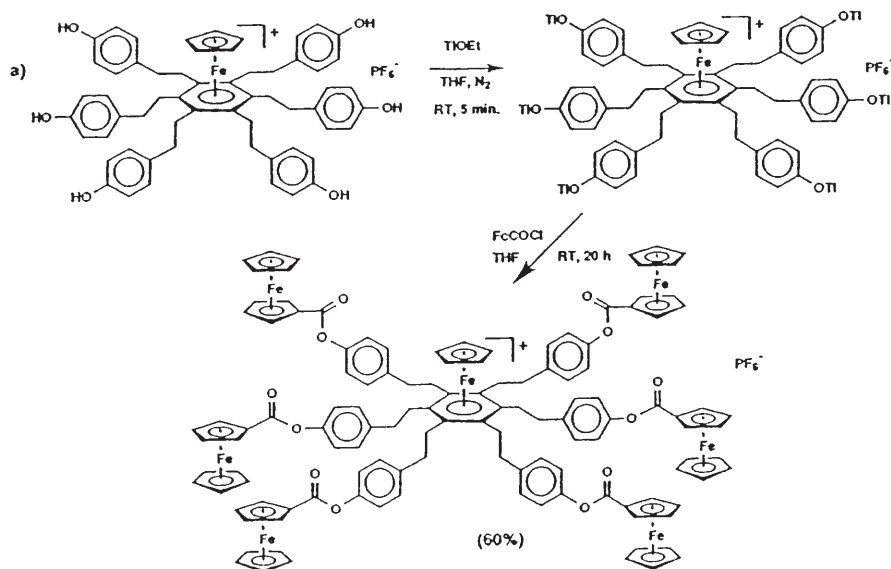
Fig. 4. MALDI-TOF mass spectrum of the 27-alcohol dendrimer showing the molecular peaks $[M + Na]$ at 3047.73 and $[M + K]$ at 3063.74

3

Syntheses of Polymetallocene Stars and Dendrimers

Iron-centered hexa-arm stars with iron-sandwich termini can be synthesized not only by direct ferrocenylalkylation (Scheme 3), but also by reactions of $[\text{FeCp}(p\text{-F-C}_6\text{H}_4\text{Me})][\text{PF}_6]$ or ferrocenoyl chloride with hexols or hexaphenols (Scheme 14) [91, 92]. A hexametallic star-shaped hexa-iron catalyst has already been described in Sect. 2.1 (Scheme 6).

The first nona-iron dendrimer was synthesized by reaction of a nonol with $[\text{FeCp}(p\text{-F-C}_6\text{H}_4\text{Me})][\text{PF}_6]$ [85] (Scheme 5). For this metallodendrimer, a single reversible wave was obtained in cyclic voltammetry at -30°C in DMF corresponding to the cathodic reduction of $d^6 \text{Fe(II)}$ to $d^7 \text{Fe(I)}$. From the intensity of the current [93], the number of electrons involved in the process was found to be 8 ± 1 [85]. However, this wave is not reversible at room temperature, and the neutral form is not water soluble. Thus, we have subsequently sought more robust and water-soluble redox systems for applications. The above polyamines were synthesized with the aim of obtaining polyamidometallocene dendrimers by reactions with metallocenylcarbonyl chlorides. The first obvious target was ferrocene units since the famous ferrocene/ferricinium redox couple had already found considerable use as a redox sensor. Reactions between the polyamine and chlorocarbonylferrocene were performed at room temperature for 1–3 d in CH_2Cl_2 in the presence of NEt_3 [90, 91] (Scheme 11):



Scheme 14. Synthesis of a hexaferrocene complex from ferrocenoyl chloride and the hexaphenol obtained by CpFe^+ induced hexaethoxybenzylation of C_6Me_6 (Scheme 3, Fig. 1) followed by O–C cleavage using BBr_3

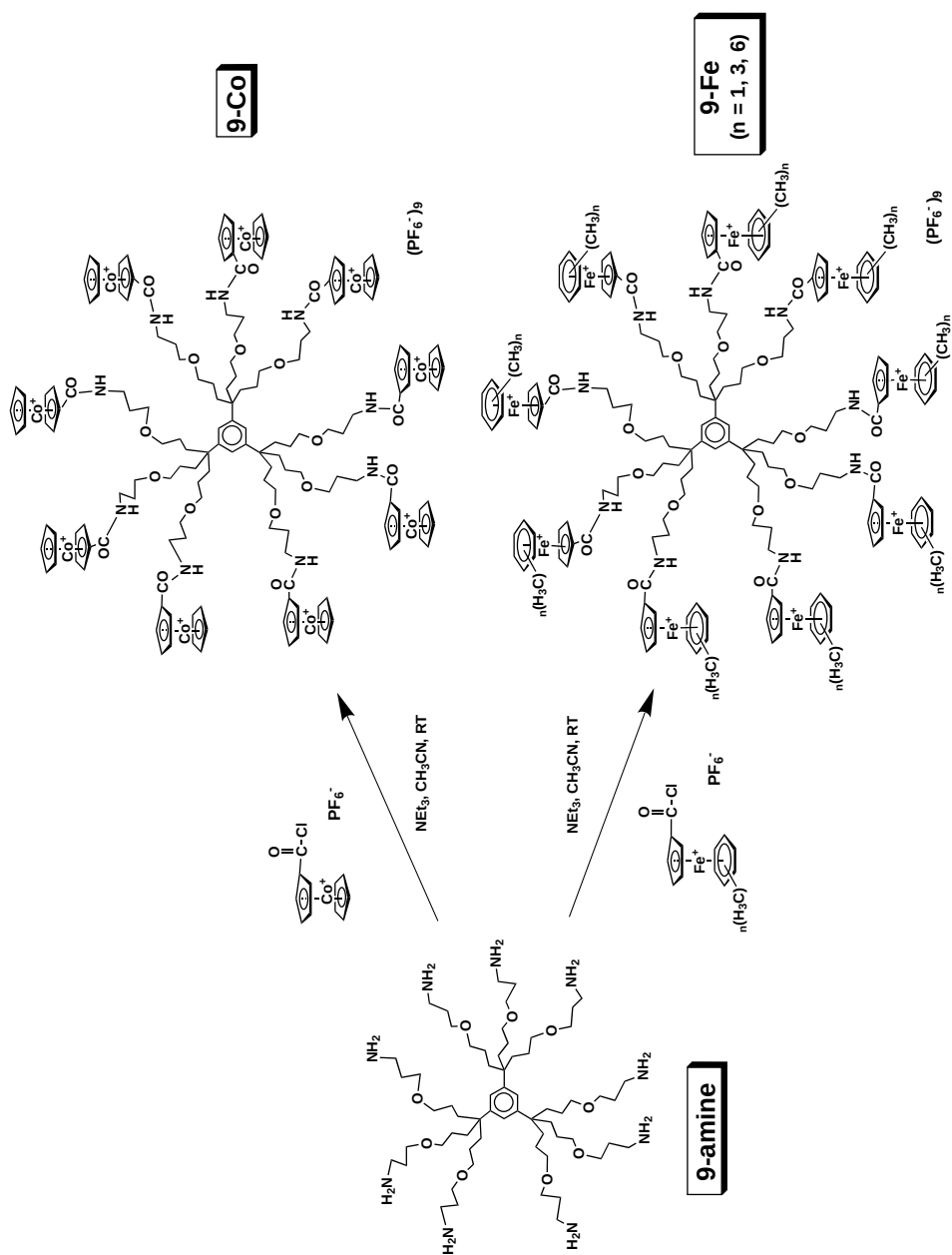
Only the 9- and 18-amine dendrimers gave soluble ferrocene dendrimers whereas the expected 36- and 72-amidoferrocene dendrimers were totally insoluble in all solvents. The insolubility reached for the 36-Fc dendrimer is a sign of steric saturation at the surface which prevents the solvents from penetrating inside the dendrimer. This also means that, at or above the 36-Fc generation, the number of ferrocene units becomes lower than expected in a default-free dendrimer, which is confirmed by elemental analyses and molecular modeling. On the other hand, the 9-Fc and 18-Fc dendrimers were characterized by ^1H and ^{13}C NMR and IR spectra, correct elemental analyses and the molecular peaks in the MALDI-TOF mass spectra (MH^+ : m/z 3066 for 9-Fc and MNa^+ : m/z 6024 for 18-Fc) [89]. These condensation reactions of the polyamines were also carried out with cationic transition-metal-sandwich complexes, namely: $[\text{Co}(\text{CpCOCl})\text{Cp}][\text{PF}_6]$ or analogues [89, 94, 95] and $[\text{Fe}(\text{CpCOCl})(\text{arene})][\text{PF}_6]$ [95] (Scheme 15). The nona-metal dendrimers with these sandwiches were synthesized and characterized by standard spectroscopic techniques and elemental analyses. Electrospray mass spectra recorded by Leize and van Dorselaer at Strasbourg University showed molecular peaks for 9-Co- and 9-Fe-toluene. Their solubilities are weaker than those of the ferrocene dendrimers, however, and decrease as the bulk of the sandwich moiety increases (i.e. when the number of methyl groups increases on the arene ligand of the iron complex). The 18-Co dendrimer was also synthesized, but its solubility in MeCN is weak, which makes NMR characterization less unambiguous, and elemental analysis suggested the inclusion of water molecules.

Metallodendrimers containing 24 amidoferrocene or cationic $\text{FeCp}^*\text{arene}$ groups were synthesized according to Scheme 16 from the 24-amine dendrimer obtained by $\text{BH}_3/\text{Me}_2\text{S}$ reduction of the 24-nitrile dendrimer whose synthesis is shown in Scheme 10. The synthesis of amidoferrocene dendrimers derived from commercial (DSM) polyamine dendrimers has also been reported by the group of Cuadrado [36]. The area of metallodendrimers has recently become very active indeed [8, 96–104].

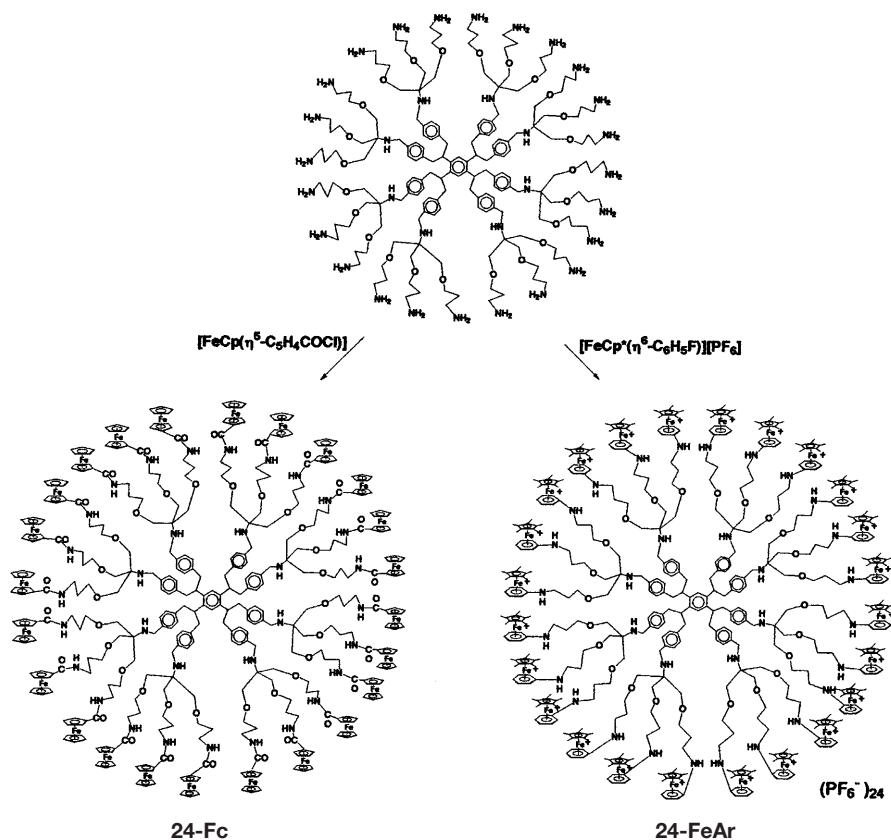
4

Redox Recognition of Inorganic Anions

The area of anion recognition, pioneered by Lehn [2, 56, 105–107], is of particular importance because of its biological implications. Various types of sensors are known, including redox sensors with macrocycles and tripods [108–112]. The anion receptors designed so far are endo-receptors [113–119]. On the other hand, dendrimers with redox sensors at the extremities of the branches could function as exo-receptors, especially if the surface covered with redox sensors is not too far from steric saturation. At this point, it could mimic the surface of microorganisms such as viruses. The ferrocene unit has long been used as a redox sensor since both Fe(II) and Fe(III) forms are stable enough for electrochemical scanning without loss of reversibility. The principle is that the redox potential of the Fe(II/III) redox system of the ferrocene unit is not the same in the presence and absence of substrate whose recognition is being sought. In the meantime, the binding constant of the substrate with the host bearing the



Scheme 15. Synthesis of amidometallocene dendrimers from metallocenyl chlorides and polyamine dendrimers



Scheme 16. Synthesis of a 24-amidoferrocene (*left*) and a polycationic 24-Fe-arene dendrimer (*right*) from the 24-amine dendrimer synthesized by reduction of the 24-nitrile dendrimer (Scheme 10) using $\text{BH}_3/\text{Me}_2\text{S}$ in THF

ferrocene unit close to the receptor is not the same in the neutral Fe(II) redox form of ferrocene and in its Fe(III) cationic form. The amidoferrocene fragment also has the benefit of the acidic amide hydrogen atom which can form a hydrogen bond with an oxygen atom of oxo anions. Amidoferrocenes have indeed been used as redox sensors in tripodal units [116–119]. We have compared the 9-Fc and 18-Fc dendrimers with mono- and tripodal amidoferrocenes of closely related structure in order to investigate dendritic effects. Recognition studies have been carried out by cyclic voltammetry and by ^1H NMR. In each case, titration of the ferrocene dendrimers were effected by $n\text{-Bu}_4\text{N}^+$ salts of H_2PO_4^- , HSO_4^- , Cl^- and NO_3^- .

By far the most informative results were obtained by cyclic voltammetry by scanning the Fe(II/III) wave (Fig. 5). Before any titration, the cyclic voltammograms of the 9-Fc and 18-Fc dendrimers show a unique wave at 0.59 V vs. SCE in CH_2Cl_2 corresponding to the oxidation of the 9 redox centers, which indicates that, as expected, the 9 or 18 redox centers are approximately electrochemically

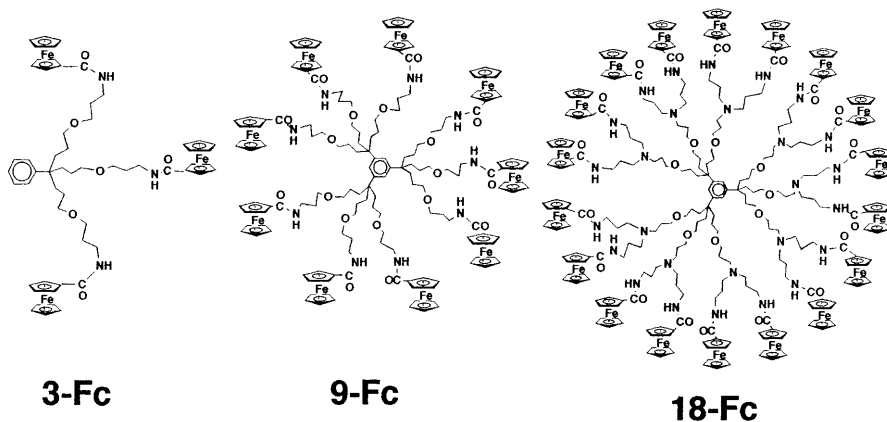
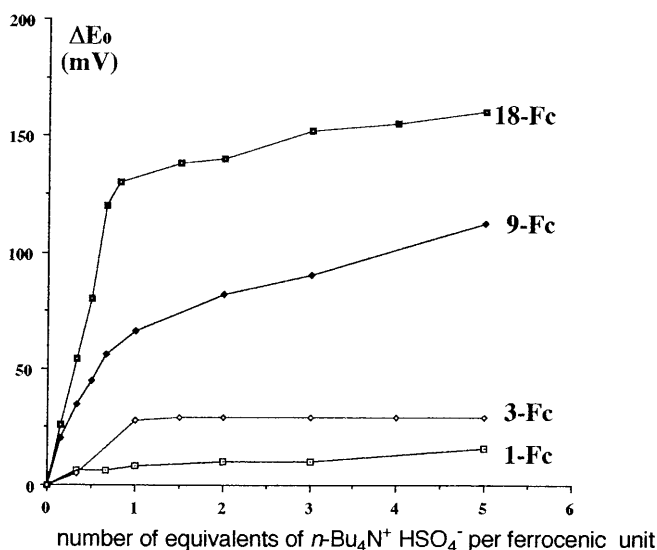


Fig. 5. Titration of 1-Fc (1-Fc = $[\text{FeCp}(\eta^5\text{-C}_5\text{H}_4\text{CONHCH}_2\text{CH}_2\text{OPh})]$), 3-Fc, 9-Fc and 18-Fc (10^{-3} M) by 0.1 M $[n\text{Bu}_4\text{N}(\text{BF}_4)]$ at 20 °C in CH_2Cl_2 using cyclic voltammetry (reference electrode: SCE; working electrode: Pt; sweep rate: 100 mV/s)

equivalent, thus independent. (When, for instance, two equivalent redox centers are not very far away from each other, two waves are observed at two distinct potentials, even if there is no electronic connection, because of the electrostatic effect. In the present situation, the redox centers are far from one another, thus the electrostatic effect is very weak and not detected.)

Upon addition of the anion, two situations can arise [120]. In the case of H_2PO_4 , a new wave starts to appear at less positive potentials and, correlatively, the intensity of the initial wave starts to decrease. When one equivalent of anion

per dendrimer branch has been added, the initial wave disappears and, upon addition of the anion, the intensity of the new wave no longer increases. In the case of the other anions, no new wave appears, but the initial wave is progressively shifted to less positive potentials upon titration until one equivalent of anion has been added per dendrimer branch. It clearly appears that the shifts (ΔE°) of potentials observed after addition of one equivalent anion per dendrimer branch considerably increases in the series: 1-Fc $\rightarrow$ 3-Fc $\rightarrow$ 9-Fc $\rightarrow$ 18 Fc, which shows the dramatic dendritic effect represented in Fig. 1 for the titration with the HSO_4^- anion. The magnitude of interaction with the anion increases in the following order: $\text{H}_2\text{PO}_4^- > \text{HSO}_4^- > \text{Cl}^- > \text{NO}_3^-$. In fact, the interactions with Cl^- and NO_3^- appear to be very weak. Both situations that can arise upon titration, i.e. appearance of a new wave and shift of the initial wave, have already been analyzed from the thermodynamic standpoint [120].

In the first situation in which H_2PO_4^- is involved, Eq. (1) applies:

$$\Delta E^\circ (\text{V}) = 0.059 \log [\text{K}(+)/\text{K}(0)] \text{ at } 25^\circ \text{C} \quad (1)$$

Measurement of ΔE° leads to $\text{K}(+)/\text{K}(0)$. The determination of $\text{K}(+)$ requires the determination of $\text{K}(0)$, the binding constant between the neutral ferrocene form of the dendrimer and H_2PO_4^- , in the present case by ^1H NMR using Hynes' EQ NMR program [121]. Indeed the shift of the amide proton also shows that the equivalence point is reached after addition of one equivalent of H_2PO_4^- per dendrimer branch (from $\delta = 6.82$ ppm before titration to 6.65 ppm after this addition).

In the second situation concerning the other anions, this binding constant $\text{K}(0)$ between the neutral ferrocene dendrimer and the anionic substrate is very small (> 1) and does not intervene in the expression of ΔE° [Eq. (2)]:

$$\Delta E^\circ (\text{V}) = 0.059 \log [\text{cK}(+)] \text{ at } 25^\circ \text{C} \quad (2)$$

where c is the concentration of added anion. Thus, $\text{K}(+)$ is directly accessible by measurement of ΔE° only (Tables 1 and 2).

^1NMR monitoring of the titrations is not as useful in the case of the other anions as in the case of H_2PO_4^- because, as indicated above, the interaction is weak. Indeed, equivalent points are very variable and very far from corresponding to one equivalent anion per branch, whereas they do for the ferricinium form which binds the different anions more strongly.

In general, the ferricinium form of the tripod or dendrimer binds the anions relatively strongly because of the synergy of the electrostatic attraction with the

Table 1. Titration of the amidoferrocene dendrimers by various $n\text{Bu}_4\text{N}^+$ salts monitored by the variation ΔE° (± 20 mV, in mV for one equivalent of anion per branch) of the standard redox potential E° of the redox couple in cyclic voltammetry. For HSO_4^- , the variation ΔE° is represented in Fig. 5 for the various dendrimers

	1-Fc	3-Fc	9-Fc	18-Fc
H_2PO_4^-	45	110	220	315
HSO_4^-	ϵ	30	65	130

Table 2. Apparent association constants $K(+)$ ($\pm 10\%$) determined in CH_2Cl_2 by cyclic voltammetry for the amidoferrocene dendrimer series from the shift in standard redox potentials using Eqs. (1) and (2). For 9-Fc, $K(+)$ was determined from the combination of $K(0)$ determined by ^1H NMR in CD_2Cl_2 and the $K(+)/K(0)$ ratio obtained from the cyclic voltammogram using Eq. (1). For 18-Fc, the $K(+)/K(0)$ ratio was found to be 219,000

	1-Fc	9-Fc	18-Fc
H_2PO_4^-	9390	216,00	
HSO_4^-	544	8530	61400

intermolecular hydrogen bond formed between the acidic amide H-atom and the anionic substrate through an oxygen atom of an oxo anion or the halogen anion. Both factors are important and, if one of them is absent, the interaction becomes loose and cannot be used for sensing (except in the case of H_2PO_4^- for the dendrimers). This effect has already been recognized and used [116–119].

Of special interest here is the dramatic dendritic effect observed for the anions. Even when the synergy between the electrostatic and H-bonding is fulfilled, the ΔE° value is unobservable or small when the amidoferrocene used is monometallic (1-Fc) or trimetallic (3-Fc). The shape selectivity designed in the dendrimer is crucial and its effect is much more marked for 18-Fc than for 9-Fc as the ferrocene termini are closer to each other when the dendritic generation increases. This dendritic effect is thus maximum for the generation (18-Fc) which precedes steric saturation by ferrocene groups on the dendrimer surface (36-Fc). It can be understood in the course of dendritic synthesis, as the insolubility of sterically saturated ferrocene dendrimers is complete in all solvents. In the amidoferrocene dendrimers, the amide H-atom is located on the branch behind the ferrocene unit which provides the surface bulk. Thus the anion must reach the inside of the microcavity formed by the amidoferrocene units at the surface of the dendrimer. These conditions become optimal for redox sensing and recognition by the close ferrocene units at the 18-Fc generation, since the channels allowing entry of the anions into the surface microcavity to reach the amide H-atom are as narrow as possible.

The polycationic 24-FeAr dendrimer shown in Scheme 16 has also proved useful for the recognition of Cl^- and Br^- , whereas the results with the oxo anions were not good. The best method appeared to be the shift of δ_{NH} monitored in the ^1H NMR spectra upon addition of the *t*-butylammonium salts of the halides. The titration with the monometallic, tripodal trimetallic and 24-FeAr dendritic complexes were compared in order to investigate the dendritic effect. Whereas the results of the titration of the monometallic and tripodal trimetallic complexes are poor and do not provide an equivalence point, titration of the 24-FeAr dendrimer yielded very good results with equivalence points for both Cl^- and Br^- . Very interestingly, however, the equivalence point for Cl^- corresponds to one equivalent of Cl^- for three dendritic branches (one dendritic tripod), whereas the equivalence point for Br^- corresponds to one equivalent of Br^- per dendritic branch (Fig. 6, Table 3). In these *N*-alkylaniline complexes, the NH group is acidic because of the electron-withdrawing properties of the Cp^*Fe^+ unit, and

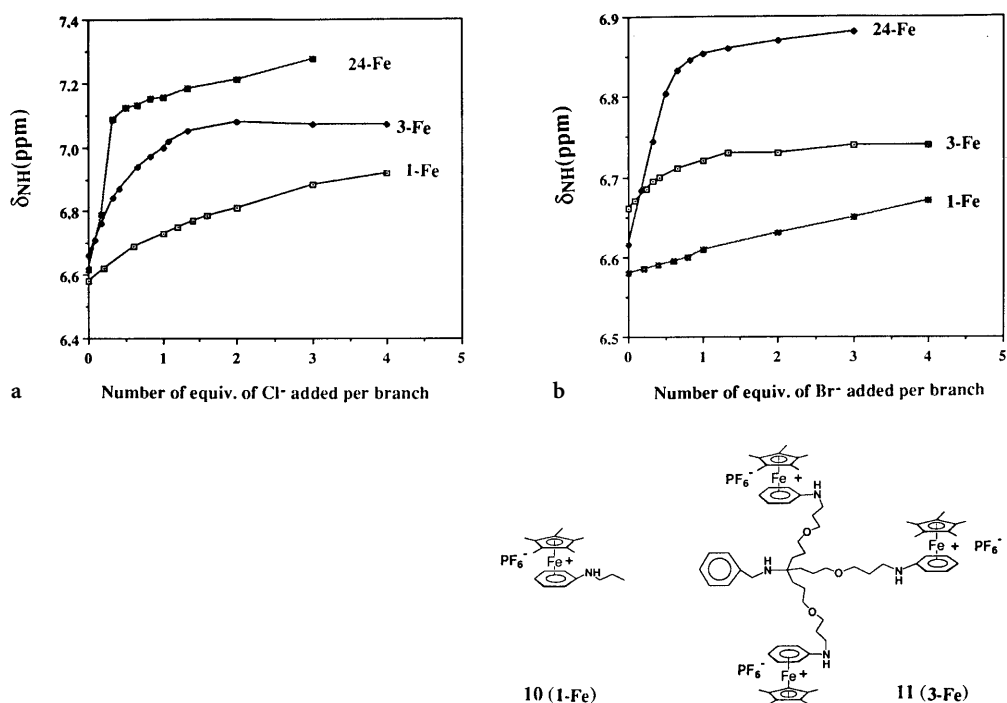


Fig. 6. Variation of δ_{NH} for the exocyclic amine proton measured by ^1H NMR spectroscopy upon addition of $n\text{Bu}_4\text{NCl}$ (a) and $n\text{Bu}_4\text{Br}$ (b), given in number of equivalents n per branch to 1-FeAr, 3-FeAr and 24-FeAr

Table 3. Apparent association constants $K(+)$ ($\text{dm}^3 \text{mol}^{-1}$) ($\pm 10\%$) determined from the variation of the δ_{NH} signal in $[\text{D}_6]\text{DMSO}$ at 20°C with the EQ-NMR program. Small values of the order of 10 (without a physical meaning) reflect the lack of equivalence point and underline the dendritic effects. For HSO_4^- , a negative dendritic effect is observed by comparing the values obtained for the 3-FeAr and 24-FeAr complexes

	1-FeAr	3-FeAr	24-FeAr
Cl^-	10	118	1221
Br^-	2	129	431
HSO_4^-	14	461	6

one hydrogen bond ($\text{N} \dots \text{H} \dots \text{X}^-$) can be formed. The size of the halide turns out to be a key factor in the interactions with the dendritic termini and exo cavities. The larger Br^- anion also interacts less strongly with the NH group than Cl^- because of the reduced electrostatic interaction.

In summary, these two series of metallo dendrimers are useful and complementary in anionic recognition, the amidoferrometallo dendrimers being best suitable for sensing the oxo anions, but not the halides, and the polycationic Fe-N-alkylaniline dendrimers being most useful to recognize halides.

5

Redox Catalysis by Metallostars

The catalysis of the electroreduction of nitrate and nitrite to ammonia by metal complexes is of environmental interest. This electroreduction can be catalyzed in water by complexes of the FeCp(arene) family [122]. However, it is necessary to solubilize the redox catalysts in basic aqueous medium in order to be able to carry out kinetic studies of the reduction of the substrates by the reduced 19-electron form of the redox catalyst in aqueous solution.

Kinetic studies were carried out by cyclic voltammetry in order to compare water-soluble mononuclear redox catalysts and hexanuclear systems in which the monomeric structure was branched to the extremities of hexa-arm stars. The enhancement of the reduction wave of the catalysts observed on a mercury cathode upon addition of the substrate (NO_3^- or NO_2^-) led to the measurement of the rate constant k according to the theory by Nicholson and Shain [123]. As indicated in the previous section, suitable molecular engineering has provided a hexanuclear catalyst which is also stable and water soluble in basic aqueous medium (0.1 N NaOH) and has the same redox potential as the monometallic compound. A preliminary comparison yielded data which showed that the hexanuclear redox catalyst was as active as the mononuclear catalyst of analogous driving force [124]. This enhancement was almost completely identical for the mono- and hexanuclear redox catalysts. The value of the rate constant of reduction of nitrate by the 19-electron form of the catalyst [$k = 3 \times 10^3 \text{ (mM s)}^{-1}$] is also in agreement with literature data [122].

6

Conclusions

The CpM^+ activation of the methyl groups in polymethylarene ($\text{M} = \text{Fe}$ or Ru) and pentamethylcyclopentadienyl ($\text{M} = \text{Co}$ or Rh) ligands of 18-electron complexes is a powerful and precise tool for the one-pot synthesis of stars and dendritic cores with various non-chiral and chiral topologies. These complexes behave as *proton reservoirs*. This methodology can also be applied to functional methylaromatics for the one-pot synthesis of dendrons which can serve as building blocks in dendrimer synthesis. From these dendritic cores and dendrons, we have subsequently synthesized large dendrimers. On the other hand, the design of organometallic stars and dendrimers has led to the achievement of a specific function in recognition or catalysis. Indeed, we have been able to demonstrate the first dendritic effects in molecular recognition and a redox-catalytic activity for the electroreduction of nitrate and nitrite to ammonia in water which is not decreased when the redox catalyst is attached to the termini of the branches of stars. Molecular recognition with stars and catalysis with sterically bulky dendrimers would not be efficient, however, that is to say appropriate engineering and design of the topology is necessary in order to achieve the function.

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Dendrimers in Diagnostics

Werner Krause · Nicola Hackmann-Schlichter · Franz Karl Maier · Rainer Müller

Schering AG, Contrast Media Research, Müllerstrasse 170–178, 13342 Berlin, Germany

E-mail: werner.krause@schering.de

Dendrimers are currently under investigation as potential polymeric carriers of contrast agents for magnetic resonance imaging (MRI), scintigraphy and X-ray techniques, i.e. computed tomography (CT). The objective for synthesizing large molecular weight contrast agents is to modify the pharmacokinetic behavior of presently available small-sized compounds from a broad extracellular to an intravascular distribution. Major target indications include angiography, tissue perfusion determination and tumor detection and differentiation. In principle, imaging moieties, e.g. metal chelates for MRI and scintigraphy and triiodobenzene derivatives for CT, are coupled to a dendrimeric carrier characterized by a defined molecular weight. The structures and sizes of these carriers are presently optimized. So far, however, no compound has reached the status of clinical application. Possible hurdles to overcome are synthetic problems such as drug uniformity, reproducible production of pure compounds and analytical issues, e.g. demonstrating purity. In principle, proof of concept for dendrimeric contrast agents as intravascular and tumor-targeting substances seems to have been established. However, a lot of effort is still necessary before a dendrimeric contrast agent will finally be available for wide-spread use in patients.

Keywords: Contrast agents, In vivo imaging, Magnetic resonance imaging, Computed tomography

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1

Introduction

Dendrimers represent a novel class of highly branched polymers which consist of essentially three different building blocks, i.e. core, branching units and functional groups for further derivatization at the surface of the molecule. Common cores exhibit three (ammonia) or four branching sites (1,4-diaminobutane). Accordingly, the number of functional surface groups of generations 1–6 is $3 \times 2^{n-1}$ or $2 \times 2^{n-1}$ with $n = 1, 2, 3$, etc. Excellent reviews on dendrimer technology are available in the literature [1–3]. Compared to classic polymers, the great promise of dendrimer chemistry is a much greater homogeneity or even monodispersity of dendrimers which could make them interesting carriers for drugs or diagnostics.

The application of dendrimer technology to diagnostics is a new and exciting field of research. There are two totally different areas of medical diagnostics, commonly referred to as *in vitro* and *in vivo* diagnostics. The first is normally *off-line* and covers analytical methods for biological samples which are normally obtained *ex vivo* from patients, such as blood or urine samples, and deals with long-known methodologies such as radio-immunoassays or enzyme-immunoassays (RIA and ELISA) and rather recent developments such as gene mapping. *In vivo* diagnostics likewise has a very long tradition dating back more than 80 years. It usually is *on-line* and covers the detection and characterization of disease in patients or animals using different imaging methodologies. Dendrimer technology might be important for both types of diagnostics. The follow-

ing sections will, however, be restricted to the field of medical in vivo diagnostics or medical imaging.

In vivo diagnostics is a very heterogeneous field covering all types of complexities from B-mode ultrasound to highly sophisticated techniques such as computed tomography (CT) or magnetic resonance spectroscopy (MRS). The context of interest here is the area of in vivo diagnostics utilizing contrast agents. At present, diagnostic agents are used for X-ray imaging, magnetic resonance imaging (MRI), ultrasound (US) and for scintigraphy, all of them with a number of sub-disciplines.

In general, the task of a contrast agent is to modify the signal response – in any technique – relative to non-enhanced procedures with the objective of improving the sensitivity and specificity of the method. Any pharmacological effects are not desired. Accordingly, the best contrast agent – from the point of view of tolerance – is that agent with the least interaction with the organism. The use of contrast agents differs widely within the different imaging modalities ranging from 100% in procedures such as angiography or scintigraphy to presently much less than 1% in ultrasound imaging. Since the physical basis of the available imaging modalities is totally different, so are the chemical nature and the requirements for the contrast agents. A summary of the characteristics, sensitivities and contrast agent features of the above-mentioned imaging techniques is given in Table 1.

Table 1. Characteristics of different imaging modalities and their contrast agents

Modality	X-ray	Magnetic resonance	Scintigraphy	Ultrasound
Principle	Attenuation of X-rays	Magnetic moment change of atoms (e.g. ^1H , ^{19}F , ^{31}P)	Detection of radioactivity (γ -rays)	Back-scatter of sound waves; stimulated acoustic emission
Time	Real time (fluoroscopy, DSA); Post-processing (CT)	Post-processing	Post-processing	Real time
Contrast	Heavy atom (e.g. iodine, metal ion)	Paramagnetic atom or group (e.g. gadolinium, iron, manganese, radical, hyperpolarized noble gas)	Radioactive element (e.g. $^{99\text{m}}\text{Tc}$, ^{131}I)	Gas (air, perfluorocarbon)
Spatial resolution	Very high	High	Very low	Low
Sensitivity	Very low	High	Very high	Very high
Quantification	Yes	(Yes)	Yes	No
Contrast agent dose (mg/kg)	100–1000	0.1–0.001	0.00001–0.000000001	0.1–0.001

Contrast agents may be characterized according to the imaging modality that they are used for (X-ray, MRI, US, scintigraphy), their chemical structure (e.g. iodinated compounds, metal chelates) or their pharmacokinetics (e.g. extra-cellular agents, intravascular compounds). In order to better understand the impact of dendrimer technology on contrast agents, all three categorizing methods will be dealt with briefly in the following sections.

2

Contrast Agents for In Vivo Diagnostic Imaging

Contrast agent research dates back to shortly after the discovery of X-rays by Röntgen in 1895. It was soon discovered that in order to increase the differences in contrast between tissues, any contrast agent requires the presence of one or more elements with high atomic weights. The higher the atomic weight, the better the contrast, since the majority of biological material contains only light atoms, such as hydrogen, carbon, oxygen and nitrogen. Only bone material is rich in calcium, an element with a significantly higher atomic weight. Sodium and lithium iodide and strontium bromide were the first water-soluble contrast agents to be used for X-ray imaging. They were introduced into clinical practice in 1923. Subsequently, iodine was identified as the element of choice with a sufficiently high atomic weight difference to organic tissue. It has been the most widely used X-ray attenuating atom in contrast agents until the present time.

New imaging modalities based on different physical principles required new types of contrast agents. For magnetic resonance imaging (MRI) elements which modify the magnetic moment of hydrogen present in tissue material are needed. Examples are paramagnetic ions such as gadolinium (III) or manganese (II/III) for water-soluble contrast agents and paramagnetic particles such as iron oxides as suspensions. In scintigraphy, a radioactive compound with the desired pharmacokinetic profile is administered into the body. Ultrasound imaging is based on the differences of the interaction of sound waves with various materials. The most effective US contrast relative to tissues is achieved with micro-bubbles.

2.1

X-ray Contrast Agents

There are two principally different types of X-ray contrast agents which might be described by positive and by negative contrast. Positive contrast means that the attenuation of radiation is higher by the contrast agent compared with the attenuation of the surrounding tissue. This requires the presence of an element of an atomic weight higher than those of biological tissue such as, for example, iodine. Negative contrast is produced by replacing biological material, e.g. blood, by compounds with a lower attenuation of X-rays, for example, gaseous carbon dioxide. The use of other gases, such as air, for negative contrast is not possible due to the formation of emboli. Carbon dioxide can safely be used in all non-neurological indications. It rapidly dissolves in blood without forming

emboli. However, its efficacy is inferior to that of iodinated contrast agents. Another gaseous contrast agent which is used for positive X-ray contrast in computed tomography applications is xenon. This contrast agent is rather new and is mainly used for perfusion measurements. The third element for positive contrast is barium. Barium sulfate is used for oral ingestion in order to diagnose diseases of the gastrointestinal tract.

Since iodinated contrast agents constitute the major portion of X-ray contrast agents, they will be dealt with in greater detail. The first X-ray contrast agent, sodium iodide, was rather toxic and subsequent research was directed towards masking the iodine in order to reduce toxicity. The first step of masking was to chemically bind iodine to an organic moiety thereby eliminating the toxicity of the iodide ions. The concentration of iodine necessary for an adequate contrast enhancement has to be rather high. For projection radiography such as angiography, it has to be greater than 10 mg/ml. For computed tomography with its higher sensitivity it still has to be greater than 1 mg/ml. To achieve such concentrations, the doses to be injected have to be very high. For CT, they are in the range 30–50 g of iodine which is equivalent to 70–120 g of drug. In order to be able to administer such high doses, the preparations of the contrast agent have to be very concentrated. Typical iodine concentrations are in the range 200–400 mg/ml. The total volume injected is still 100–150 ml. A suitable carrier for organic iodine is the benzene ring.

The first commercially available contrast agent, Uroselectan, which was introduced in 1929, contained one iodine atom in a non-aromatic six-membered ring. Subsequent generations of contrast agents contained two and finally three iodine atoms per molecule. This number could still be increased by doubling the molecule to dimers with six iodine atoms. The “non-iodine residue” of the contrast agent molecule has three purposes, first, to increase the solubility, second, to form stable covalent bonds with iodine and, third, to mask the iodine atoms to make them “biologically invisible” to the body. The last generation of agents only contains non-ionic substituents such as polyols. A typical structure of a non-ionic monomer is given in Fig. 1 (top left).

2.2

MRI Contrast Agents

The physical basis for MRI contrast agents is totally different from that of compounds suitable for X-ray imaging. Whereas for the latter the absorption of X-rays is the decisive factor, it is the influence on the magnetic moment of one single type of atoms, the protons, that determines the efficacy of MRI agents. This simply means that the contrast agent itself is not visible in MRI but only its effect on protons in its immediate neighborhood. Accordingly, the concentrations of MRI contrast agents are far less easily quantifiable than those of X-ray agents. In MRI, a magnetic field is applied to the tissue of interest which is subsequently modulated by a radio pulse. The change in distribution of the magnetic moments of the protons from random to directed and their return to normal (random) constitute the MRI signal. Contrast agents affect this return to normal by shortening T1 and/or T2 relaxation times. The signal intensity

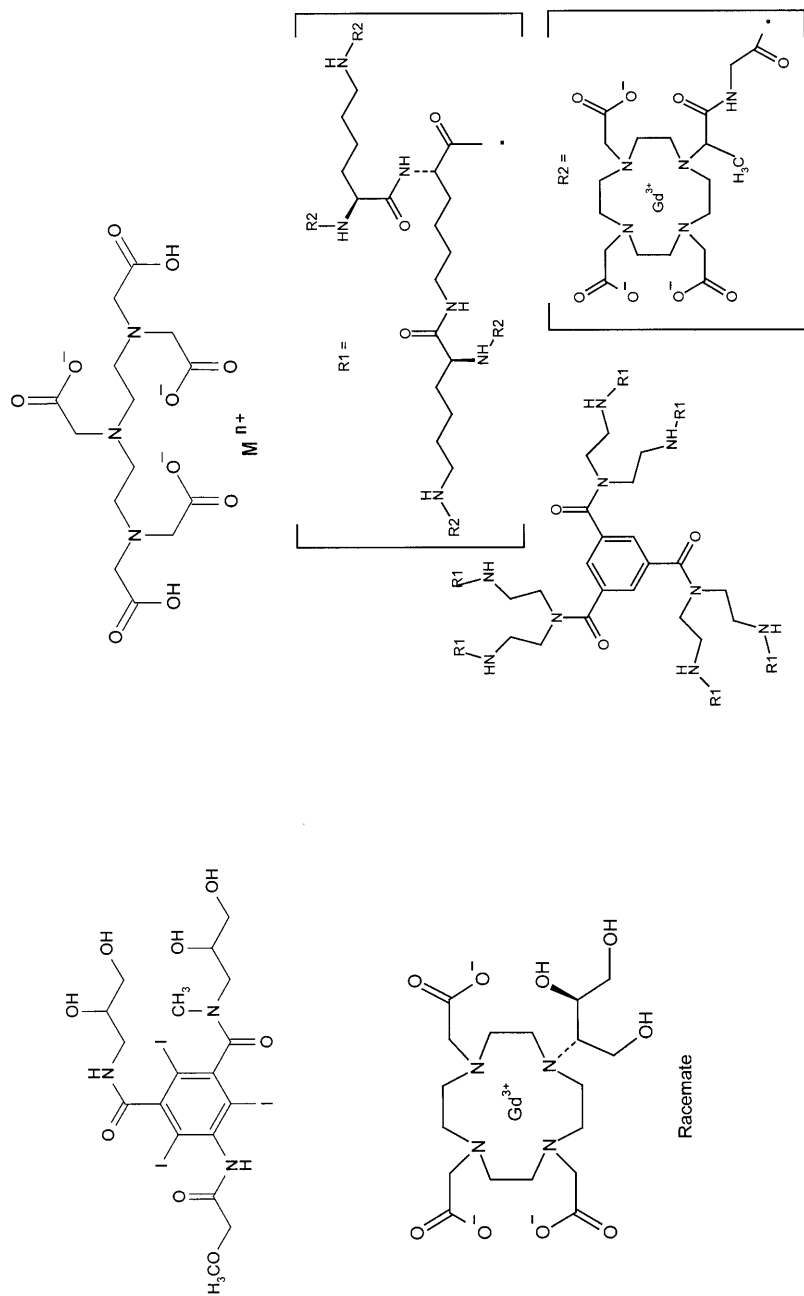


Fig. 1. Structure of an iodinated X-ray contrast agent (iopromide, *top left*), an ionic metal chelate for MRI (M-DTPA with $M = Gd^{3+}$) or scintigraphy ($M = ^{99m}TcO_2^{2+}$ or $^{111}In^{3+}$, *top right*), a nonionic metal chelate for MRI (gadobutrol, *bottom left*) and a dendrimeric blood-pool agent for MRI (Gadomer-17, *bottom right*)

depends on a number of variables such as the concentration of the agent, the relaxivity of the surrounding tissue, motion of the tissue and/or the agent, and machine parameters. Contrast agents might be differentiated according to several criteria. One of the major characteristics is whether they affect T1 or T2 relaxation times. Contrast agents that affect T1 contain paramagnetic elements such as gadolinium or manganese. Gadolinium is the metal ion with the highest T1 relaxivity because it has – as the three-valent ion (Gd^{3+}) – seven unpaired electrons in its outer sphere. Since these ions are, however, very toxic, they have to be masked in a molecule exactly like iodine has to be masked in X-ray contrast agents. In the case of MRI agents, this masking is performed by complexation with ligands such as diethylenetriaminepentaacetic acid (DTPA) for gadolinium or bis(dipyridyl) for manganese. Two typical gadolinium chelates are illustrated in Fig. 1. Strong T2 agents are, for example, iron oxides (magnetites or ferrites). Chelates of dysprosium (Dy) display a weaker effect (T2*).

2.3

Scintigraphic Contrast Agents

Scintigraphic contrast agents (radiopharmaceuticals) are compounds which contain a radioactive element offering the signal to be detected. The route of the radioactive compound and its enrichment in tissues or disease states is followed by a radioactivity detector, in most cases a gamma camera or a PET (positron emission tomography) or SPECT (single-photon emission computed tomography) machine. Unlike MRI or CT scans, which primarily provide images of organ anatomy, PET is able to measure metabolic, biochemical and functional activity. However, the resolution of PET images (> 5 mm) is much lower than that of MRI or CT images (1–2 mm). The pharmacokinetics and distribution of the radiopharmaceutical can be controlled by selecting an appropriate molecule to which the radioactive element is coupled. In standard radio-labeling techniques the radioactive marker is incorporated into a finished product shortly before administration to the patient. Alternatively, neutron activation is a technique where a small amount of stable isotope is incorporated in the contrast agent at the time of manufacture. This allows the product to be produced under normal manufacturing conditions. The stable isotope is then converted to a radioactive isotope appropriate for gamma scintigraphy by a short exposure to a neutron flux in a cyclotron. The short half-lives of the routinely produced nuclides require that the cyclotron be located very near to where the nuclides will be synthesized into a radio-tracer. As another alternative, radioactive elements are eluted from generators and incorporated into the contrast agent which is available as a kit ready for taking up the radioactivity. For example, Tc-99m is eluted from a generator and reacted with the chelate DTPA to give $^{99\text{m}}\text{Tc}$ -DTPA.

2.4

Ultrasound Contrast Agents

Ultrasound diagnostics allows for sectional imaging of the body with the signal intensity depending on the reflection of the incidental sound waves. Doppler

effects can be utilized to determine direction and rate of moving fluids such as blood. The temporal resolution of ultrasound is excellent so that on-line display is possible. The spatial resolution is proportional to the energy of the sound waves whereas the penetration depth is inversely proportional to this parameter. Ultrasound contrast agents are based on the principle of modifying the characteristics of the reflected relative to the incidental sound waves. A highly efficient modification is achieved by gas bubbles. In general, US contrast agents are therefore stabilized gas bubbles. This stabilization can be performed by entrapment in a porous material such as galactose (e.g. Levovist), by emulsifying gas bubbles (EchoGen) or by the encapsulation of gas into particles resulting in suspensions (Sonavist). Since contrast agents for ultrasound imaging are particles with entrapped gas, and since they are intravascular by nature, only linear polymers have been considered as carriers for the gas bubbles. However, if surface modifications should play a role in the future, e.g. for targeting the agent to specific sites or receptors, then a careful re-evaluation of the usefulness of dendrimers might be appropriate.

3

Pharmacokinetics of Extracellular Contrast Agents

Contrast agents can either be classified according to the imaging modality they are used for, their chemical class or their pharmacokinetics and biodistribution. The latter distinguishes between extracellular agents used for angiography, urography, myelography, etc., hepatocellular or tissue-specific agents, e.g. for cholangiography or liver imaging, and intravascular agents that are confined to the vascular space (blood pool). At present, contrast agents of this last type (blood-pool contrast agents) are only available for ultrasound and as radiopharmaceuticals, whereas macromolecular compounds for X-ray and MR imaging are at a very early research stage. Therefore, blood-pool enhancement for modalities other than US or nuclear diagnostics has to be performed with extracellular agents applying high doses and fast imaging techniques.

Extracellular contrast agents, e.g. iodinated X-ray compounds such as iopromide, MRI agents such as Gd-DTPA, or scintigraphic agents such as ^{99m}Tc -DTPA, exhibit practically identical pharmacokinetics. They are rapidly distributed after intravascular injection followed by renal elimination with a half-life of approx. 1–2 h. Their volume of distribution at steady state is approx. 0.25 l/kg which corresponds to the extracellular space volume of the body. Due to their rapid distribution over a relatively large volume, their concentrations decline very rapidly in the initial phase following injection. Accordingly, the imaging window is extremely short. Since CT needs 1 mg iodine/ml for a signal increase of 30 Hounsfield units (HU), and since for an angiogram more than 200 HU are required, imaging is possible only during the first passage of the contrast agent bolus through the region of interest.

The reason for the fast decline in concentrations is not rapid renal elimination – which is rather slow with a half-life of 1–2 h – but the leakage of the contrast agent out of the blood vessels into the extracellular space, a process

which is called extravasation. This leakage starts already during the first passage of the agent through the vessel. Blood vessel endothelium contains relatively large pores of approx. 12 nm diameter at a density of 1 pore per $2 \mu\text{m}^2$. These pores act as a filter which cannot be passed by molecules larger than approx. 20,000 Da molecular weight (MW), whereas small molecules such as water or extracellular contrast agents (MW = 500–2000) readily pass through these pores. To prevent extravasation, the molecular weight has to be increased to such a size that the molecule is no longer able to pass through the pores. One possibility for achieving this objective is to use polymeric or dendrimeric contrast agents.

Another possible target for high molecular weight contrast agents is the detection and characterization of tumors. There are two principally different mechanistic approaches which can, however, both be achieved with the same type of (polymeric) contrast agent. The first one is to make use of angiogenesis. Tumors exhibit an increased potential in recruiting new blood vessels for their nutritional support. These vessels exhibit a branching pattern that is different from that of normal tissue. Accordingly, an increased vessel density with an unusual pattern is an indication of fast-growing tumors. Intravascular contrast agents might be useful in the delineation of these new and erratic vessel systems. The second approach utilizes transport of a molecule across the vessel wall. This process is governed by several factors, including vascular permeability, hydraulic conductivity, reflection coefficient, surface area for exchange, transvascular concentration and pressure gradients [4]. Many tumor vessels are characterized by wide inter-endothelial junctions, i.e. *fenestrae* or channels, due to the lack of basal lamina. This effectively increases the permeability of the tumor vessels. However, there are some counteracting mechanisms. The interstitial pressure inside the tumor is much higher than that outside the tumor. Extravasation, therefore, has to proceed against a pressure gradient and a net fluid loss of 0.1–0.2 ml/h/g due to outward convection [5]. In addition, the vascular surface area decreases with tumor growth. In contrast, the interstitial space of tumors is much larger than that of normal tissue favoring the extravasation of macromolecules. These conflicting factors all have to be considered if an ideal contrast agent is to be designed. If the size of the agent is too small, then extravasation will already occur in the normal tissue and the compound is lost for tumor detection or characterization. If the size is too large, then the defense mechanisms of the tumor might inhibit any accumulation in the tumor. At present, it is not known which is the optimal size for a contrast agent for this indication.

4

Polymeric Contrast Agents

Polymeric contrast agents have been the focus of extensive research efforts for a long time. Since one of the major reasons for side-effects, especially of the high-dosed iodinated agents, is the extreme osmotic pressure of the concentrated solutions, the increase in iodine atoms per molecule is a natural prerequisite

for decreasing osmolality-related adverse events. Another positive aspect of polymeric contrast agents is their size, which allows them to stay within the intravascular space and thus constitute true blood-pool agents. In the following sections patents and publications of polymeric and dendrimeric contrast agents will be reviewed and our own, so far unpublished, results of dendrimer research efforts will be presented. Linear polymers were the first type to be extensively investigated, since their synthesis is relatively easy and straightforward.

4.1

Linear and Branched Polymers

4.1.1

Patents

In this section linear polymeric contrast agents will be reviewed in more detail. Efforts to synthesize polymeric imaging agents date back to the 1970s when contrast agents for the imaging of the gastrointestinal tract were investigated. Rothman et al. [95] describe an X-ray contrast preparation comprising a finely divided water-insoluble inorganic X-ray contrast producing substance and minute particles of a hydrophilic polymer containing amino groups, which is insoluble in water at body temperature and which consists of a water-insoluble, but water-swellaable, three-dimensional network held together by bonds of a covalent nature. The polymer contained a certain amount of amino groups and the average particle size lay within a certain range. The preparation is intended to adhere to the walls of the body cavities.

An X-ray contrast composition for oral or retrograde examination of the gastrointestinal tract comprising a nonionic X-ray producing agent in combination with a cellulose derivative in a pharmaceutically acceptable carrier, and methods for its use in diagnostic radiology of the gastrointestinal tract, were disclosed by Illig et al. [96, 97].

X-ray contrast compositions for the same indication comprising iodo-phenoxy alkylene ethers and pharmaceutically acceptable clays in a pharmaceutically acceptable carrier, and methods for their use in diagnostic radiology of the gastrointestinal tract, have been described by Ruddy et al. [98].

Torchilin et al. [99, 100] provided radiographic imaging agent block copolymers forming a micelle, the block copolymers including a hydrophilic polymer linked to a hydrophobic polymer, and the hydrophobic polymer including a backbone incorporating radio-opaque molecules via covalent bonds.

Tournier et al. [101] reported non-ionic triiodoaromatic compounds and compositions comprising triiodoaromatic polymers useful for X-ray imaging of the gastrointestinal tract. Disclosed compounds were acrylic acid esters of triiodobenzenes with a different degree of reticulation and their polymers/homopolymers.

Klaveness et al. [102, 103] described biodegradable polymers containing bis-ester units of the substructure $-\text{CO}-\text{O}-\text{C}(\text{R}^1\text{R}^2)-\text{O}-\text{CO}-$ or $-\text{CO}-\text{O}-\text{C}(\text{R}^1\text{R}^2)-\text{O}-\text{CO}-\text{R}^3$ which exhibit high stability in the absence of enzymes, whose linkages are degradable by esterases in the human body. Groups R^1 and R^2 represent a hydro-

gen atom or a carbon-attached monovalent organic group, e.g. an imaging moiety (iodinated agent or metal chelate) and R^3 comprises a polymeric grouping, for example, a poly(amino acid) such as a polypeptide, or a polyamide, poly(hydroxy acid), polyester, polycarbonate, polysaccharide, poly(oxyethylene), poly(vinyl alcohol) or poly(vinyl ether/alcohol) grouping.

Injectable nanoparticles or microparticles that are not rapidly cleared from the blood stream by the macrophages of the reticuloendothelial system, and that can be modified as necessary to achieve variable release rates or to target specific cells or organs as desired, were provided by Gref et al. [104]. The terminal hydroxyl groups of the poly(alkylene glycol) were used to covalently attach onto the surface of the injectable particles biologically active molecules, including antibodies targeted to specific cells or organs, or molecules affecting the charge, lipophilicity or hydrophilicity of the particle. The surface of the particle could also be modified by attaching biodegradable polymers of the same structure as those forming the core of the injectable particles. The injectable particles included magnetic particles or radio-opaque materials for diagnostic imaging.

Biodegradable polyacetals combining a glycol-specific oxidizing agent with a polysaccharide to form an aldehyde intermediate which is combined with a reducing agent to form the biodegradable biocompatible polyacetal were described by Papisov [105]. The resultant compounds can be chemically modified to incorporate additional hydrophilic moieties. A method for treating mammals, which includes the administration of an agent in which biologically active compounds or diagnostic labels can be disposed, was also disclosed.

Patents regarding linear polymers filed by our own group include iodine-containing linear and branched polypeptides which were subsequently derivatized with triiodobenzenes [106, 107]. Details of these polymers will be described later in this chapter.

An amphipathic polychelating compound including a hydrophilic polymeric moiety having a main backbone and reactive side groups, a lipid-soluble anchor linked to the N-terminal of the polymeric moiety, and chelating agents linked to the side groups of the polymeric moiety were described by Torchilin et al. [108]. The polychelating compounds are bound to liposomes or micelles for use as diagnostic and therapeutic agents.

Compositions comprising a covalently bonded adduct of deferoxamine, ferric iron and a polymer, e.g. water-soluble polymers such as polysaccharides (dextrans, starches, hyaluronic acid, inulin and celluloses) and proteins (albumin and transferrin), or water-insoluble polymers (celluloses, agaroses), for image enhancement in MR imaging were provided by Hedlund [109]. A pharmaceutical composition comprising the adduct and a method of using the composition in magnetic resonance imaging were also disclosed.

Sieving et al. [110] provided polychelants and their metal chelates which comprise a plurality of macrocyclic chelant moieties, e.g. DOTA residues, conjugated to a polyamine backbone molecule, e.g. polylysine. To produce a site-specific polychelate, one or more of the macrocyclic chelant-carrying backbone molecules were conjugated to a site-directed macromolecule, e.g. a protein.

Waigh et al. [111] described a method for the examination of internal body tissues by MRI, in particular, for the examination of the alimentary tract, by

administering an inert proton-rich organosilicon polymer, preferably a polysiloxane (dimethylsiloxane), which is not absorbed or degraded in the body. It did not contain additional contrast-giving moieties except for the protons already present in the polymer. A similar system has been reported by Block et al. [112].

Copolymer compounds which comprise at least two of a first monomer and at least one of a second monomer which is a polynitrilo chelating agent, the first and second monomers being bound to one another to form a copolymer through an ester, amide, or carboxylic thioester linkage to the second monomer, were reported by Unger et al. [113–115]. Optionally, the copolymer may also include at least one of a third monomer which is a targeting agent or a targeting agent ligand, and wherein the third monomer is also bound with the first and second monomers to form a copolymer through an ester, amide, or carboxylic thioester linkage. For magnetic resonance imaging, the copolymer may comprise a paramagnetic ion bound to the chelating agent.

An agent for modifying water relaxation times in MRI with a polysaccharide having chemically linked to it an organic complexant to which is bound a paramagnetic metal ion was described by Sadler et al. [116]. Polysaccharides included cellulose, starch, sepharose and dextran. Organic complexants included EDTA, DTPA and aminoethyl diphosphonate. The preferred metal ion was gadolinium. The agents can be administered orally or parenterally.

Gibby et al. described a polymeric contrast-enhancing agent for MRI having a chelating agent, which can be bound to metal ions having at least one unpaired electron, such as gadolinium [117]. Examples of such chelating agents include DTPA-ethylenediamide-methacrylate copolymer and poly(DTPA-ethylene-diamide).

A linear block copolymer comprising units of an alkylene oxide, linked to units of peptide via a linking group comprising a $-\text{CH}_2\text{CHOHCH}_2\text{N(R)}-$ moiety, wherein R is a C_{1-4} alkyl group, was prepared by Cooper et al. [118, 119]. The peptide can be derivatized with a metal chelating agent to give an MRI contrast agent (paramagnetic metal) or a radiopharmaceutical (radionuclide).

Novel contrast agents for use in MRI comprised of biocompatible polymers either alone or in admixture with one or more contrast agents such as paramagnetic, superparamagnetic or proton density contrast agents have been described by Unger. The polymers or polymer and contrast agent admixtures may be mixed with one or more biocompatible gases to increase the relaxivity of the resultant preparation, and/or with other components. In a preferable embodiment, the contrast medium is hypo-osmotic [120–122].

Meade et al. [123] provided bifunctional imaging agents comprising optical dyes covalently linked to at least one MRI contrast agent. These agents may include a linker, which may be either a coupling moiety or a polymer.

A peptide was provided by Sharma [124] for use as a diagnostic imaging, radiotherapeutic, or therapeutic agent, which has a conformationally constrained global secondary structure obtained by complexing with a metal ion. The peptide is of the general formula $\text{R}_1\text{-X-R}_2$, where X is a plurality of amino acids and includes a complexing backbone for complexing metal ions, so that substantially all of the valences of the metal ion are satisfied upon complexation of the metal ion with X, resulting in a specific regional secondary structure

forming a part of the global secondary structure, and where R_1 and R_2 each include from none to about 20 amino acids, the amino acids being selected so that upon complexing the metal ion with X at least a portion of either R_1 or R_2 , or both, have a structure forming the balance of the conformationally constrained global secondary structure. All or a portion of the global secondary structure may form a ligand or mimic a known biological-function domain. The peptide has substantially higher affinity when labeled with a metal ion. The peptide may be labeled with radioisotopes of technetium or rhenium for radiopharmaceutical applications.

Love et al. [125, 126] disclosed multi-site metal chelates with paramagnetic or radioactive metal ions having a linear or branched oligomeric structure comprising alternating chelant and linker moieties bound together by amide or ester moieties whose carbonyl groups are adjacent to the chelant moieties, and each polychelant comprising at least two chelant moieties capable of complexing a metal ion.

Polyazamacrocyclofluoromonoalkylphosphonic acid compounds which form inert complexes with Gd, Mn, Fe or La ions were disclosed by Kiefer et al. [127]. The complexes are useful as contrast agents for diagnostic purposes.

The invention of Snow and Hollister [128–130] provided compositions useful in MRI imaging comprising a polymer with units made up of the residue of a chelating agent linked to a poly(alkylene oxide) moiety in which the polymer has a paramagnetic metal ion associated with it. They specifically provided polymeric polychelants containing polymer repeat units of formula L-Ch-L-B (where Ch is a polydentate chelant moiety; L is an amide or ester linkage; B is a hydrophobic group providing a carbon chain of at least 4 carbon atoms between the L linkages it interconnects), or a salt or chelate thereof, with the proviso that where Ch is 2,5-biscarboxymethyl-2,5-diazahexa-1,6-diyl, the polychelant is metallated with lanthanide or manganese ions or B provides a carbon chain of at least 10 carbon atoms between the L linkages it interconnects and their salts and chelates. The paramagnetic polychelates of the polychelants of the invention have remarkably high R_1 relaxivities.

A composition suitable for use in diagnostic imaging or as a cell-killing agent comprising a chelating residue linked via an amide linkage to a poly(alkylene oxide) moiety with a molecular weight of at least 4500 was described by Butterfield et al. [131].

Although a great number of patents have been filed and granted so far, none of these contrast agents has reached practical use. The reasons include toxicity, incomplete elimination from the body and inhomogeneity or non-reproducible production of the agents. There is still a need for clearly defined, well-tolerated polymeric compounds which are completely eliminated. To overcome these issues, all hope is presently fixed on dendrimeric contrast agents.

4.1.2

Publications

Different classes of polymeric carriers have been described for use in both X-ray techniques, MRI and for scintigraphy. These include polyacrylates, dextran,

polypeptides such as albumin, polylysine, and polyaspartate, and other backbones.

Lautrou et al. [6], Revel et al. [7] and Doucet et al. [8, 9] described an iodinated polymer as a blood-pool contrast agent and its computed tomography evaluation in rabbits. The agent was composed of a carboxymethyldextran substituted by a triiodinated benzoic acid. The mean molecular weight was 32,000 Da ranging from 10^3 to 10^6 Da. The time-density curve in blood showed a prolonged vascular residence time. Additionally, in animals with segmental portal ischemia, the difference between normally perfused and ischemic liver was clearly delineated.

Triiodinated moieties, derivatized with acrylic or methacrylic acid, were co-polymerized with a non-opaque acrylic or methacrylic component by Sovak et al. [10]. Water-soluble oligomers with molecular weights ranging from 9–55,500 Da were obtained. Additionally, biodegradable bisacrylic linkers were incorporated. As general rules, Sovak et al. found that the acrylic non-opaque spacer should be present in a substantially higher proportion than the triiodobenzene moiety, and that it should be non-ionic and hydrophilic. The triiodobenzene should be ionic or should contain not more than 2 to 3 hydroxyl groups.

Trubetskoy et al. [11] published the synthesis of an iodine-containing amphiphilic block-copolymer able to micellize in aqueous solutions. The two blocks of the copolymer consisted of methoxypoly(ethylene glycol) and poly[ϵ ,N-(triiodobenzoyl)-L-lysine]. After dispersion of the polymer in water, particles were observed with an average diameter of 80 nm and an iodine content up to 45%. Following intravenous injection at 250 mg of iodine/kg in rabbits, the half-life in blood was considerably prolonged (24 h) compared with extracellular contrast agents (<1 h).

One of the first studies on blood-pool agents for MRI was that by Schmiedl et al. [12–15] who compared the contrast-enhancing properties of albumin-(Gd-DTPA) and Gd-DTPA in an experimental study in rats. Whereas Gd-DTPA was very rapidly cleared from the blood, the enhancement with albumin-(Gd-DTPA) persisted at relatively constant levels from 2 min to 1 h. Special usefulness of this type of contrast agent was found for MRI of myocardial infarction [15] since these compounds can serve as markers of perfusion and abnormal vascular permeability [16, 17].

The group of Brasch et al. [18, 19] investigated a number of polymeric contrast agents in different indications. Ogan et al. [20] also labeled albumin with Gd-DTPA through the bifunctional anhydride resulting in an average of 19 Gd-DTPA chelates which were covalently conjugated. The average molecular weight was 92,000 Da. Spin-echo images of rats demonstrated persistent enhancement of vascular tissues and slowly flowing blood. Studying polylysine-(gadopentetate dimeglumine) to allow differentiation of pulmonary fibrosis and alveolitis at magnetic resonance imaging, Berthezene et al. found that a macromolecular contrast agent can facilitate the differentiation between the exudative and fibrotic phases of interstitial lung disease [21]. For polylysine-(Gd-DTPA)40 they reported that it can be used to detect by MRI acute pulmonary embolism in a rat model [22, 23]. Using albumin-(Gd-DTPA)35 they determined an increased myocardial signal intensity in rats during adenosine infusions which was attri-

buted to increased blood volume accompanying coronary vasodilatation. The advantage of the method using a blood-pool agent was that it does not require a continuous infusion of contrast agent and therefore has potential for the clinical evaluations of coronary artery reserves [24]. Albumin-(DTPA)₃₅ was also used for the detection of focal changes in renal perfusion in a myoglobinuric acute renal failure model in the rat. Contrast-enhanced MR imaging data in this model correlated well with pathological data and microsphere perfusion results [25]. The effects of varying the molecular weight of (Gd-DTPA)-polylysine on blood pharmacokinetics and dynamic tissue MR imaging signal enhancement characteristics were studied by Vexler et al. [26] in normal rats. Blood elimination half-life increased seven-fold with an increase in molecular weight from 36 to 480 kDa. Volume of distribution was significantly smaller than that of Gd-DTPA but did not differ within the group of polymers. However, Ostrowitzki et al. [27] astonishingly reported that gadopentetate was superior to macromolecular albumin-(Gd-DTPA)₃₀ for detection of 9L brain gliomas and for measurements of hyperpermeability.

Schuhmann-Giampieri et al. [28] covalently linked gadopentetate (Gd-DTPA) to polylysine and studied this macromolecular blood-pool marker in rats and rabbits in comparison to Gd-DTPA. (Gd-DTPA)-polylysine was composed of polymers of different molecular sizes that on average were labeled with 60 to 70 Gd-DTPA moieties (average MW: 48,700 Da). Relaxivity was three times higher than that of Gd-DTPA. The volume of distribution and the significantly prolonged half-life of distribution indicate good blood-pool characteristics for this contrast agent. Chu and Elgavish [29] attached DTPA to dextran of molecular weight of approximately 6000 by an amide bond and subsequently complexed it with dysprosium or gadolinium. Relaxivity R_1 of the Dy chelate was 8.4 (mM s)^{-1} at a magnetic field of 0.23 T and 9.3 (mM s)^{-1} at 0.47 T.

A Dy-DTPA hexamethylenediamine copolymer (NC 100283) was investigated in a rabbit atherosclerosis model by Eubank et al. [30]. They compared MR angiographic results obtained in these animals with data obtained by plain MRA without a contrast agent using a black blood pulse sequence. Precontrast MRA images tended to underestimate aortic lumen diameter using conventional angiography as the standard reference.

Linear Gd-DTPA copolymer conjugates linked by α,ω -alkyldiamide bridges were synthesized by Kellar et al. [31]. Their relaxivities increased with the length of the bridge and approached those of rigid dendrimer-based Gd^{3+} chelates. Intramolecular hydrophobic interactions were found due to a dependence of relaxivities on polymer concentration.

Nolte-Ernsting et al. [32] evaluated the gadolinium polymer WIN 22181 in comparison with the ultra-small superparamagnetic iron oxide agent FeO-BPA for abdominal MR angiography in a pig model. Both agents resulted in excellent angiograms of the abdominal vascular tree. In the liver, the contrast-to-noise ratio of hepatic vessels was better for the iron oxide agent because of a T1-T2* synergistic effect. Additionally, the diagnostic window was six to eight times longer coupled with the option of in-plane imaging.

Large polysaccharide complexes, cross-linked with DTPA and chelated with Gd^{3+} of molecular weights from 17,000 to several million, were tested by Gibby

et al. [33] for MRI in rats. The larger polymers ($> 100,000$) demonstrate prolonged enhancement of the intravascular space. They were metabolized and excreted in urine.

The evaluation of a Gd-DOTA-labeled dextran polymer as an intravascular MR contrast agent for myocardial perfusion in rabbits was reported by Casali et al. [34]. The average molecular weight of the polymer was 52.1 kDa. Relaxivities in water (20 MHz, 37 °C, pH 7.4) were 10.6 (mM s)^{-1} for R1 and 11.1 (mM s)^{-1} for R2. The agent showed long retention in the blood pool and was useful for the estimation of myocardial perfusion.

Macromolecular conjugates of Gd-DTPA with dextran were synthesized by Rebizak et al. [35] from dextran 40 (about 40 kg/mol) by linking DTPA to aminated dextran via a water-soluble carbodiimide. Relaxivity R1 was 2 to 4 times as great as that of free Gd-DTPA and increased relative to the conjugate DTPA content, from 7.4 to 15.9 (mM s)^{-1} .

The synthesis of a carboxymethyl-dextran polymer with the paramagnetic macrocyclic complex Gd-DOTA, coupled via an amino spacer and a molecular weight of 50.5 kDa and a polydispersity of 1.66, was described by Corot et al. [36]. Approximately 22% of the glucose groups were replaced by Gd-DOTA and 39% were replaced by carboxyl groups. The contrast agent was well tolerated in rats and rabbits. Excretion was almost exclusively by renal elimination.

Loubeyre et al. [37] synthesized a Gd-DTPA-dextran conjugate and studied its efficacy in a transverse three-dimensional time-of-flight (TOF) MR angiography sequence of the abdominal aorta in rabbits. The polymeric contrast agent reduced, in part, the saturation effect. The authors concluded that to prevent the venous enhancement observed with the higher concentrations, a decrease in the polydispersity of the polymer should be a goal for the future.

The dynamics of tumor imaging with Gd-DTPA-poly(ethylene glycol) polymers and its dependence on molecular weight was studied by Dessier et al. [38]. They synthesized DTPA-PEG polymers in seven average polymer molecular weights ranging from 10 to 83 kDa and investigated their imaging characteristics at a dose of 0.1 mmol/kg in tumor-bearing rabbits at different time points after injection of the contrast agents. The authors found that blood-pool enhancement dynamics were observed for the Gd-DTPA-PEG polymers larger than 20 kDa, whereas polymers smaller than 20 kDa were similar to Gd-DTPA. Above the 20 kDa threshold, tumor enhancement was more rapid for smaller polymers. The authors concluded that the 21.9 kDa Gd-DTPA-PEG polymer is best suited for clinical MR imaging.

The group of Weissleder et al. published a series of papers on blood-pool contrast agents. Bogdanov et al. [39, 40] synthesized a copolymer of *O*-methyl poly(ethylene glycol)-*O'*-succinate (MPEGs, MW 5100) and poly-L-lysine (PL, average MW 32,700) by covalent grafting. The resultant MPEGs-PL had a hydrodynamic diameter corresponding to a 690 kDa protein. DTPA or succinic acid residues were conjugated to the free amino groups. The radioactively labeled copolymer accumulated in solid tumors at 1.5–2% injected dose/g of tumor in 24 h. Bogdanov et al. [41] and Frank et al. [42] labeled the chelate with Gd and found an increase in signal intensity of pulmonary vessels, an improvement in the quality of MR angiography, and an increase in the detectability of pulmo-

nary emboli. Callahan et al. [43] studied a ^{99m}Tc -labeled analog of this polymer preclinically and in a phase I trial. They found long circulation times in humans and expected clinical applications in cardiovascular imaging, gastrointestinal bleeding studies, and capillary leak imaging. Harika et al. [44] determined the pharmacokinetic and MR imaging properties of DTPA conjugated with a polyglucose-associated macrocomplex, which accumulated after intravenous injection in lymph nodes of tumor-bearing rats and was able to differentiate between normal and metastatic lymph nodes. In a further study, Marecos et al. [45] were able to show that the tumoral drug delivery in vivo of long-circulating polymers such as MPEGs-PL can be equally high compared with antibody-labeled polymers because of slow extravasation at the tumor site.

A polyaspartate of average molecular weight 30,000 binding in solution up to 40 Mol Gd^{3+} ions per mole of polyaspartate has been described by Cavagna et al. [46]. The relaxivity of the solutions was much higher than that of Gd-DTPA .

4.2

Dendrimers

4.2.1

Patents

Patents on dendrimers date back to the 1980s when Tomalia et al. described “star polymers and dense star polymers” [132, 133]. Later, the patent scope was enlarged such as to additionally comprise agricultural chemicals and pharmaceuticals including diagnostic moieties coupled to the dendrimeric core [134, 144].

Biological or synthetic macromolecular polyamine compounds, optionally of the dendrimer type, characterized in that they carry at least three radio-opaque iodine-containing derivatives, were filed by Meyer et al. [135]. The general formula was $\text{P-NK}_x\text{-A-G}_n$ wherein P represents a macromolecular radical of said macromolecular polyamine compound, N represents a nitrogen atom, K is selected from the group consisting of a hydrogen atom, lower linear or branched alkyl group, lower linear or branched hydroxy- or polyhydroxyalkyl group, lower linear or branched alkoxyalkyl group, lower linear or branched alkoxyhydroxy- or alkoxypolyhydroxyalkyl group, and group -A-G, x is an integer equal to 0 or 1, G is an iodine-containing radio-opaque benzenic derivative.

A number of patents on dendrimeric contrast agents with triiodobenzenes as the imaging moiety were also filed by our group. Cascade polymers with triiodobenzenes are described [136]. For example, in the patent WO 96/41830, we described dendrimeric iodine-containing contrast agents according to the general formula $\text{A}\{-\text{X}\{-\text{Y}\{-\text{Z}\{-\text{W}(\text{D}_w)_z\}_y\}_x\}_a$ with A standing for a nitrogen-containing cascade core of multiplicity a, X and Y are either direct bonds or a cascade sub-unit of multiplicity x or y, and Z and W are cascade sub-units of multiplicity z or w, and D represents a group containing a triiodobenzene moiety.

Margerum et al. [137] reported on a dendrimeric bioactive moiety which had linked to it a plurality of diagnostically or therapeutically active moieties characterized in that the molecular skeleton of the said compound contains at least one biodegradable cleavage site such that, on cleavage, these active moieties

are released in renally excretable form. The compounds exhibit the structure $Y(X-Y_q)_q$ in which X is carbon, oxygen, or nitrogen, each X, independently, is unsubstituted or substituted with R or $Y'-X'_q$; Y is boron or phosphorus, each Y, independently, is unsubstituted or substituted with R or $X'-Y'_q$; X' and Y' are as defined for X and Y, respectively, but cannot carry side chains, $Y'-X'_q$ or $X'-Y'_q$; each R, independently, is hydrogen, oxo, or a bond; and q is 2–5; and two non-adjacent Y groups can together represent a single Y group thereby, together with the intervening X and Y groups, creating a 4- to 10-membered ring; and said backbone moiety is linked to a plurality of diagnostically or therapeutically active moieties.

Cascade polymer complexes containing complexing ligands of the general formula $A-\{X-Y-(Z-(W-K_w)_z)_{yx}\}_a$, in which A represents a nitrogen-containing cascade nucleus of base multiplicity a; X and Y, independently of one another, stand for a direct bond or a cascade reproduction unit of reproduction multiplicity x or y; Z and W, independently of one another, stand for a cascade reproduction unit of reproduction multiplicity z or w; K stands for a radical of a complexing agent; a is a number between 2 and 12; x, y, z and w, independently of one another, stand for numbers 1 to 4, and that at least one of the cascade reproduction units X, Y, Z, W stands for (a) 1,4,7,10-tetraazacyclododecane or 1,4,8,11-tetraazacyclotetradecane reproduction unit, (b) at least 16 ions of an element of atomic numbers 20 to 29, 39, 42, 44 or 57–83, (c) optionally cations of inorganic and/or organic bases, amino acids or amino acid amides, as well as (d) optionally acylated terminal amino groups, are valuable compounds for diagnosis and therapy that were described by Schmitt-Willich et al. [138–140].

A macromolecular contrast agent for MRI of the vascular system was constructed of a polymeric backbone structure with a plurality of spacer arms bonded to the backbone structure, each spacer arm terminating in at least one paramagnetic complex [141]. The polymeric backbone thus served as an amplifier by supporting a multitude of paramagnetic complexes, and the spacer arms contributed to the molecular weight. The spacer arms further contributed useful properties to the agent, such as hydrophilicity and the ability to cleave at a relatively rapid rate in blood. The general formula was $R^1\{-R^2(-R^3)\}_n$, in which R^1 is a polymeric group which is non-toxic and non-antigenic; R^2 joins R^1 to R^3 and is a member selected from the group consisting of $X-R^4-Y-R^5-Z$ and $X-R^5-Y-R^4-Z$, in which R^4 is poly(ethylene glycol) having a formula weight between about 100 and 20,000 Da; R^5 is S–S; and X, Y, and Z are the same or different and are inert linking groups; R^3 is a complex of a ligand and a paramagnetic metal cation capable of altering contrast in magnetic resonance imaging; n is at least 3; and m is 1.

Dendrimeric X-ray contrast agents wherein the contrast-giving moieties are bismuth atoms which represent the branching points of the dendrimer have been described by our group [142]. The general structure may be represented by $X-[L-(BiR^1R^2)_n]_b$, where X stands for a central unit such as O, S, N, P, C, Si, Sn, Ge, or Bi, an aryl, heteroaryl, alkyl or cycloalkyl group, which could be substituted, and a multiplicity of b, L for an optionally substituted alkyl group and n for 1–10. R^1, R^2 represent another $L-BiR^1R^2$ group or an optionally substituted alkyl or aryl group.

Similarly, we have synthesized tin-containing dendrimers of the general structure $X-(L-SnR^1R^2R^3)_n$. In this case, tin atoms were positioned at the branching points and were responsible for X-ray contrast [143].

4.2.2

Publications

Wiener et al. [47–52] described starburst dendrimer-based contrast agents on the basis of polyamidoamines and the chelator 2-(4-isothiocyanatobenzyl)-6-methyl-DTPA. The relaxivity per gadolinium ion of the polymeric contrast agent was greater by a factor of up to 6 compared with that of Gd-DTPA. These factors are more than twice those observed for analogous metal-chelate conjugates formed with serum albumins, polylysine, or dextran. One of the dendrimer-metal chelate conjugates had 170 gadolinium ions bound, and exhibited a molecular relaxivity of 5800 (mM s)^{-1} . The plasma half-life of dendrimeric chelates with molecular weights of 8508 and 139,000 were 40 ± 10 and 200 ± 100 min, respectively. Their usefulness in MR angiography was demonstrated.

Bourne et al. [53] studied another dendrimeric contrast agent with Gd chelates, TG(5)(FDDO3A), in rabbits. They performed MR angiography at different dose levels ranging from 0.03–0.005 mmol/kg. The images demonstrated a dose-related reduction in saturation effects and improved visualization of vascular structures of the pelvic circulation in the axial and coronal planes, with an optimum at 0.03 mmol/kg. A dose of 0.02 mmol/kg was found to be the minimal effective dose at the three vascular regions. These doses are lower by a factor of more than 10 compared with Gd-DTPA.

A ^{17}O -NMR study with macrocyclic Gd complexes attached to polyamidoamine dendrimers using variation of magnetic strength, temperature and pressure was performed by Tóth et al. [54]. They found 4–8 times longer rotational correlation times compared to monomeric chelates. However, due to the relatively slow water exchange rate, relaxivities were lower than expected from the rotation times.

Macromolecular chelates on the basis of 1-(4-isothiocyanatobenzyl)amido-4,7,10-triacetic acid tetraazacyclododecane coupled to the terminal amino groups of different generations of polyamidoamines were synthesized by Margerum et al. [55]. Molecular weights ranged from 18.4 kDa (11 Gd ions) to 61.8 kDa (57 Gd ions). MR relaxivities and blood elimination half-lives in rats increased with molecular weight. However, retention in the body also increased reaching 40% of dose at 7 d for the largest molecule. Grafting poly(ethylene glycol) onto the polymer decreased body retention to 1–8%. A correlation between molecular weight and retention was, however, not found.

Bulte et al. [56] studied Dy-chelated PAMAM dendrimers of generation 5 as macromolecular T2 contrast agents. They used DOTA as chelator instead of DTPA in order to achieve a greater complex stability. This is – according to the authors – an important factor in the design of blood-pool agents with long half-lives. They linked ammonia-terminal PAMAM dendrimers to the bifunctional ligand p-SCN-Bz-DOTA and subsequently Dy^{3+} was titrated at a 90% molar

ratio. The resultant dendrimeric metal chelate had 76 DOTA and 68 Dy^{3+} ions per molecule. T1 relaxivity [approx. 0.20 (mM s)^{-1}] was independent of the field strength in the investigated range from 0.05 to 1.5 T. $1/T_2$ was up to three times higher for the dendrimer compared with the single chelate molecules and increased quadratically with field strength, with a strong dependence on temperature. These results were explained by the “inner sphere” theory of susceptibility effects (Curie spin relaxation). Temperature-dependent effects were due to contact interaction with the proton residence time dictating the primary time constant.

Dendrimer chelates targeted to tumors and tumor cells expressing the high-affinity folate receptor were reported by Wiener et al. [47, 49].

A comprehensive review of the value of macromolecular contrast agents for the characterization of benign and malignant breast tumors has been published by Daldrup et al. [57–59]. It was hypothesized by the authors that polymeric contrast agents increase the specificity of MR mammography. Whereas in benign tumors the contrast agent is confined to the intravascular space, they leak out into the interstitium of carcinomas. Compounds described in that review include (Gd-DTPA)-albumin, (Gd-DTPA)-polylysine, and blood-pool iron oxides such as AMI-227.

Nilsen et al. [60] reported dendritic nucleic acids potentially useful for the development of nucleic acid diagnostics as signal amplification tools. Due to the relatively large size of nucleic acid molecules, nucleic acid dendrimers can be readily labeled with fluorescent compounds. They presented a model of a new class of dendrimers, constructed entirely from nucleic acid monomers initiated from a single monomer and proceeding in layers, the first comprising four monomers, which provides 12 single-stranded arms. Thus, the second layer adds 12 monomers resulting in 36 single-stranded arms. After addition of the 6th layer, the dendrimer was comprised of 1457 monomers, of which 972 reside in the 6th layer, which possessed 2916 single-stranded arms.

The biodistribution in tumor-bearing mice of indium- and yttrium-labeled G2 polyamidoamine dendrimers (PAMAM) conjugated with 2-(p-isothiocyanatobenzyl)-6-methyl-DTPA was reported by Kobayashi et al. [61]. They found a high accumulation in the liver, kidney, and spleen, which significantly decreased when the chelates were saturated with the stable element. The authors additionally conjugated the dendrimeric chelate to humanized anti-Tac IgG and labeled the agent with ^{111}In and ^{88}Y . Specific tumor (ATAC4) uptake was higher than that in nonspecific tumor (A431).

Bryant et al. [62] described PAMAM dendrimers corresponding to generation 5, 7, 9, and 10 which were conjugated with the bifunctional chelate 2-(4-isothiocyanatobenzyl)-DOTA and complexed with Gd^{3+} . The synthesis resulted in compounds with an average of 127 chelates and 96 gadolinium ions per generation 5 dendrimer to an average of 3727 chelates and 1860 Gd^{3+} ions per G = 10 dendrimer. The authors found a “saturation” of ion relaxivity for high-generation dendrimers due to a slow exchange of bound water molecules with the bulk solvent.

The most advanced investigations so far were performed with a cascade polymer synthesized by Radüchel et al. [63]. They first attached 24 DTPA groups

to the polymeric backbone and then exchanged DTPA for DO3A which resulted in more stable Gd complexes. The structure of this agent (Gadomer-17) is represented in Fig. 1.

Adam et al. [64, 65] compared the Gd-DTPA cascade polymer with (Gd-DTPA)-polylysine, in a pig model after injection of 20 $\mu\text{mol/kg}$. They measured relative signal intensities in different tissues and organs and found a similar pharmacokinetics for both contrast agents.

The Gd-DTPA 24-cascade polymer was also compared with albumin-(Gd-DTPA)30 in the MR angiography of peritumoral vessels in rats by Schwickert et al. [66, 67]. The animals received 0.05 mmol Gd/kg of the polymers or 0.1 mmol Gd/kg of Gd-DTPA. Whereas Gd-DTPA produced a transient and low-scoring vessel definition (0.2 ± 0.1), but strong rim enhancement (score 1.7 ± 0.1), the cascade polymer resulted in better vessel delineation (score 1.6 ± 0.3 , S/B 5.0 ± 0.2) and strong rim enhancement (score 1.8 ± 0.1). Albumin-(Gd-DTPA)30, on the other hand, produced the best and longest lasting angiograms (score 2.6 ± 0.2 , S/B 7.4 ± 0.2), but minimal rim enhancement (score 0.3 ± 0.2).

The same dendrimeric MR contrast agent was studied by Tacke et al. [68] in rabbits with hypovascularized VX-2 liver tumors in comparison to Gd-DTPA. They found a higher absolute signal in the tumor after Gd-DTPA but a better contrast-to-noise ratio between liver and tumor for the dendrimeric agent.

Dick et al. [69] investigated the polymer in an experimental pyogenic liver abscess model in rabbits in comparison to Gd-DTPA. The doses were 25 $\mu\text{mol/kg}$ for the dendrimeric contrast agent and 100 $\mu\text{mol/kg}$ for Gd-DTPA. A higher contrast ratio, abscess center-liver, was found after the application of the gadolinium polymer and, accordingly, a better and prolonged visibility of the abscesses compared with Gd-DTPA.

Dynamic MR imaging was used by Su et al. [70] to determine the enhancement kinetics of three Gd chelates [Gd-DTPA, Gadomer-17, 30 kDa, and polylysine-(Gd-DTPA), 50 kDa] in three different animal tumor models. The vascular permeability of the tumors was evaluated by means of the rate of entry of the contrast agent into the interstitial space. Gd-DTPA was not useful for the determination of vascular permeability. With the two polymeric agents it was shown that faster-growing tumors had a greater vascular permeability than the slower-growing ones.

A similar study was performed by Roberts et al. [71] who investigated by T1-weighted MRI the endothelial permeability towards Gadomer-17 and albumin-(Gd-DTPA)30 of different tissues (normal myocardium, infarcted myocardium and subcutaneously implanted adenocarcinoma) in rats. The doses were 0.02 mmol Gd/kg. The fractional leak rates of Gadomer-17 were 8.24/h in normal myocardium, 39.17/h ($P < 0.01$) in infarcted myocardium and 8.55/h in tumors. Corresponding values for albumin-(Gd-DTPA)30 were 0.33/h, 7.94/h ($P < 0.001$) and 0.66/h ($P < 0.002$), respectively. Whereas in mildly increased microvascular permeabilities, the utility of the cascade polymer Gadomer-17 is of limited value, it might be useful for severely injured tissue.

Adam et al. [72] studied the time course of enhancement of spontaneous breast tumors in dogs comparing Gd-DTPA and Gadomer-17. For Gd-DTPA a fast signal increase followed by a rapid decline was observed in tumors. Similar

kinetics were found in benign lesions after injection of Gadomer-17. In malignant tumors, the blood-pool agent showed a different kinetic profile, characterized by a slower delivery, a delayed peak enhancement, and a slower clearance or even a signal plateau. The authors concluded that large molecular weight contrast agents might be able to differentiate between benign and malignant lesions.

Recently, Nguyen-minh et al. [73] compared the contrast enhancement of recurrent herniated disk fragments and scar after intravenous injection of Gadomer-17 with that after injection of Gd-DTPA and reported a greater contrast between scar and recurrent herniated disk with Gadomer-17 than with Gd-DTPA. The difference between the high and low molecular weight contrast media increased with maturation of the scar tissue.

Dong et al. [74] investigated Gadomer-17 for abdominal and thoracic MR angiography in dogs and found an improved visualization of vascular anatomy compared with Gd-DTPA.

A totally different class of dendrimers, dendritic bismuthanes, were prepared by Suzuki et al. [75]. They lithiated tris[2-(diethylaminosulfonyl)phenyl]bismuthane with *tert*-butyllithium followed by reaction with bis[2-(diethylaminosulfonyl)phenyl]bismuth iodide. The final stage was a Bi₁₀ bismuthane.

5

Synthesis and Characterization of Dendrimeric X-ray Contrast Agents

In the following sections, our own, and so far unpublished results, on dendrimeric X-ray contrast agents will be described. We have synthesized a number of high molecular weight X-ray contrast agents consisting of a dendrimer backbone and triiodobenzenes as contrast-giving moieties coupled to amino groups at the surface of the polymer. Additionally, commercially available dendrimers of the polypropylenimine type were used. These new contrast agents were characterized both analytically and pharmacologically in different models and by different methods. The analytical procedures included gel permeation (size-exclusion) chromatography using various types of detectors, gel electrophoresis, field-flow fractionation, and isoelectric focusing. Molecular characteristics such as weight and diameter were determined via intrinsic viscosity and density measurements.

5.1

Synthesis and Characterization of the Building Blocks

Some of the dendrimeric building blocks, especially polyamidoamines and polylysines, were synthesized in our own laboratory whereas others, mainly (propylenimines, are commercially available and were purchased from the supplier (DSM). Details have been published by Brabander et al. [76–78].

5.1.1

Polyamidoamines

The divergent synthesis of polyamidoamines was performed according to Tomalia et al. [79–81]. Briefly, the reaction sequence started by adding three mole equivalents of methacrylate to ammonia followed by reacting the esters with ethylenediamine to yield the respective amides. This generation 0 dendrimer was then consecutively reacted according to the described scheme to higher dendrimers up to generation 6. By then the density on the surface reaches a maximum and larger molecules probably would only be present as a mixture with many deficient species.

5.1.2

Polypropylenimines

Polypropylenimines of different generations were purchased in the terminal amino form from DSM. Batches delivered at the beginning of our research efforts were not very pure according to size-exclusion chromatography (see Sect. 5.2.4) but improved significantly later.

5.1.3

Polylysines

The synthesis of different structural types of exactly defined polylysines was performed by solid-phase procedures according to Merrifield [82, 83]. Boc-protected lysine was reacted with the solid carrier, subsequently converted to the free amine and derivatized with an activated, Boc-protected lysine. This process was repeated until the desired branching and chain length was obtained.

5.1.4

Triiodobenzene Moieties

As contrast-giving substituents, triiodobenzenes were coupled to free amino groups at the surface of the dendrimers. The different triiodobenzenes contained substituents which met the following requirements; first, an activated group was necessary which allowed coupling to the dendrimeric amino groups. This was in general an activated carboxylic group. Second, if the dendrimeric backbone contained basic amino groups, for example, in the polypropylenimines, an additional carboxylic group was needed to compensate for the charge of the molecule. Otherwise, the final compound would bear positive charges (Fig. 2).

The number of positive charges would be equivalent to the number of tertiary amino groups. For a polypropylenimine with 64 amino groups at the surface, the corresponding number of positive charges would also be 64. Accordingly, polypropylenimines are zwitter-ions after derivatization with the carboxylate group containing triiodobenzenes. The third characteristic of triiodobenzene substituents is high hydrophilicity. This feature is necessary to obtain sufficient water

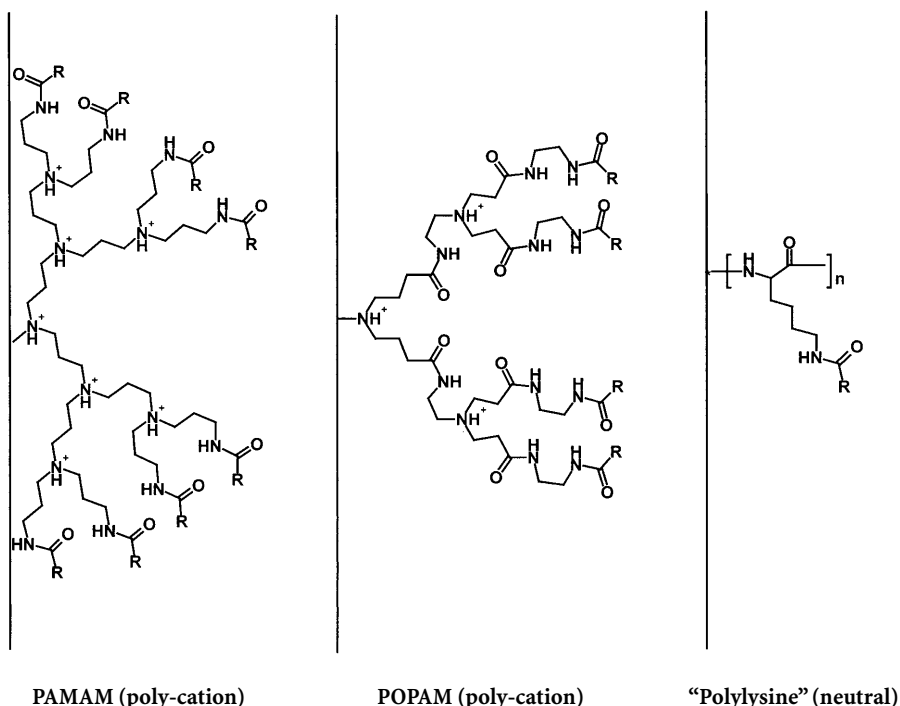


Fig. 2. Internal structural components of polypropylenimine (PAMAM), polyamidoamine (POPAM) and polylysine dendrimers determining the electrical charge of the molecule

solubility of the contrast agent. It is achieved by adding side chains with hydroxyl groups. A selection of substituted triiodobenzenes is given in Table 2.

5.2

Characterization of the Dendrimeric Contrast Agents

The dendrimeric contrast agents were characterized by a number of different analytical methods [94]. Whereas some of them had to be specifically adapted to the analysis of this type of molecules, others were not able to produce useful results. Among the last category, surprisingly, field-flow fractionation appeared.

5.2.1

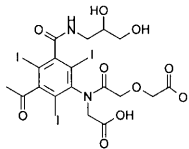
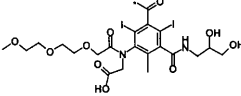
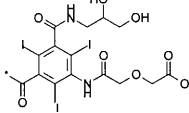
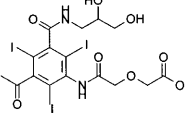
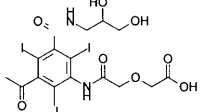
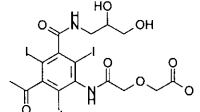
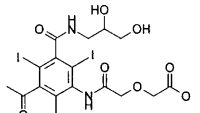
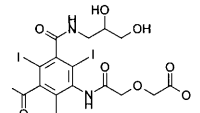
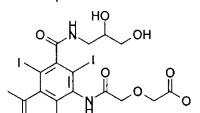
Heat Sterilization

Sterilization is an essential prerequisite of all parenteral drugs. It is normally, and most conveniently, performed by heating the preparation to 120°C for approx. 10 min. If this process is not possible, more time-consuming and costly methods of sterilization have to be applied. We used 134°C at 2 bar for 25 min. The contrast media were analyzed by size-exclusion chromatography before and

Table 2. Structures of selected dendrimeric contrast agents synthesized

Code, MW	Polymer type	Imaging moieties
YD 751-1, 22,076.2 g/mol	Polyamidoamine, 24 NH ₂ groups	
163200, 45 kDa	Polyamidoamine, 32 NH ₂ groups	
YD 718-2, 45,459.0 g/mol	Polyamidoamine, 48 NH ₂ groups	
YD 810-1, 44,691.1 g/mol	Polyamidoamine, 48 NH ₂ groups	
YD 804-1, 26,873.6 g/mol	Polypropylenimine, 32 NH ₂ groups	
188879 Ca ²⁺ salt, 29.3 kDa	Polypropylenimine, 32 NH ₂ groups	
YD 849-2, 26,873.6 g/mol	Polypropylenimine, 32 NH ₂ groups	
JP 569-1, 27,737.6 g/mol	Polypropylenimine, 32 NH ₂ groups	
YD 977-1, YD 977-2, 54,785.1 g/mol	Polypropylenimine, 64 NH ₂ groups	
JP 591-1, JP 591-3, 57,986.9 g/mol	Polypropylenimine, 64 NH ₂ groups	

Table 2 (continued)

Code, MW	Polymer type	Imaging moieties
YD 1032-1, 59,008.5 g/mol	Polypropylenimine, 64 NH ₂ groups	
231138, YD 1166-1, 60.4 kDa	Polypropylenimine, 64 NH ₂ groups	
YD 855-1, 28,125.6 g/mol	Polypeptide, K=lysine, A=alanine, [(R ₂ K)(R-K) ₂] ₈ K ₄ K ₂ K-A-OH	
YD 871-1, 35,166.8 g/mol	Polypeptide, K=lysine, A=alanine, [(R ₂ K)(R-K) ₃] ₈ K ₄ K ₂ K-A-OH	
YD 811-1, 41,152.8 g/mol	Polypeptide, K=lysine, A=alanine, [(R ₂ K)(R-K) ₄] ₈ K ₄ K ₂ K-A-OH	
YD 860-1, 41,152.8 g/mol	Polypeptide, K=lysine, A=alanine, [(R ₂ K)(R-K) ₁₀] ₄ K ₂ K-A-OH	
YD 862-1, 41,152.8 g/mol	Polypeptide, K=lysine, A=alanine, [(R ₂ K)(R-K) ₂₂] ₂ K-A-OH	
YD 863-1, 49,249.1 g/mol	Polypeptide, K=lysine, A=alanine, [(R ₂ K)(R-K) ₅] ₈ K ₄ K ₂ -A-OH	
YD 864-1, 77,413.8 g/mol	Polypeptide, K=lysine, A=alanine, [(R ₂ K)(R-K) ₉] ₈ K ₄ K ₂ K-A-OH	
WB 4818, WB 5090	Polypeptide (trimesinic acid core), 24 amino groups	macrocyclic ligand with Gd ³⁺

after this procedure. Polyamidoamines of different sizes (24 and 48 amino groups) proved to be unstable towards heat sterilization, whereas polypropylenimines did not change during this process (Fig. 3). Polylysines were also stable and could be sterilized without degradation.

5.2.2

Polyacrylamide Gel Electrophoresis

Polyacrylamide gel electrophoresis (PAGE) was considered a useful analytical method for dendrimeric contrast agents since it is able to separate compounds according to their size and charges. We used a collecting gel for the start zone in order to sharply focus the zones. The collecting and separating gels were prepared as described in Table 3.

Five gels were prepared in parallel and used immediately after preparation. However, storage in the refrigerator for up to two weeks before use is possible. The buffer for the analytes consisted of 10 ml 0.5 M Tris/HCl, pH 6.8, 1 g sodium dodecyl sulfate (SDS), 1.93 g dithiothreitol, 14.3 ml glycerol (87%), 0.01 g bromophenol blue dye, and water to give a final volume of 25 ml. The electrophoresis buffer was made from 15 g Tris base, 72 g glycine, 5 g SDS and water to give a volume of 5 l. For the separation of the analytes, an electric voltage of 100 V was applied for 15 min, followed by 175 V for 60 min. Staining of the gels was performed with Coomassie Blue (0.2% solution in methanol/water, 1:1, 10% acetic acid) by shaking the gels for 30 min in a bath with the staining reagent and subsequent washing with 10% acetic acid/20% methanol. Alternatively, silver nitrate staining was used according to Hochstrasser et al. [84]. Therefore, the gels were washed in water and fixed in a bath of ethanol/acetic acid/water (40:10:50). After 1 h, the fixing bath is exchanged for a mixture of ethanol/acetic acid/water (5:5:90). After 3 h to 3 d, the gels are washed in water, and shaken in a 10% glutaraldehyde solution. After careful washing with water, the gels are immersed in a bath with silver nitrate (6 g in 1 l NaOH/NH₃). Developing was

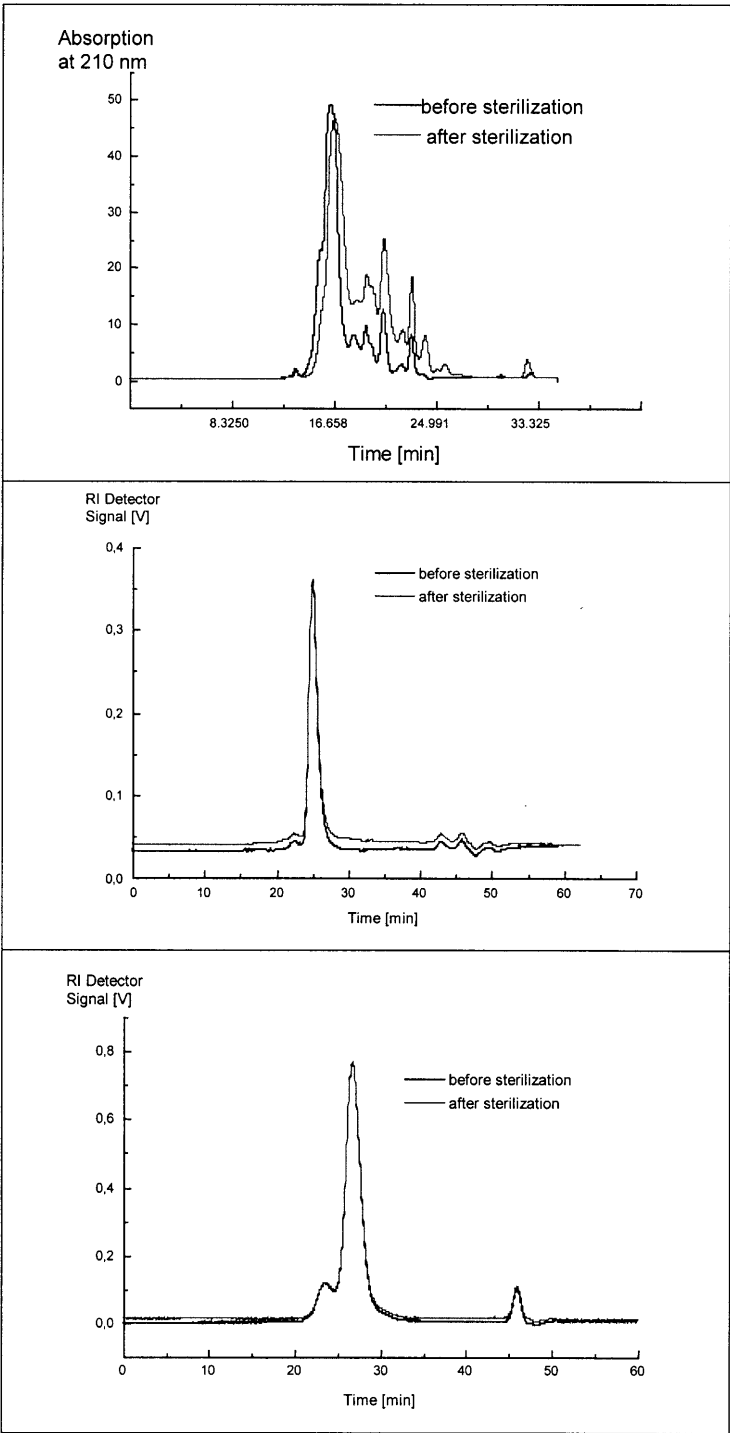
Table 3. Preparation of collecting and separating gels in PAGE

	Acrylamide/ bisacrylamide (30%:0.8%)	Tris/HCl (ml)	10% SDS (ml)	Water (ml)	10% Ammonium persulfate (μl)	TEMED (μl)
Collecting gel	1.67 ml	2.5 ml, 0.5 M, pH 6.8	0.1	5.73	100	30
Separating gel, 20% used	20 ml	7.5 ml, 1.5 M, pH 8.8	0.3	2.2	300	

Tris: tris(hydroxymethyl)aminomethane.

SDS: sodium dodecyl sulfate.

TEMED: *N,N,N',N'*-tetramethylethylenediamine.



performed with a solution of 0.1% formaldehyde. The process is stopped with acetic acid/water (5:95). As a third alternative, commercially available "Stains-all" (Sigma) was used. The commercially available solution was diluted with formaldehyde (5 ml + 45 ml) and mixed with 50 ml of water. The gel was shaken in this solution for 1 h in the dark. Quantification of the zones after separation was performed by densitometry (molecular dynamics) versus standard curves.

Staining with Coomassie Blue gave good results for polyamidoamines and polypropylenimines. On the other hand, polypeptides could not be stained with this reagent. With silver staining neither of the polymers could be detected. "Stains-all" resulted in excellent detection of all types of dendrimers investigated (Fig. 4).

A comparison of the band width of dendrimeric compounds and the protein test substances shows that the latter exhibit much narrower bands. In order to exclude concentration-dependent effects (saturation), the dependence of band width on the amount of sample applied to the gel was determined. However, at all concentrations studied (1–20 µg), band width did not change indicating significant inhomogeneity of the dendrimeric contrast agents.

In a further experiment, Gadomer-17 was applied to gel electrophoresis both in the fully complexed form (24 gadolinium ions per molecule), partially complexed and the non-complexed ligand without any gadolinium ions (Fig. 5). The free ligand is negatively charged with a molecular weight of 14,000 Da. Its electrophoretic behavior is similar to that of the trypsin inhibitor (6500 Da) and cytochrome c (12,500 Da). The compound with 24 gadolinium atoms is electrically neutral and has a molecular weight of 17,500 Da. This compound was similar in its migration behavior to egg albumin (45,000 Da). It has to be concluded from these results that, in addition to molecular weight, electric charge also makes an impact on electrophoretic migration. This finding is, however, not in agreement with results reported by Smisek [85] who did not observe this strong dependence on charge.

In order to compare the efficiency of PAGE and size-exclusion chromatography (SEC), the polypropylenimine JP 591-3 was studied in both analytical systems. First, the target compound and any impurities were separated by preparative SEC and, second, the fractions obtained were analyzed by PAGE. The result was that whereas PAGE exhibited a better resolution, concentrations were more easily quantified by SEC. Both methods therefore seem to complement each other nicely.

Fig. 3. Size-exclusion chromatograms of dendrimeric carriers derivatized with triiodobenzenes before and after heat sterilization. *Top* polyamidoamine with 48 amino groups (MW 22 kDa) (120 °C, 1 bar, 45 min) *Middle* polypropylenimine with 64 amino groups (MW 59 kDa) (120 °C, 2 bar, 45 min) *Bottom* polylysine (MW 49 kDa) (134 °C, 2 bar, 25 min)

Compounds are identified as follows:

Track	Code name	Amount (µg)	Compound	Track	Code name	Amount (µg)	Compound
1				2	YD 856-1	20	Protein test mixture
2	Standards	5	Protein test mixture	3	YD 804-1	20	Polyamidoamine
3				4	YD 860-1	20	Polypropylenimine
4	YD 811-1	30	Polypeptide	5	YD 862-1	20	Polypeptide
5	YD 804-1	30	Polypropylenimine	6	YD 863-1	20	Polypeptide
6	YD 810-1	30	Polyamidoamine	7	YD 864-1	20	Polypeptide
7	YD 811-1	15	Polypeptide	8			
8	YD 804-1	15	Polypropylenimine	9	Standards	5	Protein test mixture
9	YD 810-1	15	Polyamidoamine				

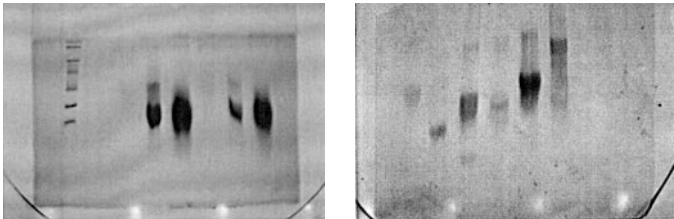


Fig. 4. Staining of dendrimeric contrast agents on gel electrophoresis plates with Coomassie Brilliant Blue (*left*) and „Stains-all“ (*right*).

Compounds are identified as follows:

Track	Code name	Amount (µg)	Compound	Track	Code name	Amount (µg)	Compound
1				2	YD 849-21	20	Polypropylenimine
2	Standards	5	Protein test mixture	3	YD 849-21	15	Polypropylenimine
3				4	YD 849-21	10	Polypropylenimine
4	WB 4814	50	Non-complexed	5	YD 849-21	5	Polypropylenimine
5	WB 4814	50	Partially complexed	6	YD 849-21	1	Polypropylenimine
6	WB 4814	50	Partially complexed	7			
7	WB 4814	50	Partially complexed	8	Standards	5	Protein test mixture
8	WB 4814	50	Fully complexed	9	Standards	5	Protein test mixture
9							

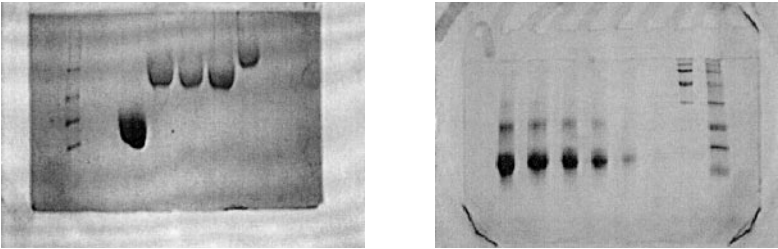


Fig. 5. *Left* Gel electrophoresis of a fully, partially and non-complexed dendrimeric metal chelate (Coomassie Brilliant Blue staining). *Right* Dilution experiment of a polypropylenimine derivatized with triiodobenzenes

5.2.3

Isoelectric Focusing

Commercially available pre-coated plates (Servalyt Precotes, Serva) were used for the analysis of dendrimeric contrast agents. The analytes were added to the gels in an aqueous solution. The applied voltage was continuously increased to a final value of 3000 V. The total analysis time was 3 h. The plates were cooled at 10 °C during the whole procedure. After focusing and fixation of the gel by shaking in 20% aqueous trifluoroacetic acid, Coomassie Blue staining was performed. Two polypropylenimines with different triiodobenzenes were analyzed:

1. YD 849-2: 32 amino groups (G4), triiodobenzene with one COOH group
2. JP 569-1: 32 amino groups (G4), triiodobenzene with two COOH groups
3. YD 977-1: 64 amino groups (G5), triiodobenzene with one COOH group
4. JP 591-1: 64 amino groups (G5), triiodobenzene with two COOH groups

All dendrimers showed very broad bands, especially in comparison with the protein standards (Fig. 6). The band width increased from the G4 to the G5 dendrimer indicating an increased deviation from the ideal structure of the larger dendrimer, probably due to both missing sequences and incomplete derivatization.

5.2.4

Size-Exclusion Chromatography

Size-exclusion or gel permeation chromatography is an analytical method based on the principle of molecular separation according to the hydrodynamic size of the compound. The substance is retained by entering pores in the gel. If the compound is too big, it cannot enter the pore. Accordingly, large molecules are eluted first and small molecules last. The parameter characteristic of a compound is its partition coefficient, k_s . The selection of appropriate column material and elutes is essential.

Column materials published in the literature are polyacrylates, dextrans, cross-linked poly(vinyl alcohols) or modified silica [86, 87]. We first started with polymethacrylate gels which are either neutral or carry a negative charge depending on pH. However, judging from elution volumes greater than the dead volume of the column, interactions of the dendrimeric contrast agent with the column material were observed. Probably better suited therefore are neutral column materials which are no longer able to interact with the charged contrast agents. Additionally, these materials are often more stable over a broad pH range. We tested Superose 12 [88], Superdex 75 [89] (both from Pharmacia) and a PL Aquagel OH-40 column [90] from Polymer Laboratories. Details of the columns are given in Table 4.

A comparison of the separation efficiency of different columns using a polymeric contrast agent composed of a dendrimeric polypropylenimine with 64 amino groups (JP 591-1) and 0.05 M potassium phosphate buffer at pH 9 as eluent showed that whereas the Superose 12 and Superdex 75 columns resulted in a separation into three peaks, the Aquagel OH-40 column only produced two peaks indicating inferior resolution of this material. Dextran standards from

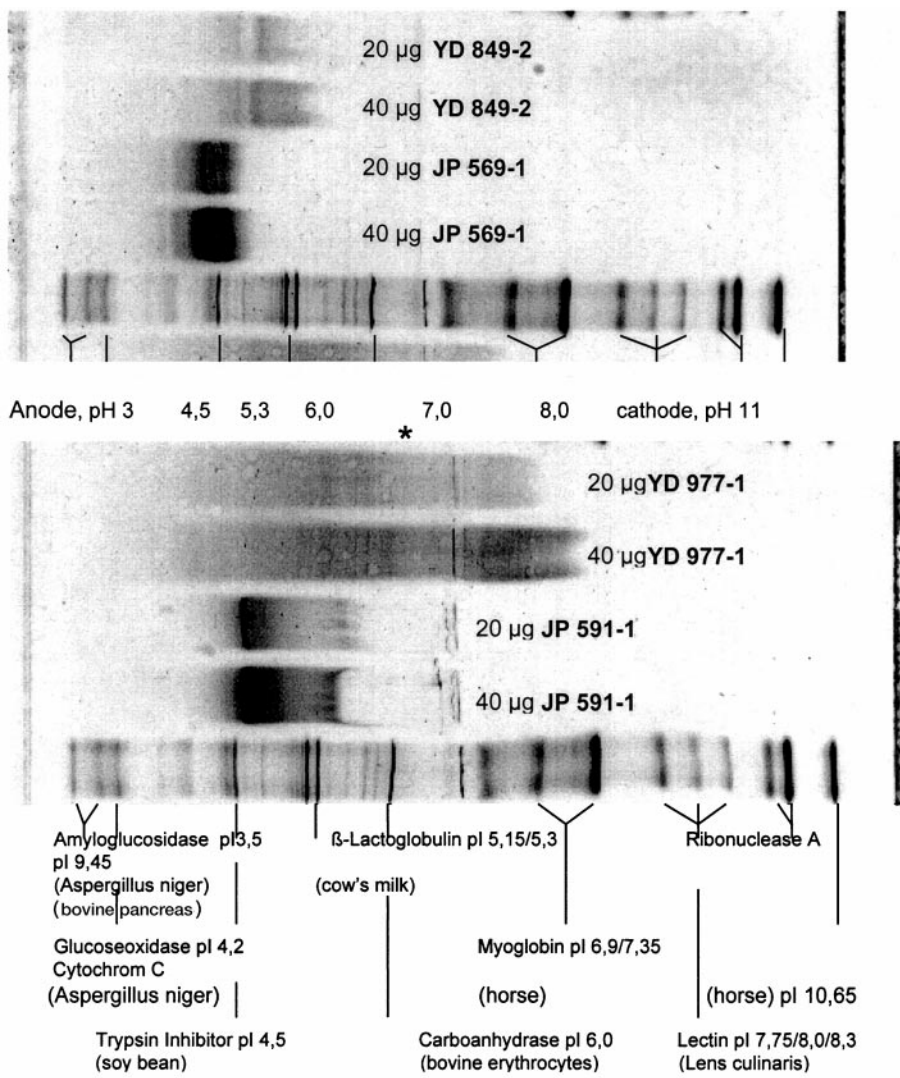


Fig. 6. Isoelectric focusing of four dendrimeric contrast agents

5 to 230 kDa (Pharmacosmos) were separated using the three columns and calibration curves were established. Calculation of separation quality factors B (slopes of the linear range of the calibration curves) resulted in 0.69 for the Aquagel OH-40 column and approx. 0.16 for the agarose columns indicating a significantly better resolution for the latter two columns. Resolution, R, was calculated as 0.32–0.44 for Superose 12, 0.36–0.45 for Superdex 75 and 0.17–0.30 for Aquagel OH-40. As a consequence, we used a combination of one Superose 12 and one Superdex 75 column for further experiments. With this approach, one further peak could be resolved.

Table 4. Summary of column materials used for SEC (according to manufacturer's data)

	Superose 12	Superdex 75	PL Aquagel OH-40
Manufacturer	Pharmacia Biotech GmbH	Pharmacia Biotech GmbH	Polymer Laboratories
Material	Cross-linked agarose	Dextran covalently coupled to cross-linked agarose	"Polyhydroxyl" material
Pore diameter	No data	No data	No data
Particle size (μm)	10 ± 2	13–15	8
Buffer additives and salts	No data	Aqueous up to 20% acetonitrile, ion strength up to 6 M	Aqueous up to 50% methanol, ion strength up to 5 M
pH area	1–14	3–12	2–12
Efficiency (theoretical plates/m)	>40,000	>30,000	25,000
Separation range (Da)	1000–150,000	3000–70,000	200–100,000

The theoretical molecular weight of JP 591-1 is 57,086 g/mol. Using the elution volume of JP 591-1 and its theoretical molecular weight, the respective point would lie above the calibration curve obtained with dextran standards indicating that the size of the molecule is smaller compared with dextrans of identical molecular weight. The reason for this is the greater density of dendrimers compared with non-dendrimeric polymers and the high atomic number and relatively small volume of iodine. One molecule of JP 591-1 contains 192 iodine atoms which is equivalent to 43% of the total molecular weight. Another conclusion from these results is that dextran standards are not very useful for the determination of molecular weights of this type of dendrimers.

For further optimization of SEC, the eluent (potassium phosphate + 1 mM NaN_3) was varied using different ionic strengths and pH values. As model compounds YD 1032-1 (a polypropylenimine with 64 terminal amino groups), YD 849-2 (a polypropylenimine with 32 amino groups), and YD 871-1 (a polypeptide with 40 amino groups) were used. YD 1032-1 contained triiodobenzenes with two carboxylic groups whereas the other two polymers were substituted with triiodobenzenes which contained only one carboxylic group. Accordingly, the partition coefficients determined by SEC (K_{SEC}) as a function of ionic strength showed a different behavior for the two types (Fig. 7).

The SEC behavior of YD 1032-1 was tested in 0.05 M phosphate buffer at pH 4, 9 and 12. Newkome et al. [91] reported a pH dependency of elution for dendrimers with terminal acid functions. They dissolved the polymers at pH 6.8 and 2.0, respectively, and then performed SEC in the same system at pH 6.8. Significant differences in elution volumes were observed. With our dendrimeric contrast agents, however, we could not find any difference in elution volume for samples dissolved at different pH values and separated at pH 9. We therefore modified the pH value of the whole system and determined elution volumes

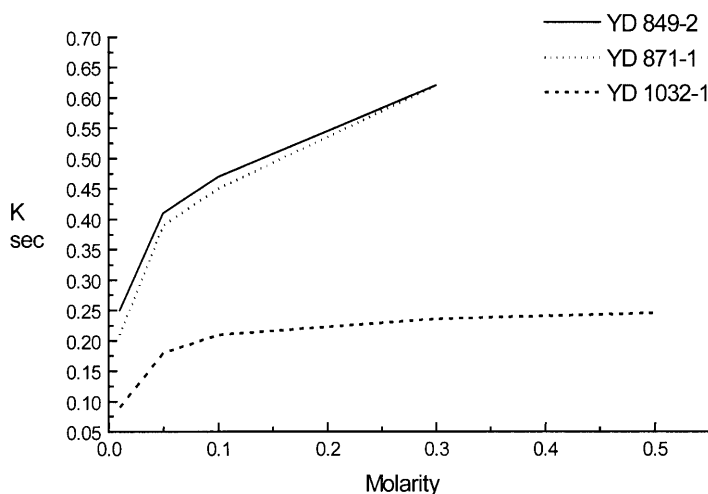


Fig. 7. Comparison of the partition coefficients, K_{SEC} , of three dendrimeric contrast agents of different sizes and polymeric backbones as a function of ionic strength of the eluent

with the Superdex 75 column and a flow rate of 0.4 ml/min at different pH values. Detection was performed by refractive index. We found an elution volume of 11.4 ml at pH 4, of 10.3 ml at pH 9, and of 9.7 ml at pH 12.

This result is in contradiction to that of Newkome who described an increase in elution volume after lowering the pH value from 6.8 to 2.0. Newkome explained this behavior by a reversible contraction of the molecule upon pH change. In his experiment it was sufficient to modify the pH of the solution medium whereas in our study this was not sufficient and the whole system (dissolution medium and SEC eluent) had to be modified. We expected a molecular expansion upon decreasing pH, because the positively charged amine groups in the interior of the dendrimer system should increasingly be protonized and should repel each other. As a result, a decrease in elution volume would be the result. However, we found an increase. We hypothesize that the molecules contract due to decreasing dissociation of the terminal carboxyl groups and their decreasing electrostatic interaction. This means that the hydrodynamic behavior of this type of dendrimers is mainly determined by the electric charge of the terminal carboxyl groups. Sufficient resolution was found for a pH of 9.

Chromatograms of the underivatized polypropylenimine dendrimers were obtained on a Superdex 75 column with 0.3 M Na_2SO_4 + 0.1 % trifluoroacetic acid and a flow rate 0.3 ml/min. Tremendous quality differences were observed between early and later batches commercially available from DSM. Mass spectrometric confirmation was found for the major peak (MW 7166). Other components probably included a dimer or larger oligomers.

In order to check the analytical efficacy of SEC, dendrimers with terminal amino groups of different generations were injected as a mixture onto a Superdex 75 column using the above-mentioned conditions. Figure 8 shows that base-line separation is possible.

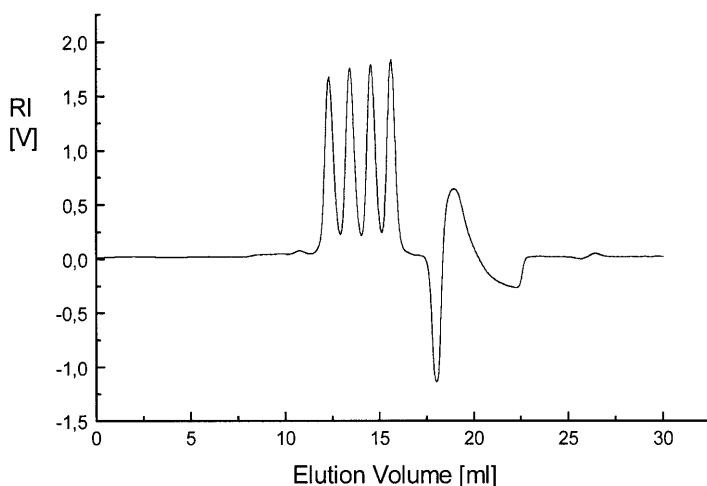


Fig. 8. SEC chromatograms of a mixture of dendrimeric polypropylenimines with terminal amino groups of different sizes. DAB(PA)_{64, 32, 16 and 8}• (Column: Superdex 75; Eluent: 0.3 M Na₂SO₄ + 0.1 % trifluoroacetic acid; flow rate: 0.3 ml/min)

Another important issue is whether derivatization of terminal amino groups with triiodobenzenes modifies the impurity profile. A comparison of two qualitatively very different polypropylenimine batches shows that coupling of the imaging moiety does not have an impact on the impurity profile of relatively pure polypropylenimines (Fig. 9). Using an ultraviolet (UV) diode array detector for further characterization of impurities showed that all purities exhibited the same UV spectrum. It can be concluded therefore that impurities detectable by UV, other than dendrimers of different size, were not present in the sample.

In a further study, SEC was used to correlate the molecular size of a contrast agent with its pharmacokinetic behavior *in vivo*. The objective was to study whether, for example, biological half-lives can be predicted from the SEC elution behavior. For this purpose, two X-ray agents, YD 1032-1 and Yd 977-2 (polypropylenimines), and one MR agent, WB 5090, were separated on a combination of a Superose 12 and a Superdex 75 column using 0.05 M potassium phosphate buffer at a flow rate of 0.4 ml/min and a refractive index detector. The elution volumes were 22.4 ml for YD 1032-2 (59 kDa), 23.3 ml for YD 977-2 (55 kDa) and 26.3 ml for WB 5090 (20 kDa). The *in vivo* behavior was determined by injecting anesthetized rats (Han-Wistar, 250 g body weight, $n = 3$ per compound) intravenously with a dose of 400 mg iodine/kg (YD 1032-2 and YD 977-2) and 240 mg/kg (WB 5090), respectively, and measuring the iodine or gadolinium concentrations in the blood of the animals after definite time points. Iodine was measured in the blood samples by X-ray fluorescence analysis and gadolinium by ICP-AES. YD 1032-2 showed the highest concentrations at 5 min after injection (60 % of the dose in blood) followed by YD 977-2 (43 %) and WB 5090 (22 %; Fig. 10, top). There seemed to be a good correlation between the elution volume of the contrast agents and their concentration in the blood of the rats 5 min after administration (Fig. 10, bottom).

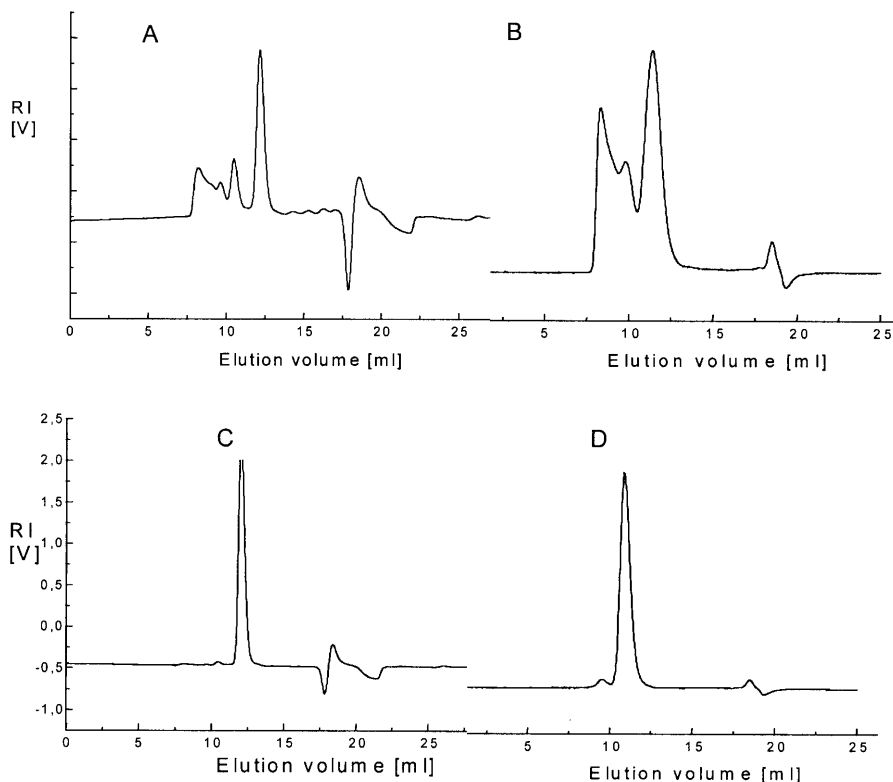


Fig. 9. SEC chromatograms of two different batches of polypropylenimines with 64 terminal amino groups before (A, C) and after (B, D) derivatization with triiodobenzenes

5.2.5

Field-Flow Fractionation

The analysis of dendrimeric contrast agents by field-flow fractionation was performed using three pumps. The first pump provided the channel flow and the second and third pumps the perpendicular flow. The membrane was a hydrophilic YM-10 membrane from Amicon with a size exclusion of 10 kDa relative to dextran standards. Detection was performed by a UV detector, a refractive index detector and a multi-angle laser light scattering (MALLS) device. Polystyrene beads of 103 to 1335 nm diameter (Duke Scientific Corp.) and dextrans of 79.8 to 11.6 kDa molecular weight (Pharmacosmos) were used as standards. Both types of standards were analyzed without any problems. Dendrimeric contrast agents, on the other hand, showed no retention under the conditions tested. Even at extremely high perpendicular flow rates of 7 ml/min, retention was not observed. There was a flow-dependent recovery of the compounds with 100 % at flow zero and < 20 % at 2 ml/min indicating that the membrane used with a dextran-determined cut-off of 10 kDa

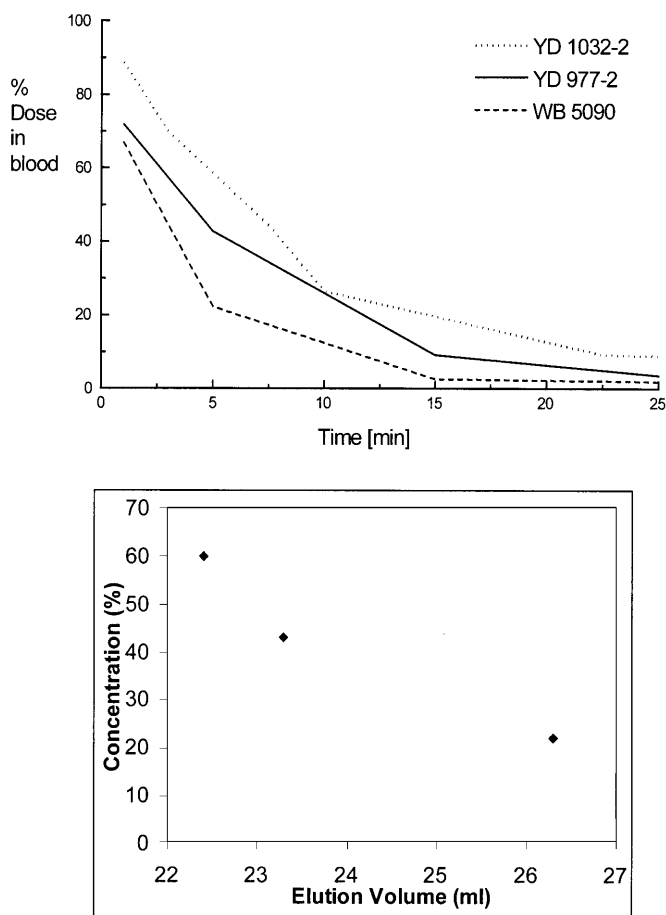


Fig. 10. Comparison of the blood levels in rats of three different polymeric contrast agents (*top*) and relationship between 5-min concentrations and elution volume in SEC (*bottom*)

was not appropriate for the dendrimers having nominal molecular weights from 30–46 kDa.

5.2.6

Multi-Angle Laser Light Scattering

Molecular dimensions can be roughly estimated from SEC by comparison with standard curves. However, the standards have to closely resemble the analyte in their chemical structure in order to allow for good agreement of results. However, commercially available standards such as dextrans are not very well suited to determine molecular sizes of dendrimeric contrast agents. We therefore studied the use of a multi-angle laser light scattering (MALLS) detector coupled on-line to SEC for the determination of absolute molecular parameters such as

molecular weights and dimensions. A MALLS detector (DAWN DSP F, Wyatt Technology) was introduced on-line into the SEC system and the molecular weights of the eluted compounds were registered. By plotting molecular weights versus elution volumes, a check can be made as to whether the elution is exclusively due to size exclusion or whether additional adsorption processes play a role. In combination with specific refractive index increments, this curve represents the calibration curve of the individual compound. In SEC, this curve has an S-like shape. An example of an early-batch dendrimer (JP 591-1) with many impurities and a newer relatively pure batch (JP 591-3) is given in Fig. 11.

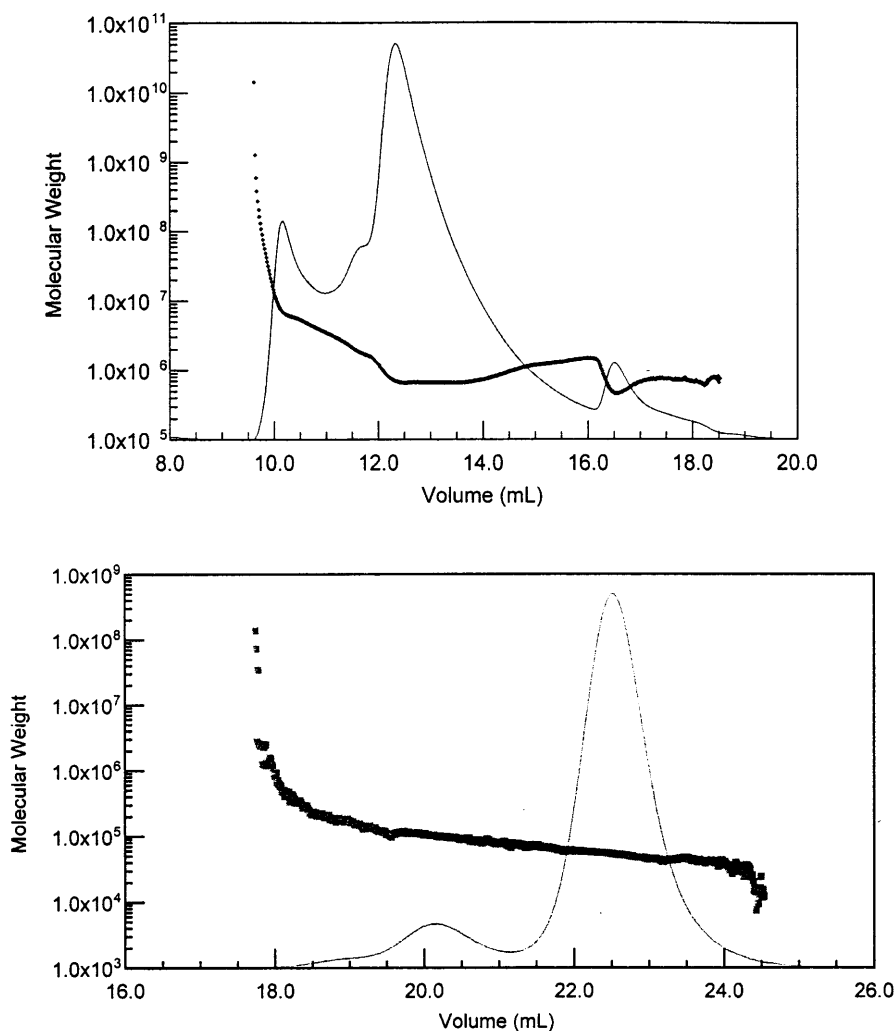


Fig. 11. Size-exclusion chromatograms of an early (*top*) and later batch (*bottom*) of a dendrimeric contrast agent (JP 591, polypropylenimine) using a differential refractometer (*thin line*) and a MALLS detector (*solid line*)

Size-exclusion chromatography of chromatogram A was performed using two TSK 3000 PWHR columns (TosoHaas) and 0.05 M phosphate buffer, pH 9. Elution started with large molecular weight compounds and continuously decreased up to 14 ml (peak 1 and shoulder 2) and then remained constant (peak 3). Thereafter, an increase in molecular weight was observed during an elution volume of approx. 2 ml. Peak 4 represents the smallest molecules. This elution behavior indicates that, in addition to size exclusion, adsorption processes seem to play a role. SEC of chromatogram B was performed using one Superose 12 and one Superdex 75 column (Pharmacia) and the same eluent as in A. A typical S shape was obtained.

The absolute molecular weight can be determined with the MALLS detector using the specific refractive index increment, dn/dc . This is a parameter which depends on wavelength and temperature and which may either be determined on-line or off-line by comparison with a concentration-dependent calibration curve. We used JP 591-3, a polypropylenimine, as a model compound and prepared a dilution curve ranging from 5.25×10^{-5} to 3.50×10^{-4} g/ml. Before measurements, the polyelectrolyte solution was extensively dialyzed in order to exclude preferential solvation of the polymer. From the calibration curve, dn/dc was obtained from the slope of the respective regression line after plotting dn versus concentration. For JP 591-3, dn/dc was determined as 0.134 ± 0.001 ml/g at 628 nm and 25 °C. Using the MALLS detector software program, dn/dc was also determined on-line. A prerequisite for any on-line measurement of dn/dc is complete recovery of the compound from the column and no loss is allowed. The result of 0.13425 ± 0.0029 ml/g was in good agreement with the data obtained off-line.

Using a dn/dc value of 0.134 ml/g, a molecular weight of 57,080 Da was calculated for JP 591-3 with a nominal weight of 57,086. The standard deviation was 3 %. A minor peak in the chromatogram had a weight of 113,600 Da with a standard deviation of 14.7 %. The higher standard deviation might be explained by the much lower concentration of this dimeric impurity (14–15 % of the main compound). The molecular weight of the impurity suggests its structure to be a dimeric version of the main product. The polydispersity index for the main peak was determined as 1.007 and for the impurity as 1.056 indicating highly monodisperse polymers.

Figure 12 illustrates the differential distribution curves of the two peaks describing the proportion of a sample with molecular weight M and $M + dM$. Since $dM \rightarrow 0$, the proportion of a polymer with any molecular weight can be determined. The figure shows a somewhat polydisperse character of the sample which is not in agreement with the extremely low polydispersity index.

5.2.7

Intrinsic Viscosity and Density

From the intrinsic viscosity of a dendrimer the hydrodynamic volume can be calculated according to $\eta_{rel} = \eta/\eta_0 = 2.5 \Phi + 1$, where η_{rel} , the relative viscosity of a solution with ball-shaped colloidal particles, exclusively depends on the relative volume, Φ , of the dissolved phase. Modification of this equation results

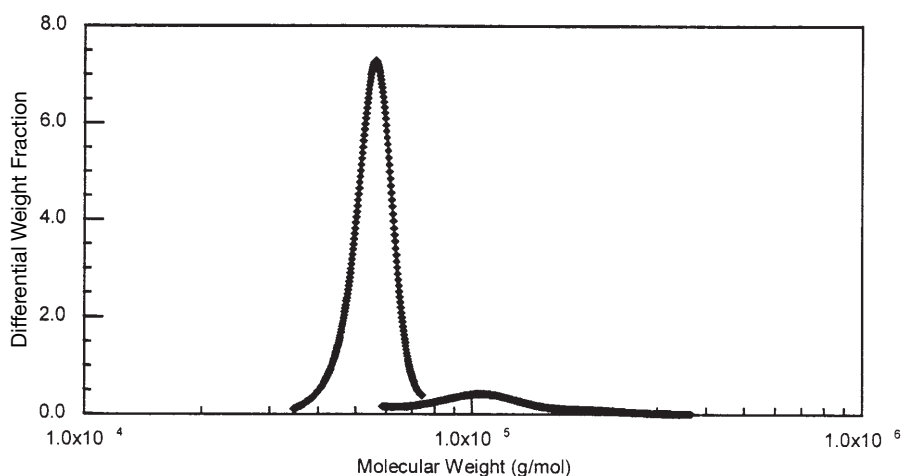


Fig. 12. Differential molecular weight distribution of the polymeric contrast agent, JP 591-3 ($dn/dc = 0.134 \text{ ml/g}$)

in the intrinsic viscosity, η , as $[\eta] = 2.5/\rho_{\text{equ}} = 2.5V_h/M$ with ρ_{equ} indicating the equivalent density of the polymer. Since the rheological behavior of dendrimers is assumed to be similar to that of balls, the equation is simplified to $[\eta] = 2.5V_h/M$ where V_h represents the hydrodynamic volume and M the molecular weight. From a dilution experiment, intrinsic viscosities were determined for JP 591-3 (a polypropylenimine with 64 amino groups). The resulting graph is illustrated in Fig. 13. Taking into account the standard deviation of 0.2 for the intrinsic viscosity, a hydrodynamic diameter of 5.03 nm (range: 4.84–5.21 nm) was obtained.

An alternative route of calculation uses the Solomon-Ciuta equation.

$$[\eta] = [2(\eta_{\text{sp}} - \ln \eta_{\text{rel}})]^{1/2}/c$$

With this equation the hydrodynamic diameter of JP 591-3 is 4.78 nm.

A third way is the calculation via the partial specific volume according to the following equation:

$$\bar{v}_2 = \frac{1}{\rho_0} \left(1 - \frac{\rho - \rho_0}{c} \right)$$

with $\bar{v}_2$ being the partial specific volume, ρ_0 the density of the solvent and ρ the density of the solution with concentration c . Modification results in the apparent molecular volume, V_m , being expressed as:

$$V_m = \frac{\bar{v}_2}{N_L}$$

with $N_L = 6.023 \times 10^{23} \text{ mol}^{-1}$. Plotting density versus concentration gives a regression curve with slope 0.468629 and a y-intercept of 1.00859, resulting finally in a molecular diameter of 4.51 nm.

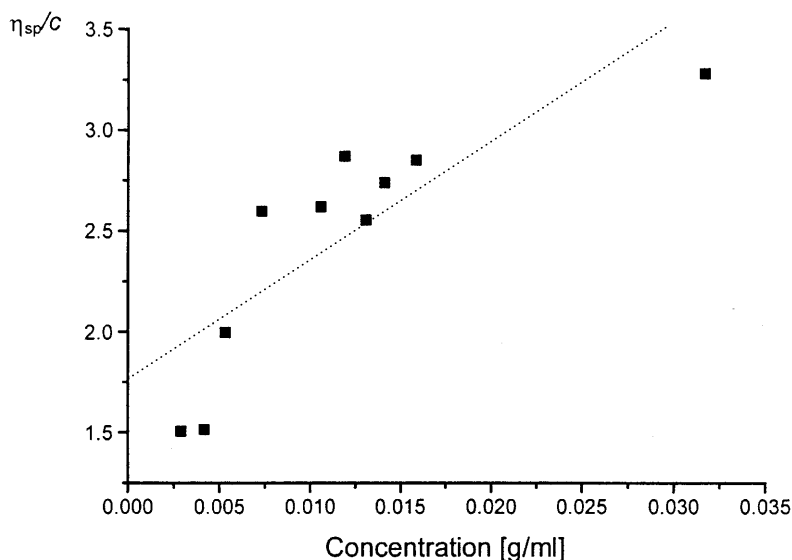


Fig. 13. Plot of η_{sp}/c versus c for JP 591-3 at 25 °C. The y-intercept of the resulting line gives an intrinsic viscosity of 1.76 ml/g

This value is smaller than that obtained by the intrinsic viscosity method. The reason is that by using density, the water sphere around the dendrimers is not taken into account, while with the viscosity method this is included. Accordingly, a water sphere of 0.25 nm thickness seems to surround the dendrimeric X-ray agent in solution.

Molecular size is one of the major determinants for renal excretion. All extracellular X-ray contrast agents are eliminated from the body by glomerular filtration. Likewise, polymeric compounds are exclusively eliminated through the kidney. Chang [92] and Bohrer [93] determined the size limits for the renal elimination in rats of anionic, neutral and cationic compounds as a function of molecular size. They found that cationic substances are more easily eliminated than neutral and anionic compounds (Fig. 14).

Fractional renal clearance is defined as the ratio of renal clearance of a compound relative to inulin which is eliminated exclusively by glomerular filtration. Accordingly, for a negatively charged molecule with a diameter of 5 nm (radius 2.5 nm), the fractional clearance is approximately 0.3 indicating slower elimination from the body than inulin.

5.2.8

Structure-Activity Relationships

Some of the polymeric contrast agents were studied *in vivo* in animals, mainly by determining their toxicity. The LD_{50} value was roughly estimated in mice following intravenous injection of increasing doses to groups of three animals.

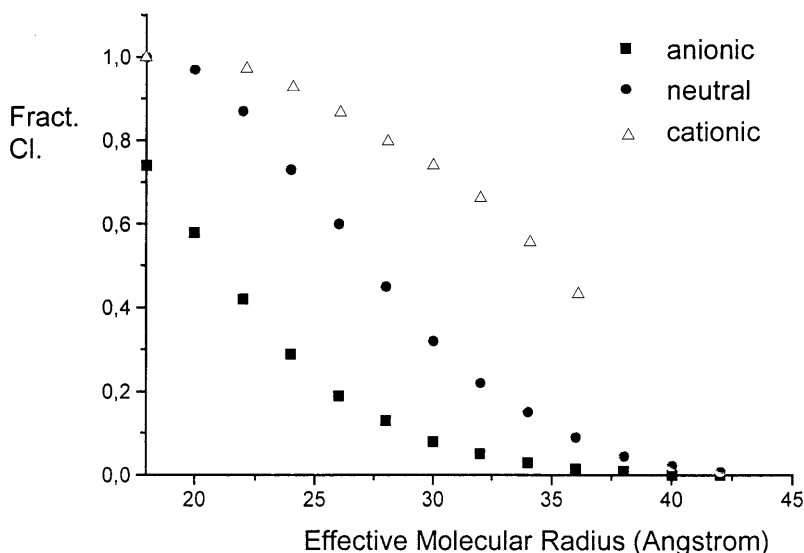


Fig. 14. Fractional clearance (clearance of compound x/clearance of inulin) as a function of molecular weight for anionic, neutral and cationic dextrans according to Chang [92] and Bohrer [93]

Table 5. Summary of physicochemical (osmolality, viscosity) and biological results (retention in body, LD₅₀ in mice) for selected dendrimeric X-ray contrast agents

Compound	MW (kDa)	Body retention at 14 d (%)	LD ₅₀ (gI/kg)	Osmolality (osm/kg)	Viscosity (mPas)	Solubility (mgI/ml)
163200	45.4	18.8	≈ 5	0.222	3.86	100
YD 804-1	26.9	3.3	< 3	0.644	7.09	150
188879/Na	29.3	7	3	0.043	66.65	150
188879/Ca				0.060	5.30	100
213138	60.4	15	> 3, < 6	0.359	2.13	100
YD 871-1	35.2	0.27	> 3			100
YD 862-1	41.2	0.91	< 3			100
YD 864-1	77.4	2.43	> 0.75	0.313	8.79	150

The mice were observed over a time period of seven days. The results are summarized in Table 5.

From the data obtained some general structure-toxicity relationships can be established. These include that an increase in hydrophilicity of the triiodobenzene moiety improved tolerance in mice. In multi-acid compounds, the selection of the cationic counterion seems to play a significant role. Calcium ions rather than sodium resulted in improved tolerance.

Increasing the molecular weight generally resulted in a prolongation of blood circulation times. The upper size limit was probably not reached in our studies

since even molecules with 72 kDa were renally excreted. However, retention in the body was a general problem for both polyamidoamines and polypropylenimines. Renal elimination was not totally complete for any of these compounds, irrespective of their nominal molecular weight. The reason most likely can be seen in high molecular weight impurities which are so big that they are no longer excreted by the kidneys. In contrast, polylysines did not show this behavior. Retention in the body was much lower for this class of polymers than for the other two classes. However, since production costs for polylysines are considerably higher than for polyamidoamines or polypropylenimines, these polymers will most likely not be used for X-ray technologies where extremely high doses (in the gram range) are necessary. On the other hand, for magnetic resonance imaging, which is more sensitive by a factor of 20 or more, these compounds might be of interest. In that case, the triiodobenzenes would have to be replaced by metal chelates with paramagnetic ions. An example is Gadomer-17. If instead of a paramagnetic ion a radioisotope is introduced into the chelate, then a scintigraphic contrast agent is obtained. Since the sensitivity of this modality is greater by a factor of nearly one million compared with X-ray imaging, costs of the polymer no longer play a role. Therefore, scintigraphy most probably will be the entry modality for dendrimeric contrast agents.

6 Conclusions

Dendrimers as carriers of contrast agents represent a new field of research in which a number of groups are currently extensively working. Although compounds suitable for radiopharmaceutical application should be quite easily achievable, efforts to date have been mostly directed at MRI and X-ray imaging. For this purpose, metal chelates and triiodobenzenes were coupled to dendrimeric carriers of different structures and sizes. However, to date, no compound has reached the status of broad clinical use. Possible hurdles still to overcome are drug uniformity, reproducible production of pure compounds, and economic synthesis. Until now, only mixtures of the desired end-product with a number of impurities have been synthesized. In principle, proof of concept for dendrimeric contrast agents as intravascular and even tumor-targeting substances seems to have been established. However, a lot of effort is still necessary before a dendrimeric contrast agent will finally be available for wide-spread use in patients.

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7

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