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The Synthesis and Properties of Novel Functional Dendritic Molecules

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1. Introduction

The research emphasis in dendrimer chemistry has recently switched to an exploration of the practical usefulness of functional dendritic molecules. As a result, functionalisation of dendritic systems has taken preference over the simplified version of synthesising large dendrimers for their own sake. Although

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dendrimer chemistry was initially a spin-off from the conventional polymer arena in the early forties,[1] it is now commencing to play a unique role not only in the polymer and materials industries, but also in various medical and pharmaceutical areas. Nowadays, dendrimers with novel physical, material, electrochemical, optical, photophysical/photochemical, biological and catalytic properties are beginning to emerge.

Dendrimers, in contrast to linear polymers, are highly branched, fractal-like macromolecules of defined three-dimensional size, shape and topology which can be prepared with very narrow molecular weight distribution. They also possess a large number of untangled chain-ends and surface functional groups with an identical micro-environment. Due to their structural homogeneity and regularity, the structural-property relationship of dendritic molecules can be rationalised in a more precise manner. Though synthetically more challenging, dendritic molecules can be tailor-made to contain discrete functional domains having unique physical and chemical characteristics. Amongst these properties are controllable nanoscale dimensions, predetermined molecular shape, precise molecular mass and tuneable interior/surface features. Furthermore, due to their relatively large molecular size and topology, dendrimers possess unusual chemical and physical assets which are not displayed by small molecules. During the last decade, a variety of dendritic polymers possessing organic, inorganic and organometallic functionalities have been synthesised, and intense research efforts are being devoted to identifying their practical applications.

The term "functional dendrimer" is used to describe dendritic molecules which possess useful or reactive functional groups that can participate in chemical/physical processes without degrading the dendritic matrix. The purpose of this manuscript is to review the key characteristics of functional dendrimer chemistry, consider issues involved in the design, synthesis and properties of functional dendritic molecules, and highlight their developments in various applications. The first part begins with a summary of the various synthetic approaches to functional dendrimers. The main theme of this review will be focused on their properties. Due to the vast number of dendrimers known in the literature, our selection is restricted to functional dendrimers for which well-defined properties and applications have been reported. Literature work detailing synthetic information solely will normally not be included here, since a significant amount of this information has recently been summarised in several excellent reviews/monographs[2] and highlight articles.[3] Hyperbranched polymers are also excluded because they often show different properties from "perfect" dendritic molecules prepared by stepwise, controlled processes.

2. Design of Dendritic Molecules

Most functional dendrimers reported in the literature have design strategies which fall into one of the following categories (Figure 1). One approach is to encapsulate a functionality of interest into the central core of a dendrimer. This type of design allows one to monitor the influence of the dendritic envelope on the property of the core functional group. Alternatively, the functional group may be appended on the dendrimer surface. In this case, the effect of the surface sector on the properties of the functional moiety can be addressed. If more than one functional group is attached to a dendritic surface, the resulting multi-functional dendrimer can be considered as an ideal model for the study of cooperativity and allosteric interactions amongst these surface functional units. Last but not least, both the surface and the interior domains could be decorated with functional units. As will be seen, each one of these designs gives rise to unique structural characteristics which provide us with diverse opportunities to further exploit the potential usefulness of functional dendritic molecules.

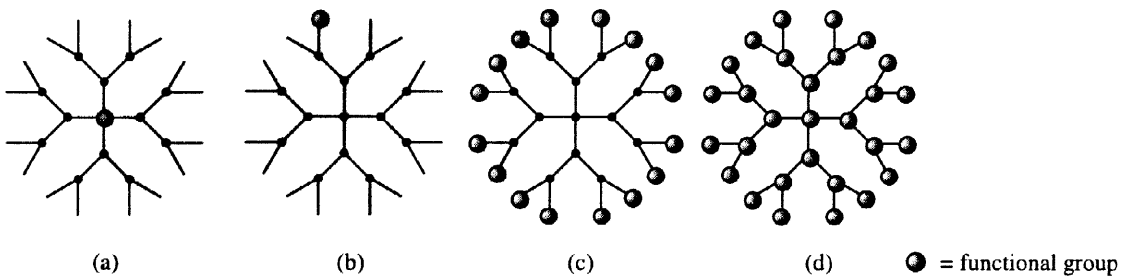


Figure 1. Functional dendrimers with (a) one functional moiety inside the core, (b) one functional group on the surface, (c) multiple functional groups on the surface and (d) multiple functionalities on both the surface and interior of the dendritic matrix.

It should be emphasised here that dendrimers without functional moieties can still exhibit interesting chemical or physical properties. Based on experimental[4] and computer simulation[5] studies, the interior of dendrimers has been shown to consist of solvent-filled voids which may serve as hosts for encapsulation of small molecules. Such entrapment of guest molecules is one of the unique attributes of dendritic macromolecules and is not normally observed for linear polymeric systems.

3. Synthesis of Dendritic Molecules

One of the most important breakthroughs in dendrimer synthesis in the past decade was the development of novel synthetic methodologies which enabled precise control of the architecture. Today, a number of sophisticated synthetic armouries are available to us for exerting complete control over the size and shape of a dendrimer as well as its molecular cavities by varying the nature of the dendritic branch and the branching juncture, and on the surface properties by proper selection of the peripheral functionality. On the other hand, one-step preparations of dendritic molecules based on polymerisation of $[(f_c)_n \bullet f_r]$ type monomers are also known. Although synthetically these approaches are much more efficient and less time consuming, they invariably produce dendrimers of high polydispersity and with substantial skeletal defects.[6] Hence, structurally perfect dendrimers with high purity and narrow polydispersity are usually prepared under controlled polymerisation conditions using iterative synthetic procedures.

3.1 Divergent Methods

The divergent synthetic approach was developed during the period between the late seventies and the early eighties with key contributions from Vögtle,[7] Denkewalter,[8] Tomalia[9] and Newkome.[10] The principle of this method involves growth from a central core, whereas branching is encouraged *via* a series of repetitive addition and activation steps which multiply the number of branches. This method is characterised by a rapid increase in the number of reactive groups at the periphery of the growing macromolecule. Thus, growth of the dendrimer is from the central core to the periphery.

The initial central core contains multiple copies of reactive functionality f_r which react with an excess of a bifunctional monomer $[f_c \bullet (f_p)_2]$[11] to give the first generation (G1) dendrimer (Figure 2). In reality, only one of the functionalities $[f_c]$ can form a linkage to $[f_r]$ while the other protected functional moiety $[f_p]$ remains intact under the coupling condition. The end-groups of the first generation dendrimer, $[f_p]$, can be converted into the reactive group $[f_r]$ for further coupling reaction with additional monomers to give the G2 dendrimer. Iteration of these processes allows rapid geometric growth in the number of surface groups while the radius of

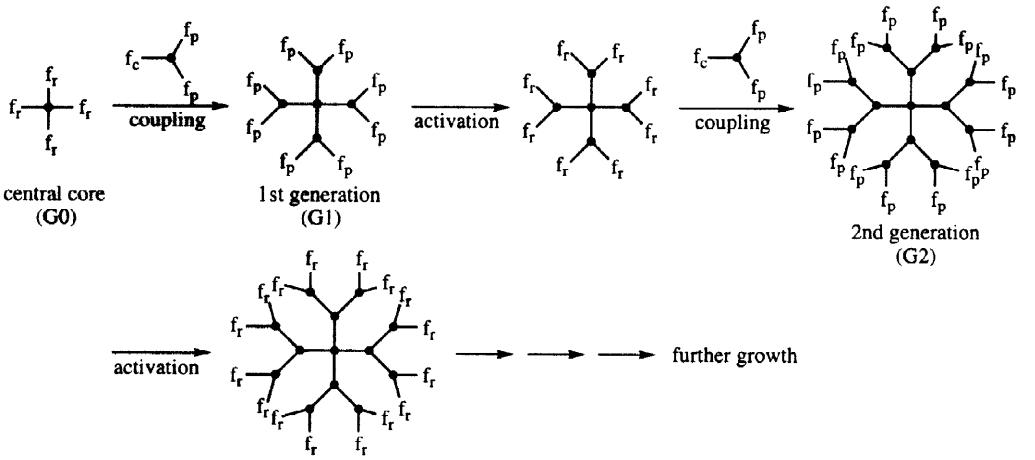


Figure 2. Divergent synthetic strategy of dendrimers

the dendrimer increases in an arithmetic fashion. As a result, a self-limiting size (generation) will occur for any dendrimer series once the surface groups are too congested for further growth without creating structural defects.

Because the number of terminal functional groups increases sharply with each generation, incomplete reaction of all of the terminal groups is a potential problem, and consequently, the occurrence of structural defects, especially for higher generation dendrimers, is virtually inevitable. Moreover, the large excess of reagents which are required to force the reaction to completion may lead to difficulties in product purification. Nevertheless, the divergent method is the most efficient and rapid procedure to construct dendrimers of high generation. Since it is impossible to achieve selective conversion of only one or several of the reactive surface moieties [f_r], the divergent procedure does not allow for the selective functionalisation of only part of the surface sector. Examples of dendrimers prepared by this approach are the polyamidoamine (PAMAM),[9] polyamide,[12] poly(trimethyleneimine)[7,13] and organosilane[14] dendrimers.

3.2 Convergent Methods

The alternative convergent approach toward dendrimer synthesis was developed independently by Fréchet[15] and Miller.[16] The synthesis begins at what will ultimately become the peripheral sectors of the dendrimers and propagates toward the central core. This involves an iterative coupling of branching fragments to produce a focal point functionalised dendritic sector followed by a divergent core anchoring step to produce the target dendrimer.

In the convergent synthetic strategy, each successive generation is synthesised in stepwise fashion to produce a new dendritic fragment in which a single reactive group [f_r] located at the focal point of all branches is used for further growth (Figure 3). The surface functionality [Δ], is connected to the branching bifunctional monomer [f_c•(f_p)$_2$] to form a dendritic wedge [(Δ)$_2$•f_p] containing two surface moieties. Upon activation (f_p $\rightarrow$ f_r), the reactive dendritic fragment [(Δ)$_2$•f_r] is then coupled to additional branching monomer to give a dendritic wedge of a higher generation [(Δ)$_{2\times2}$•f_p]. These dendritic wedges can be anchored to a central core [(f_c)$_4$][17] to give dendrimers of various generations. In contrast to the divergent approach, the low number of possible side reactions and the readily controllable number of reactive groups required for generation growth

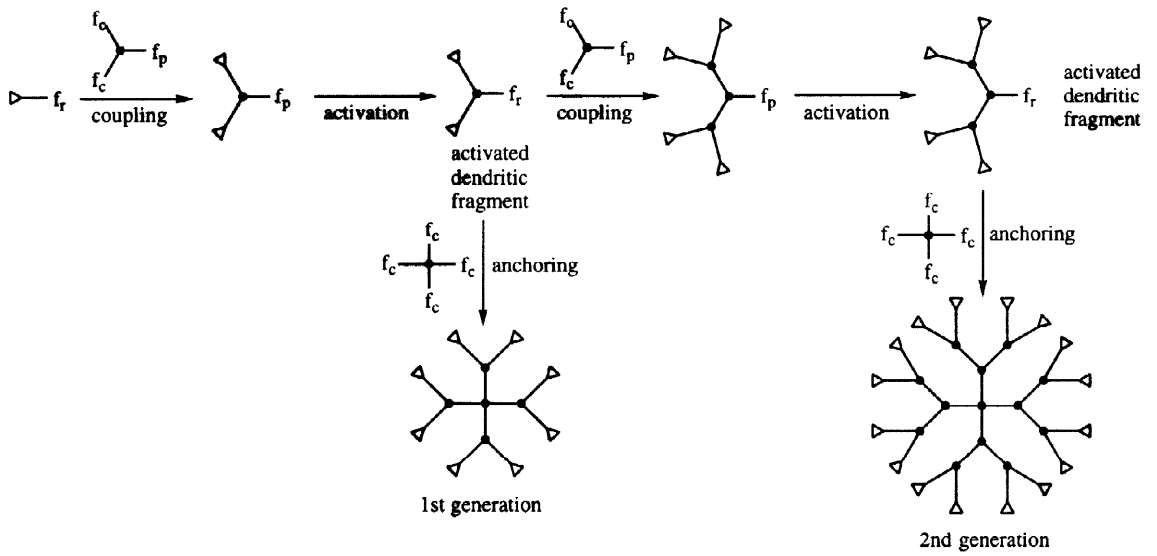


Figure 3. Convergent synthetic strategy of dendrimer

allow the synthesis of monodispersed dendritic molecules with a high degree of control. However, the convergent approach may suffer from steric inhibition at the focal point [f_r], particularly for the higher generation dendritic wedges. Examples of dendrimer synthesis employing this strategy are the polyether,[15] polyester,[16] and the phenyleneacetylenic[18] dendrimers. Because this approach has a high degree of control over the number and placement of functional groups at the periphery as well as in the interior regions of the dendritic macromolecule, novel types of dendritic layer-block and segment-block copolymers[19] as well as specific surface-functionalised dendrimers[20] can now be prepared in straightforward fashion (Figure 4).

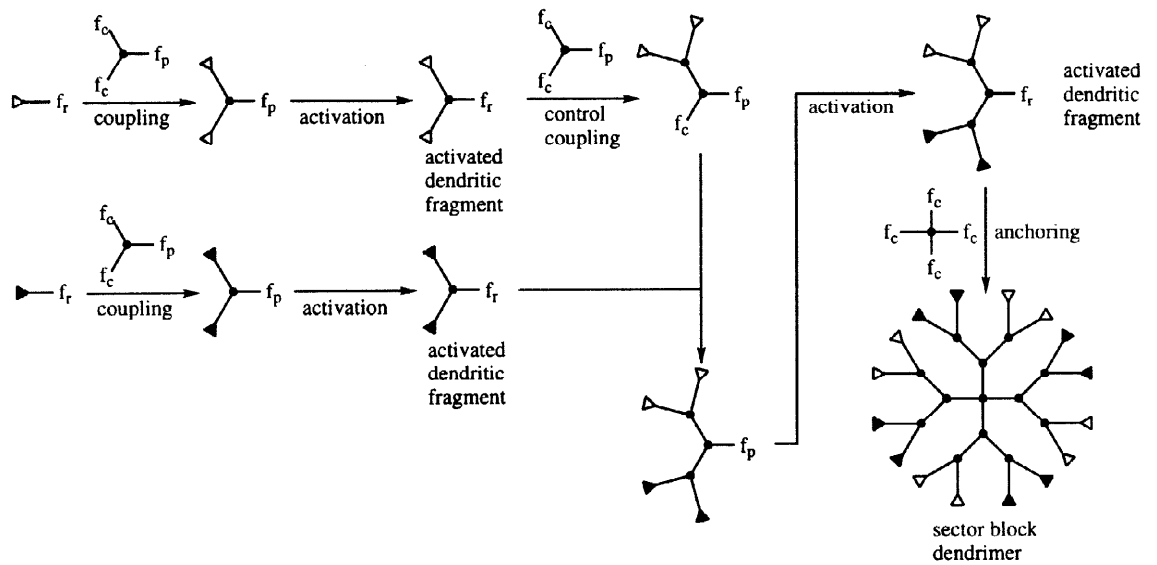


Figure 4. Convergent synthetic strategy for a block co-dendrimer

3.3 Accelerated Approaches

The convergent and divergent growth approaches described above involve stepwise and tedious operations and purifications. To facilitate the preparation of higher molecular weight dendrimers of narrow

dispersity in large quantities, alternative accelerated synthetic strategies which can speed up the preparative procedure and simplify the purification process have evolved.[21]

Double-stage hypercore convergent growth

This approach, initially coined by Fréchet as double-stage convergent growth,[22] allowed the rapid preparation of higher generation monodispersed dendrimers. The key feature of this process involves the anchoring of small dendritic wedges onto a hyperbranched dendritic core ("hypercore") which carries a large number of reactive surface functional group [f_s] at its numerous chain ends. This hypercore, in turn, is prepared by a convergent growth protocol (Figure 5). The working assumption of this technique is that the surface functionality of the hypercore is less sterically hindered than those of a simple non-dendritic core molecule used in the conventional convergent methodology. This is primarily due to the segregation of the reactive functionalities by the side branches, thus providing ample spacing between the reactive groups at each chain end for efficient coupling.

Two monomers [$(f_c)_2$•f_p] and [$(f_{p'})_2$•f_r] utilising two different protective groups [f_p] and [$f_{p'}$] are required in this strategy. The second monomer [$(f_{p'})_2$•f_r] can be prepared by the coupling of two molecules of [f_p–f_r] to one equiv. of [$(f_c)_2$•f_p] *via* the reactive functional groups [f_r] and [f_c], followed by chemoselective functional group activation ([f_p] → [f_r]). The masked monomer [$(f_{p'})_2$•f_r], upon coupling to [$(f_c)_2$•f_p], followed by activation and subsequent anchoring to a central core [$(f_c)_3$], can then be transformed to a symmetrical hypercore [$(f_{p'})_{2\times2\times3}$] containing a large number of end groups [$f_{p'}$]. This hypercore, after activation of the protected end groups to the reactive surface functionality [f_s], can then be coupled to dendritic wedges of different generations (*e.g.* [$(f_{p'})_4$•f_r]) to give dendrimers of higher generations.

A slight variation of this synthetic theme has recently been described by Moore,[23] and is known as the double exponential dendrimer growth process. In this strategy, a higher generation hyperbranched dendritic wedge, instead of a simple lower generation dendritic sector, is used to anchor to a hypercore. Using this strategy, a G7 (255-mer) phenylacetylene dendritic fragment of 40 kDa could be prepared in 9 steps, while the conventional convergent growth scheme would require 15 synthetic operations.

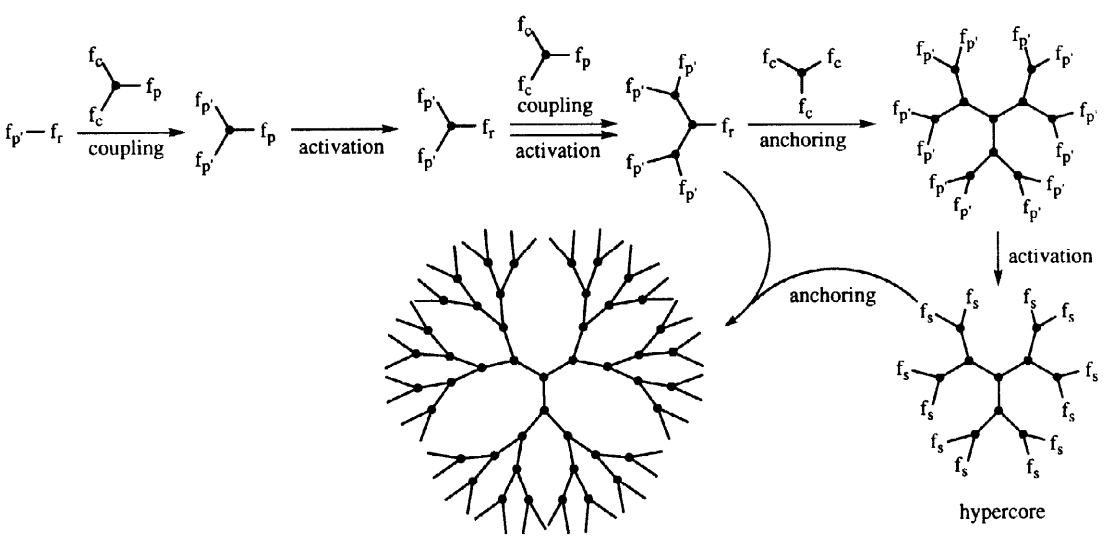


Figure 5. The double-stage convergent synthetic strategy of dendrimer formation

Branched monomer approach

In 1994, Fréchet disclosed the use of hyperbranched fragments as monomers[24] for the rapid synthesis of higher generation dendrimers. Conceptually, the use of a hyperbranched monomer of high generation such as $[f_c{\bullet}(f_p)_{2\times2}]$ or even $[f_c{\bullet}(f_p)_{2\times2\times2}]$ instead of a doubly branched monomer $[f_c{\bullet}(f_p)_2]$ in the growing process (Figure 6) allows the addition of two or three dendritic layers in one iterative cycle.[25]

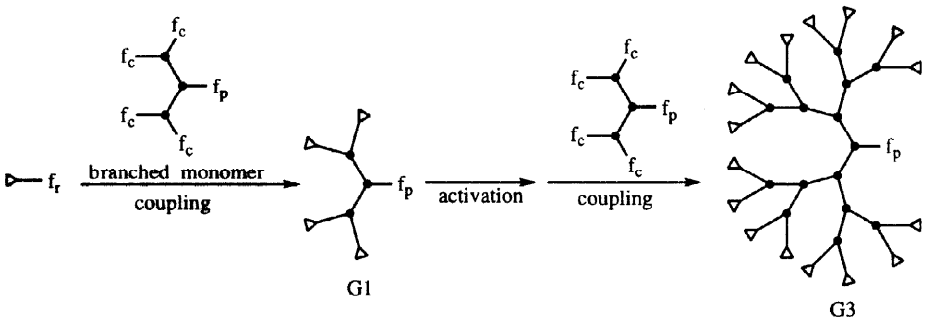


Figure 6. Branched monomer approach

Two monomer approach

This method, also known as the two-step approach[26] or the orthogonal coupling strategy,[27] was again pioneered by Fréchet. In contrast to the other approaches, this method utilises two different monomers $[(f_c)_2{\bullet}f_{r'}]$ and $[(f_{c'})_2{\bullet}f_r]$ with a set of orthogonal functionalities which react with each other in a specific and selective manner (Figure 7). Thus functionality $[f_r]$ can only be coupled to $[f_c]$ and $[f_{r'}]$ can only react with $[f_{c'}]$. On the other hand, neither $[f_{c'}]$ nor $[f_{r'}]$ reacts with functionality $[f_r]$. The advantage of this approach is that both protection and deprotection reactions are eliminated and this greatly simplifies the synthetic operations. However, since the chemical linkages between alternative layers are different, the resulting dendrimer therefore has a layered-block architecture.

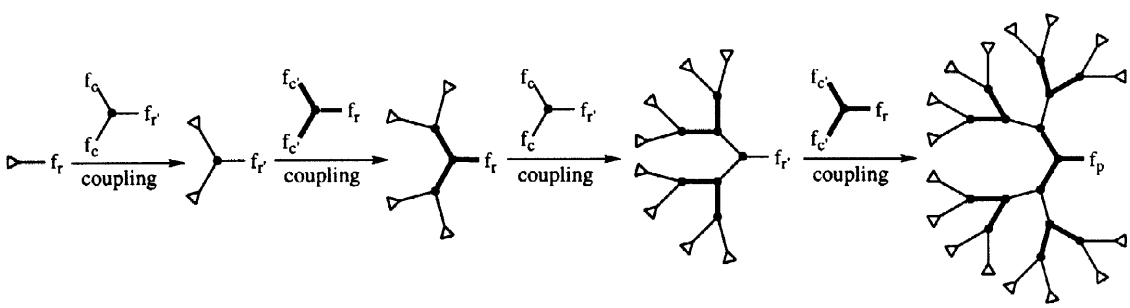


Figure 7. Two monomer approach

3.4 Solid Support Synthesis

Solid phase synthesis has proven to be a powerful tool in making biopolymers such as polypeptides[28] and polynucleotides which require repetitive, stepwise reactions in which large excesses of reagents are used. In principle, the divergent synthetic method is very similar to solid-phase peptide methods. In 1991, Fréchet reported the first use of polystyrene supports for the synthesis of polyamide dendrimers (Figure 8).[29] In this method, the monomer $[(f_c)_2{\bullet}f_p]$ is coupled to a reactive moiety $[f_r]$ tethered to a solid support. After activation, excess monomer was added to initiate the next iterative cycle. This solid support technique

simplifies the purification procedure for each generation as the excess reagents used to ensure complete reaction of the surface functional groups can be removed easily by washing the polymer-bound dendrimer. The desired dendritic polymer is then isolated by cleavage of the macromolecule from the solid support. In reality, the yields of the coupling reactions were extremely poor. Furthermore, higher generation dendritic fragments prepared by this method have severe structural defects.[30]

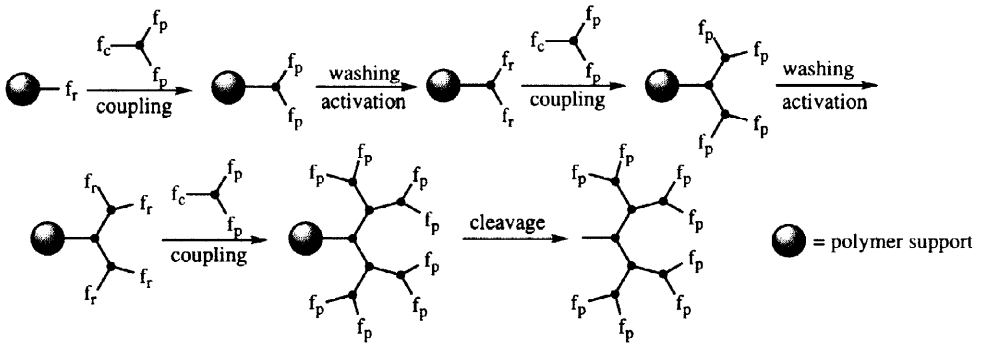


Figure 8. Divergent solid phase synthesis of polyamide dendrimer

A solid-phase convergent synthesis of a nucleic acid dendrimer was disclosed by Damha (Figure 9).[31] In this procedure, a number of short oligonucleotide chains were anchored on the surface of a long-chain alkylamine controlled-pore glass. They were then annealed to a branching nucleotide to form a G1 dendritic nucleotide. Chain elongation and branching steps were then repeated to form successive generations, each with twice as many chain ends as the previous generation. Unfortunately, the purities of the resulting dendrimers were poor and this method was not amenable to the preparation of higher generation species.

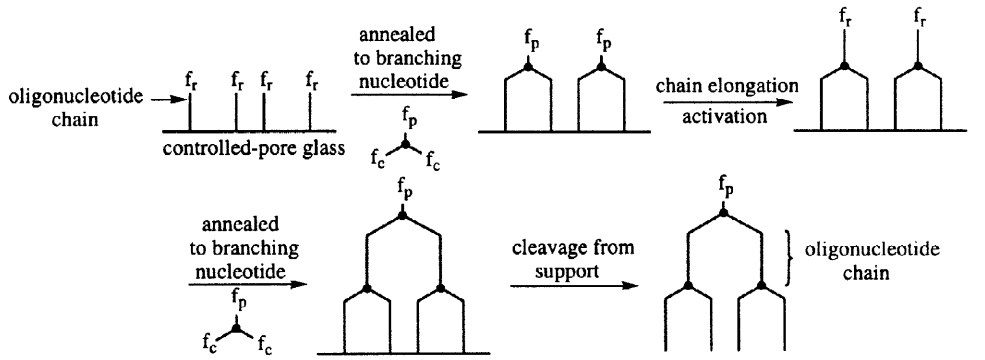


Figure 9. Convergent solid-phase synthesis of nucleotide dendrimer

Recently, another solid-phase convergent synthesis of phenylacetylenic dendritic fragments was reported (Figure 10).[32] The product of the solid phase coupling reaction was cleaved and activated to yield an activated fragment of one higher generation, which was then used to couple to the same polymer support agent. The yields of the coupling reaction in this convergent approach were higher than those of the divergent method, although the coupling reaction became extremely sluggish with higher generation dendritic fragments. An optical microscopy study revealed dramatic changes in the appearance of polymer support beads from lower to higher generations, suggesting a sudden change of the accessibility of the reactive sites.

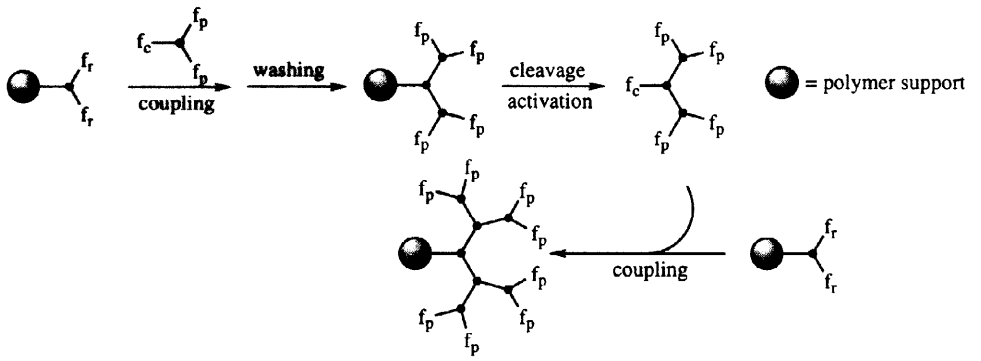


Figure 10. Convergent solid phase synthesis of dendrimer

The above synthetic approaches, whether divergent, convergent or accelerated, should be considered as complimentary and not competitive. The divergent method offers a rapid preparation of higher generation dendrimers in large scale with potential structural defects. On the other hand, the convergent method, although labour intensive, is the method of choice for preparing perfect dendritic structures. While the accelerated methods combine the advantages of divergent and convergent approaches, there are still practical problems with regard to reactant solubility and steric accessibility. The method of choice for dendrimer synthesis, is primarily determined by the nature of the branching functionality, the length of the branches, the peripheral groups, the compatibility of the protective groups under the reaction conditions and the physical as well as the solubility properties of all the intermediates and the final products. An excellent comparative synthetic study of phenylacetylene dendrimers using these three different approaches has been reported.[33]

4. Characterisation of Dendritic Molecules

Dendrimers are usually characterised by standard polymer characterisation techniques such as size exclusion chromatography (SEC), viscosity and light scattering measurements. Due to the structural regularity of dendritic architecture, nuclear magnetic resonance spectroscopy is often a better method in providing structural information for a dendrimer macromolecule.

One of the critical issues on dendrimer purity is the question of accessing structural defects, especially for the higher generations. Although viscosity and light scattering measurements can provide information regarding their molecular weights and sizes, they provide little information about dendrimer homogeneity. On the other hand, SEC technique can produce data about molecular weight distributions of dendritic species. Generally speaking, a structurally pure dendrimer will give narrow SEC peaks of polydispersity less than 1.05. Some examples of those which have been characterised by SEC analyses includes polyether,[15a,22,34] polyester,[35] phenylacetylene,[33] organosilane,[36] and phenylene dendrimers.[37] However, a polydispersity near to 1.0 does not guarantee the structural homogeneity of a dendrimer sample, this is especially true for dendrimers of high generations. One such example was demonstrated in the synthetic study of a phenylacetylene dendrimer[23] *via* the double exponential dendrimer growth approach, wherein a SEC peak of polydispersity of 1.05 was actually a mixture of four dendritic components as revealed by mass spectrometry.

Nuclear magnetic resonance spectroscopy, especially of ^{13}C and heteronuclei, has been extremely useful in accessing dendrimer purity. Since any structural defects will lead to an unsymmetrical structure and result in the multiplicity of ^{13}C signals. The use of the ^{13}C-NMR technique to confirm perfect dendrimer structure

has been demonstrated in synthetic studies of polyether[20b,22,38] and organosilane dendrimers.[36] ^{31}P-NMR spectroscopy is also extremely useful in determining the structure of phosphorous containing dendrimers.[39] On the other hand, ^{1}H-NMR appeared to be less convincing as a technique in accessing structural defects,[23] at least for cases when the ^{1}H signals were extremely complex.

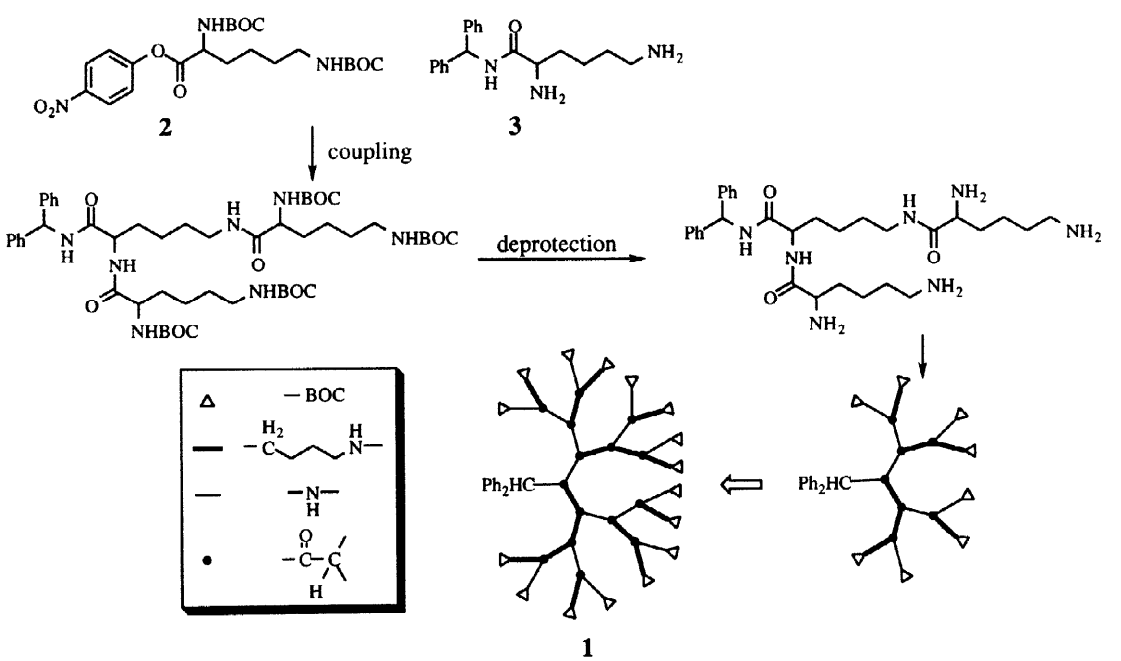
With the advent of modern techniques in mass spectroscopy, it has now become possible to ionise dendritic molecules and to determine their molecular mass with high precision. For example, by using the matrix-assisted laser desorption ionisation (MALDI) technique, aromatic polyester dendrimers of MW up to 5200 could be determined within 1 amu.[40] Other ionisation techniques such as fast atom bombardment (FAB), electrospray (ES) and MALDI-time of flight are especially useful for structural characterisation of high molecular weight dendrimers[41] and metallodendrimers.[42] Furthermore, metallodendrimers are prone to form multiply-charged ionic species, which greatly facilitates their molecular mass determinations.[43]

5. Properties of Dendritic Molecules

The main purpose of this article is to review the properties of the various functional dendrimers reported in the literature over the past decade. In contrast to the conventional way of categorising dendritic macromolecules by their structural type or by their method of preparation, they are classified herein according to their physical or chemical properties. Due to the increasing "cross fertilisation" between these subdivisions, a dendritic molecule may exhibit more than one kind of property and may therefore fall into more than one category.

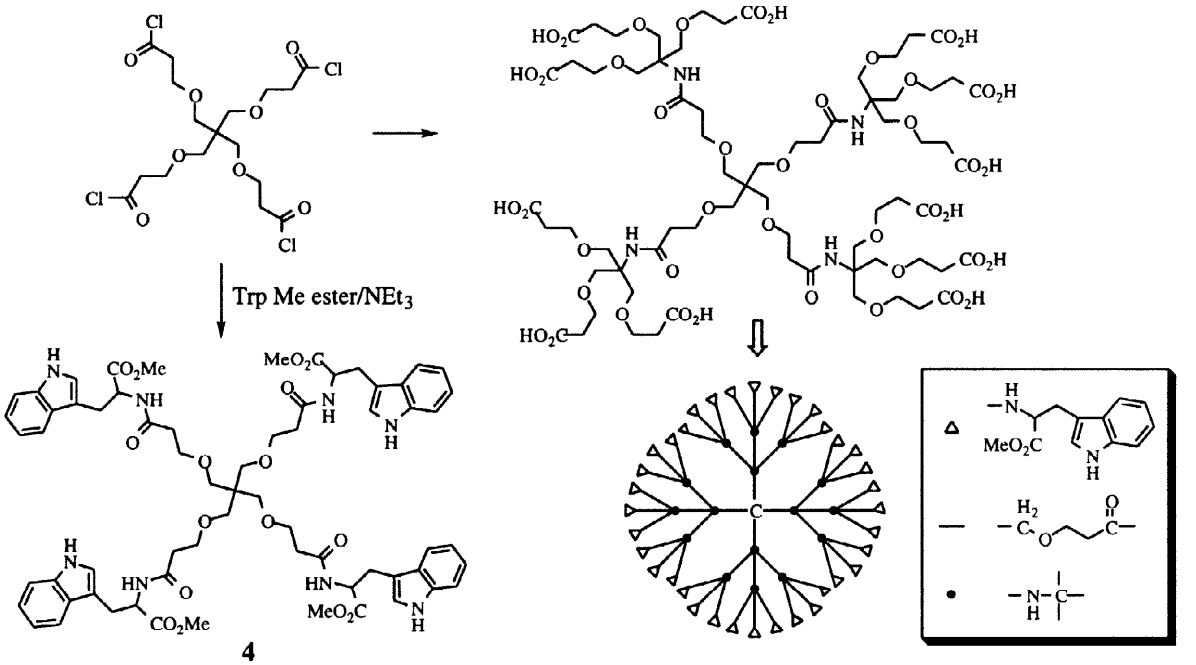
5.1 Chiral Dendrimers[44]

The introduction of chiral elements into a dendritic structure should result in the formation of non-symmetrical, nonspherical molecules having a chiral surface and chiral cavities. The chiral surface can serve as chiral *exo*-receptors while the chiral cavities may function as chiral *endo*-receptors. Chiral dendrimers are therefore potentially useful materials for chiral recognition and enantioselective binding of guest molecules.



The first chiral dendritic series were the polypeptide dendrimers **1*** reported by Denkewalter.[45] Their preparation involved a divergent addition of a protected lysine derivative **2** to a lysine core **3** prepared from L-lysine and benzhydrylamine. Removal of the BOC protecting groups released the four amino functionalities which allowed further growth of the dendrimer. Repeating this procedure, dendrimers of generation up to G10 were prepared. However, no chiroptical properties were revealed in this study. Soon afterwards, a number of biological dendrimers containing chiral sugar, nucleotide and amino acid units (for details see section 5.7) were synthesised. Because the majority of these studies were focused on the biological properties of these macromolecules, their structural-chiroptical property relationship was not disclosed.

In 1991, Newkome described the first study of the chiroptical properties of a series of tryptophane-based dendrimers **4**.[46] They were synthesised by a divergent addition of the chiral amino acid derivatives to the periphery of a polyamido dendritic core. A linear relationship between the molecular ellipicity of these compounds and the number of chiral tryptophane units in the molecule was noted. However, attempts to incorporate the chiral units within the interior of the dendritic structure resulted in a complete loss of chirality, presumably due to racemisation during the coupling process.



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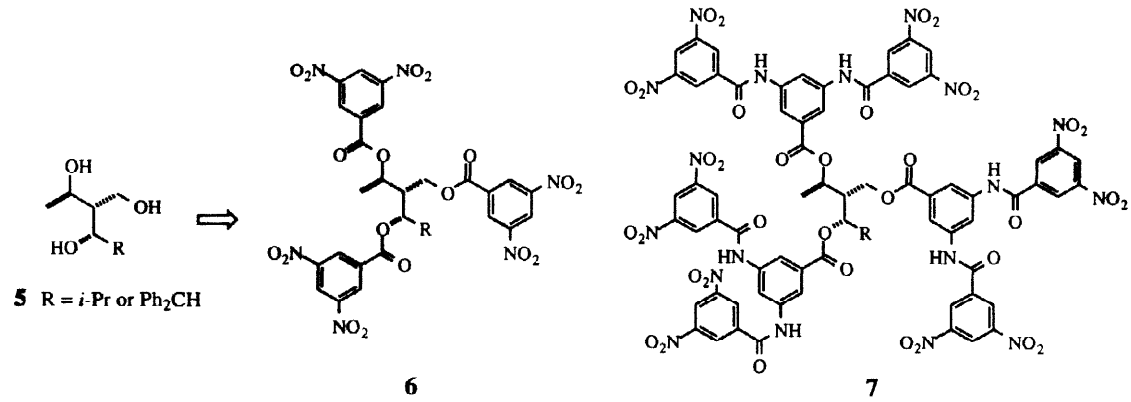
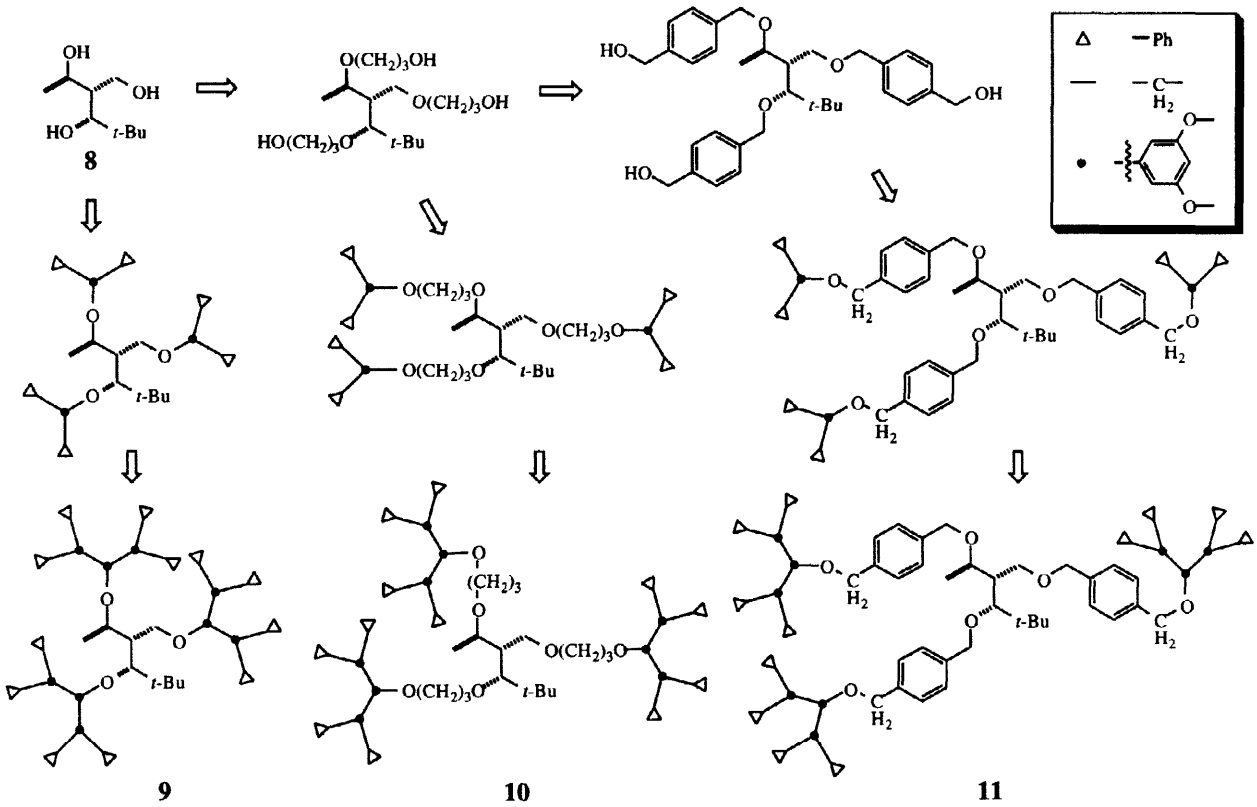
In a quest to explore the use of chiral dendrimers as hosts for chiral recognition, Seebach described the synthesis of a number of chiral dendrimers using optically active triols **5** derived from poly-(3*R*)-hydroxybutanoate as the central core.[47] Polyester-based **6** and polyester/polyamide-based dendrimers **7** were prepared by a divergent addition of aromatic branches to the chiral triol **5**. A dramatic change in the optical rotation was observed on going from G1 to G2, but no trend could be established. In a related study, three different chiral dendrimer series **9**, **10** and **11** were prepared by employing a chiral triol **8** as the central core and Fréchet's achiral polyether wedges as the branches. The specific rotation of these chiral dendrimers, along

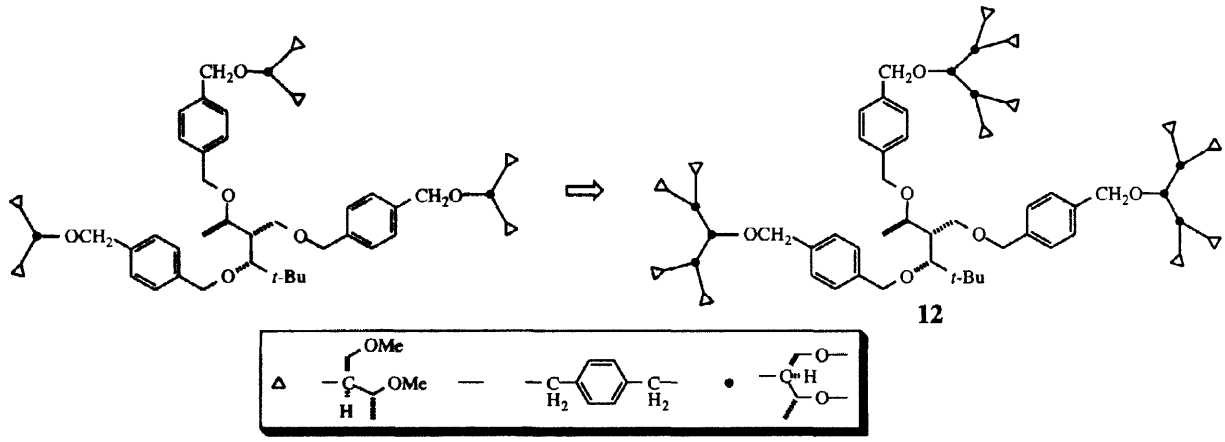
* Schematic drawings are used here to reduce space, where Δ = surface group; — = branch; • = branching juncture. In the structural key, the left hand side of the dendritic branch and branching juncture denotes the attaching point toward the central core. The full structure of a lower generation dendrimer is usually given to provide a glimpse of the chemical linkages.



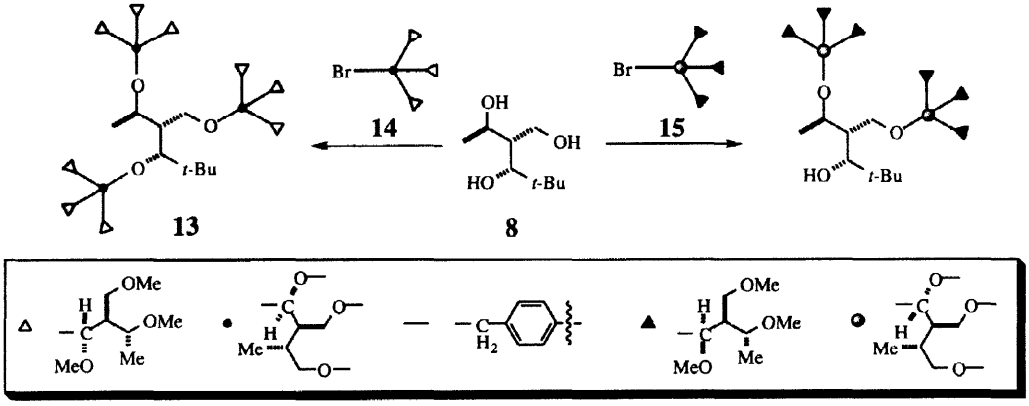
the same series, decreased toward the higher generation while the molar rotation remained essentially constant. Hence, attachment of achiral branches to a chiral core led simply to an optical dilution effect. In fact, the circular dichroism (CD) spectra of the aliphatic branch series **10** does not show any Cotton effect from 220 to 400 nm.



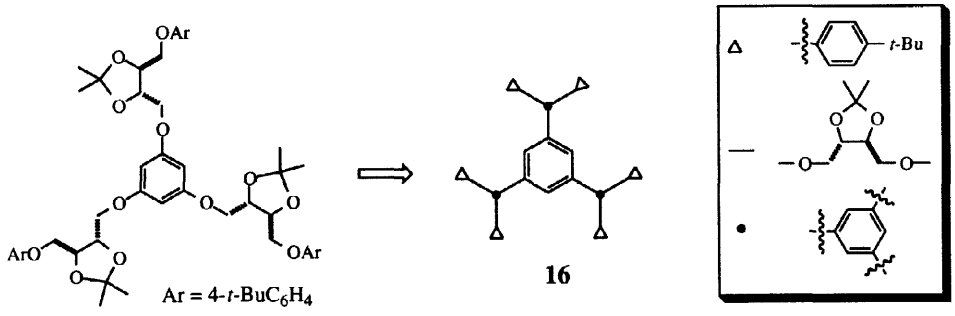
Seebach later extended this work by incorporating both chiral branching junctures and chiral core into two different dendritic structures **12** and **13**.[48] Using a convergent strategy, the doubly branched series **12** could be prepared up to G3. However, the triply branched series **13** could only be synthesised up to G2, presumably due to a higher degree of branching and increased steric hindrance. Interestingly, a kinetic diastereoselectivity was noted where the coupling efficiency of different chiral wedges to the chiral central core **8** was dependent on the absolute configuration of the chiral wedge. Hence, three equiv. of chiral sector



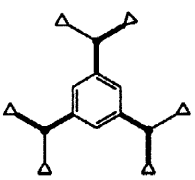
14 could be anchored to the chiral triol **8** to give **13**, but only two equiv. of the diastereomeric fragment **15** could be attached to **8**. The CD spectra of the doubly branched series **12** varied from generation to generation with significant changes in moving from G2 to G3. This was likely caused by a change from an open to a closed structure across generations. Likewise, a reversal of the sense of specific rotation was also observed on going from G1 to G2 in the triply branched series **13**.



Shortly after these developments, Chow reported the convergent preparation of optically active (L)-tartrate-based dendrimers **16** containing multiple chiral branches.[49] It was found that each tartrate unit contributed to the same extent to the overall molar rotation of this dendrimer series. In a subsequent paper, two chiral layer block dendrimers **17** and **18** containing both (D)- and (L)-tartrate chiral elements were reported.[50] As expected, the molar rotation of these lower generation dendrimers is proportional to the



number of chiral units in excess. In other words, the chiroptical effect of one (D)-unit cancels that of an (L)-unit. CD studies, however, suggested that this cancellation effect was more effective when both (D)- and (L)-chirons were deposited within the same layer. Attempts to prepare the higher generation analog of this series were unsuccessful as the convergent growth method failed to produce dendritic wedges of higher generation, probably due to solubility and steric reasons. However, the problem could be circumvented if an achiral C-3 spacer was used to replace all the internal chirons while keeping all of the peripheral (L)-tartrates intact.[51] For this extended chiral series **19**, it was again noted that each tartrate unit contributed to the overall molar rotation to the same extent, with the absolute contribution per chiral unit matched well with that of the **16**, **17** and **18** series. These results suggest that for sterically non-congested dendrimers with symmetrically branching patterns, each chiral unit behaves independently of each other and each contributes to the overall molecular chiroptical properties to the same extent.



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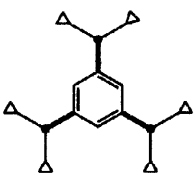

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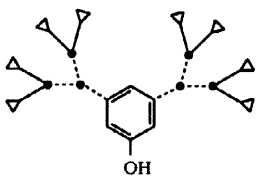

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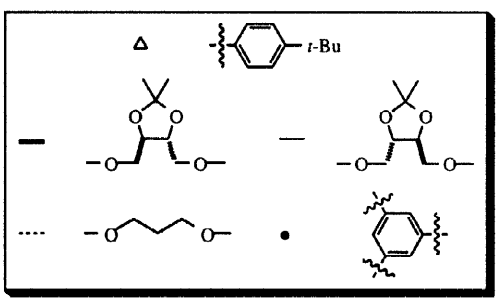
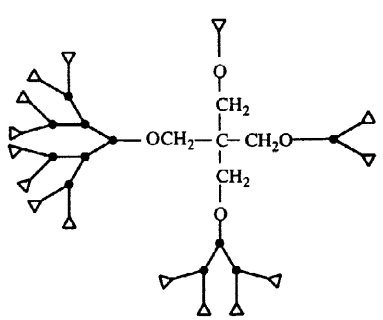


To address the stereochemical concept of cryptochirality, Meijer described the preparation of racemic polyether dendrimers **20** and **21** bearing a chiral sp^3-carbon linked to four dendritic branches of different generations.[52] Unfortunately, failure to resolve **20** by chiral HPLC precluded a chiroptical study of the pure enantiomer. It was noted that the 4 sets of methylene protons belonging to the pentaerythritol core appeared as 4 sharp singlets with little sign of diastereotopicity in the ^{1}H-NMR spectrum of **20**. In order to make a detailed chiroptical study possible, Meijer replaced the pentaerythritol core with an optically active triol to obtain both enantiomers of a chiral dendrimer **22**.[53] The (*S*)-enantiomer was shown to be devoid of optical activity by polarimetry, CD and ORD measurements. Molecular modelling of **22** suggested that the dendritic side arms still possessed significant conformational freedom and thus there was little enantiomeric difference in the geometry and chiroptical properties between (*S*)-**22** and its enantiomer.



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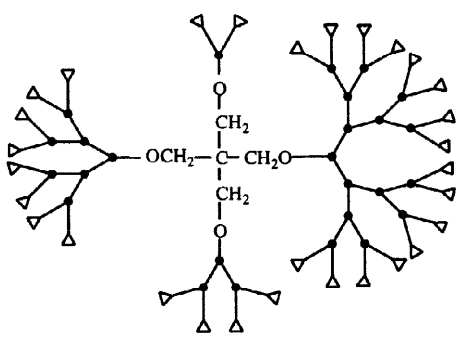

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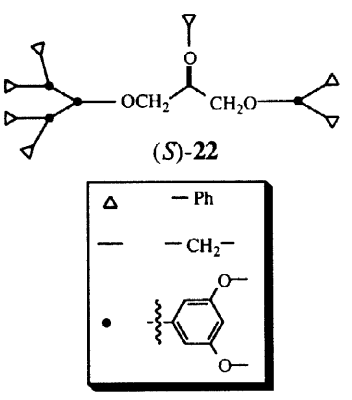
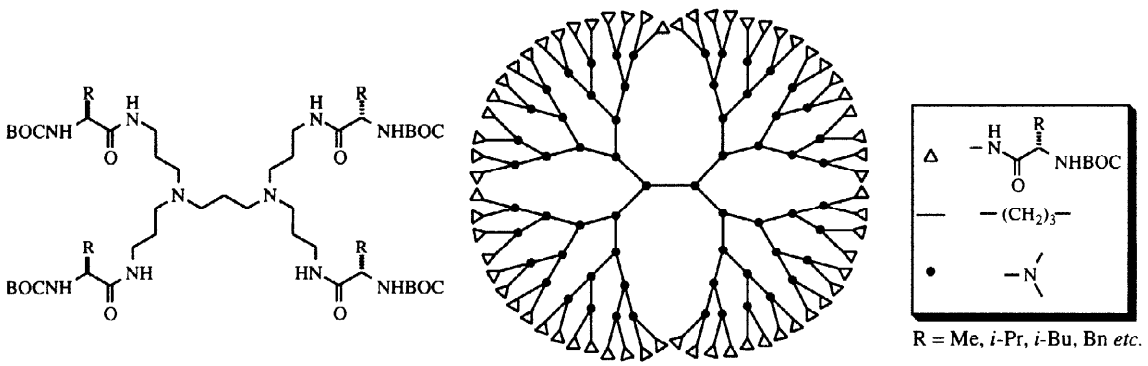
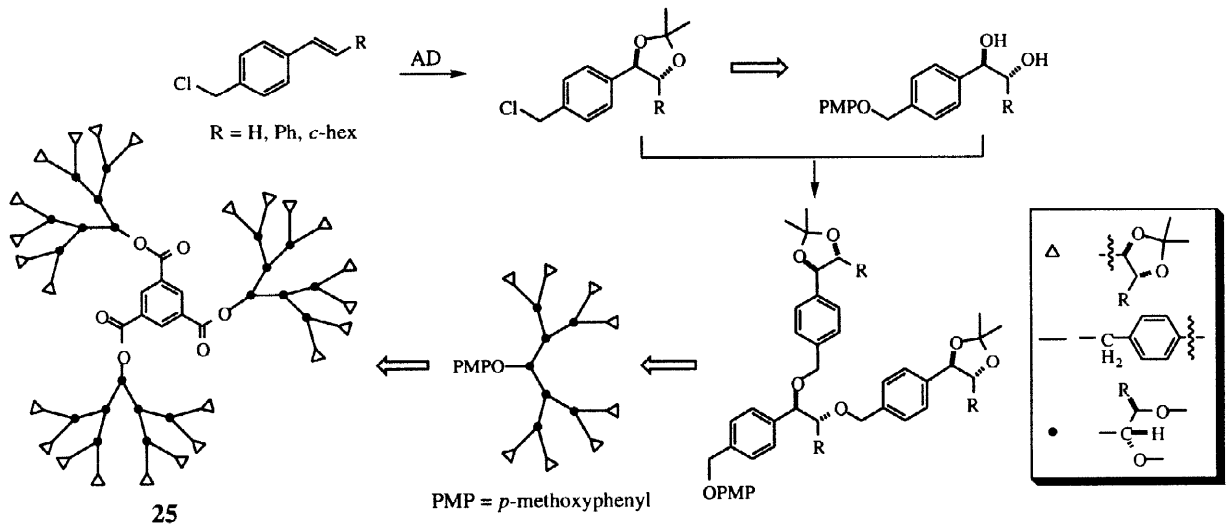


Recently, Meijer has reported one of the most intriguing chiroptical properties of dendrimers during the preparation of a series of amino acid-coated poly(propyleneimine) dendrimers.[54] It was found that both the specific rotation and Cotton effect diminished from G1 **23** to G5 **24** when the amino acid side chain R was relatively large (*i.e.* R = CH_2Ph, C_6H_4OH).[54a] On the other hand, this decrease of the chiroptical properties toward the higher generation was less pronounced for the dendrimers decorated with smaller amino acid residues (R = Me, *i*-Pr and *i*-Bu). Due to the presence of a large number of amide and carbamate groups, the surface of the G5 dendrimer **24** had a highly dense solid-like packing in solution. The rigidity of the shell was further enhanced by multiple inter-chain H-bonding. It was therefore suggested that the conformations of the chiral surface moieties were frozen in a pseudo mirror-image relationship, leading to the observed disappearance of optical activity. To substantiate this argument, this "drop" in the chiroptical properties with increasing generation was not observed when the carbamate groups were replaced by non H-bonded acetal linkages.[54b]



23 **24**

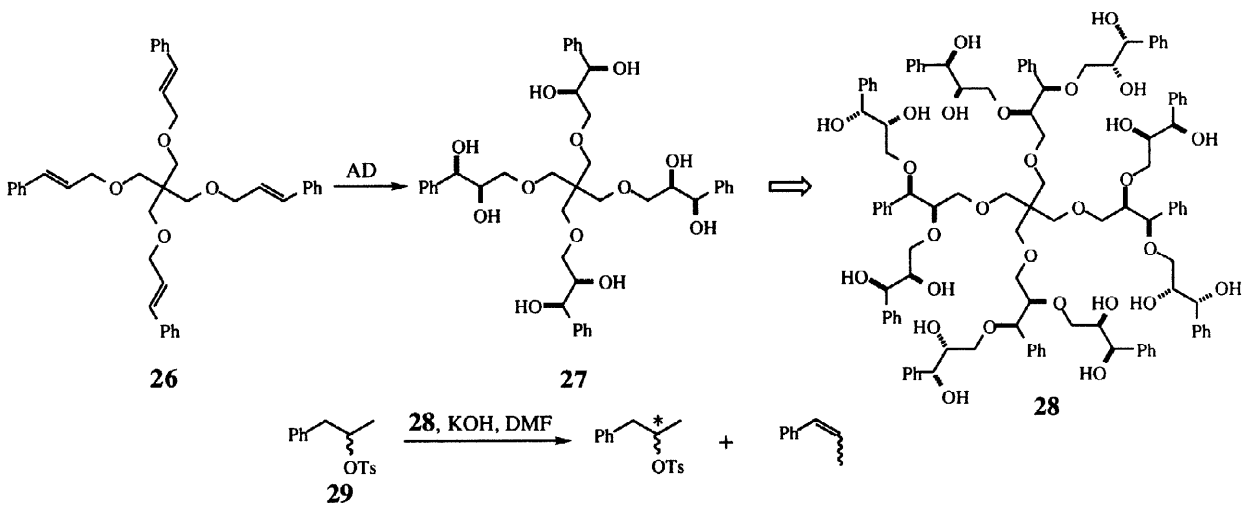
In contrast to all of the above-mentioned methods wherein the chirality of the dendrimer originated from optically pure chiral pool substrates, Sharpless reported a double exponential dendrimer growth method for the preparation of chiral polyether dendrimers **25**[55a] in which all of the chiral centres were generated by an asymmetric dihydroxylation (AD) of prochiral olefins.[56] Similar to the cases reported earlier,[49-51] the molar rotation of the sterically less encumbered styrene series (R = H) was approximately proportional to the number



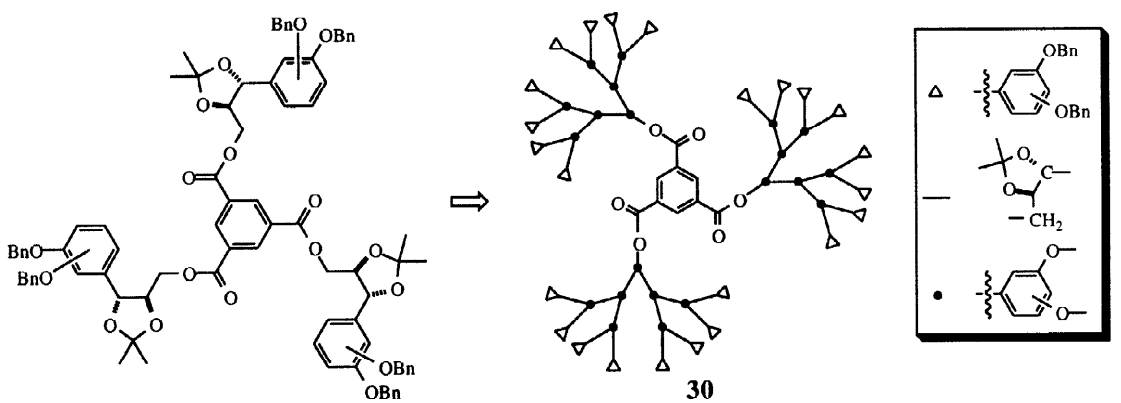
25

of chiral repeating units. For the sterically demanding stilbene-based series (R = Ph), the molecular rotation per repeating unit decreased as the generation increased.[55b] The latter situation was similar to that reported by Meijer,[54] and was again attributed to the larger phenyl group which created a sterically bulky, conformationally frozen pseudo-enantiomeric environment.

Sharpless further demonstrated that chiral polyether dendrimers up to G3 could also be prepared by a divergent method starting from pentaerythritol as the central core.[55b] The key reaction again relied on the highly enantioselective AD process, by which an 8-ol **27** could be obtained in 92% e.e. from a tetraene **26**. Subsequent alkylation of **27** with cinnamyl bromide followed by a second stage AD gave the 16-ol **28** in somewhat lower enantioselectivity. However, further growth of **28** was hampered by the poor efficiency of the AD process. Interestingly, dendritic polyols **27** and **28** exhibited some unusual chemical reactivities. For example, the G1 polyol **28** underwent a much faster base-induced *O*-alkylation reaction than G0 **27**, which in turn reacted faster than pentaerythritol. This result was rationalised by a tighter complexation of the metal cations by a larger crown ether-like structure such as **28**, leading to a relatively naked alkoxide anion, as compared to its lower generation analogues. The 8-ol **27** had also been used as a chiral phase transfer catalyst for the kinetic resolution/elimination of racemic tosylate **29**. Preliminary experiments showed that recovered **29** had a moderate enantiomeric excess (15%) at 50% conversion.[55b]

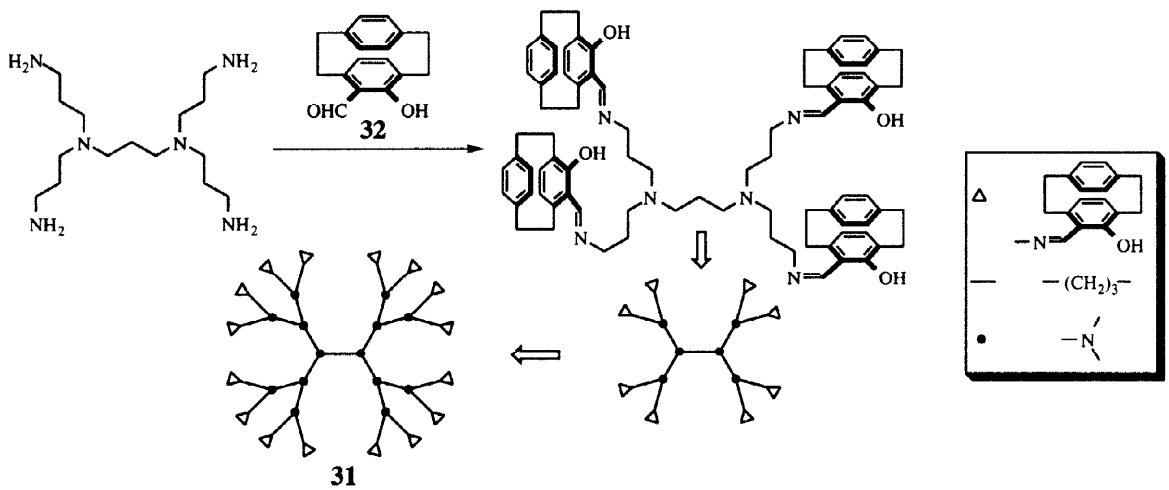


Using the AD strategy, McGrath described the convergent preparation of a number of chiral dendrimers **30** with a highly functionalised internal structure.[57] Dramatic changes in optical activity with increasing

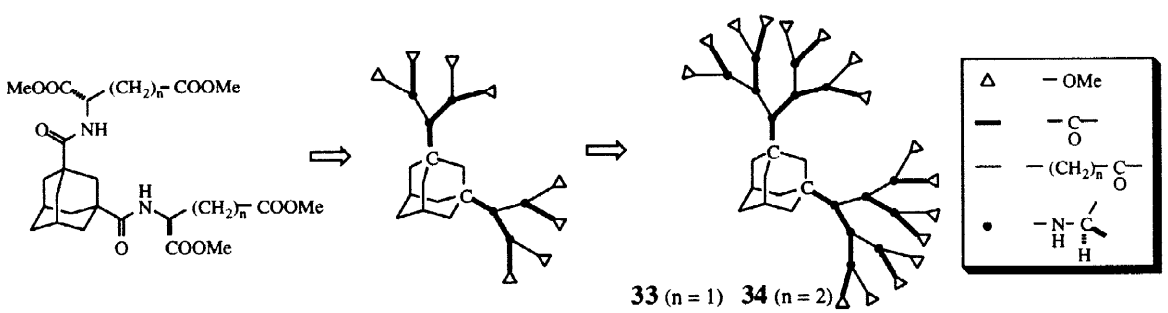


generation were observed, but the effects were due to constitutional changes rather than conformational transitions induced by an increasing sterically hindered environment. Monte Carlo conformational searches on **30** revealed a series of low-energy conformers which all had a helical conformation. These highly functionalised dendrimers have chiral cavities which could be useful for enantioselective host-guest complexations and catalytic transformations.

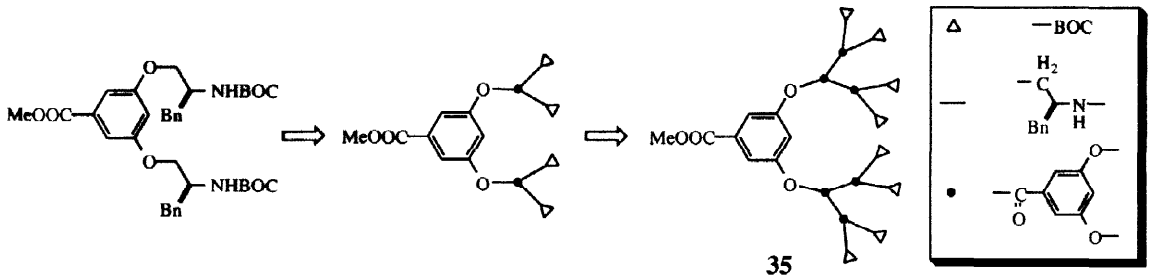
Vögtle reported the preparation of chiral dendrimers **31** bearing planar chiral paracyclophane moieties on the surface.[58] Treatment of amino-terminated poly(propyleneimine) dendrimers of various generations with optically active paracyclophane **32** gave **31** in good yields. From CD measurements, these dendrimers had nearly constant optical activity regardless of generation. These dendritic ligands could be transformed into the corresponding manganese complexes which were known to possess water splitting properties.



Reports on optically active amino acid-based dendrimers have appeared. Mitchell[59] and Ranganathan[60] independently disclosed the use of (L)-glutamic and (L)-aspartic acids as chiral branches in the construction of peptide dendrimers. While little chiroptical information was disclosed in Mitchell's work, the signs and magnitudes of the specific rotation did not follow any particular trend for both the aspartic **33** and glutamic **34** series prepared by Ranganathan. Since the branching patterns are unsymmetrical in these dendrimers, it is premature to assume that each chiral unit offers the same degree of chiroptical contribution to the overall macromolecular asymmetry.

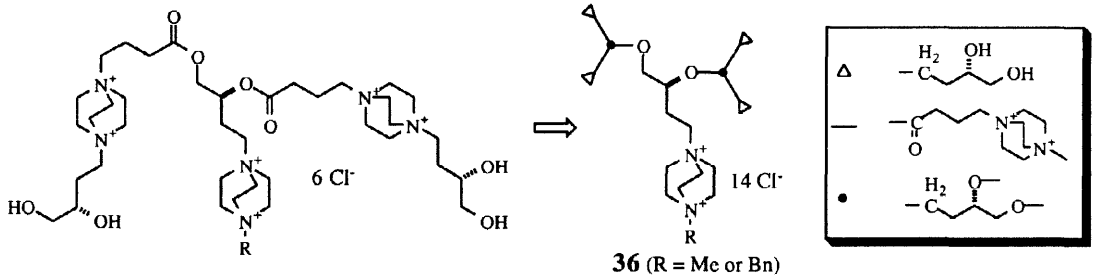


Very recently, Liskamp documented the use of phenylalaninol for the preparation of amino acid-based dendrimers having chiral units located both within and on the surface of the macromolecule.[61] Using standard peptide coupling procedure, a G3 peptide dendrimer **35** could be prepared in low yield. The optical activity of



this series of compounds remains essentially constant irrespective of dendrimer generation.

Cationic dendrimers **36** containing chiral (–)-1,2,4-butanetriol derived branches had been prepared by Engel.[62] They are useful materials for chiral ion exchange resins and supports for chiral capillary electrophoretic chromatography. Due to the unsymmetrical branching patterns, no structure-chiroptical relationship could be established.



36 (R = Me or Bn)

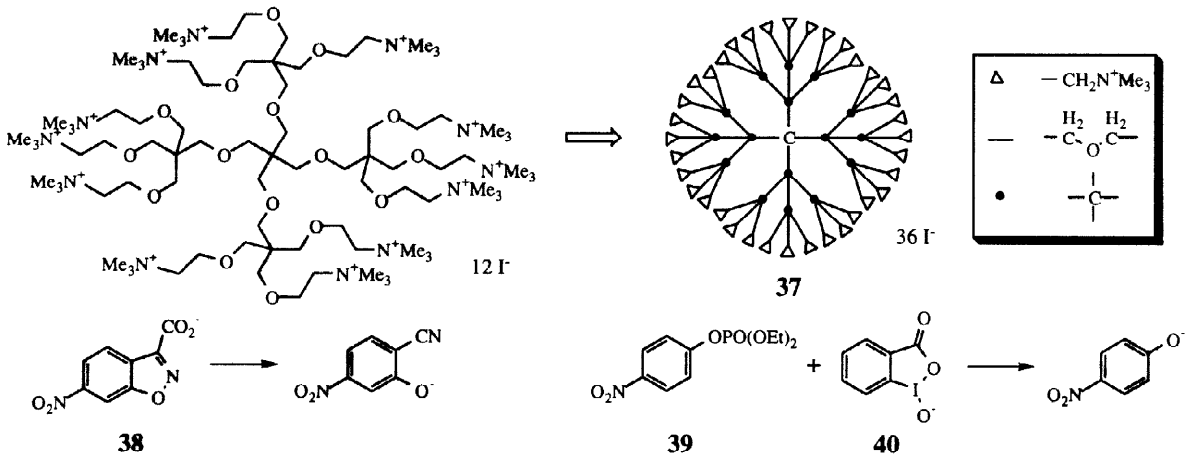
5.2 Catalytically Active Dendrimers

One of the important developments in dendrimer chemistry is the preparation of catalytically active dendritic systems, within which two broad categories have evolved. The first strategy involves those in which the catalytic sites are incorporated at the periphery of the dendrimer while in the second type, a catalytic site is encapsulated within a dendritic matrix. Both approaches have their own advantages and disadvantages. While the former strategy allows one to examine potential cooperative or allosteric effect amongst the catalytic centers, the latter offers opportunities to modulate catalyst reactivity and selectivity by dendrification.

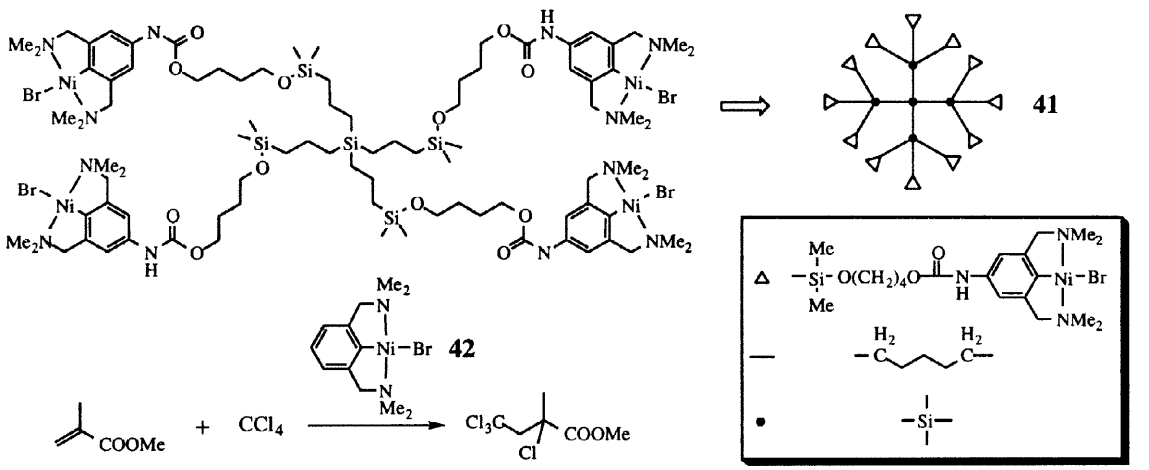
Multiple catalytic site systems

Typical examples of multiple catalytic centre systems were the polyether-based dendrimers **37** carrying catalytic quartenary ammonium ions on the surface.[63] They were prepared by a divergent protocol and were shown to accelerate the unimolecular decarboxylation of *p*-nitrobenzisoxazole-3-carboxylate **38** and the bi-molecular hydrolysis of *p*-nitrophenyl diphenyl phosphate **39** in the presence of *o*-iodosobenzoate ion **40**. Although both reactions were substantially slower than those catalysed by cationic polymeric colloids, however, positive cooperativity was observed for the decarboxylation reaction. Thus, while the G0 analog was not catalytic active, the analogous G1 dendrimer speeded up the reaction by 2 fold and G2 **37** by 20 fold. This result implied that the higher generation dendrimer was catalytically more reactive than the lower ones on a per catalytic unit basis. However, the mechanism of the rate enhancement remains to be explored.

Aryl nickel(II) complexes located at the periphery of a silane dendrimer provide the second example of multiple centre catalysts.[64] A number of diamino aryl moieties were attached to a polysilane core followed by

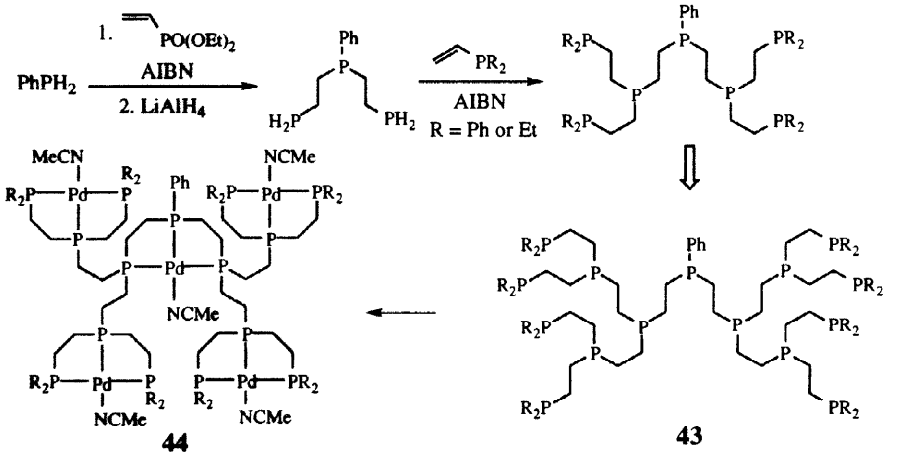


an oxidative addition of nickel tetrakis(triphenylphosphine) into the diamino aryl units to furnish the active catalyst **41** as an orange solid. This homogeneous catalyst system was found to be highly effective in promoting the Kharash addition reaction of polyhaloalkanes to olefins. In a comparative study between the catalytic activities of the dendrimer **41** and the monomeric complex **42**, a 20% reduction of catalyst reactivity was noted for catalyst **41**. However, its recycling potential which is an important factor in large scale applications far outweighs this disadvantage.

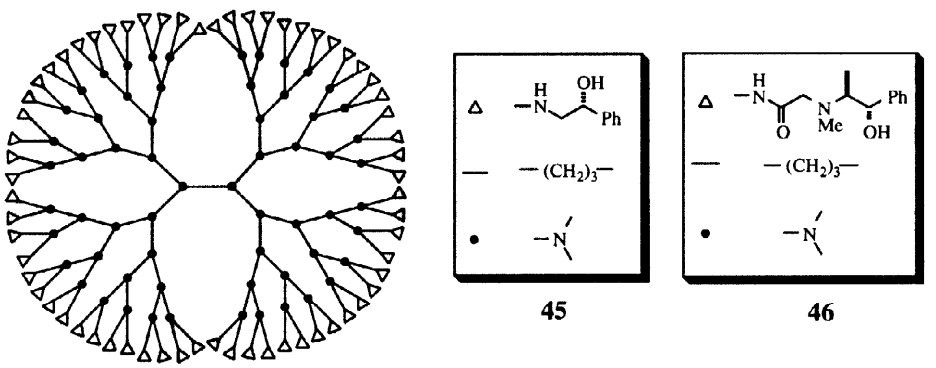


Using the free-radical addition reaction of a primary phosphine to a vinylphosphonate and subsequent reduction of the adduct with $LiAlH_4$, DuBois reported the divergent preparation of dendritic organophosphine ligands **43** for use in the electrochemical reduction of CO_2 to CO catalysed by the corresponding palladium complexes **44**.[65] Metallation of the polydentate ligand **43** turned out to be a complex process in which **44** appeared to be the dominant species in solution. These dendritic catalysts possessed almost the same catalytic reactivity and selectivity as the analogous mono-palladium catalysts.

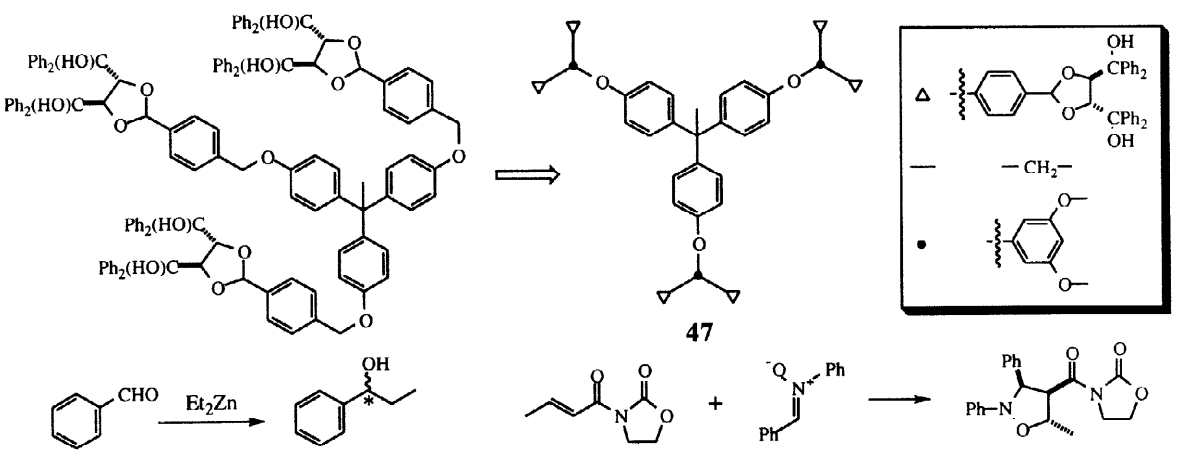
To exploit the usefulness of chiral dendritic catalysts in asymmetric synthesis, optically active amino alcohol-terminated dendrimers **45** were synthesised and used as ligands for the asymmetric addition of diethyl zinc to benzaldehyde.[66] As it turned out, the reaction enantioselectivity diminished with increasing catalyst generation, starting from 10% e.e. with G0 and reaching essentially 0% with the G5 catalyst. Conformational



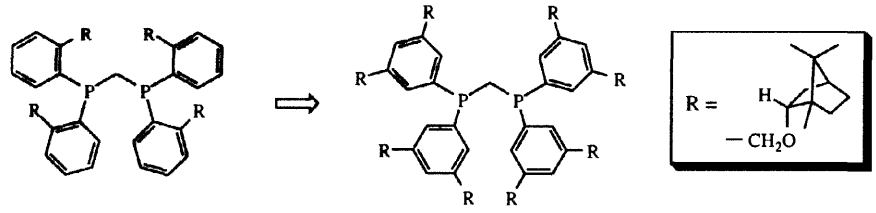
rigidity and surface crowding of the catalytic shell are the possible causes for the drop in the asymmetric induction. Surprisingly, no enantioselectivity was observed in the same reaction catalysed by ephedrine-modified poly(propyleneimine) dendrimers **46**.



Seebach reported the preparation of chiral polyether dendritic ligands **47** having TADDOL units on the dendrimer surface.[67] The corresponding titanium derivatives were capable of promoting the nucleophilic addition of diethylzinc to benzaldehyde and the [3 + 2] cycloaddition between 3-crotonyl-1,3-oxazolidino-2-one and (*Z*)-*N*-benzylidenephenylamine *N*-oxide. No significant improvement of diastereo- and enantio-selectivity was noted for this series of catalysts as compared to non-dendritic titano-TADDOL derivatives.



Single catalytic unit systems



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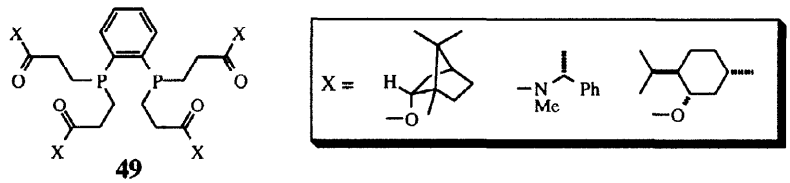
Placing a catalytic centre in the interior of a dendrimer with the aim of modulating catalyst reactivity represents a second approach toward catalytic dendrimer design. A common synthetic protocol is to append one or several dendritic fragments to a catalytic reactive functionality. Brunner provided the first example by synthesising a series of chiral "expanded ligands" for use in asymmetric catalysis.[68] These dendritic ligands **48** were prepared by attaching several optically active (–)-borneol moieties to an α,ω-bis-(phosphino)alkane. Unfortunately, the product e.e. from the rhodium-**48** complex-catalysed hydrogenation of *N*-acetamidocinnamic acid was disappointingly low (2 ~ 5 %). Subsequent work with dendritic ligands **49** and **50** gave no promising results with regard to product e.e. on the rhodium-catalysed hydrogenation, palladium-catalysed allylation or copper-catalysed cyclopropanation reactions.[69]



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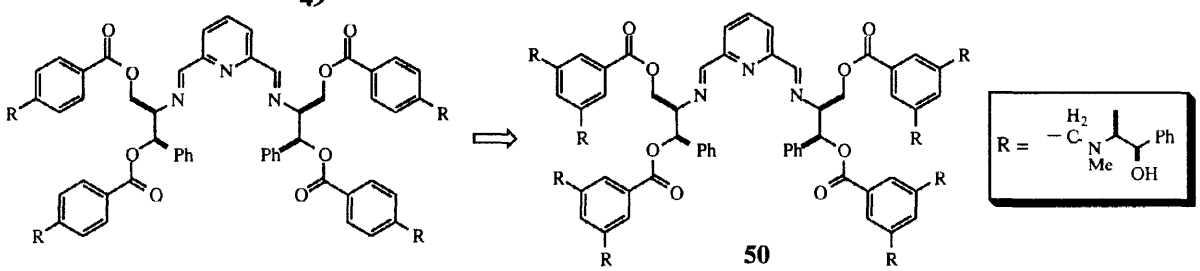

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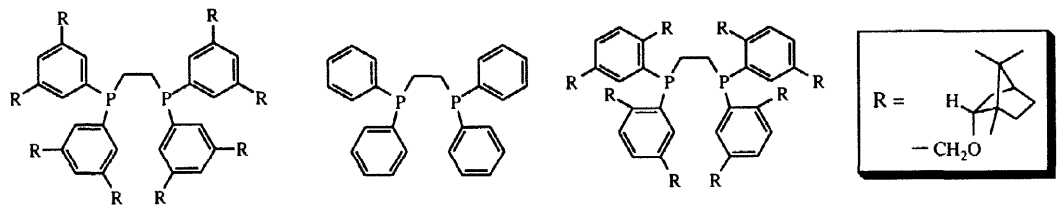
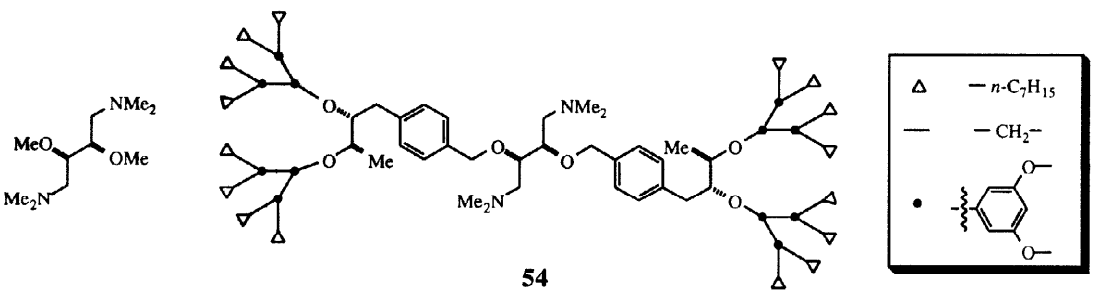
Gratifyingly however, the rate of the rhodium-catalysed hydrogenation of acetamidocinnamic acid was enhanced in the presence of an expanded ligand **51** relative to a non-dendritic analogue **52**.[70] This rate acceleration was shown to be dependent on the stereospatial arrangement of the dendritic branches on the bis-(phosphine) core, as the corresponding hydrogenation reaction involving a 2,5-substituted dendritic ligand **53** exhibited a 300 fold rate retardation. However, the enantioselectivities of the reactions were extremely poor.



51 **52** **53**

Seebach recently described the preparation of a dendritic analog of (*S*,*S*)-1,4-bis(dimethylamino)-2,3-dimethoxybutane (DDB). The target compound **54** was used as a mediator to improve the enantioselectivity of the [2 + 2] cycloaddition of ketene to chloral, nucleophilic 1,4-addition of thioacetic acid to cyclohexenone and nucleophilic addition of butyllithium to benzaldehyde.[48b] Both the enantioselectivities and yields of these catalysed reactions matched well to those mediated by DDB itself.



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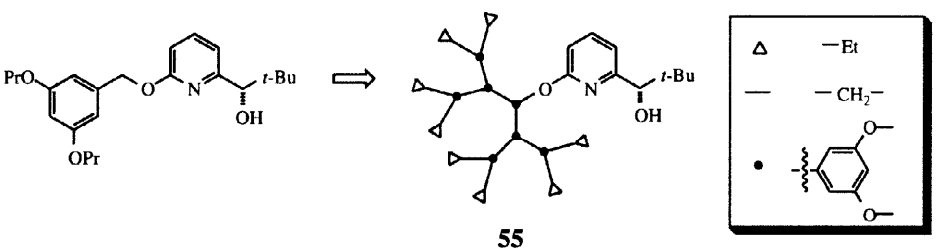
Although higher generation chiral dendritic catalysts tend to give products with poor enantioselectivity, the chiral pyridinyl alcohols **55** synthesised by Bolm have proved to be an exception.[71] These dendrimers were prepared by tethering a chiral amino alcohol to a series of polyether dendrimers and were used as ligands in the asymmetric diethylzinc alkylation of benzaldehyde. No significant changes in enantioselectivity (~88%) were found using ligands of different generations. However, slightly lower e.e.'s (~80%) were noted for the higher generation catalysts when the catalytic loading was low.



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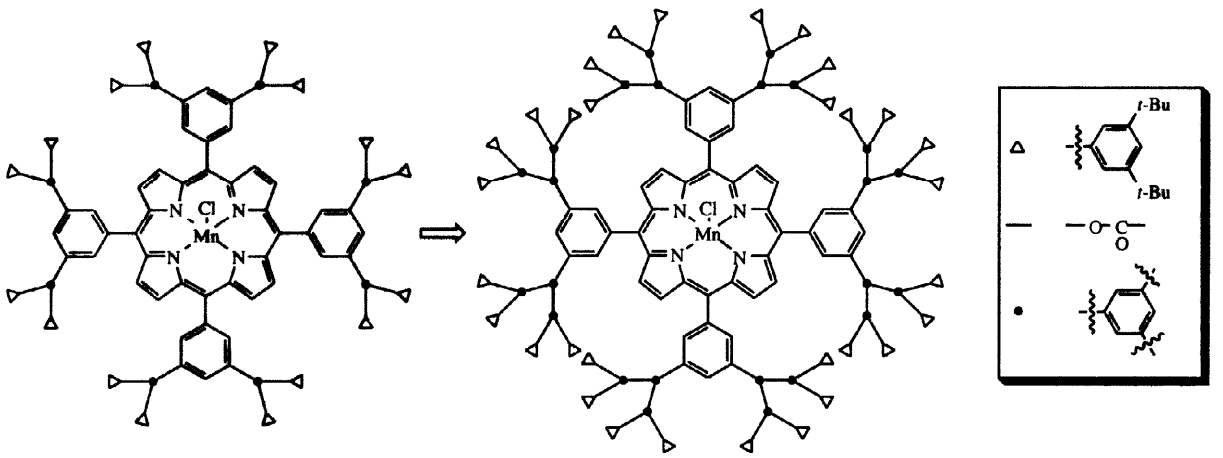
The placement of catalytic reactive functionalities inside the interior of a dendritic matrix is similar to the creation of an active site within an enzyme pocket. Similar to enzyme molecules, such dendritic catalytic systems are therefore expected to provide enhanced substrate selectivity. Inspired by the successful applications of metalloporphyrins in the regio- and enantio-selective epoxidation of olefins, Moore reported the use of manganese containing dendritic porphyrins **56** in the substrate selective epoxidation of olefins.[72] The catalysts were constructed by linking several polyether dendritic fragments to the *meso*-positions of a porphyrin followed by metallation to form a cage structure protecting the metal centre from oxidative degradation. Using iodosylbenzene as the oxygen donor, the G2 catalyst **56** exhibited considerable selectivity towards the least hindered double bond of unconjugated dienes such as 1,4-heptadiene and limonene when compared with the unsubstituted 5,10,15,20-tetraphenylporphyrinato-manganese(III) cation. Similarly, in the epoxidation of a mixture of 1-alkene and cyclooctene, the G2 metalloporphyrin showed two to three-fold higher selectivity towards 1-alkenes, relative to the nondendritic catalyst. The increase in selectivity was attributed to a steric factor rather than an electronic factor.



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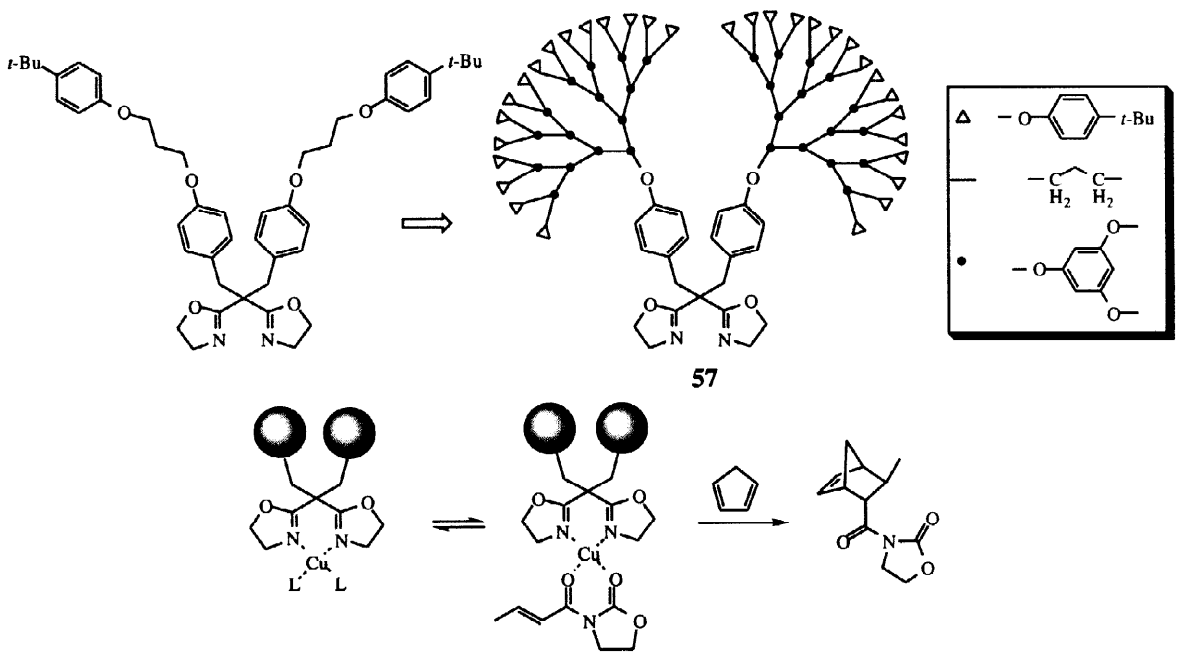
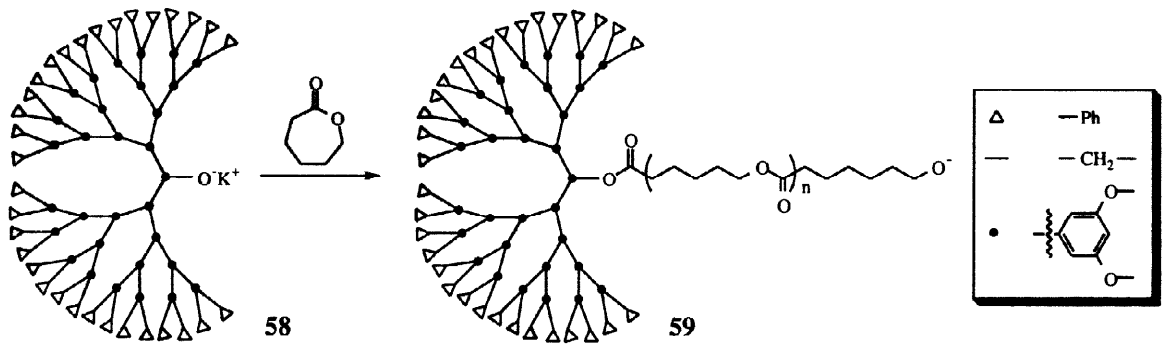
In a study designed to address the effect of the size of dendritic sectors on the reactivity of a catalytic centre, Chow reported a kinetic and mechanistic study of the Diels-Alder reaction catalysed by a series of dendritic bis(oxazoline) ligands **57** in the presence of copper(II) triflate.[73] Two important mechanistic steps were identified in this Diels-Alder reaction. First, a reversible binding between the catalyst and the dienophile. Secondly, a bimolecular reaction between the catalyst-dienophile complex and the diene. Based on kinetic studies, it was established that a larger dendritic sector had a stronger destablisation effect on the binding strength between the catalyst and the dienophile. On the other hand, the bimolecular rate constant remained the same from G0 to G2, but dropped suddenly for G3. These observations were rationalised by a folding-back of the dendritic sectors toward the catalytic unit at G3, resulting in an *exo*- to *endo*-active site transition which hindered the approach of the diene toward the catalyst-dienophile complex. For the earlier generations, due to the smaller size of the respective dendritic sectors, the catalytic center remained exposed to the surroundings and thus the bimolecular rate constant was insensitive to the generation.

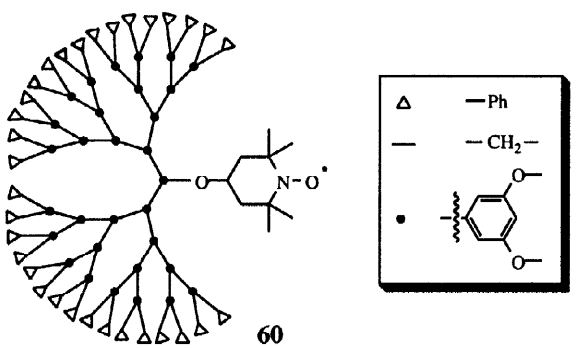


57

Figure 11. Mechanism of the bis(oxazoline)copper(II) catalysed Diels-Alder reaction



Dendrimers can also be used as macroinitiators for polymerisation reactions.[74] For example, in the presence of a G4 polyether dendritic alcoholate **58**, a high molecular weight (MW 3×10^5) hybrid polymer **59** was obtained from the anionic polymerisation of ε-caprolactone. In contrast, polymerisation with a G1 alcoholate gave only oligomers of ε-caprolactone, which were formed by intramolecular transesterification of the propagating polymer chain. Due to steric factors, such intramolecular back-biting side cyclisations were greatly suppressed when a bulky G4 initiator was used. Dendritic radical **60** containing a TEMPO radical has also been utilised as an initiator for the radical polymerisation of styrene, although the polymerisation control was not better than using TEMPO itself.[75]



5.3 Electrochemically Active and Conductive Dendrimers[76]

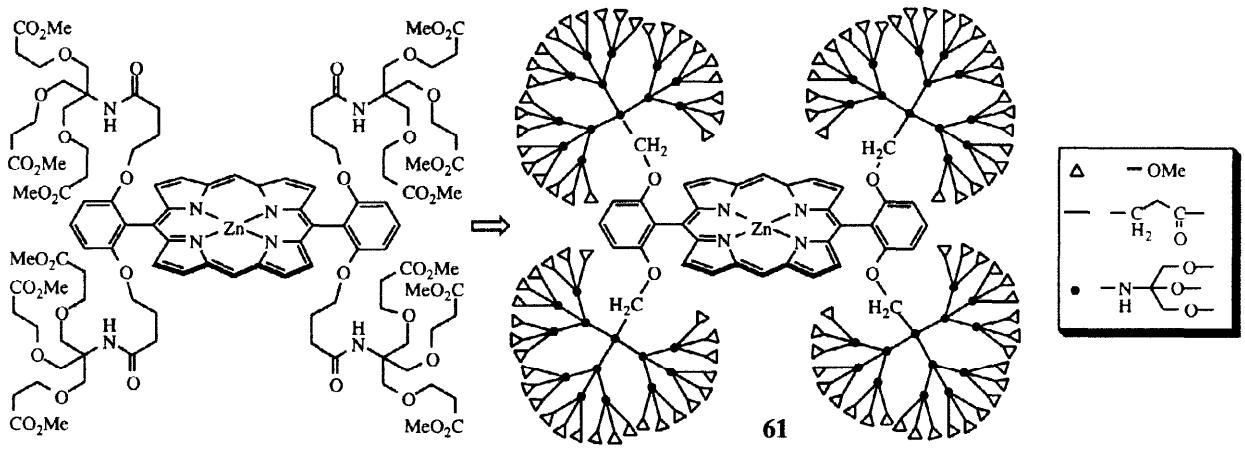
Electrochemically active/conductive dendrimers represent another area of potential interest in dendrimer study. A variety of redox-active organic and organometallic functionalities have been blended into different dendritic architectures. These structurally defined redox systems were prepared with objectives to study the dynamics of electron transfer at surfaces or within restricted reaction spaces, to explore new polymeric materials for electron storage or electron conducting/semiconducting applications, and to simulate biological redox processes. Because electron transfer reactions can also be initiated by photochemical means, some electrochemically active dendrimers are also photochemically active. In this section we will focus on redox processes which are initiated by electrochemical methods such as cyclic voltametry (CV), electrolysis *etc.*. Electron transfer processes triggered by photochemical means will be discussed in Section 5.4.

In similar fashion to catalytic dendrimers, redox active dendrimers can be broadly divided into two categories; those containing a single redox-active unit and those having multiple ones. The former plans to address how electron transfer behavior can be modulated by the physico-chemical properties and the shielding

effect of the dendritic sector, while the latter plans to examine the global redox behavior, whether independent, interactive or cooperative, of multiple redox units in multi-electron transfer processes.

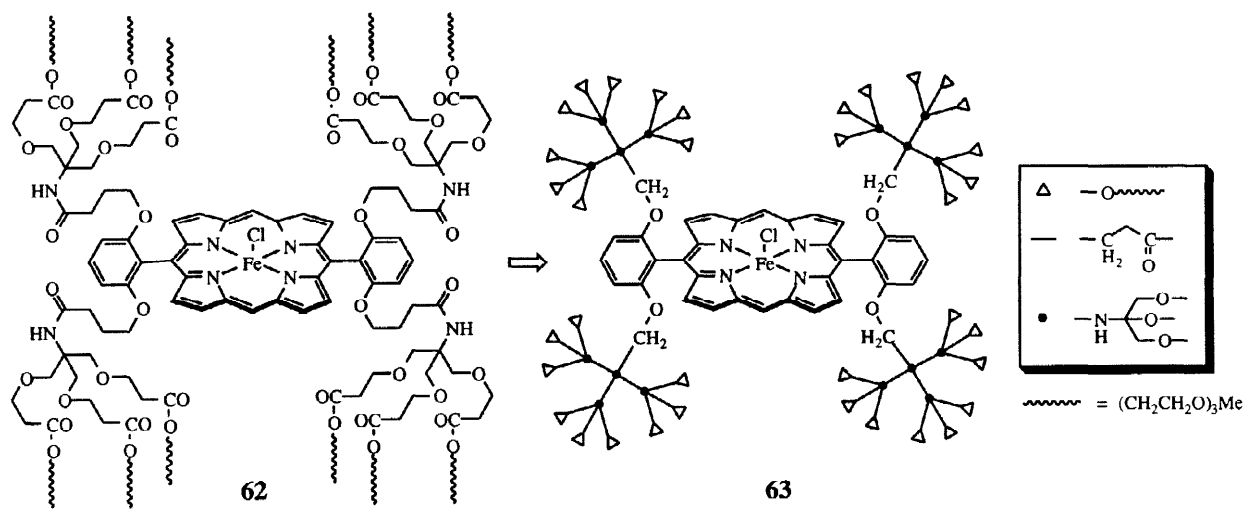
Single redox site systems

Encapsulated electroactive functionalities are of important relevance to the understanding of biological electron transfer processes because a number of metalloproteins also have their redox center buried within a polypeptide envelope. Diederich first described the electrochemical behavior of a dendritic series of zinc-porphyrins **61** in which the porphyrin nucleus was surrounded by four polyamide-based dendritic sectors of different generations.[42a] The modulation effect of the increasingly electron-rich dendritic pendants on the redox behavior of these metalloporphyrins was manifested by a gradual decrease of both of the oxidation and reduction potentials toward the higher generation. Hence, the electron rich dendritic sectors exerted their influence by discouraging the addition of electron but facilitating electron removal from the ring system. Furthermore, the redox processes of the higher generation compounds tended to be increasingly irreversible.



61

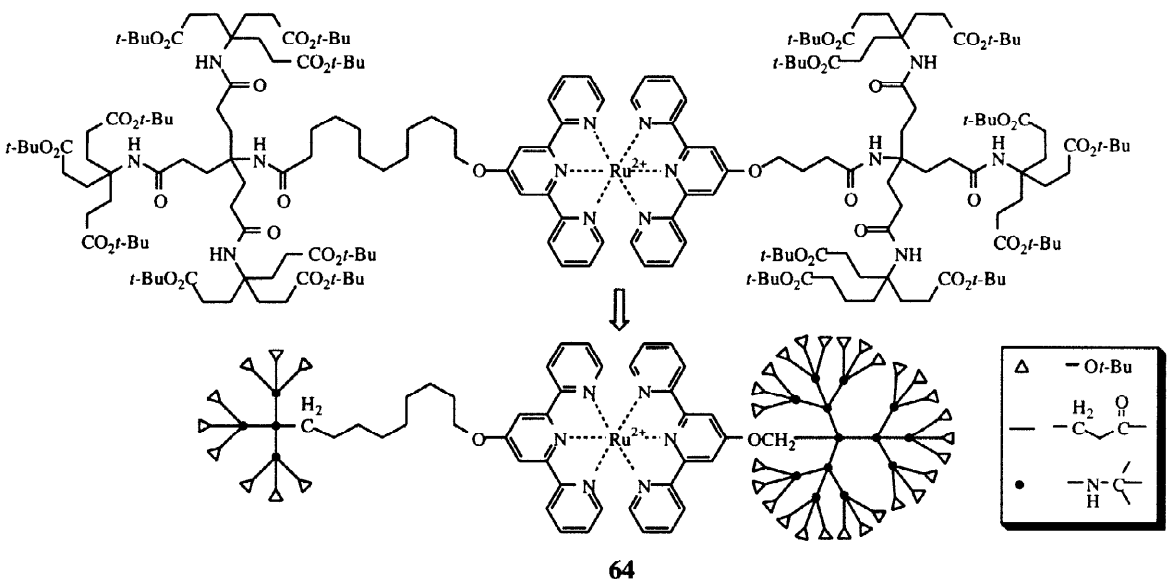
To examine the solvent effect on the redox behavior of metalloporphyrins, Diederich extended his work by preparing a new series of aqueous and organic soluble dendritic iron porphyrins **62** and **63**.[42b] The water solubility of these dendrimers was obtained by using the highly hydrophilic triethyleneglycol monomethyl



62 63

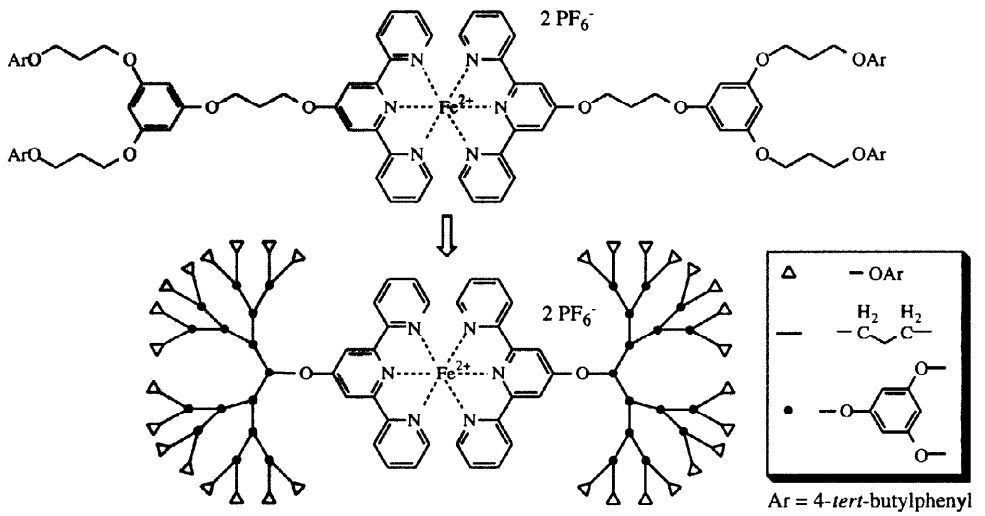
ether end groups attached to the zinc porphyrin core. CV studies indicated that the redox potentials of these iron porphyrins were solvent dependent. In CH_2Cl_2 solution, the potential difference for the Fe^{3+}/Fe^{2+} couple between the G1 **62** and G2 dendrimer **63** was 80 mV, while in aqueous solution this difference was increased by more than four fold (420 mV). It was suggested that in CH_2Cl_2 solution, the iron porphyrins in the exposed **62** and the densely packed **63** experienced very similar microenvironments; hence similar potentials for the Fe^{3+}/Fe^{2+} couple were measured. In water solution, the sterically less hindered dendritic shell of **62** could not impede aqueous solvation of the iron porphyrin centre, whereas the sterically demanding hydrophobic dendritic superstructure in **63** shielded off water molecules from the oxidised, more charged ionic state. This large difference in the degree of aqueous solvation of the porphyrin nucleus thus led to the large difference of observed redox potential between the two dendritic metalloporphyrins.

In contrast to Diederich's findings, heteroleptic ruthenium(II) complexes **64** reported by Newkome did not exhibit any generation dependent shift of redox potential.[77] Instead, the redox profiles of the ruthenium and bis(terpyridine) electrophores became increasingly irreversible as the size of dendritic sectors increased. The rationale for this increasingly irreversible voltammetric response toward higher generation remains unknown.



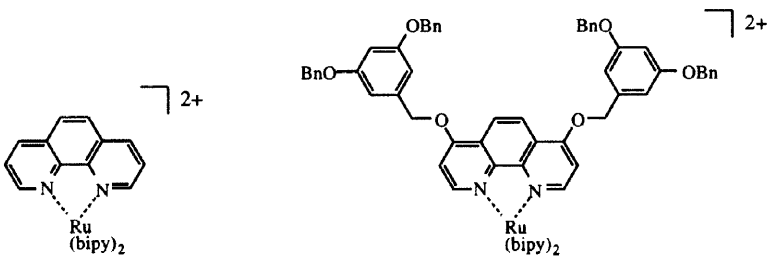
64

In a related model study by Chow,[78] dendritic bis(terpyridine) iron(II) complexes **65** exhibited similar CV profiles to those of **64**. The absence of a flexible hydrocarbon linker in model **65**, in comparison to **64**, reduced the conformational flexibility of the dendritic moieties with respect to their positions around the iron centre. Such structurally rigid systems could be used to correlate the redox property change to the molecular dimension of the dendritic fragments more precisely. According to CV examinations, the redox potentials of these metallodendrimers were generation independent. In line with Newkome's results, the reversibility of the redox reactions decreased with increasing generation number. This decrease of reversibility was rationalised by the increasing insulating effect of the larger polyether dendritic sectors, which hindered the electron-transfer process between the terpyidine-iron(II) complex and the electrode surface. X-ray photoelectron spectroscopic measurements showed that the solid-state coordinating environments of the iron(II) ion of different generations were very similar.



65

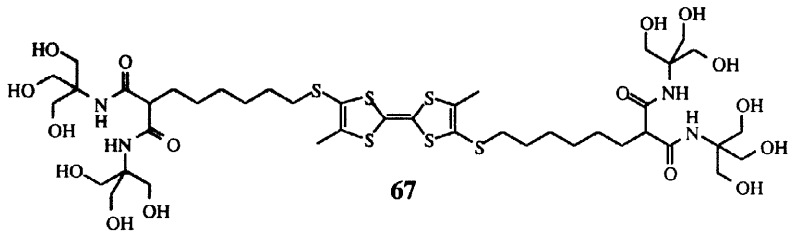
In contrast to compounds **64** and **65**, ruthenium(II) complexes **66** containing a dendritic polyether-substituted 1,10-phenanthroline (phen) ligand exhibited generation dependent redox behavior.[79] These complexes are known to undergo one metal-centered oxidation and three ligand-centered reduction processes. Owing to the better electron donating power of the polyether-based dendritic phen ligand, the metal oxidation process was shifted toward to a less positive potential when compared with that of the nondendritic $[Ru(bipy)_2(phen)]^{2+}$ complex (bipy = bipyridine). In a similar manner, the reduction potentials of the two residual bipy ligands were moved to slightly more negative values, as compared with those of $[Ru(bipy)_2(phen)]^{2+}$. As the dendritic ligands were better electron donors than phen, the third reduction process, which was due to the phenanthroline ligand, occurred at a less negative potential. Similar to those of **64** and **65**, the second and third reduction waves of **66** were not completely reversible.



$Ru(bipy)_2(phen)^{2+}$ **66**

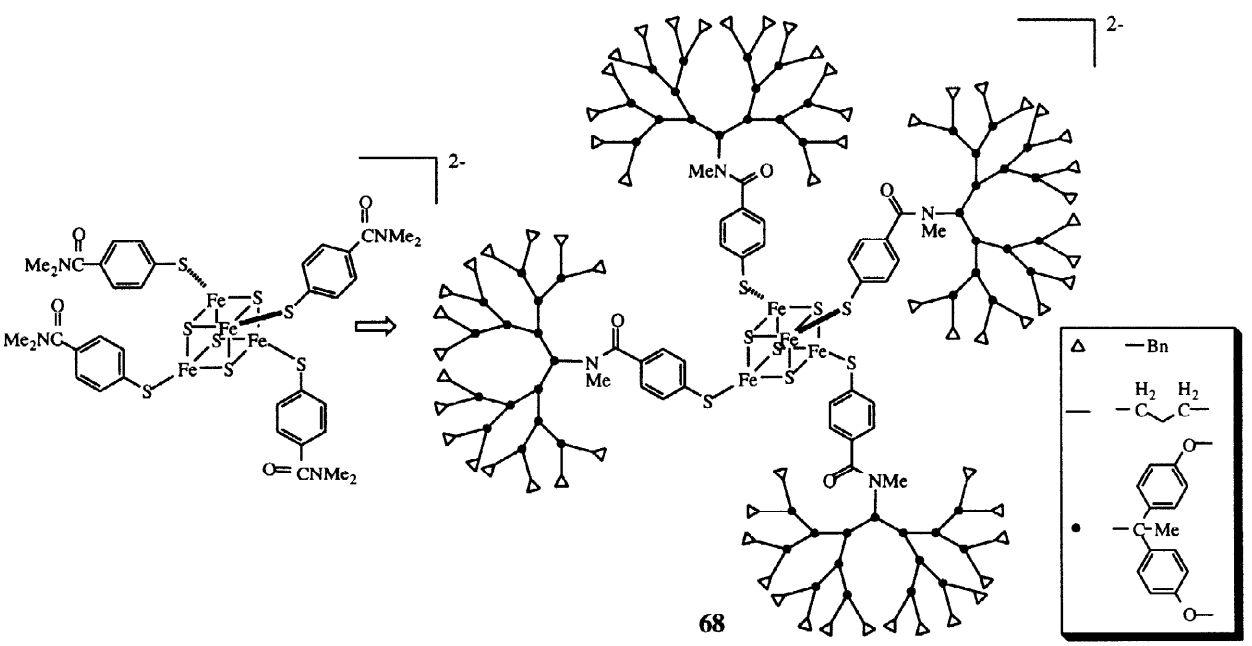
Instead of changing the electron transfer properties of redox active centers by controlling their locations within a dendritic matrix, one can also tune their redox behavior by modifying their stacking properties in the solid/solution state. Jørgensen reported the synthesis and self-assembling properties of a dendritic tetrathiafulvalene (TTF) **67**.[80] This compound is made up of a central hydrophobic TTF moiety surrounded by hydrophilic polyols. Such dumbbell-shaped molecules are known to form strings of helical structures with the hydrophobic core stacking on top of each other.[81] Indeed, atomic force microscopy revealed that compound **67** had string-like superstructures with lengths of the order of microns and diameters ranging from thirty to

several hundred nanometers. Despite this stacking behavior, the redox potentials of the TTF moiety were not significantly altered by the dendritic polyols.



67

A number of hybrid organic/inorganic dendritic architectures having an iron-sulfur cluster core surrounded by a polyether dendritic envelope have recently been disclosed by Gorman.[82] These molecules were synthesised *via* a ligand exchange reaction between aromatic dendritic thiols with the aliphatic thiols in FeS clusters of the formula $[Fe_4S_4(SR)_4]^{2-}$. These hybrid dendritic molecules appear as black, shiny, slightly air-sensitive solids and are readily soluble in organic solvents such as dichloromethane and THF. The CV profiles of these molecules were very similar to those of Diederich's. The G4 dendrimer **68** was found to have a more negative reduction potential in comparison to the lower generation ones. This was attributed to the increased steric bulk of the higher generation ligand, which rendered the molecule both kinetically and thermodynamically more difficult to reduce. The progressively larger voltage difference between the redox peak separation toward the higher generation, further supported the increasing difficulty of the reduction process.



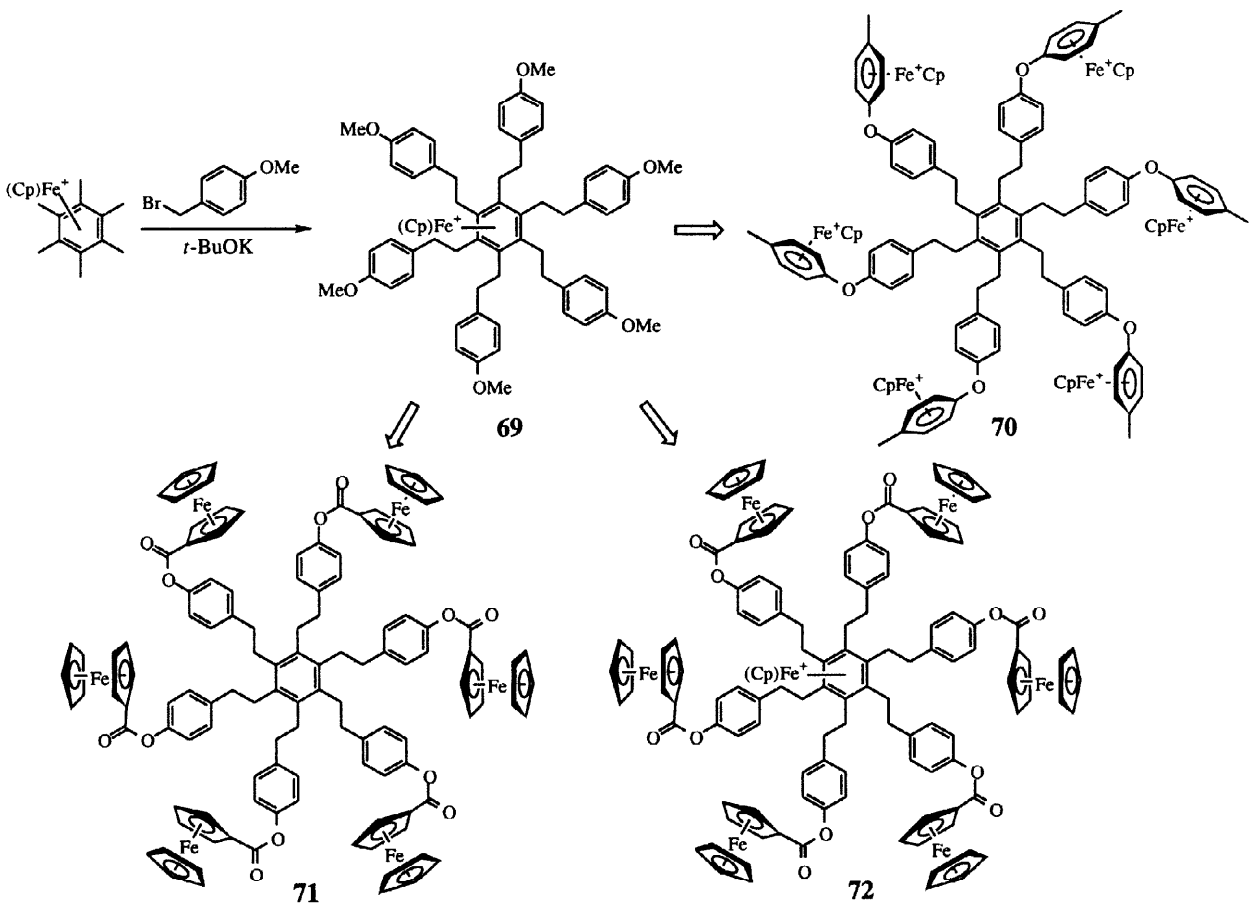
68

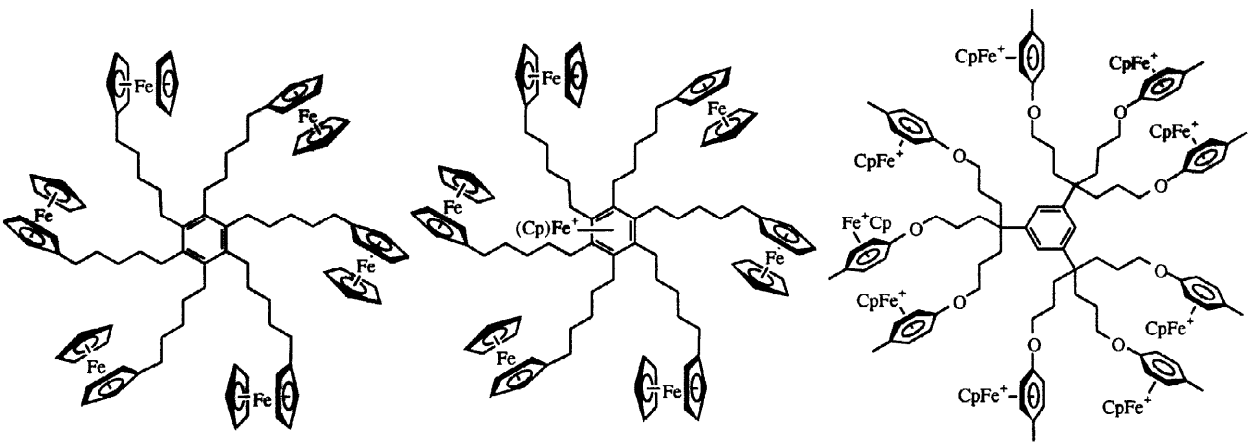
Multiple redox center systems

The most widely studied multiple redox-active dendritic systems are those involving ferrocene and its derivatives.[83] The ferrocenyl unit has been a popular building block for redox active materials due to its high chemical stability, reversible redox behavior, and ease of derivatisation. It is also used as a component in molecular devices such as molecular ferromagnets, molecular sensors and non-linear optical materials.

Astruc reported a number of metallodendritic systems containing multiple ferrocenyl units for use as multielectron redox catalysis.[84] The key intermediate involved was a multifunctional aromatic compound **69** which was prepared *via* polyalkylation of the $Fe(Cp)^+$ complex of hexamethylbenzene. Functional group conversion followed by attachment of different ferrocenyl appendages to this intermediate gave hexa-iron sandwich complexes **70** and **71** and the hepta-iron derivative **72**. The hexakis $[FeCp(arene)]^+$ dendrimer **70** exhibited a single reversible couple at -1.30 V due to the simultaneous transfer of six electrons. Similarly, only one oxidation wave at +0.78 V was observed for the other hexa-iron compound **71**, indicating that all six ferrocene units had the same oxidation potential. For the hepta-iron derivative **72**, the central $[FeCp(arene)]^+$ moiety gave a redox wave at -1.34 V. The redox potential of the six peripheral ferrocene units, in the presence of the central iron center, was slightly perturbed to +0.88 V. This result suggested that the central and surface iron centers were interacting with each other. However, the shift of redox potential appeared to be dependent on the structural environment around the metal vicinities. Thus, the redox potentials of the peripheral ferrocene units in both compounds **73** and **74** had the same value (+0.44 V), despite the presence of an additional $[FeCp(arene)]^+$ moiety in the latter compound.[85] The preparation of a triple branched nonairon complex **75** was also described by Astruc.[86] As expected, all nine peripheral $[FeCp(arene)]^+$ moieties appeared as independent redox centers and had the same redox potential at -1.37 V.

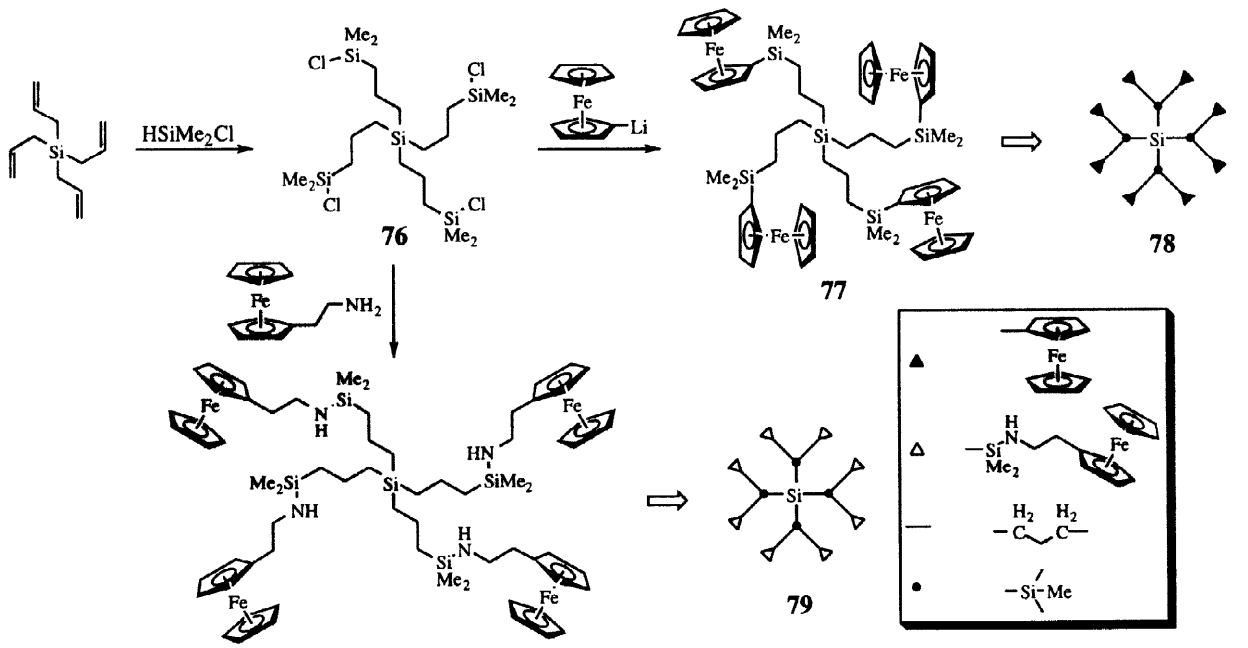
The second group of ferrocenyl metallodendrimers are those having the ferrocenyl moieties embedded in a dendritic organosilicon skeleton. The organosilane dendrimer was prepared by a divergent synthetic strategy involving a repetitive hydrosilylation/Grignard alkylation sequence. Reaction of the chlorosilane dendrimer





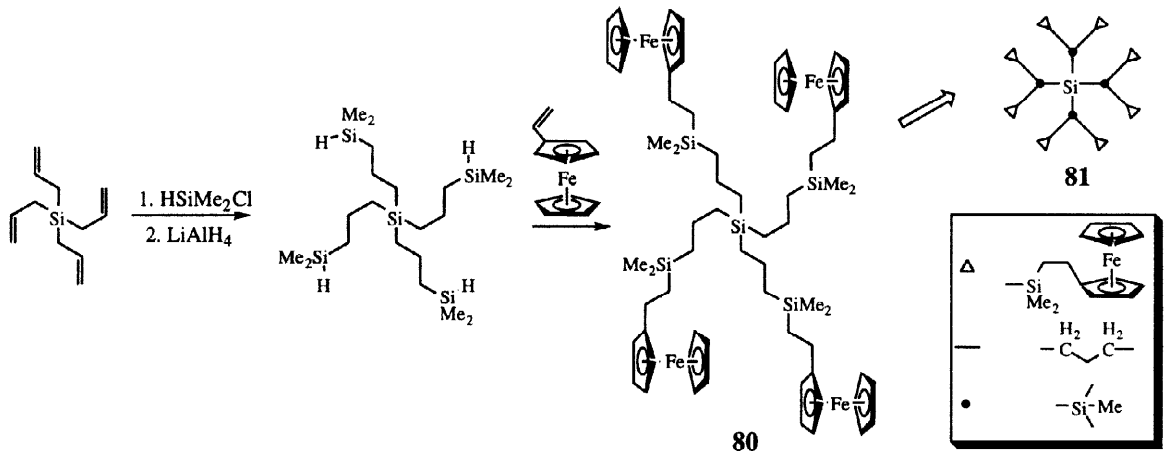
73 74 75

76, prepared *via* hydrosilylation of tetraallylsilane, with ferrocene-containing nucleophiles gave metallodendrimers **77** - **79** of various generations.[87] Electrochemical studies employing CV and differential pulse voltammetry techniques showed that all ferrocenyl units within each compound were non-interacting and had the same redox potential. Upon oxidation, these metallodendrimers could be deposited onto electrode surfaces to form electroactive materials with persistent redox properties and high stability toward electrochemical cycling.[88] The formal potential of these deposited films is nearly identical to the redox potential of the corresponding dendrimer in solution. The very narrow splitting between the oxidation and reduction peaks suggested that the rate of electron transfer was rapid on the experimental time scale.

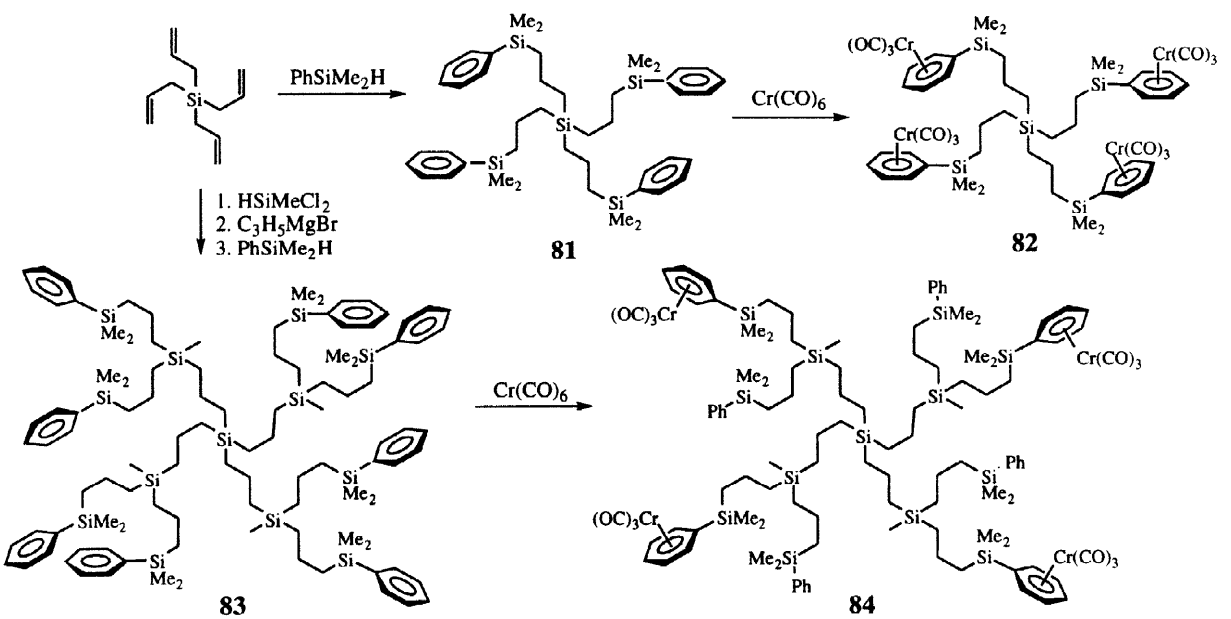


Ferrocenyl dendrimers **77** and **78** or their chain-extended analogues **80** and **81** could be immobilised on electrodes to serve as mediators or electron-shuttling redox couples in various amperometric enzyme electrodes.[89] Such sensors were prepared by pasting the metallodendrimer, glucose oxidase and graphite powder together and then cementing the composite to the end of an electrode. Because the enzyme, mediator

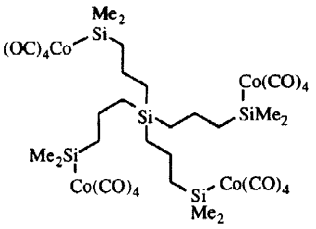
and sensing sites are located in close proximity, the current response to the enzyme substrate (glucose) is very rapid. In contrast to monomeric mediators such as ferrocene, these high molecular weight dendritic compounds have little tendency to diffuse away from the electrode surface and therefore long term durability can be sustained. Successive scans of the electrodes demonstrated that none of the dendritic mediators lost their electrochemical activity on repetitive cycling. The G1 octanuclear analogues **78** and **81** exhibited consistently higher sensitivity to glucose than the corresponding G0 tetranuclear compounds **77** and **80**. On the other hand, the chain-extended series **80** and **81**, displayed slightly higher sensitivities than **77** and **78**. This could be due to the higher flexibility of the ferrocene units in the elongated series, leading to a more efficient interaction between the dendritic relay and the enzyme molecules.



π-Arene chromium tricarbonyl units could also be tethered to the surface of the silicon-based dendritic network.[90] Thermal displacement of CO from chromium hexacarbonyl by a phenyl-terminated silane-based dendrimer **81** gave the tetranuclear organochromium complex **82**. Surprisingly, π-complexation of the octaphenyl compound **83** failed to give the anticipated octanuclear complex, instead a tetranuclear dendrimer **84**



was isolated as the major product. Other silane-based dendrimers having σ-bonded silicon-cobalt **85**, σ-bonded silicon-iron **86** and cobaltcene moieties **87** have also been introduced.[91] Similar to earlier findings, electrochemical studies on these metallodendritic systems indicated that the metal centers in these complexes were essentially non-interacting.



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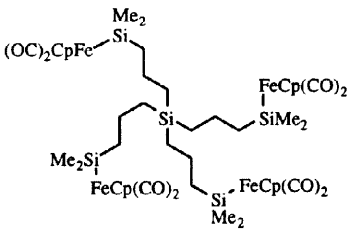

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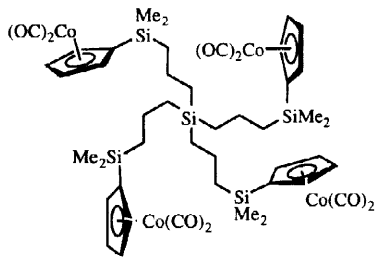
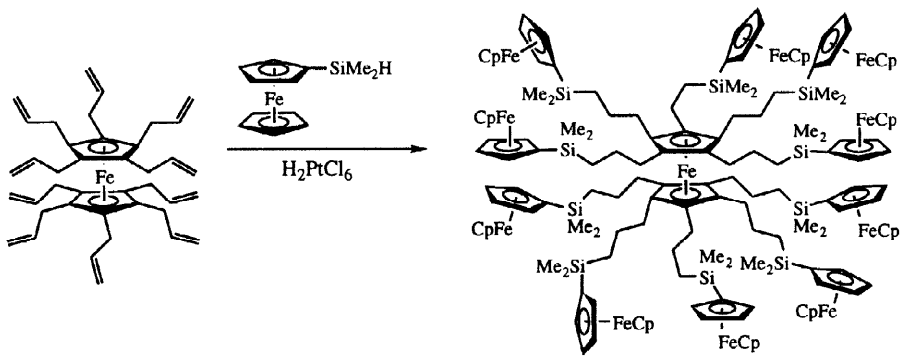


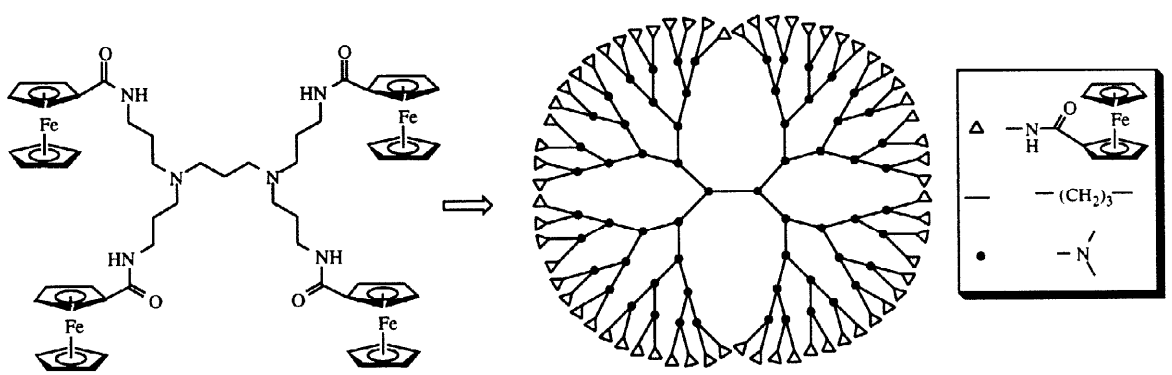
87

Hydrosilylation of deca(allyl)ferrocene **88** with dimethylsilylferrocene led quantitatively to the deca-ferrocenyl ferrocene dendrimer **89**.[92] This compound was contaminated with 10% of the isomeric compound resulting from hydrosilylation with opposite regioselectivity. CV studies of **89** showed that the outer ferrocenyl moieties were electrochemically equivalent at an oxidation potential of 0.40 V. The inner ferrocenyl moiety was oxidised at -0.10 V, which was typical of decasubstituted ferrocenes.



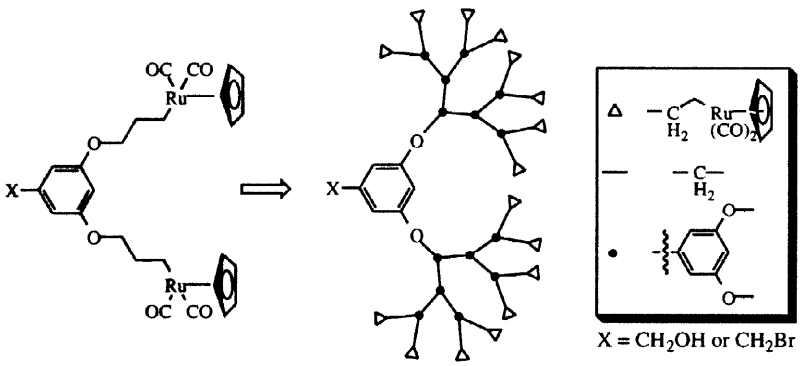
88 **89**

Organometallic dendrimers containing up to 64 peripheral ferrocenyl moieties (G5) **90** were recently described by Cuadrado.[93] This series of air-stable organoiron dendrimers were prepared by coupling excess ferrocenyl carboxylic acids to amino-terminated poly(propyleneimine) dendrimers. Based on ^{1}H-NMR data,



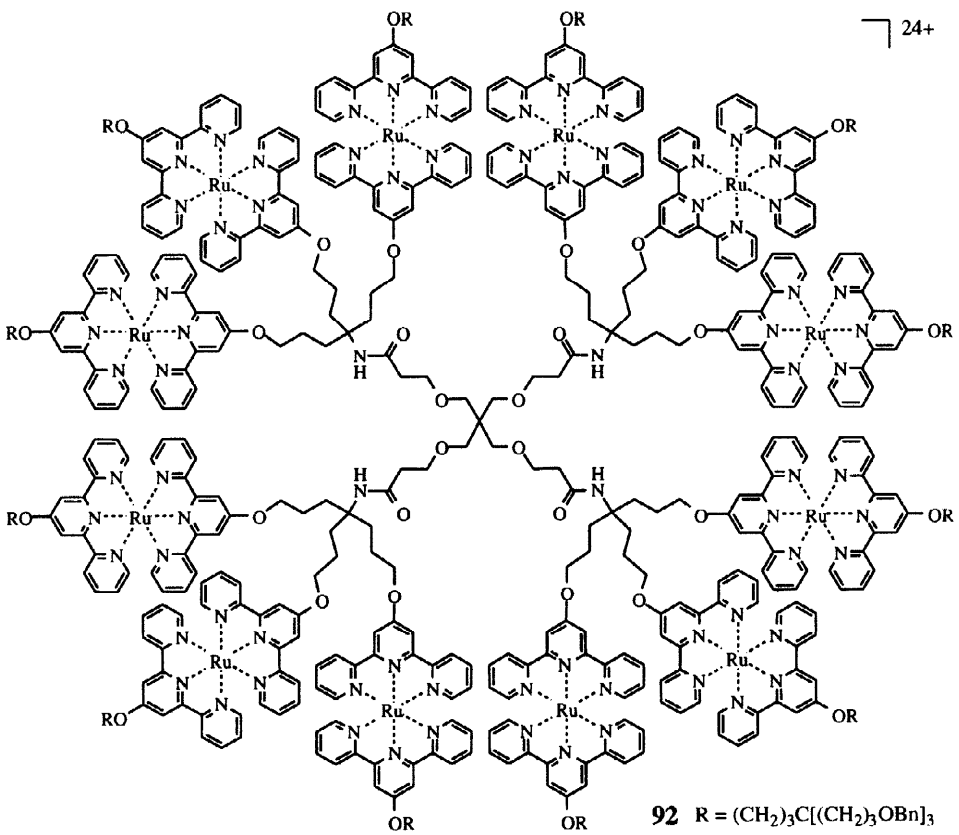
90

interbranch H-bonding interactions were strong for the higher generations, as the chemical shift of the amido protons moved increasingly downfield (δ from 6.8 → 7.7) on going from G1 to G5. The increase in the H-bonding interaction for the higher generation dendrimers is probably due to a closer contact between the peripheral ferrocenyl moieties on adjacent dendritic branches. As anticipated, all ferrocenyl moieties attached to the dendritic surfaces behaved independently and were oxidised at the same redox potential.



91

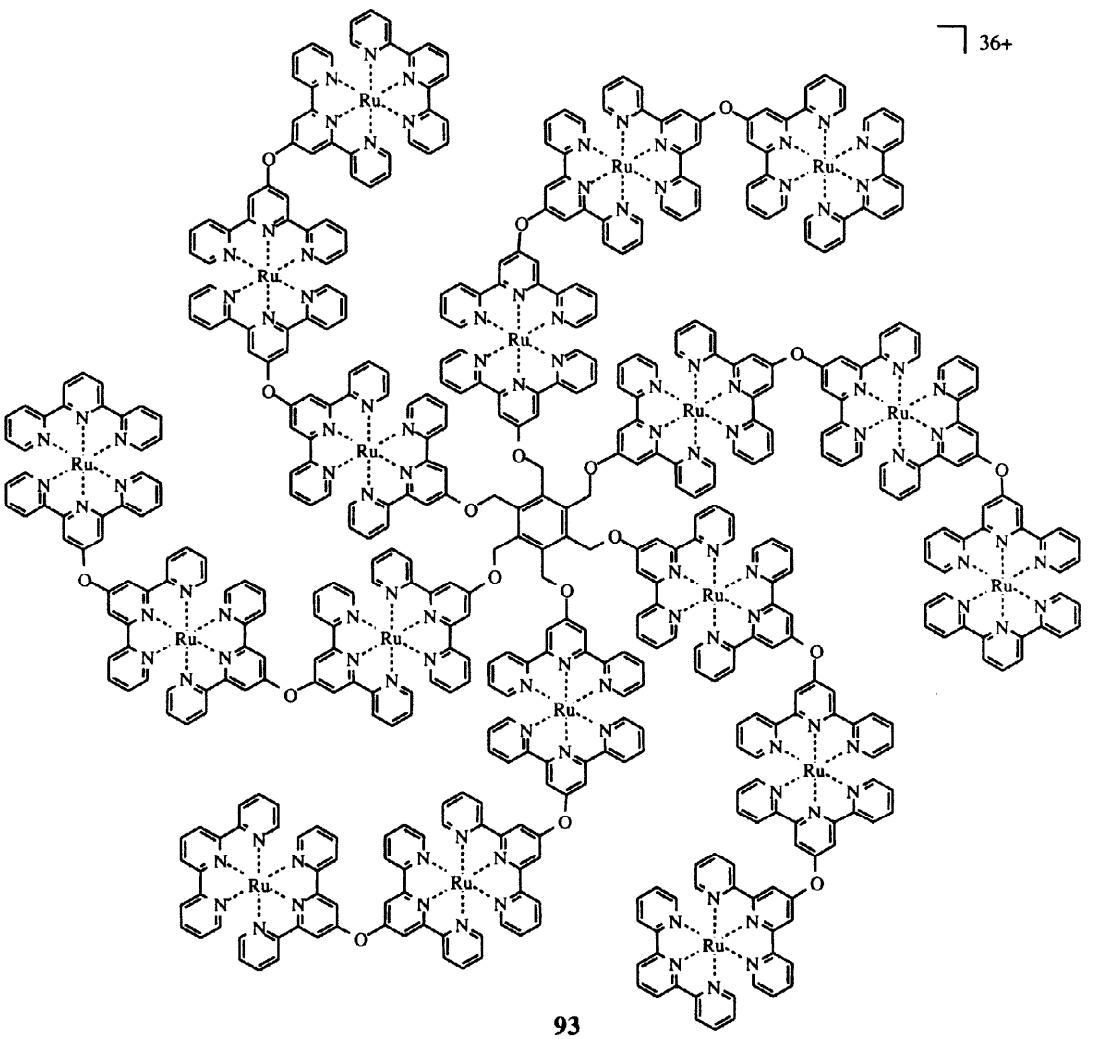
Metallodendrimers containing cyclopentadienyl ruthenium moieties on the surface have also been synthesised.[94] Using 3,5-dihydroxybenzyl alcohol as the branching monomer, successive generations of metallodendritic fragments up to G3 **91** were prepared by a convergent approach. The structures of these organoruthenium dendrimers were established by ^{1}H-NMR spectroscopy. However, attempts to characterise them by mass spectroscopic techniques were unsuccessful although their molecular sizes could readily be estimated by SEC. No redox data were reported in the study.



92 R = $(CH_2)_3C[(CH_2)_3OBn]_3$

Metallodendrimers containing polypyridine-based ligands represent another popular group of redox responsive dendritic systems. Polypyridine ligands can form complexes with a variety of metal ions with interesting redox and photophysical properties.[95] Most importantly, all of these properties can be fine tuned within rather broad ranges by changing either the ligands and/or the ligand substitutents. Polypyridine metal complexes are readily prepared by mixing polypyridine ligands and metal ions together. The resulting complexes are extremely stable with no evidence of ligand exchange. They also play an important role for the construction of self-assembly dendritic systems.

Several low generation metallodendrimers were prepared by metal complexation of dendritic terpyridine (terpy) ligands. For example, Newkome and Constable reported the synthesis of a red crystalline dodeca-ruthenium heteroleptic bis(terpy) macromolecular complex **92**.[96] This compound was prepared by coupling of twelve (terpy)$RuCl_3$ units to a polyamido-based dendritic core containing twelve substituted terpy ligands on the surface. The CV properties of this dodecanuclear complex were not reported in this study. Constable later elaborated this chemistry to the preparation of snowflake-like metallodendrimers bearing six directional **93**[97] and three directional skeletons **94**.[98] Electrochemical studies of these compounds were hampered by their strong adsorption to the surface of glass carbon or platinum electrodes. Nonetheless, for the three directional ruthenium dendrimer **94**, only a single broad CV peak was observed. On the other hand, the hexadirectional



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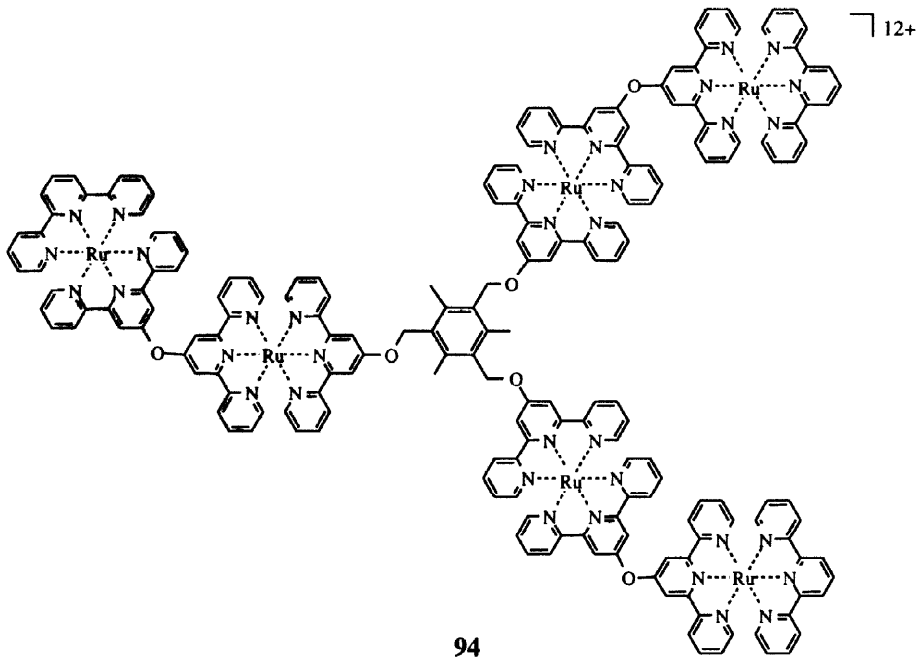
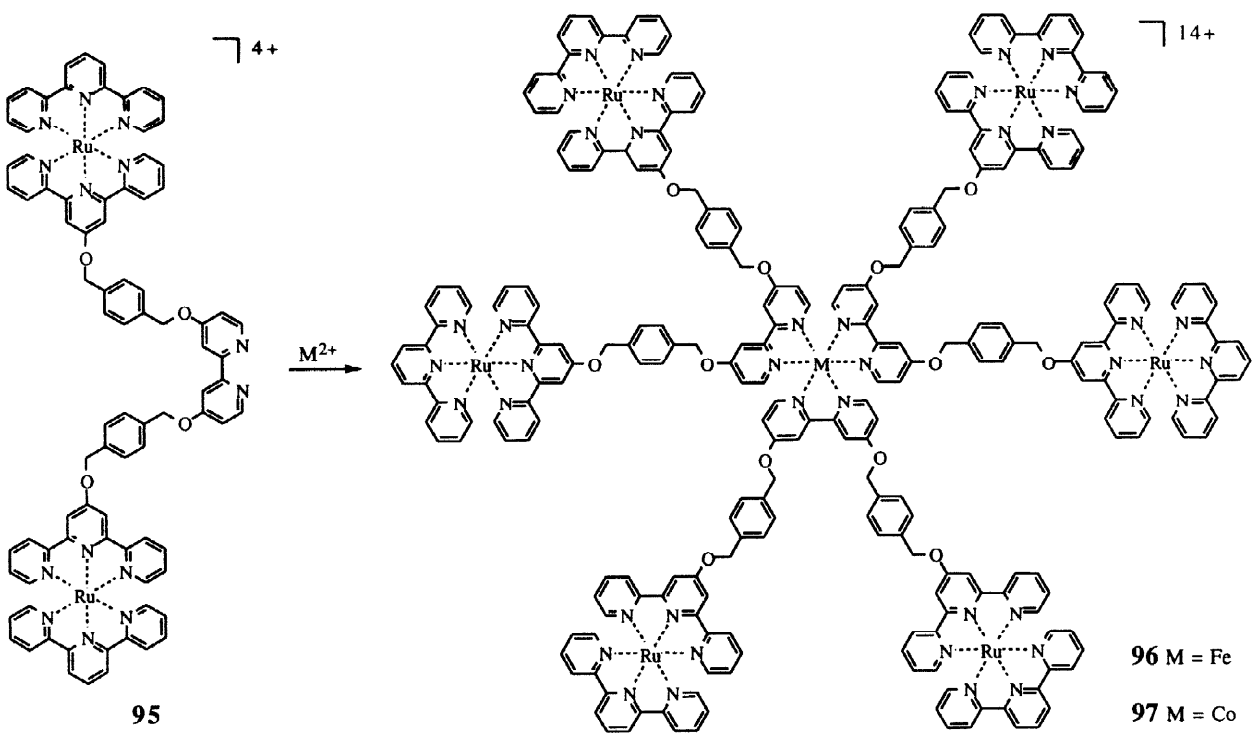


94

dendrimer **93** exhibited a single quasi-reversible Ru^{3+}/Ru^{2+} process at +0.87 V, indicating that the 18 ruthenium centers behaved as independent domains with no significant ground state electronic interaction.

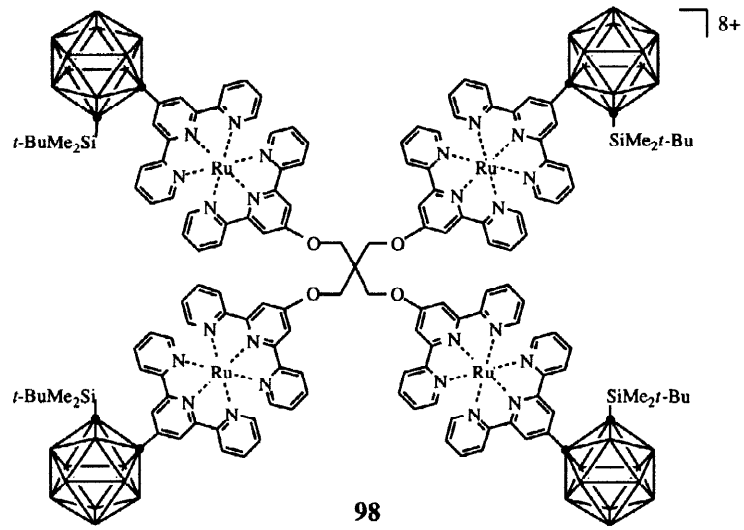
Metallodendrimers containing bis(terpy)-metal periphery units and a tris(bipy)-metal core have also been disclosed by Constable.[42d] The bis(terpy)ruthenium(II)-containing bipy ligand **95**, readily complexed with iron(II) to give a brown tris(bipy)iron(II) metallodendrimer **96**. In the CV study of **96**, the Ru^{3+}/Ru^{2+} redox couple could be detected as a fully reversible process at +0.81V, while the Fe^{3+}/Fe^{2+} process was not



95

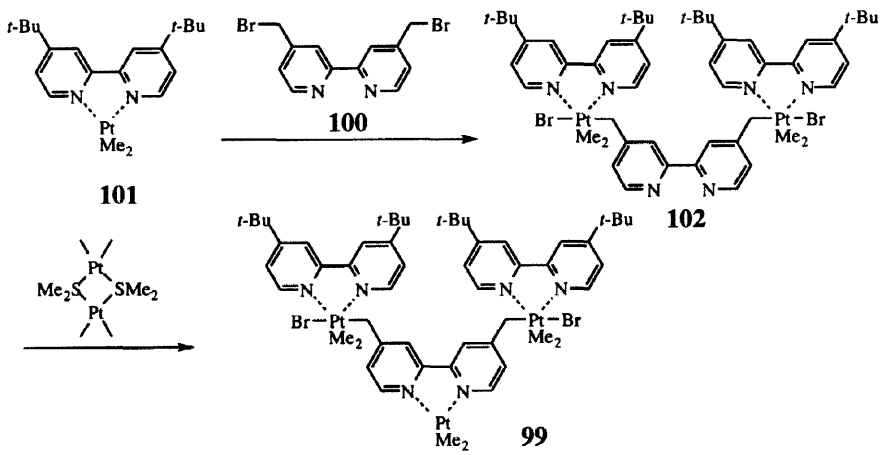
observable. Similarly, bipy **95** could also be converted to a tris(bipy)-cobalt(II) complex **97**. The electrochemical behaviour of **97** closely resembled that of the iron analogue. Hence, a fully reversible Ru^{3+}/Ru^{2+} redox wave was noted at +0.82V with no detectable Co^{3+}/Co^{2+} process.

Constable also described the preparation of a ruthenium metallodendrimer **98** having boron-rich carborane groups on the surface sector.[99] The presence of the four sterically bulky carbaboranyl moieties gave rise to conformational restriction such that the 4 methylene signals at the central core as well as the two methyl groups on the silyl protecting groups were magnetically non-equivalent. Despite the diastereotopicity of the methylene and methyl residues, all ruthenium ions were equivalent and displayed a single reversible redox couple at +0.79V.



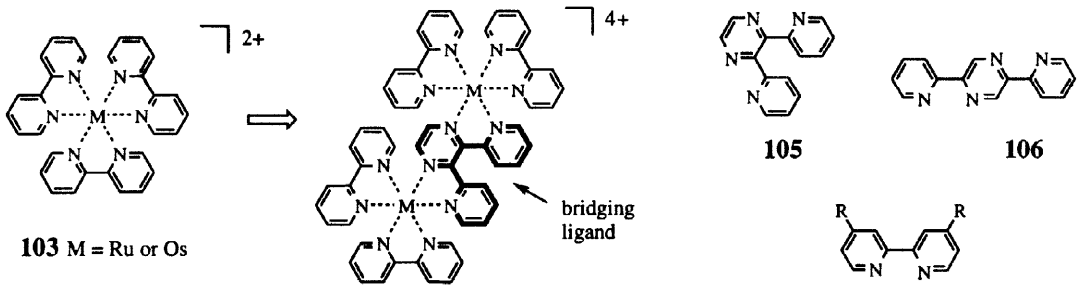
98

Metallodendrimers **99** containing transition metals in every layer of the dendrimer were reported by Puddephatt.[100] They were prepared by a convergent method involving the oxidative addition of 4,4'-bis-(bromomethyl)bipyridine **100** to a dimethyl(bipy)platinum(II) complex **101**. The resulting bipy ligand **102** was then metallated by displacement of dimethyl sulfide from $[Pt_2Me_4(\mu\text{-}SMe_2)_2]$ to give metallodendrimer of the next higher generation **99**. By repetition of this iterative cycle, organometallic dendrimers containing up to 16 surface platinum units were prepared. A divergent route to related organoplatinum and organoplatinum-



palladium dendrimers was also reported.[101] The redox properties of these dendrimers were not described.

Perhaps the most complex bipyridinyl polynuclear metallodendrimers known to date are those synthesised by Balzani *via* a "small-upward" approach.[102] The fundamental repeating units for these supramolecular species are the tris(bipy)ruthenium(II) or osmium(II) complexes **103**. In order to assemble these complexes into an oligomeric array such as **104**, 2,3-bis-(2-pyridyl)pyrazine (2,3-bpp) **105** and 2,5-bis-(2-pyridyl)pyrazine (2,5-bpp) **106** were employed as bridging ligands, while simple 2,2'-bipyridines **107** were used as terminal ligands.



103 M = Ru or Os

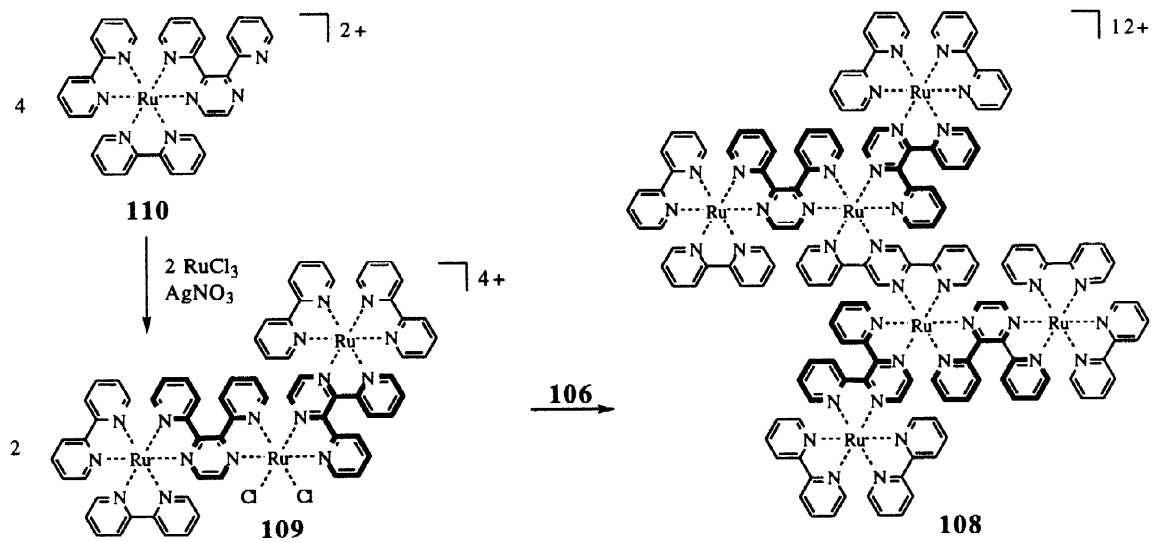
104 M = Ru or Os

105

106

107 R = Me or *t*-Bu

Mononuclear transition metal complexes (ML_n) are often synthesised by mixing a metal ion (M) and free ligands (L) in a stoichiometric ratio ($M + nL \rightarrow ML_n$). In order to prepare oligonuclear metal complexes of desired nuclearity, the use of complexes in place of both M and/or L is necessary. The role of M can be taken by mono- or oligonuclear complexes that possess easily replaceable ligands such as chloride ions, and L can be replaced by mono- or oligonuclear complexes that contain free chelating sites. This procedure is also known as "complexes as metals" and "complexes as ligands" synthetic strategies.[102a] Using this methodology, a hexanuclear metallodendrimer **108** could be synthesised by reacting two equiv. of a trinuclear complex **109** with the bridging ligand (2,5-bpp) **106**. Compound **109** in turn was obtained by reacting 2 equiv. of a mononuclear complex **110** with 1 equiv. of $RuCl_3$.[103] Homo- and hetero-metallic decanuclear polypyridine complexes **111**, were similarly prepared by mixing 1 equiv. of the expanded ligand **112** and 3 equiv. of the metal complex **113** together.[104] A tridecanuclear ruthenium(II)-polypyridine metallodendrimer



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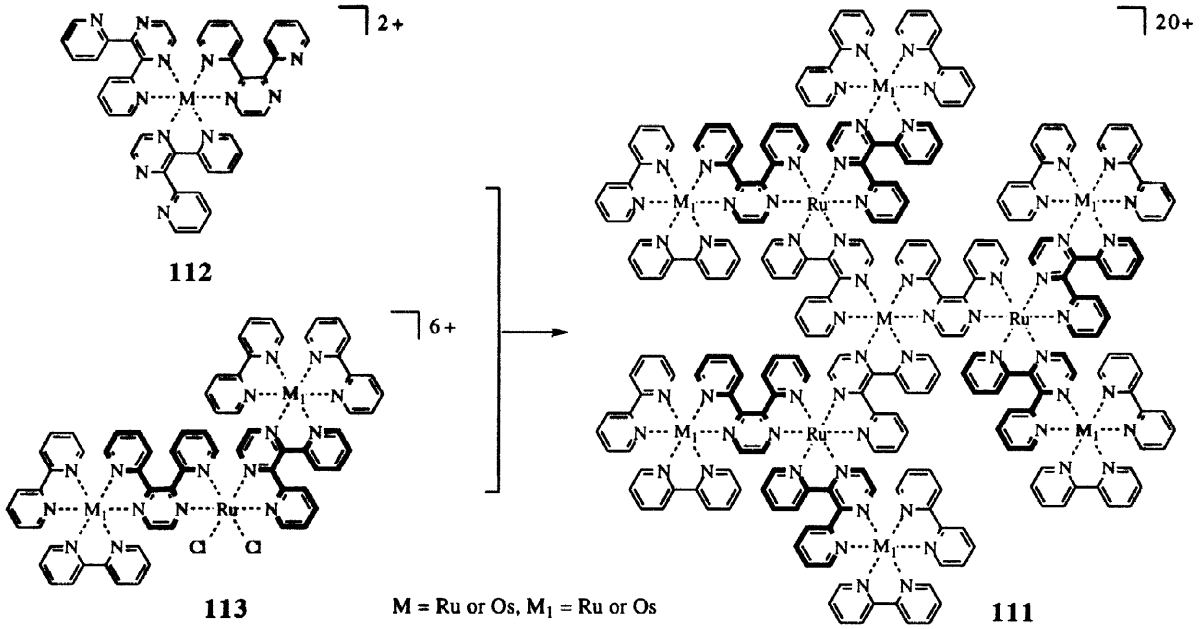
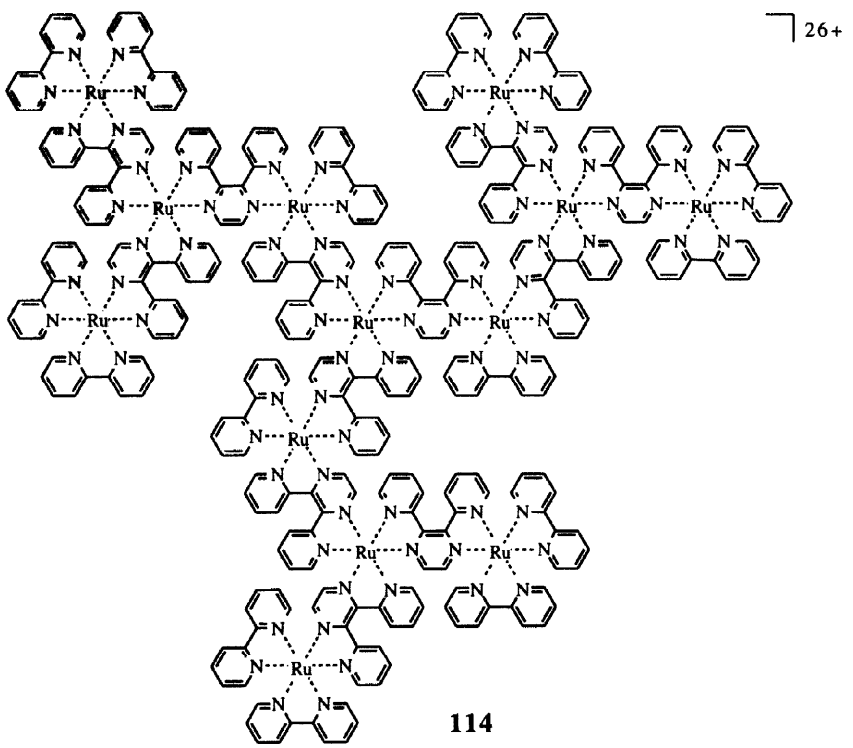
109

108



114 was likewise synthesised.[105] Because the two coordinating nitrogen atoms of each chelating site of the bridging ligands are nonequivalent, different geometrical isomers can form for metal ions coordinate to more than one bridging ligand. Furthermore, each complex actually exists as a mixture of diastereisomeric species due to the inherent chiral nature of the tris(bipy) units.



The electrochemical properties of these dendrimeric ruthenium or osmium complexes were investigated by CV and differential pulse voltammetry. In similar fashion to the related tris(bipy) metal complexes, it was

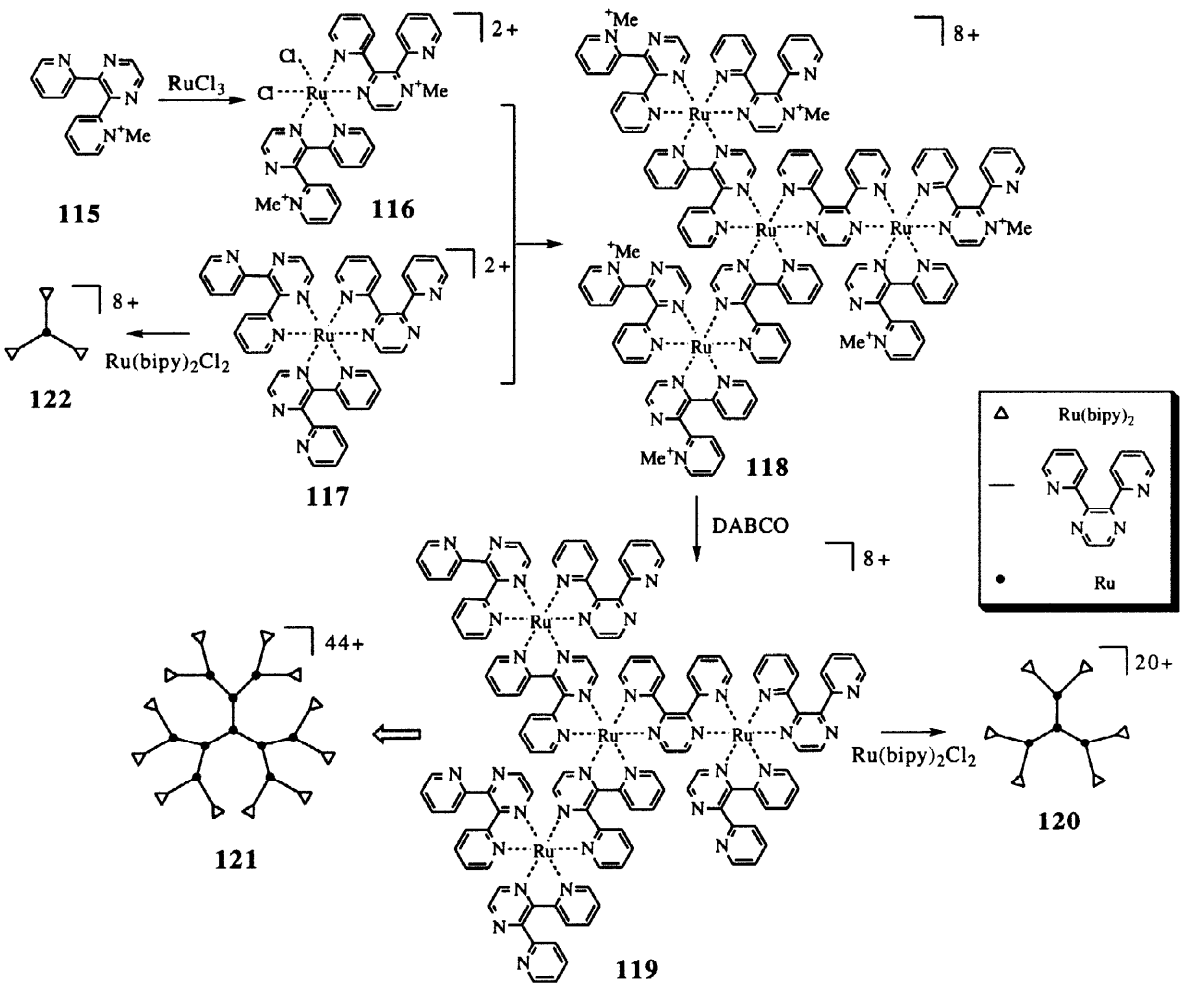
found that oxidations of these metallodendrimers were metal centered while the reduction processes were ligand centered and that bridging ligands were reduced in preference to terminal bipy units.[103] Furthermore, electronic communications between equivalent metals or equivalent ligands was noticeable for metals coordinated to the same bridging ligand and for ligands coordinated to the same metals, whereas it was small for metals or ligands that were sufficiently far apart. In line with this observation, the four positional equiv. peripheral Ru^{2+} ions of the hexanuclear complex **108** showed a single reversible oxidation potential at +1.4 V.[103] On the other hand, oxidation of the two inner Ru^{2+} ions was not observed within the potential window examined (< +2.0 V). They are expected to be less readily oxidised because of the weaker electron-donating power of 2,3-bpp and 2,5-bpp as compared to that of bipy, and the unfavorable electrostatic effect due to the presence of the already oxidised peripheral Ru^{2+} ions. With regard to the reduction processes, two broad multielectronic signals around -0.50 and -1.1 V ascribed to the first and second one electron reduction of the five bridging ligands, respectively, were noted. Two narrower multielectronic signals at -1.4 and -1.6 V, assignable to the two sets of equivalent bipy ligands, were also observed.

With regard to heterometallic polypyridine complexes, it was found that oxidation of Os^{2+} was more readily achieved than that of Ru^{2+}. A differential pulse voltammogram of the osmium-centered nona-ruthenium(II) complex (**111**, M = Os, M_1 = Ru) exhibited two oxidation peaks at +1.17 and +1.50 V with a relative peak area ratio of 1 : 6, which corresponded to the oxidation of the central Os^{2+} ion and of the peripheral Ru^{2+} ions inside the six equivalent $[Ru(bipy)_2(2,3\text{-bpp})]^{2+}$ residues, respectively.[104] Oxidation of the three intermediate Ru^{2+} ions could not be detected in the potential window examined. The heterometallic layer-blocked complex with Os^{2+} ions situated both at the centre and at the periphery (**111**, M = M_1 = Os) gave two oxidation peaks at +1.05 and +1.39 V with a relative peak area ratio of 6 : 1, which were assigned to the oxidation of the six peripheral and the central Os^{2+} atoms respectively. The central Os^{2+} ion had a more positive potential because of the weaker donating power of the three bridging 2,3-bpp ligands. Due to the perturbation effect induced by the already oxidised Os^{2+} ions, oxidation of the intermediate Ru^{2+} ions were not observed. Finally, the homometallic complex (**111**, M = M_1 = Ru) showed a single oxidation peak at +1.43 V, attributable to the oxidation of the six peripheral Ru^{2+} ions. Oxidation of the central and intermediate Ru^{2+} ions were not detected in the potential window studied.[104]

To facilitate the synthesis of metallodendrimers of less symmetric superstructures, Balzani recently developed a new procedure involving protection-deprotection chemistry.[106] The key intermediate of this approach was a protected 2,3-bpp unit **115** having one of the pyridyl nitrogens quarternized. Reaction of two equiv. of compound **115** with 1 equiv. of $RuCl_3$ afforded a propagating unit **116**, which was then anchored to a central core **117** to yield a tetranuclear ruthenium complex **118** with no defective by-products. The methyl groups were deprotected with diazabicyclo[2.2.2]octane in refluxing acetonitrile to give a tetranuclear complex **119**, which was then further reacted with $Ru(bipy)_2Cl_2$ to give the G1 decanuclear metallodendrimer **120**. Further elaboration of **119** produced a G2 dendrimer **121** containing 22 Ru^{2+} ions.

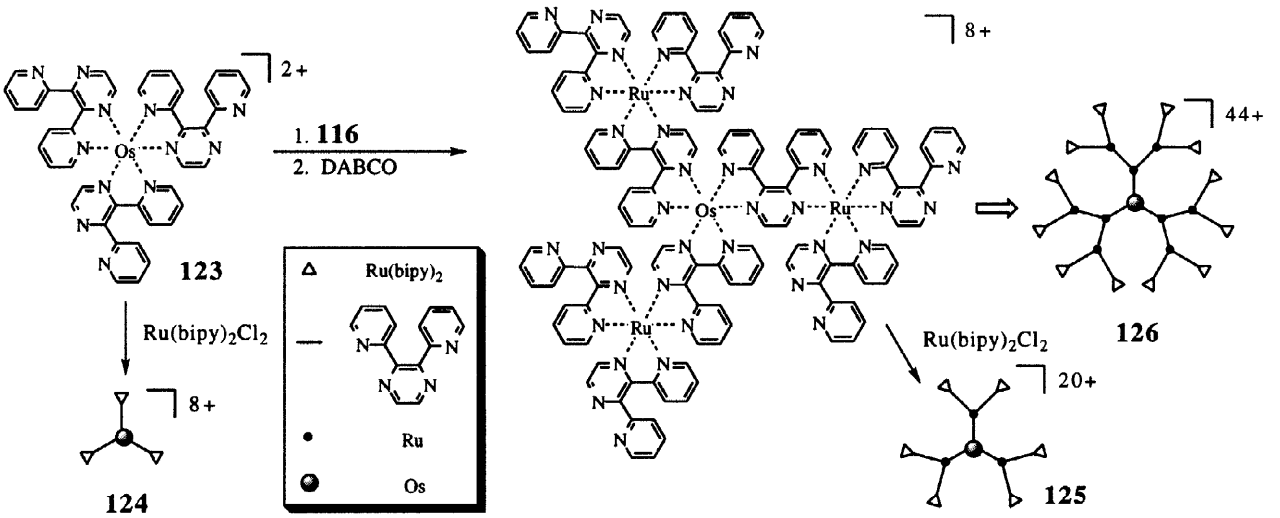
Upon electrochemical oxidation, dendrimers **122**, **120** and **121** each produced a reversible signal corresponding to three, six and twelve electron transfer, respectively, at the same potential value (+1.53 V). This picture was consistent with the simultaneous oxidation of all the equivalent and weakly interacting peripheral Ru^{2+} units within each dendrimer. The oxidation potentials of the central and intermediate metal ions would be displaced to more positive values after the preferential oxidation of the peripheral units, and hence was not observed within the potential window examined. Interestingly, a reversal of the oxidation

sequence was noted for the protected dendrimeric series. Due to the poor electron donating ability of the cationic 2,3-Mebpp$^+$ unit **115**, oxidation of the central metal took place in preference to those of the peripheral ones, with a one electron oxidation wave located at +1.82 V for 2,3-Mebpp$^+$-terminated metallodendrimer **118**. On the other hand, the deprotected species **117** and **119** containing free metal coordination sites on the periphery tended to adsorb strongly on the electrode surface and meaningful redox values could not be obtained. The electrochemical reduction behavior of these metallodendrimers were extremely complex due to the presence of a large number of different polypyridine ligands, each capable of undergoing several reduction processes. For the G0 dendrimer **122**, noticeable ligand-ligand interactions through the central metal was found, as the three bridging ligands were reduced at different potentials (-0.62, -0.77 and -1.23 V). However, such metal-mediated ligand-ligand interaction was significantly reduced for the G1 dendrimer **120**, since the three core bridging ligands in **120** were reduced at nearly the same potential (-1.22 V).

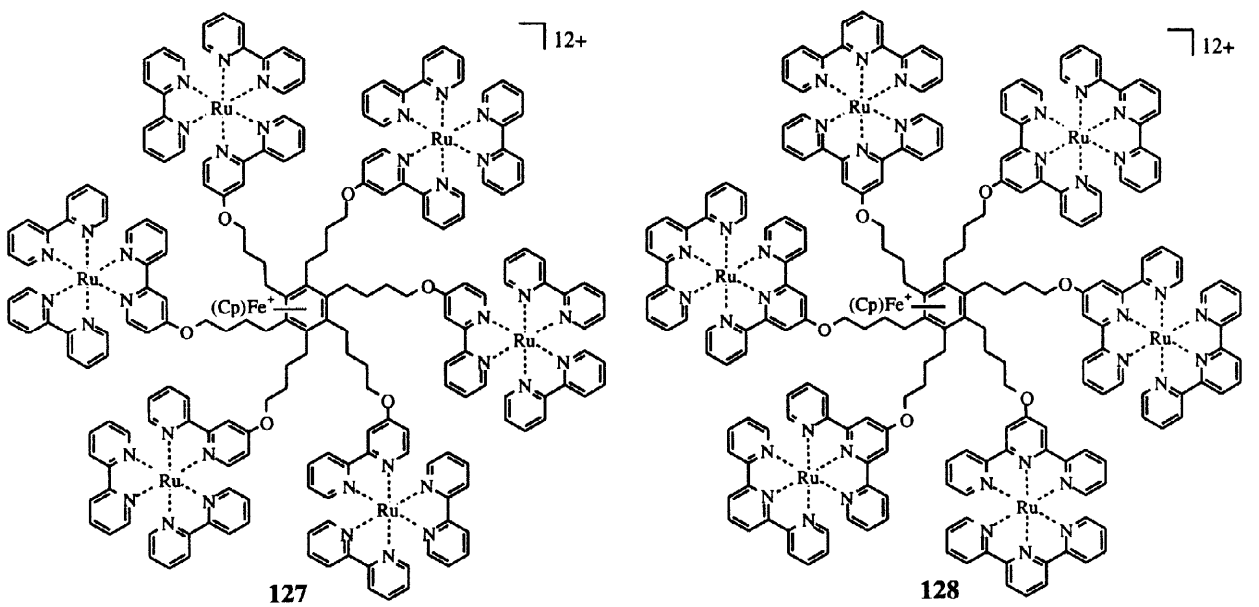


Extending this protection/deprotection chemistry, Balzani further synthesised layer-blocked metallodendrimers **124** - **126** having a central Os^{2+} ion surrounded by several Ru^{2+} ions.[107] Reaction of an Os^{2+} cored intermediate **123** with the 2,3-Mebpp$^+$-protected Ru^{2+} species **116** afforded a monoosmium triruthenium species which could be further elaborated into the target compounds. Due to the preferential oxidation of the core Os^{2+} relative to the peripheral Ru^{2+} ions, these molecules provided another case study for the effect of dendrimerisation on the redox properties of the internal Os^{2+} ion. In contrast to the findings by Newkome[77]

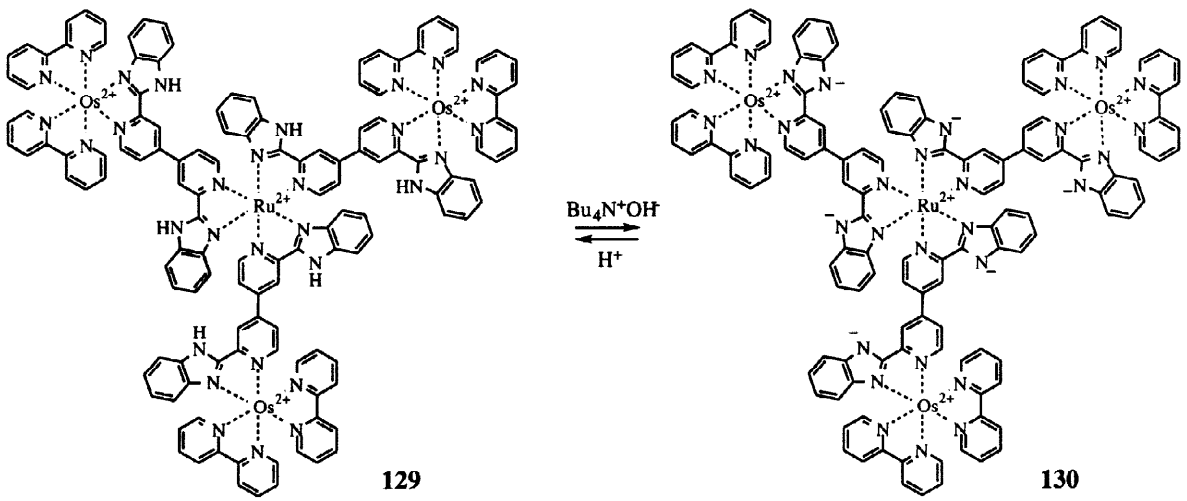
and Chow,[78] the oxidation process involving the Os^{2+} ion was completely reversible irrespective of the dendrimer generation. While there was little change of the oxidation potential on moving from G1 **124** to G2 **125**, a notable potential shift (+1.35 → +1.42 V) was observed for the G3 dendrimer **126**. The second oxidation process involved the peripheral Ru^{2+} ions; a three electron process was noted at +1.61 V for G1 **124**, a six electron process at +1.55 V for G2 **125**, and a twelve-electron process at +1.54 V for G3 **126**. The slightly more positive potential observed for the G1 complex was likely due to the closeness of the Ru units to the already oxidised Os core. It was further established that the potential at which oxidation of the peripheral units took place did not depend on the nature of the interior core, since the observed potential values for Ru^{2+} centers were very similar to those found for the homonuclear ruthenium dendrimers **120** - **122**.



Astruc also reported the preparation of layer-block metallodendrimers **127** and **128** containing an outersphere of Ru^{2+} ions surrounding a core Fe^{2+} ion.[108] The structural identities of these complexes were confirmed by NMR and MS studies. Electrochemical studies on **127** and **128** each gave a single reversible anodic wave due to the Ru^{3+}/Ru^{2+} couple at +0.82 and +0.79 V (*vs.* Fc-Fc$^+$), respectively.

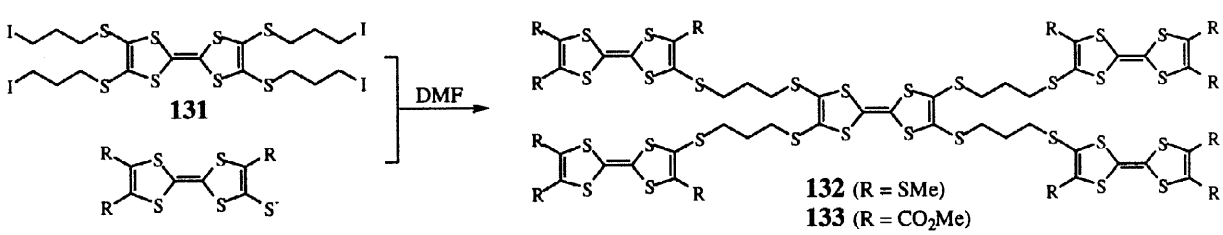


Haga recently disclosed the synthesis of a heteronuclear Os_3Ru dendrimer **129** which showed pH dependent redox properties.[109] In its neutral form, compound **129** exhibited two oxidation peaks centered at +0.38 and +0.71 V, which were due to the three-electron Os^{2+}/Os^{3+} and one-electron Ru^{2+}/Ru^{3+} oxidations, respectively. However, the oxidation preference of these two peaks was reversed (Os^{2+}/Os^{3+}: +0.38 → +0.06 V; Ru^{2+}/Ru^{3+}: +0.71 → -0.34 V) for the deprotonated species **130**, which was formed by treatment of **129** with $Bu_4N^+OH^-$. Thus, deprotonation of the benzimidazole NH protons switched the site of the first oxidation from the Os centres to the Ru core. This switching was fully reversible as acidification of the fully deprotonated species quantitatively regenerated the original CV profile.



129 **130**

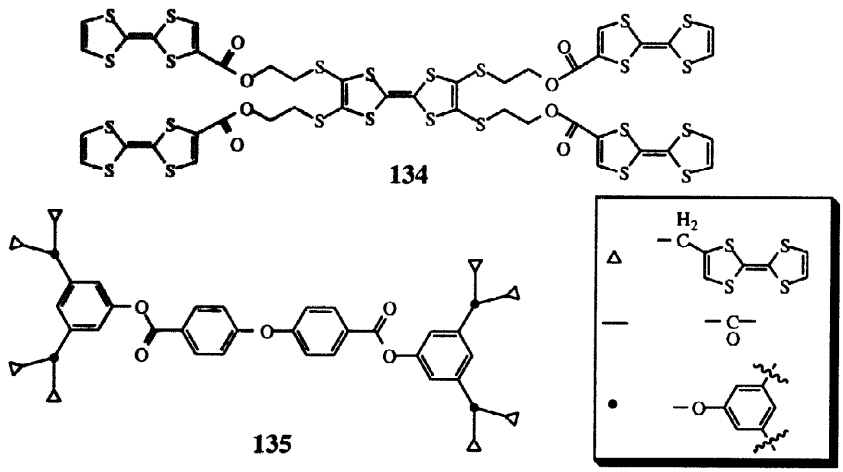
The redox active tetrathiafulvalene (TTF) unit has also been incorporated into a wide variety of dendritic structures. TTF can be sequentially and reversibly oxidised to a stable radical cation and a dicationic species which can further interact with other TTF units. It was suggested that through the interactions of two or more electrophoric TTF moieties, tuneable and thermodynamically stable molecular conducting materials could be produced.[110] Adopting this idea, Becher prepared a number of functional TTF building blocks such as the tetraiodide **131** and used them to construct a G1 TTF-based dendrimer **132** consisting of five TTF units.[111] CV studies on **132** gave two reversible redox couples at +0.52 and +0.82 V, ascribed to the 1st and 2nd oxidation of all five TTF units. The result implied that there was no interaction amongst the TTF moieties. Similar CV profiles were noted for related dendrimeric TTF derivatives **133**[111] and **134**.[112] When TTF-containing dendrimer **135** was mixed with tetracyano-*p*-quinodimethane (TCNQ), a conductive charge transfer salt with conductivity of 2×10^{-3} S cm^{-1} was formed.[113]



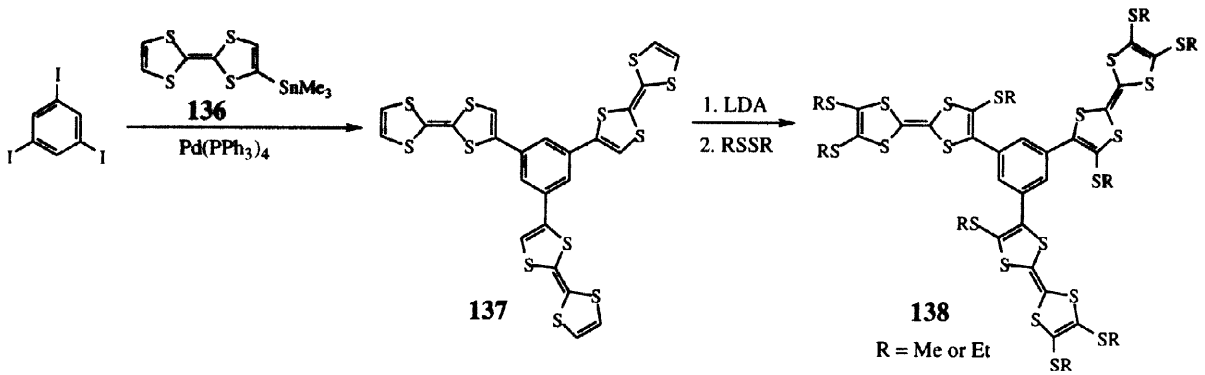
131

132 (R = SMe)
133 (R = CO_2Me)

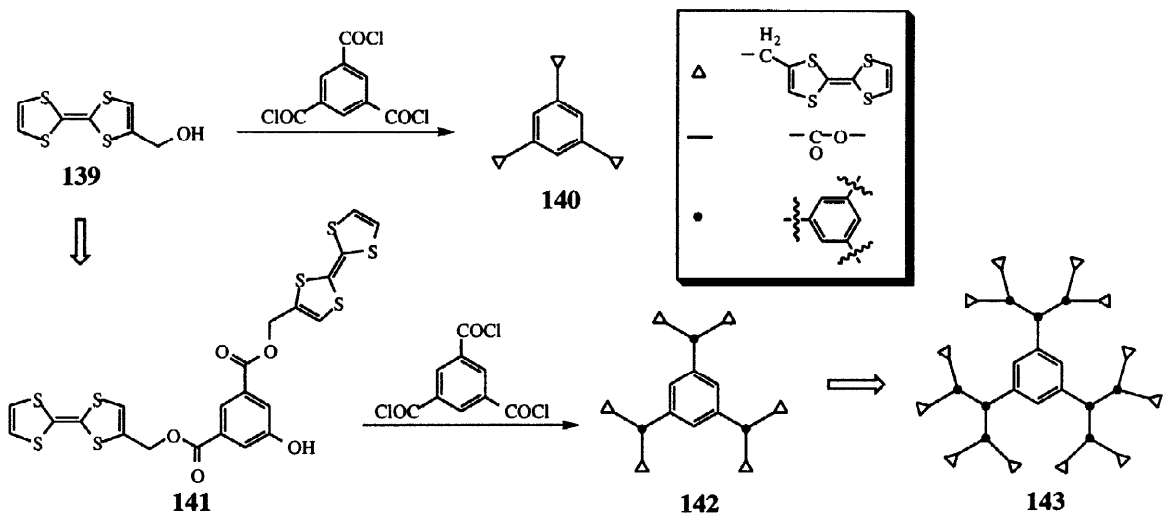
Iyoda described the use of palladium-catalysed cross coupling between trimethylstanyl-TTF **136** and 1,3,5-triiodobenzene to give a G1 dendritic TTF compound **137**, which could further be converted into a



nonaalkylthio derivative **138** upon deprotonation and subsequent quenching with dialkyldisulfide.[114] CV studies of **137** and **138** again indicated the redox independence amongst the TTF units. Upon mixing with TCNQ, compound **137** gave a 2 : 1 CT-complex with a fairly high conductivity (30 Scm^{-1}).

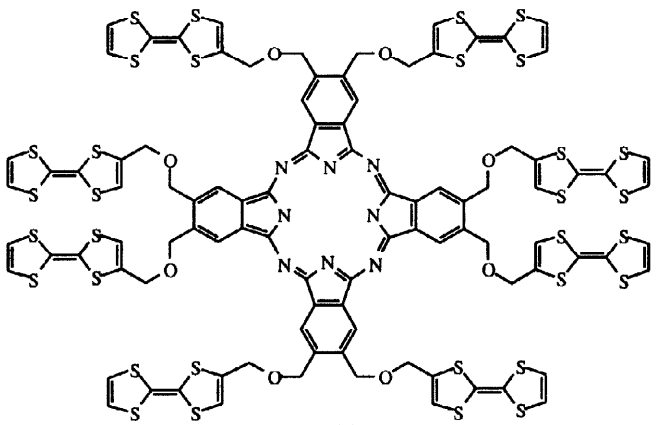


Using a convergent synthetic strategy, Bryce reported the preparation of a series of polyester-based dendrimers consisting of up to twelve TTF units on the surface sector.[115] Esterification of 1,3,5-benzenetricarbonyl chloride with TTF-methanol **139** gave a G0 dendrimer **140** having three TTF units. The alcohol



139 could also be elaborated into a bis(TTF) dendritic wedge **141** which was used as a monomer for subsequent convergent construction of the higher generation TTF analogs **142** and **143**. These TTF dendrimers exist as yellow or orange oils with a limited lifetime at room temperature. CV studies on **140**, **142** and **143** showed the characteristic redox behavior of the TTF system with two quasi reversible redox couples at +0.45 and +0.85 V with little electronic interactions amongst the charged TTF units.

A dendritic phthalocyanine derivative **144** with eight TTF units located at the peripheral sector was also reported.[116] Compound **144** gave two oxidative CV peaks at +0.51 and +0.83 V. While the first signal had the same potential value as that of a model monomeric analogue **145** (+0.51 and +0.74 V), the second oxidation wave was significantly broadened and slightly shifted to higher value. The data implied that there were some interactions amongst the oxidised TTF units in compound **144**.



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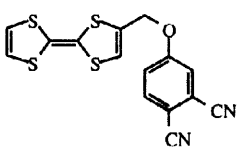
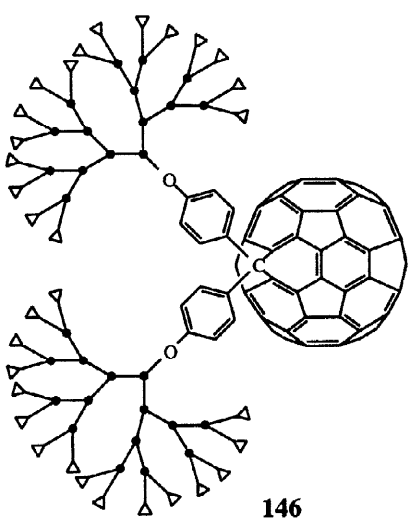
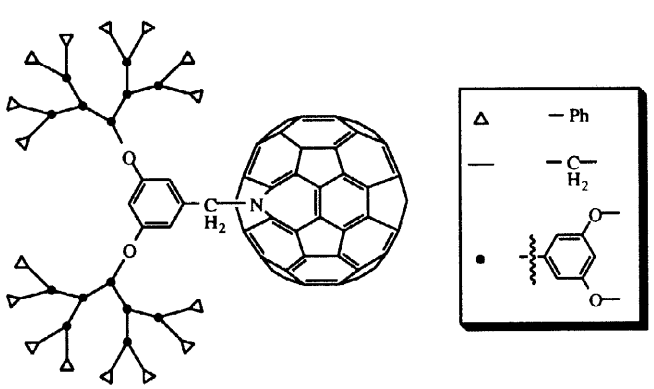


145

Following the exciting developments in fullerene chemistry, Fréchet described the synthesis of two fullerene-bound dendrimers **146**[117] and **147**.[118] Compound **146** was formed from coupling of two polyether dendritic sectors onto a bis(phenolic) fullerene derivative prepared *via* carbene addition to C_{60}. Compound **147**, on the other hand, was constructed by the direct insertion of a dendritic nitrene to C_{60}. When a large excess of the dendritic nitrene was used, the di-adduct was also obtained but with no detectable higher adducts. The inability to obtain tri- or higher-addition products may be due to steric hindrance around the C_{60}



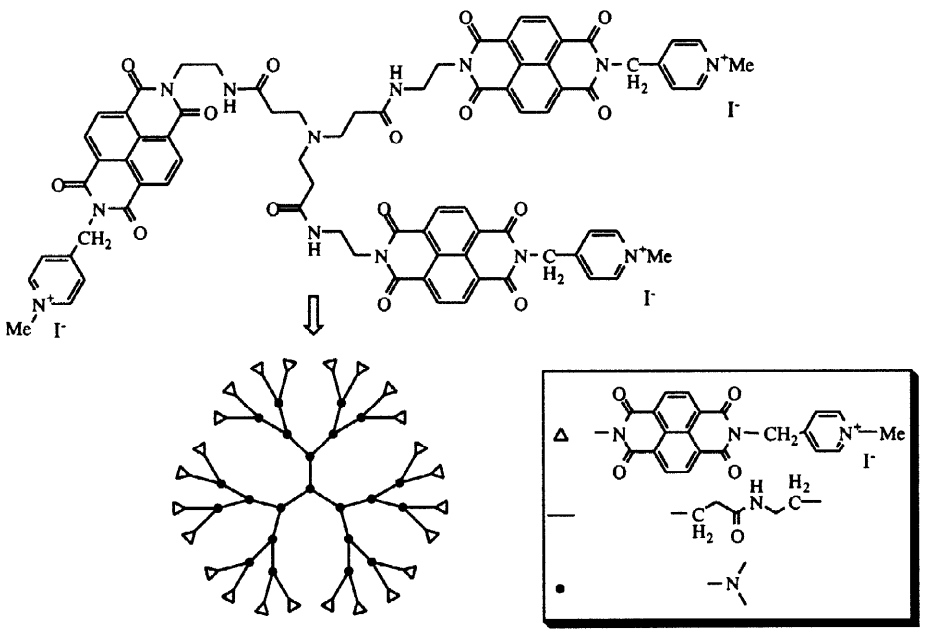
146



147

core already possessing two dendritic umbrellas. In contrast to C_{60}, these dendritic fullerenes are extremely soluble in a variety of organic solvents. Such properties could be advantages for material processing purposes. The cyclic voltammogram of **147** showed a multi-reduction pattern with the first three reduction potentials shifted to lower values (about 10 mV more negative) than those reported for other non-dendritic analogues, presumably due to the presence of the electron-rich polyether dendritic envelopes.

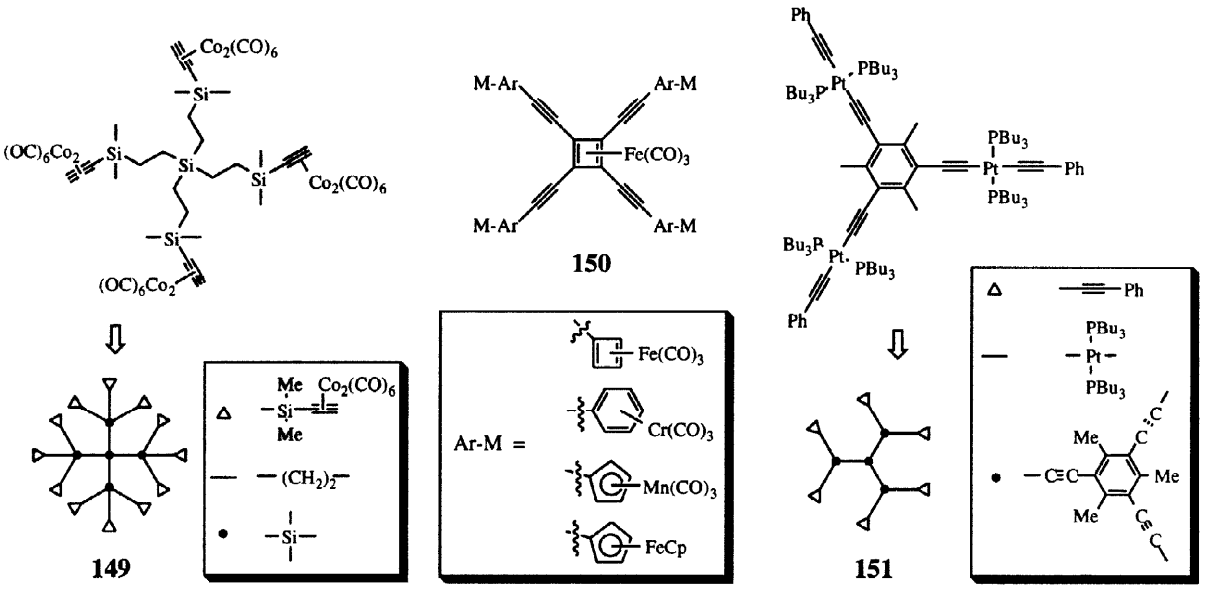
A number of naphthalene diimide-terminated PAMAM dendrimers **148** were prepared by Miller and Tomalia.[119] Upon chemical reduction with $Na_2S_2O_4$, each of the diimide units was transformed into the corresponding radical anion. It is well established that these anionic radicals can aggregate into a π-stacked network to provide the mechanism for conductivity. Amongst dendrimers of various generation, the fully reduced G3 analog could form a conducting film with a conductivity of 2×10^{-4} Scm^{-1} when cast at 120°C. Significantly higher conductivity (2×10^{-3} Scm^{-1}) was realised when the film was cast at 60°C, suggesting that stacking was more effective at a lower casting temperature. Surprisingly, a partially (55%) reduced film had even better conductivity (6×10^{-3} Scm^{-1}) than the fully reduced one. This was rationalised by the formation of mixed valence stacks containing both neutral diimide and anion radical diimide moieties. Furthermore, the conductivity of such films could reach values as high as 18 S cm^{-1} with increasing humidity. It was also noted that the conductivity of these radical anion-terminated dendrimers was higher than those reported for diimide anion radicals anchored on a linear polymer. The findings suggested that the naphthalene diimide moieties of these conducting dendrimers formed more efficient π-stacks than similar radical anion units in a polymer chain.



148

Other organometallic dendrimers with potentially interesting redox activities have been disclosed, notably carbosilane-based dendrimers **149** with peripheral acetylenedicobalt hexacarbonyl substituents,[120] star-shaped tricarbonyl(cyclobutadiene)iron complexes **150**,[121] and platinum-containing dendrimers **151**.[122] Despite the novel structures, their redox properties have not been reported. Dendrimeric ligands having a multitude of ligating sites for metal ions have also been synthesised but research focus is concentrated on the

metal complexation ability of these ligands and not on the redox properties of the metal centers. The chemistry of these dendrimeric ligands will be discussed in Section 5.5.



5.4 Photoresponsive Dendrimers

The design of dendritic molecules having chromophores capable of absorbing light energy and transmitting the excitation energy by means of an antenna effect to selected traps within the dendrimer has been a main theme in photoresponsive dendrimer research.[123] Such systems can be utilised as components in photochemical molecular devices for solar energy conversion, information storage and redox catalysts.[124] Photochemical and photophysical active dendrimers can also be employed as probes to investigate the microenvironment and microstructure of dendrimers.

One of the most thoroughly studied photoresponsive dendritic systems are the poly(pyridinyl) metal complexes reported by Balzani. It is well established that Ru or Os complexes of bipy have a relatively long-lived luminescence in the red spectral region, intense ligand centered (LC) absorption bands in the UV region and moderately intense metal to ligand charge transfer (MLCT) bands in the visible region.[102c-e] As expected, Ru and Os polypyridine metallodendrimers **108**, **111**, **114**, **120 - 122** and **124 - 126** displayed luminescent properties similar to those of their nondendritic analogs. Based on the results of photochemical studies of these compounds, several generalisations can be formulated. First, metal-metal interaction is weak for metals coordinated with the same bridging ligand and almost negligible for metals that are far apart. Similarly, ligand-ligand interaction is appreciable only for ligands coordinated with the same metal. As a consequence, the energy levels of the component building blocks are essentially maintained. Secondly, photoexcitation of these polynuclear metal complexes leads to the population of the ^{1}MLCT singlet excited states in the various components, which then relaxes to the lowest energy triplet ^{3}MLCT level. Thirdly, energy transfer from the lowest luminescent level of each unit to the lowest one of the entire supramolecular structure is fast and hence the luminescence property of the whole metallodendrimer originates from such a lowest excited state. Such argument is consistent with the formation of only one luminescence band from most of these metallodendrimers. Obviously, the rate of energy transfer will depend on the energetics of the process and on the electronic interaction between the components. Exoergonic energy transfer between components

connected by the same bridging ligands is expected to be much faster than luminescence and radiationless decay. The energy of the luminescent level, in turn, is influenced by the nature of both the metal ion and its ancillary ligands. Since these polynuclear dendritic complexes possess excellent light absorption properties over the entire visible region and efficient energy transfer can take place among their components, they are capable of channelling the resulting excitation energy toward a specific site in the dendritic array and are therefore useful light harvesting devices.

Based on experimental measurements, the energy of the lowest MLCT excited state of each unit was shown to depend on the metal and ligand environment in a predictable manner: $Os(bipy)_2(\mu\text{-}2,5\text{-}bpp)^{2+}$ < $Os(bipy)_2(\mu\text{-}2,3\text{-}bpp)^{2+}$ < $Os(\mu\text{-}2,5\text{-}bpp)_3^{2+}$ < $Os(\mu\text{-}2,3\text{-}bpp)_3^{2+}$ < $Ru(bipy)_2(\mu\text{-}2,5\text{-}bpp)^{2+}$ < $Ru(bipy)_2(\mu\text{-}2,3\text{-}bpp)^{2+}$ < $Ru(bipy)(\mu\text{-}2,5\text{-}bpp)_2^{2+}$ < $Ru(bipy)(\mu\text{-}2,3\text{-}bpp)_2^{2+}$ < $Ru(\mu\text{-}2,3\text{-}bpp)_3^{2+}$.[102c,e] Balanzi demonstrated that the direction of energy flow within a polynuclear metallodendrimer could be synthetically tuned. For example, the tetranuclear complexes **122**, **124** and **152** and their corresponding energy migration patterns are shown in Figure 12.[102c] For the homonuclear complex **122**, all three peripheral Ru units [$Ru(bipy)_2(\mu\text{-}2,3\text{-}bpp)^{2+}$] are equivalent and their lowest energy excited state is located at lower energy than that of the central Ru unit [$Ru(\mu\text{-}2,3\text{-}bpp)_3^{2+}$], the luminescence of the central unit is thus quenched while that of the peripheral ones is sensitised. On the other hand, the lowest energy excited state of the central Os unit [$Os(\mu\text{-}2,3\text{-}bpp)_3^{2+}$] in the heteronuclear complex **124** has a lower energy than those of the peripheral Ru atoms, and so the energy migration pattern is reversed. In complex **151**, because the peripheral [$Ru(bipy)_2(\mu\text{-}2,5\text{-}bpp)^{2+}$] unit has the lowest energy excited state amongst the others, all excited state energy from other metal centers is channelled toward this single Ru unit. Obviously, energy transfer from the two peripheral [$Ru(bipy)_2(\mu\text{-}2,3\text{-}bpp)^{2+}$] units to [$Ru(bipy)_2(\mu\text{-}2,5\text{-}bpp)^{2+}$] must either overcome a barrier at the central Ru core or proceed through space.

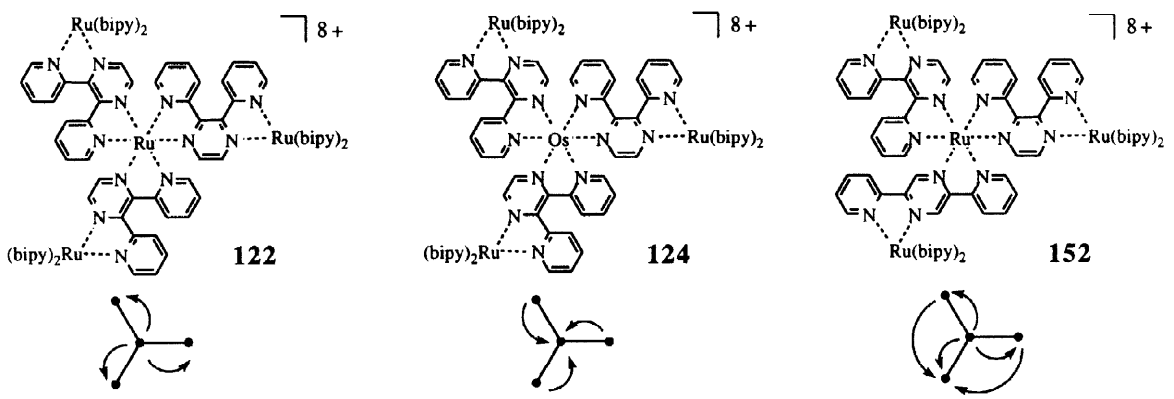


Figure 12. Energy migration patterns for tetranuclear metallodendrimers **122**, **124** and **152**.

The same rationale was used to explain the photochemical behavior of decanuclear complexes **120** and **125.** The homonuclear Ru complex **120** showed one single luminescent band at 809 nm that could be assigned to the peripheral Ru units as the luminescents of central and internal Ru atoms were efficiently quenched (Figure 13).[104] On the other hand, the heteronuclear species **125** with one central Os core gave a predominant luminescence band at 808 nm, together with a shoulder at 860 nm. The former emission was assigned to the peripheral Ru units while the latter was considered to originate from the lower energy [$Os(\mu\text{-}2,3\text{-}bpp)_3^{2+}$] unit. Based on these observations, it was established that energy transfer from the peripheral units to the central core by either a two-step energy transfer mechanism *via* the intermediate Ru units or a direct through space transfer

mechanism was very slow. Energy transfer from peripheral Ru units to the central Os center was also disfavored for the heteronuclear $OsRu_{21}$ metallodendrimer **126**.[107]

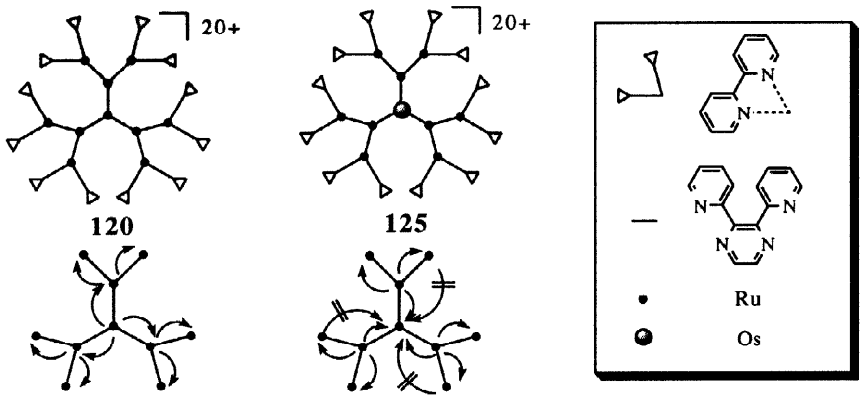
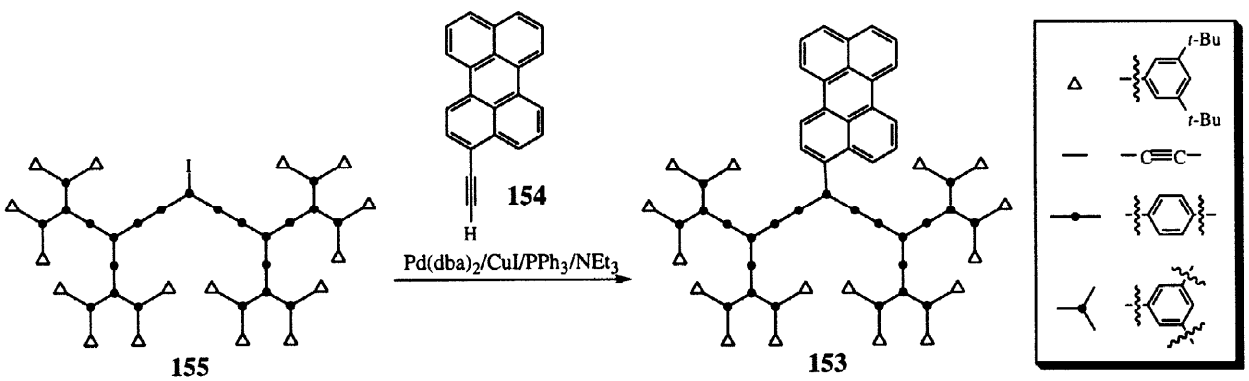


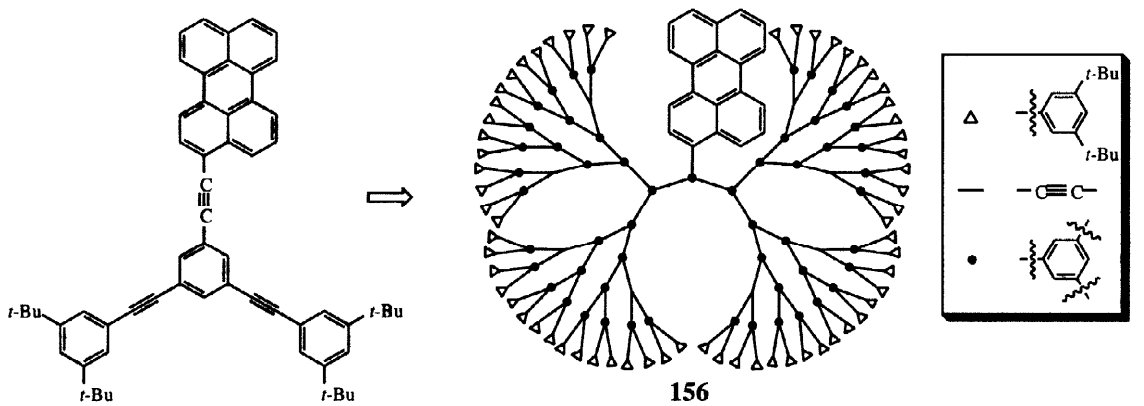
Figure 13. Energy migration patterns for decanuclear complexes **120** and **125**.

Structurally rigid dendrimers were shown to be better candidates than linear polymers for photo-harvesting systems since they possessed a convergent constitution which could be site specifically functionalised to create an energy funnel. One such light harvesting dendritic device having a luminescent probe at the focal point was reported by Moore.[125] The luminophor chosen was a perylene derivative whose excited state represented an energy sink relative to the dendrimer. The synthesis of this molecular antenna **153** involved a palladium-catalysed coupling between 3-ethynylperylene **154** and a dendritic aryl iodide **155** which was prepared by an iterative synthetic procedure.[126] Preliminary photophysical experiments showed that perylene emission from **153**, when excited at a wavelength corresponding to the absorption maximum of the dendrimer's peripheral groups, gave an intensity enhancement of more than two orders of magnitude compared to that from a nondendritic perylene **154**. Furthermore, the excitation energy cascaded to the focal point with a high energy transfer quantum yield (98%).



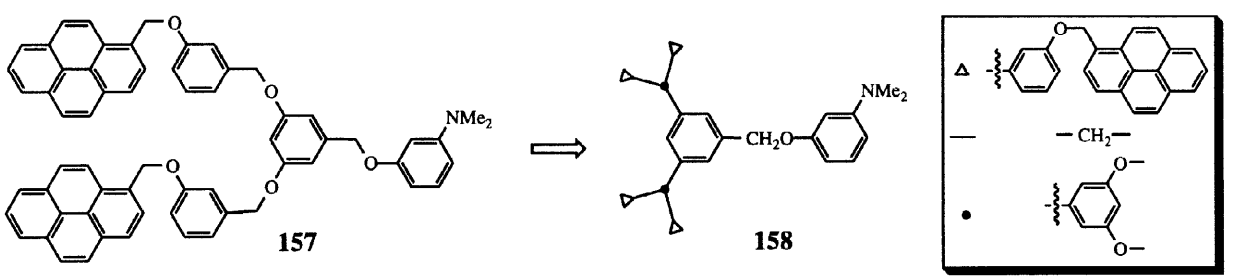
To examine the effect of the dendrimer size on the efficiency of energy transfer from the peripheral groups to the focal perylene moiety, Moore synthesised a series of perylene-terminated dendritic wedges **156** and demonstrated that the light-harvesting ability of these compounds improved with increasing generation.[127] The improvement of light-harvesting ability was mainly due to the increase of molar extinction coefficient of the larger dendritic fragments. Excitation of the phenylacetylene dendritic sector at 310 nm resulted in the fluorescence emission from the perylene chromophore with two maxima at 482 and 517 nm. These λ_{max}

values did not vary significantly from one generation to another and matched reasonably well with those of 3-(phenylethynyl)perylene (479 and 512 nm). However, the efficiency of this energy transfer was shown to decrease with increasing generation. In comparison to the layer block dendrimer **153**, the energy transfer process in dendrimer **156** was much slower. The unique property of compound **153** was attributed to the presence of a smooth energy gradient created by the gradually increasing length of the oligophenylene-acetylene branch toward the focal point.



156

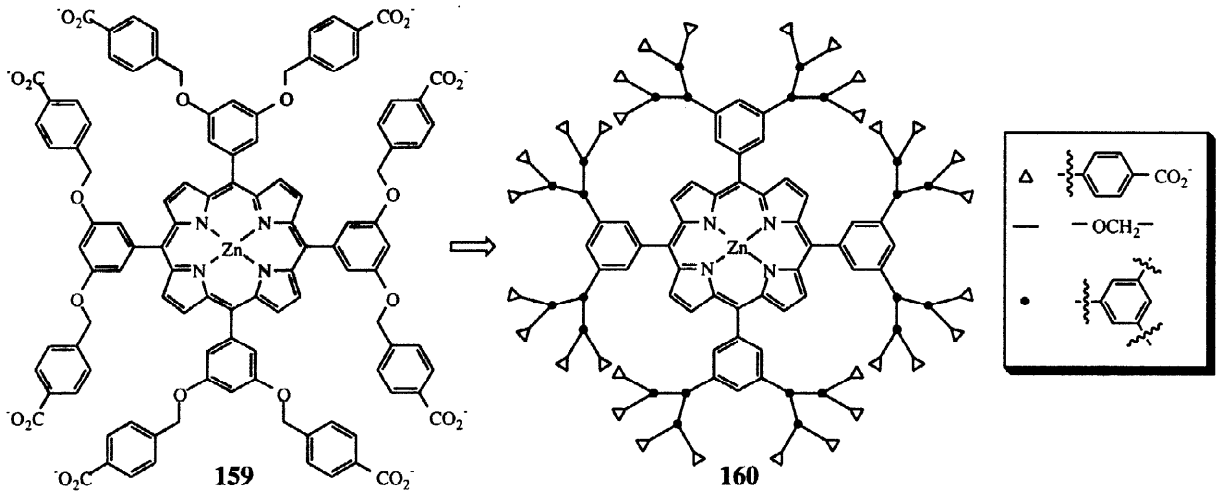
Light harvesting dendritic antennas **157** and **158** bearing pyrene electron acceptors at the periphery and an electron donor 3-(dimethylamino)phenoxy group at the focal point were reported by Fox.[128] It was shown that the fluorescence of the pyrene surface groups were effectively quenched by the dimethylamino-phenoxy group *via* an intramolecular mechanism. Quenching was always less efficient in the higher generation wedge **158** than in the lower one **157**. The decreased ratio of donor to acceptors and the increased separation distance between the donor and acceptors are the principal factors responsible for the diminishing quenching efficiency for higher generation compounds.



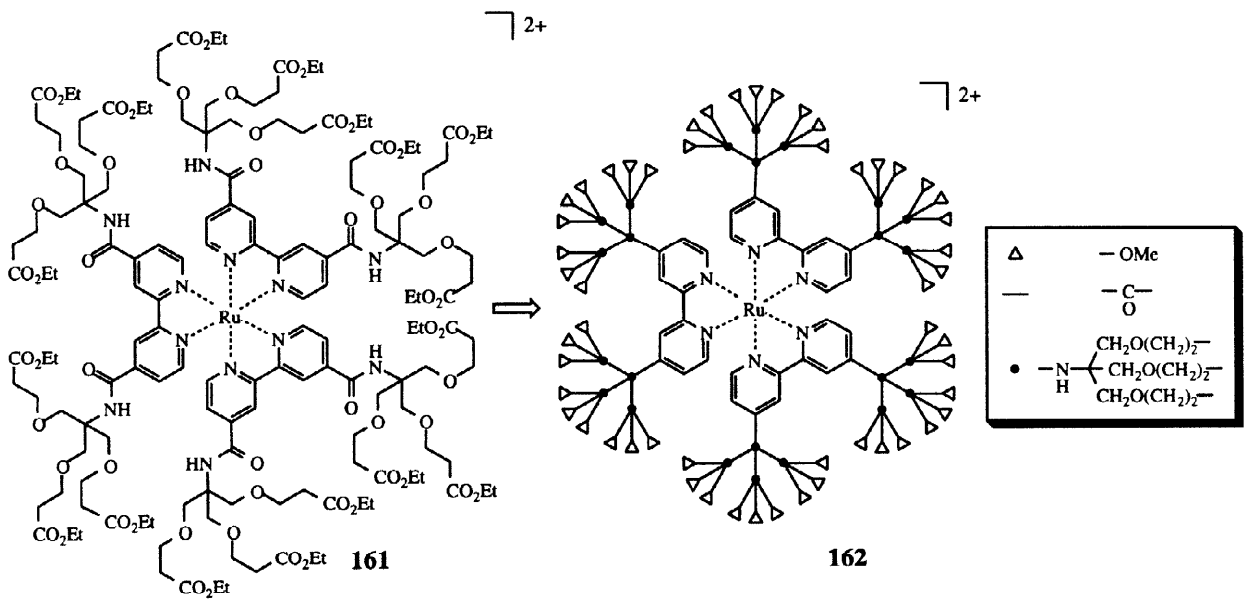
157 **158**

Photoinduced electron transfer could also be realised from a dendrimer core through a dendritic matrix to non-covalently assembled electron acceptor molecules on the exterior surface.[129] Water soluble dendritic zinc porphyrins terminated with carboxylates **159** and **160** were prepared by coupling of 20-tetrakis-(3',5'-dihydroxyphenyl)porphine with methoxycarbonyl-terminated polyether dendritic bromides followed by metallation with zinc acetate and subsequent base-catalysed hydrolysis of the ester groups. These two dendritic zinc porphyrins exhibited generation dependent photophysical properties. First, the UV absorption pattern of the lower generation porphyrin **159** was strongly influenced by the addition of either positively charged methyl viologen (MV^{2+}) or negatively charged naphthalenesulfonate electron acceptors, while that of the higher generation one **160** remained unperturbed by these additives. The result was consistent with an open architecture of the lower generation porphyrin so that the internal porphyrin core could interact with both

electron acceptors. On the other hand, in the higher generation one the core is sterically shielded by the dendritic cage from access by acceptor molecules. Secondly, the fluorescence of **159** was effectively quenched by MV^{2+}, while that of **160** exhibited a saturation profile. Because of the closed shell structure of **160**, fluorescence quenching could only be due to a long-range photoinduced electron transfer through the dendrimer network with the positively charged MV^{2+} molecules assembled *via* electrostatic interaction on the negatively charged dendrimer surface. Hence the saturation behavior was due to the limiting charge density on the dendrimer surface.

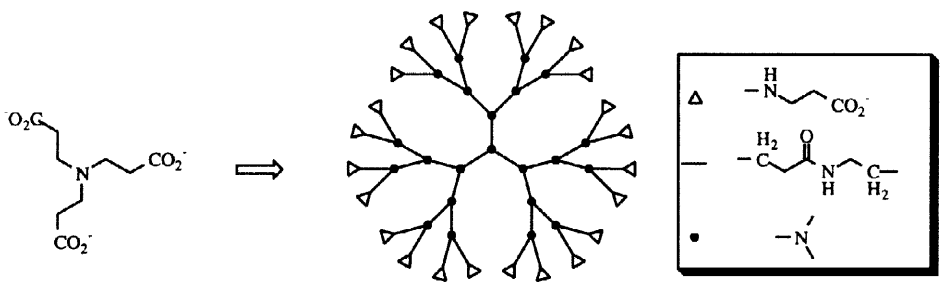


Recently, Vögtle and Balzani showed that a larger dendritic envelope had a pronounced shielding effect and diminished the quenching efficiency of molecular oxygen on a $Ru(bipy)_3^{2+}$ central core.[130] Tris-(bipyridine)ruthenium(II) complexes **161** and **162** having multiple ester functionalities on the surface were synthesised by a divergent procedure. Both the absorption and emission spectra of **161** and **162** are very similar to those of nondendritic $Ru(bipy)_3^{2+}$ complexes. In deaerated solution the lifetime of the higher generation complex **162** was shorter than that of the complex **161**. On the other hand, in air equilibrated



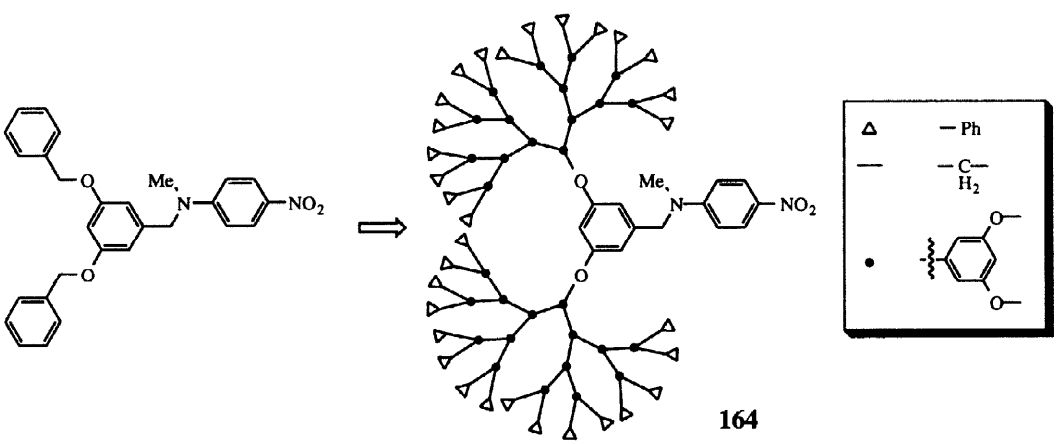
solution the situation was reversed, and both **161** and **162** had a longer excited state lifetime than the parent $Ru(bipy)_3^{2+}$ molecule. Hence, the larger dendritic shell served as a better shielding envelope against the quenching of the photochemically active unit by molecular oxygen in aerated solution.

Photoinduced electron-transfer reactions have also been used to probe the structure of starburst dendrimers as a function of their generation. The quenching of the ^{3}MLCT excited state of $Ru(bipy)_3^{2+}$ by MV^{2+} in the presence of different generations of carboxylate-terminated dendrimers **163** was reported.[131] In the presence of the lower generation species, the quenching behavior was very similar to those in homogeneous solutions. However, the quenching process became highly efficient in the presence of later generations. The result was consistent with an open structure for the lower generation dendrimers, where both $Ru(bipy)_3^{2+}$ and MV^{2+} interacted weakly with the dendrimers. On the other hand, a compact, closed-shell and negatively charged structure was proposed for the high generation dendrimers, into which positively charged $Ru(bipy)_3^{2+}$ and MV^{2+} could be brought into close proximity leading to efficient quenching. Similar transitions from open to closed shell structures toward higher generations were also detected by a similar photophysical investigation using pyrene as a photoluminescence probe.[132]



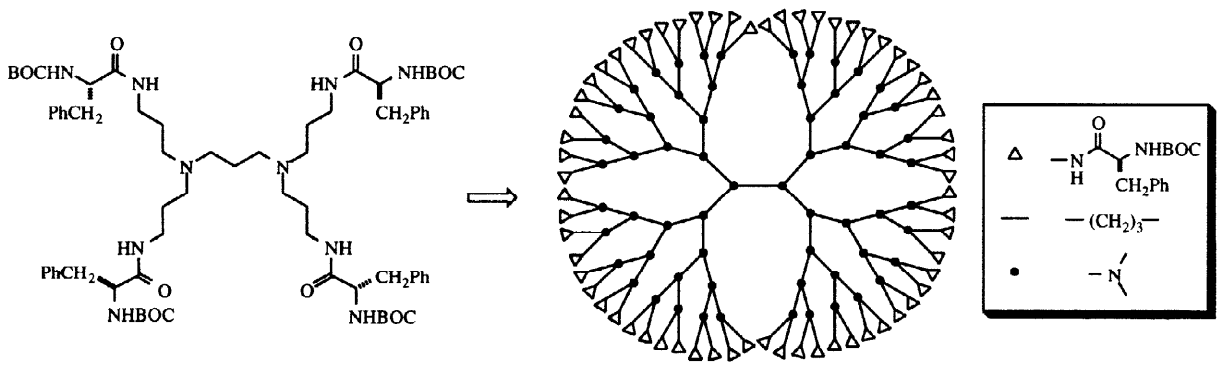
163

Solvatochromic devices were similarly used to probe the polarity of dendritic molecules.[133] Fréchet described the synthesis of a series of polyether dendritic fragments **164** up to G6 by attaching a solvatochromic 4-(*N*,*N*-dialkylamino)nitrobenzene functional group at the focal point. UV spectrophotometric analysis of this series of compounds exhibited a bathochromic shift of λ_{max} with increasing generation number, together with the presence of a noticeable discontinuity on going from G3 to G4. This was due to a transition from an extended to a globular structure as the steric environment of the dendritic branches increased.



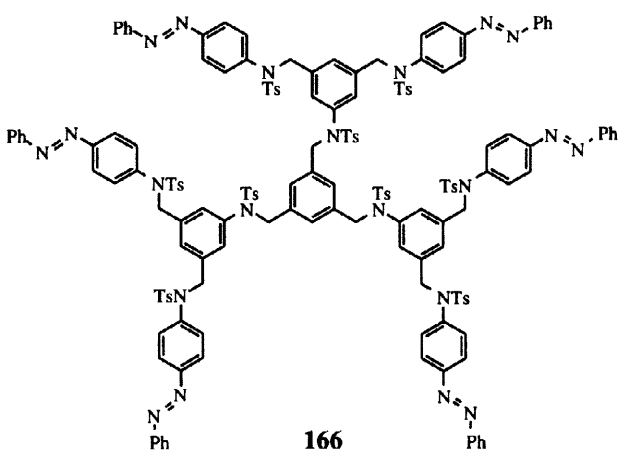
164

Functionalised poly(propyleneimine) dendrimers **165** decorated with *N*-(*tert*-butoxycarbonyl)-L-phenylalanine moieties on the surface were also shown to be effective electron donors in quenching the photoexcited states of the C_{60} molecule to form a radical anion $C_{60}^{\cdot -}$.[134] Interestingly, persistent photoinduced electron transfer only occurred for dendrimers with generation higher than G1. Small model molecules containing either the core structure or the dendrimer shell were less effective electron donors.



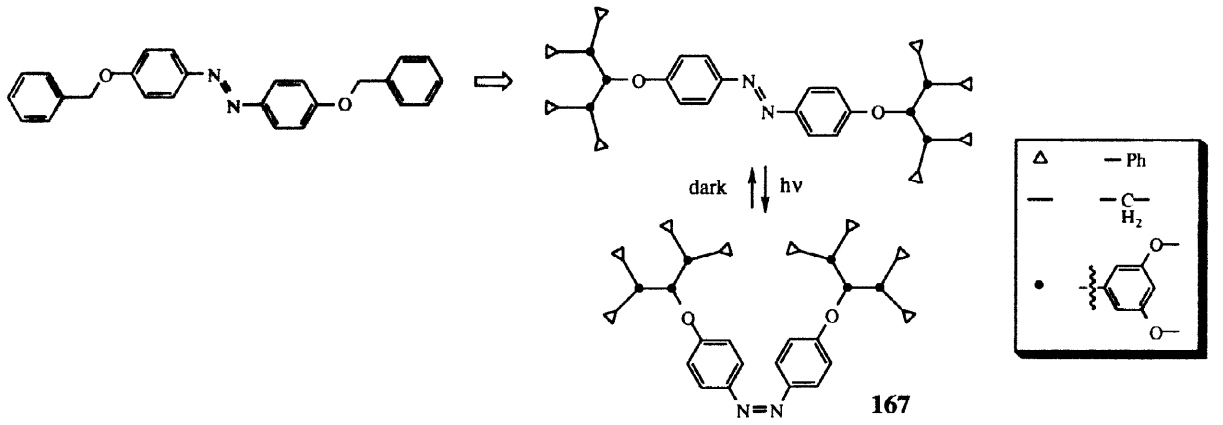
165

Photoresponsive dendrimers which undergo conformational or configurational changes upon photoactivation have also been prepared. The first example of such a photoactive dendrimer was reported by Vögtle.[135] The target dendrimer **166**, synthesised *via* a divergent strategy, has six azobenzene side chains located at the peripheral sector. Thermal equilibration of **166** in the dark converted all the azo groups to the *E*-configuration. Irradiation of the all *E*-dendrimer at 313 nm for 5 min resulted in the predominant formation of the *Z*-isomer which could be re-isomerised back to the *E*-configuration upon subsequent irradiation at 436 nm.

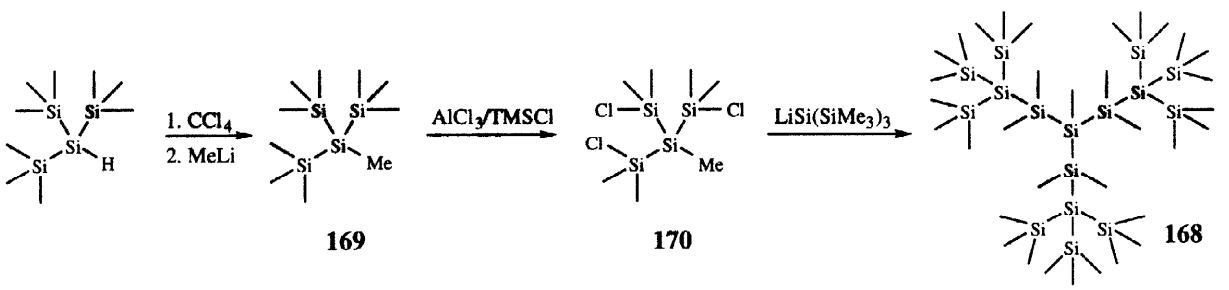


166

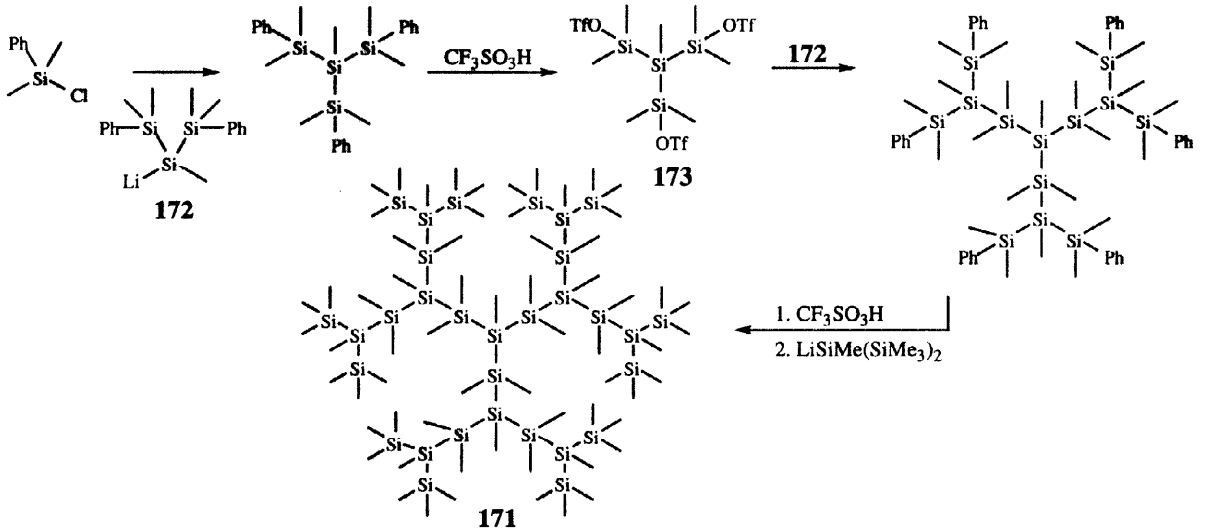
McGrath also reported the preparation of a number of polyether dendrimers **167** having an azobenzene central linker connected to two dendritic sectors.[136] After dark incubation, the *E*-isomer could be photoisomerised to the corresponding *Z*-isomer on irradiation with 350 nm light. Thermal reversion to the original *E*-isomer was shown to follow a first order process with a half-life of 40 min. This value was similar in magnitude to those of other non-dendritic azobenzenes, and apparently there was little steric influence on the thermal isomerisation process. This study also represents the first investigation on the gross topological change of a dendrimer induced by light.



Polysilanes are another interesting class of compounds with novel photoluminescence, semiconducting, photoconducting, thermochromic and nonlinear optical properties.[137] Polysilane dendrimers, having most of the fragile Si-Si bonds buried in the interior, could offer better stability than their linear analogs. Lambert described the preparation and crystal structure of a G1 polysilane dendrimer **168** having 16 silicon atoms.[138] The longest polysilane chain contained within the structure consists of 7 silicon atoms which is repeated 27 times in the dendritic structure. Dendrimer **168** was prepared from tris(trimethyl-silyl)silane, which could be converted to methyl[tris(trimethylsilyl)]silane **169** by reaction with carbon tetrachloride and methyllithum. Subsequent demethylative chlorination of **169** with $AlCl_3$/TMSCl afforded a tris-(chlorosilane) intermediate **170** which was then reacted with tris(trimethylsilyl)silyllithium to give the target polysilane dendrimer **168**. The UV λ_{max} of **168** is at 272 nm, which is lower in energy than that of the linear heptasilane (266 nm), and almost identical to that of octasilane (272.5 nm). The molar extinction coefficient of **168** is 10 times larger than those of the corresponding linear heptamer, demonstrating that the multiplicity of heptasilicon pathway dramatically enhances the extinction coefficient without changing the absorption maximum. This dendritic polysilane **168** could also be prepared by a different route.[139]



The corresponding G2 polysilane dendrimer of **168** was recently reported by Sekiguchi and Sakurai.[140] A divergent synthetic strategy was used in which the key step involved the replacement of Si-aryl bonds with silyl triflate functionalities. The Si-Si single bond was then created by coupling of a silyl lithium reagent **172** to a tris(silyl triflate) **173**. Repetition of this procedure afforded the G2 polysilane dendrimer **171**. The longest polysilane chain in **171** has 11 directly connected Si atoms. The UV λ_{max} of **171** is at 279 nm, which is lower in energy than that of the corresponding G1 analog **168**. Compound **171** has an extinction coefficient which is 2 times larger than that of **168**.

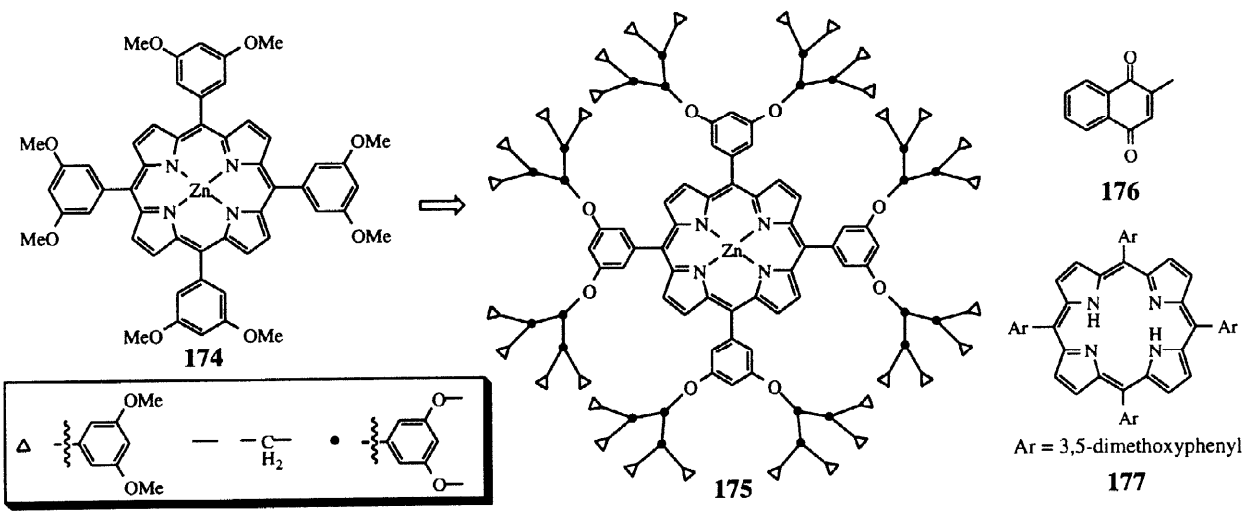


5.5 Dendrimers as Receptors or Complexation Agents

Since the discovery of crown ethers and their ability to form stable host guest complexes with metal ions, studies in the design, synthesis and properties of artificial receptors have become one of the main themes in host-guest complexation chemistry. Not surprisingly, a number of dendrimers with novel host properties have been reported. Encapsulation of small guest molecules within the internal cavities of sterically congested dendrimers is another mode of binding which is normally not observed with simple host molecules.

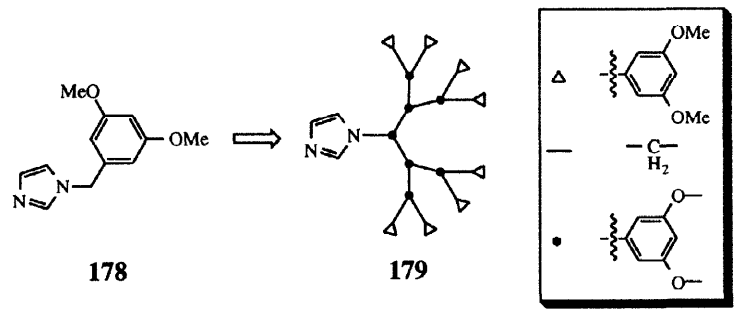
Dendritic receptors for neutral guests

The formation of a clathrate between a dendrimer and a neutral solvent molecule has already been documented.[47a] In terms of popularity, the most studied dendritic receptors for neutral guest molecules are those derived from porphyrin, due to their close resemblance to biological molecules such as haemoglobin and myoglobin. The first series of examples **174** and **175** are porphyrin dendrimers having a zinc porphyrin core encapsulated within a polyether dendritic cage.[141] They were prepared by a divergent anchorage of polyether dendritic fragments to a 5,10,15,20-tetrakis-(3',5'-dihydroxyphenyl)porphine followed by metallation with zinc acetate. The fluorescence quenching profiles of these macromolecules were very different and were related to



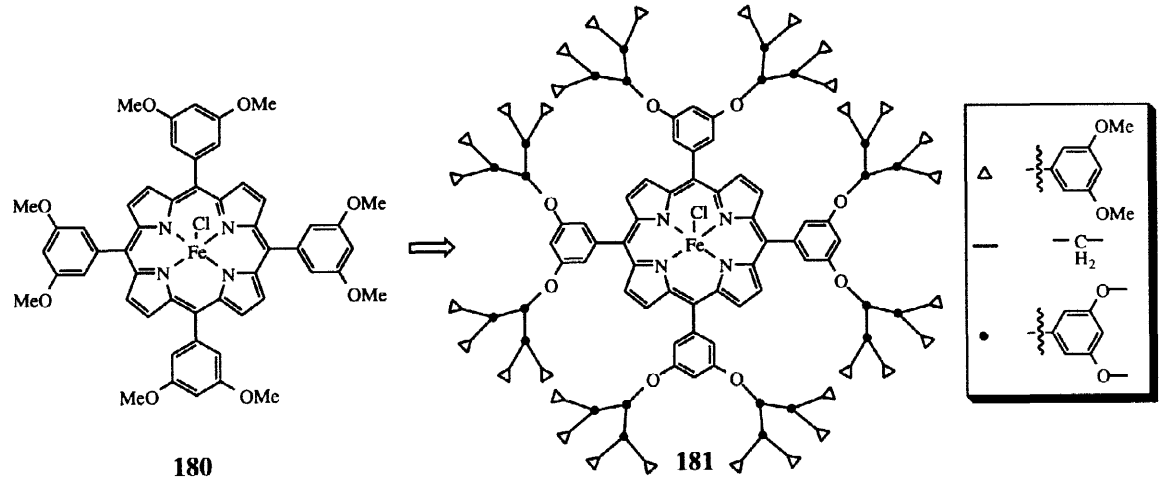
both the dendrimer generation and the size of the quencher. The G1 zinc porphyrin **174** was quenched to a similar extent by either the smaller vitamin K_3 **176** or the sterically bulkier porphyrin **177**. On the other hand, porphyrin **177** was a poor quencher for the G4 zinc porphyrin complex **175**, while vitamin K_3 was a more efficient one. Hence, the larger polyether dendritic envelope served as a steric barrier for the larger quencher but acted as a host for trapping the smaller vitamin K_3 molecule.

The binding properties of these zinc porphyrins to imidazoles **178** and **179** of different sizes were disclosed in a follow-up study.[142] UV spectroscopic analysis of the Soret bands of the G4 dendritic porphyrin **175** indicated that the zinc porphyrin core was almost shielded from its surroundings by the dendritic sectors. The densely packed nature of the dendrimer surface was also confirmed by ^{1}H-NMR pulse relaxation time (T_1) measurements, which showed that the conformational motion of the peripheral methoxy groups became less mobile with each successive increment of the number of generations. The binding stoichiometry between the zinc porphyrin and the imidazole was established by spectrophotometric titration to be 1 : 1. The binding constants (K_a) become smaller as the generations of both the porphyrin and imidazole components become higher. For example, the K_a between the smallest porphyrin-imidazole pair **174** and **178** is 9.2×10^4, whereas that of the largest pair **175** and **179** is 2.4×10^2. A sudden drop of binding constant across G3 and G4 porphyrins was noted, again indicating a change from an open to a semiclosed architecture.



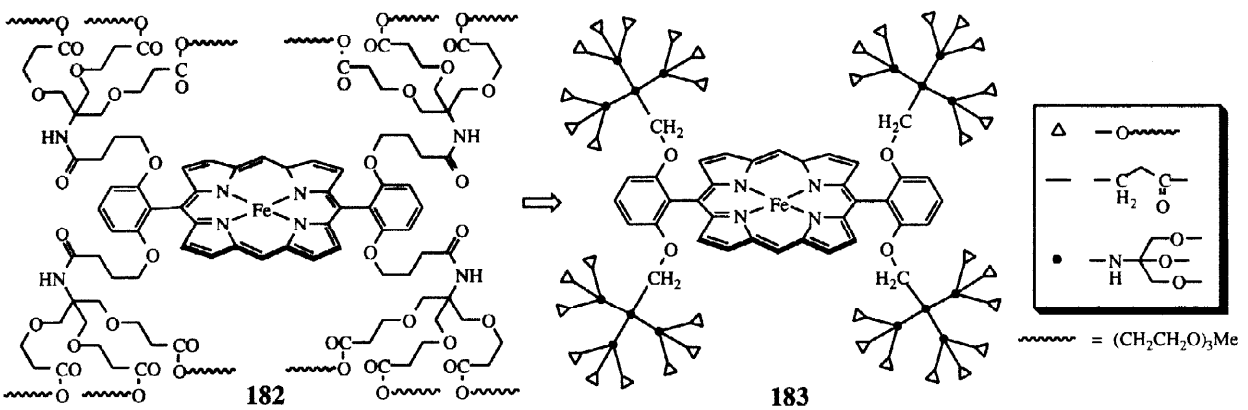
178 **179**

On switching the metal ion from zinc(II) to iron(II), metalloporphyrins **180** and **181** capable of binding to dioxygen and carbon monoxide were obtained.[143] In the presence of 30 equiv. of 1-methylimidazole, the smaller porphyrin **180**, without any steric protection around the active site, was instantly and irreversibly oxidised by O_2 to give a μ-oxo dimer. On the other hand, iron(II) porphyrins of G3 to G5 did not show any

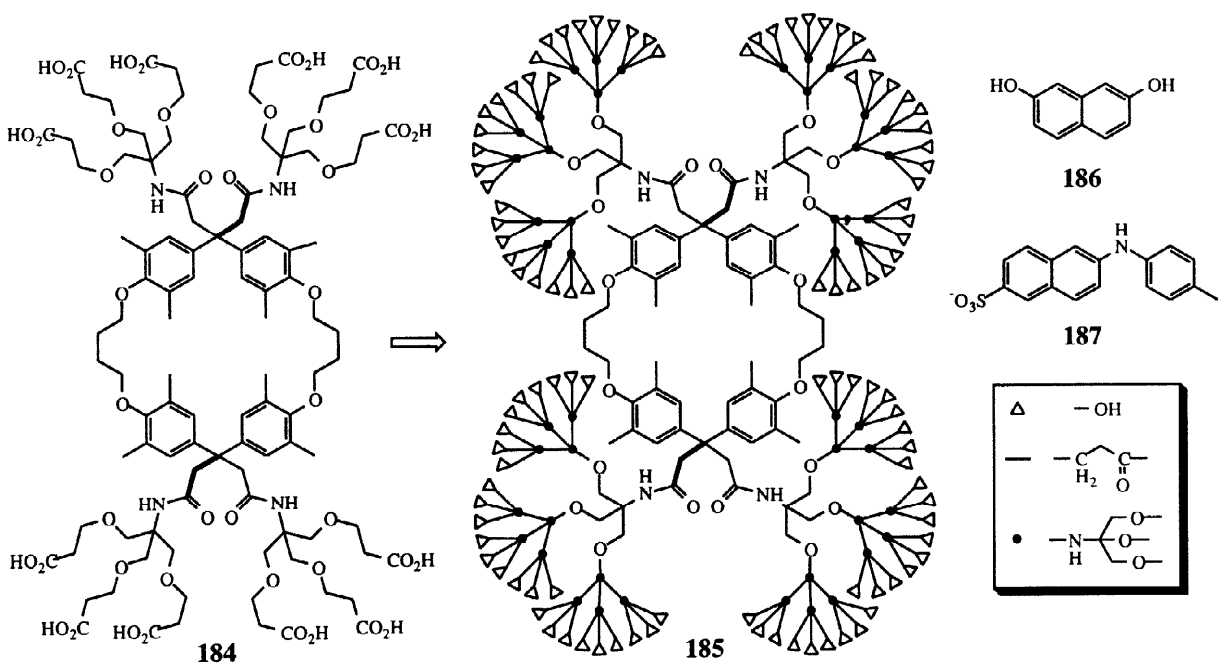


180 **181**

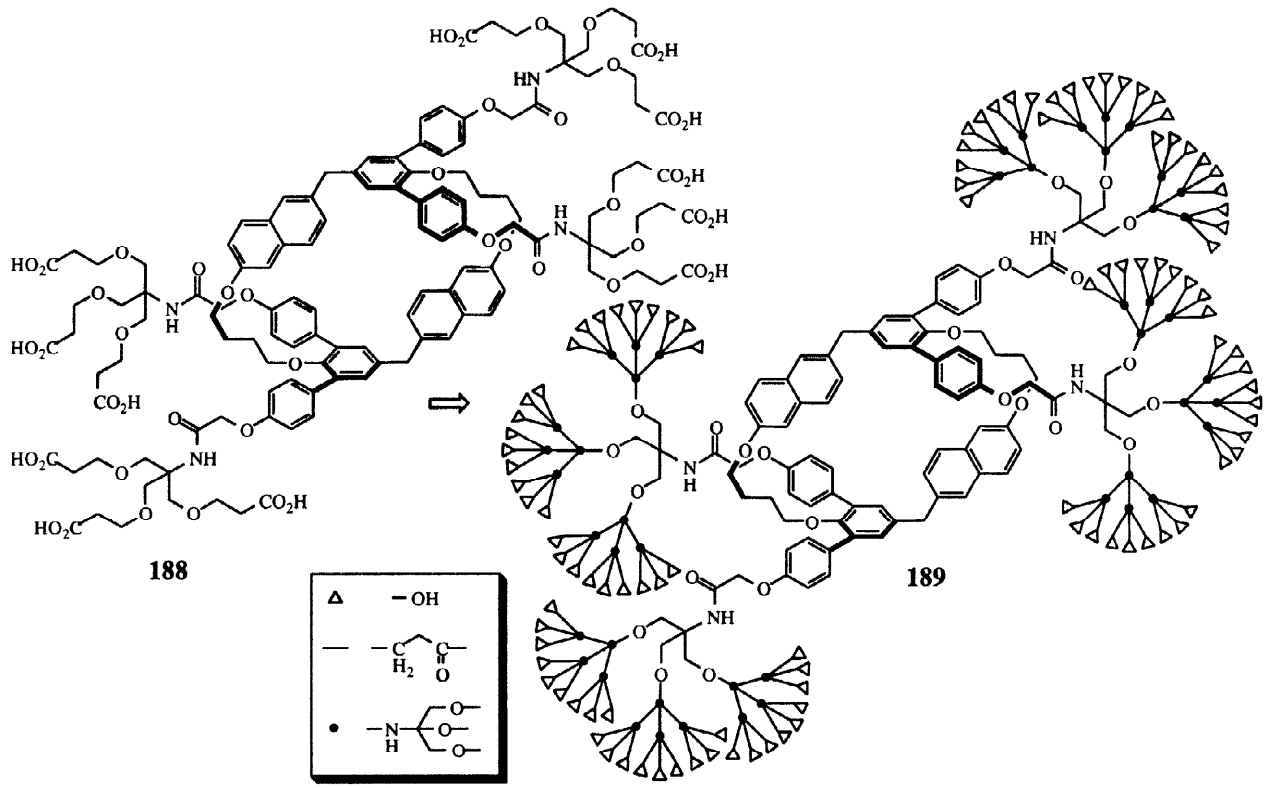
sign of dimer formation, and instead bound reversibly with O_2. When the oxygen-bound G3 or G4 porphyrin complex was treated with water-saturated toluene, an irreversible autoxidation occurred with a half life of 1.5 and 6 h, respectively. However, the dioxygen adduct derived from the G5 porphyrin **181** could survive over a period of two months in wet toluene. Thus, the large dendritic fragments not only inhibited bimolecular oxidation but also provided a hydrophobic barrier against permeation of water molecules. Furthermore, gas permeation studies indicated that even small molecules such as O_2, N_2 and CO diffused much more slowly through the packed G5 dendrimer framework than through a network of lower generation. Other structurally related dendritic iron(II)porphyrins **182** and **183** also exhibited reversible O_2 and CO binding in the presence of 1,2-dimethylimidazole.[144] Remarkably, the O_2 binding affinity of these dendritic porphyrins were 10^3 greater than those of T-state haemoglobin, implying the possibility of H-bonding between the terminal oxygen of the bound O_2 and an amide N-H group.



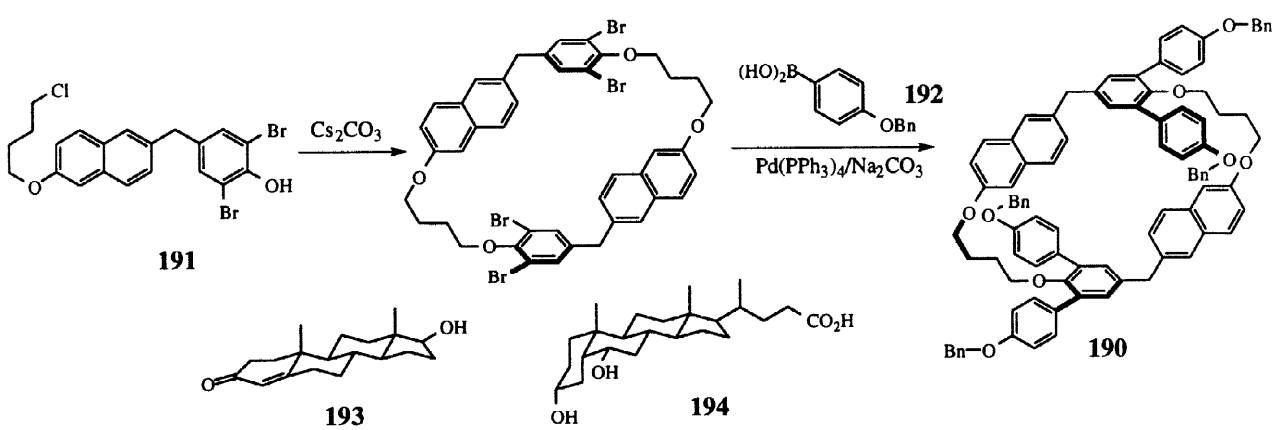
Water soluble dendritic cyclophanes **184** and **185** also possessed interesting host properties.[41a] They were synthesised by a divergent addition of polyamide branching units onto a cyclophane core. These receptors possess a hydrophobic cavity for binding to nonpolar aliphatic and aromatic substrates. ^{1}H-NMR



and fluorescent quenching studies confirmed the formation of 1 : 1 inclusion complexes with naphthalene-2,7-diol **186** ($K_a \sim 2 \times 10^3$) and 6-(*p*-toluidino)naphthalene-2-sulfonate (TNS) **187** ($K_a \sim 10^4$) in aqueous solution. Both the thermodynamic complexation constants and the kinetic complexation rates were shown to decrease with increasing dendrimer generation. The fluorescence emission maximum of TNS was notably blue-shifted when changing from the complex of a lower to a higher generation, suggesting that the microenvironment around the binding cavity became more nonpolar with increasing branching.

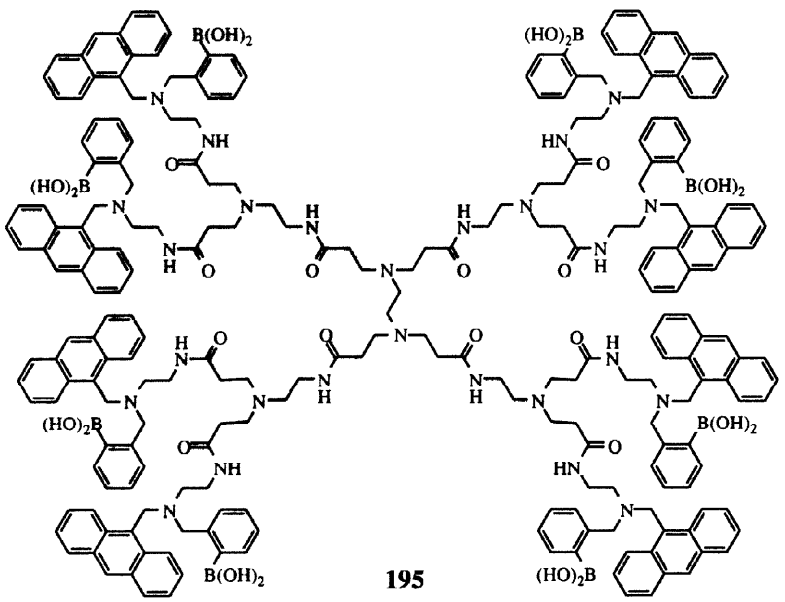


Dendrophanes **188** and **189** capable of forming 1 : 1 inclusion complexes with steroids were also prepared.[41b] The central core unit **190** was prepared *via* a macrodimerisation of a chlorophenol **191** followed by a Suzuki cross-coupling of the cyclisation product with a boronic acid derivative **192**. The polyamido dendritic branches were then added to the core to give the target dendrophanes. The binding constants with nonpolar steroids such as testosterone **193** were high ($K_a \sim 10^3$) and were almost independent of dendrimer



generation. Significant substrate selectivity was noted since a polar steroid such as hyodeoxycholic acid **194** was less tightly bound (K_a ~ 40) than a nonpolar steroid.

The dendritic receptor **195** having 8 boronic acid residues located on the surface a PAMAM dendrimer was found to have improved binding ability to sugar molecules.[145] This dendritic receptor binds 10^2 times more tightly to sugar derivatives such as D-galactose and D-fructose than a monomeric boronic acid analog **196**. The enhanced binding ability of **195** was ascribed to the cooperative action of two boronic acids to form an intramolecular 2 : 1 complex.



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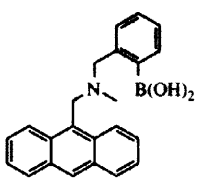
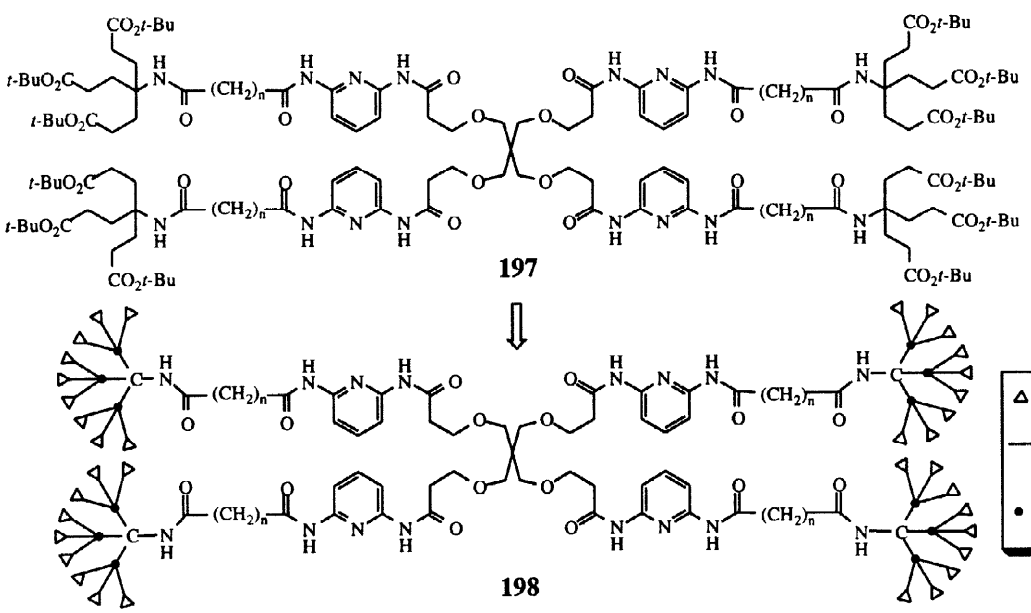


196

Dendritic receptors **197** and **198** capable of binding to glutarimide were synthesised by Newkome.[146] They were obtained by a divergent addition of polyamido dendritic fragments to a tetrahedral core containing four 2,6-diaminopyridine units. The association constants between these dendrimers with glutarimide were about 7×10^1, as determined by a ^{1}H-NMR titration experiment.

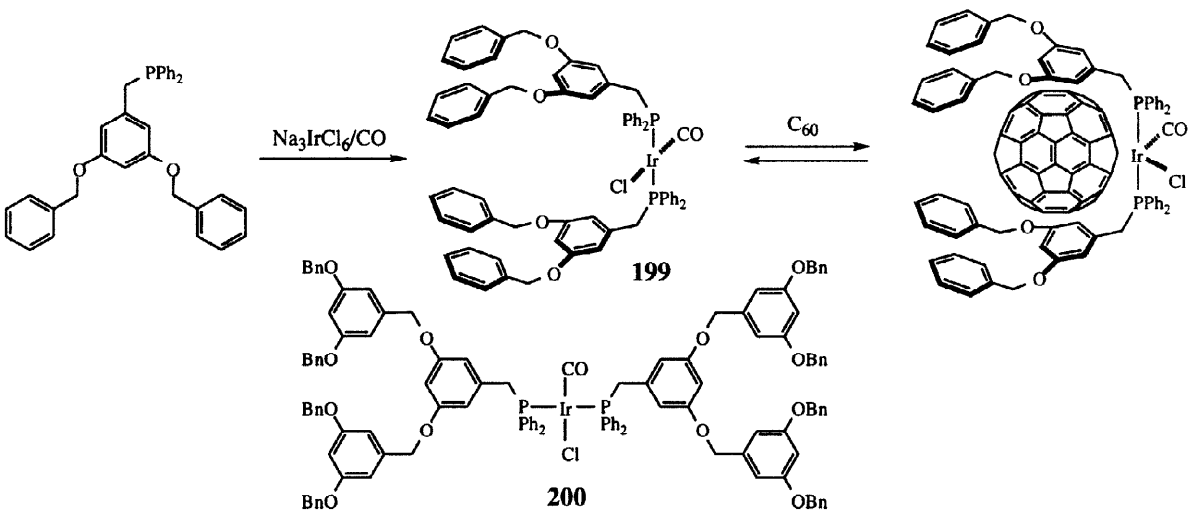


197

198

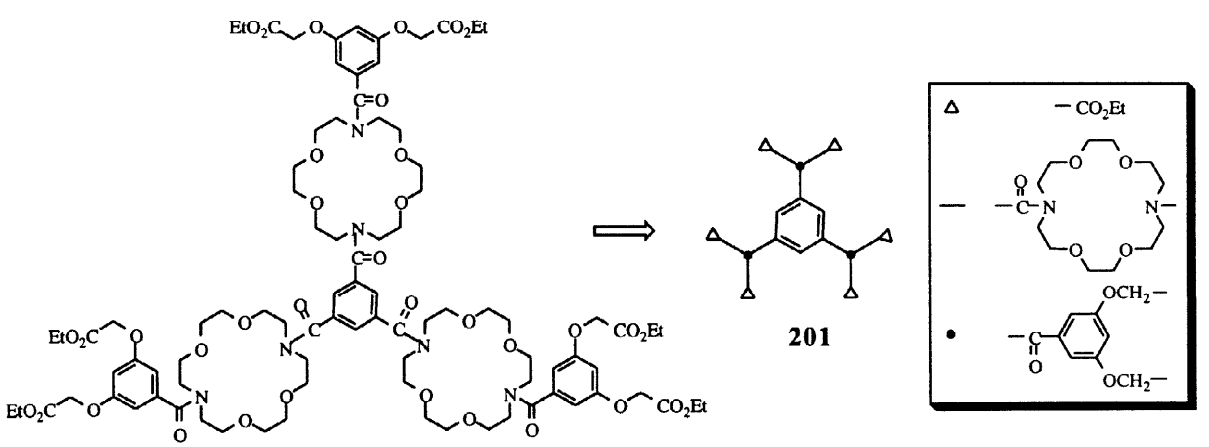
n = 3 or 11

Catalano recently reported the preparation of dendritic receptors capable of reversibly binding to C_{60}.[147] These are iridium complexes **199** and **200** with two aromatic polyether dendritic appendages. The metal complexes were prepared by CO reduction of Na_3IrCl_6 followed by the addition of two equiv. of an aromatic dendritic phosphine ligand. Addition of C_{60} to a bright yellow degassed chlorobenzene solution of **199** or **200** resulted in the formation of a deep green color typical of C_{60}–$Ir(CO)Cl(PPh_2R)_2$ complexes. The binding of C_{60} by these ligands was due to a favorable arene-fullerene interaction through the aromatic dendritic arms. The equilibrium constants for the formation of **199**•C_{60} and **200**•C_{60} were 18 M^{-1} and 22 M^{-1}, respectively, with the larger ligand **200** being a consistently better host for C_{60} than **199** at various temperatures.

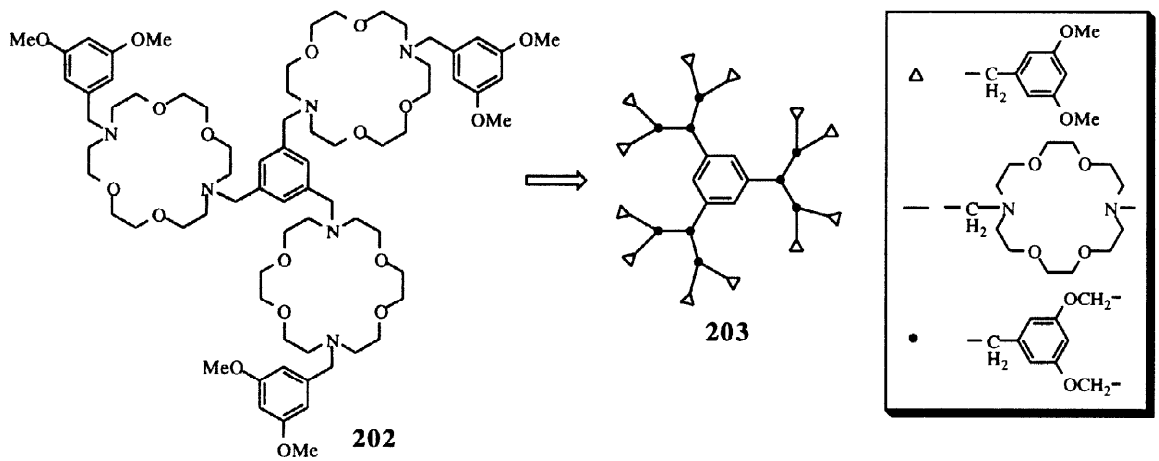


The previously mentioned poly(propyleneimine) dendrimers **90** with multiple ferrocene groups on the surface could form stable cyclodextrin (CD) inclusion complexes.[148] For the G1 analog of **90**, all 8 ferrocene residues were shown to complex with CD, as only one redox wave was observed in CV studies. On the other hand, two CV peaks were observed for the G2 analog, implying that only part of the peripheral ferrocene moieties were bound to CD. Further addition of excess CD did not change this redox pattern. This result suggested that substantial steric congestion was developed on the dendrimer surface of the G2 analog, which limited the number of ferrocene residues that could be included by the bulky CD molecule.

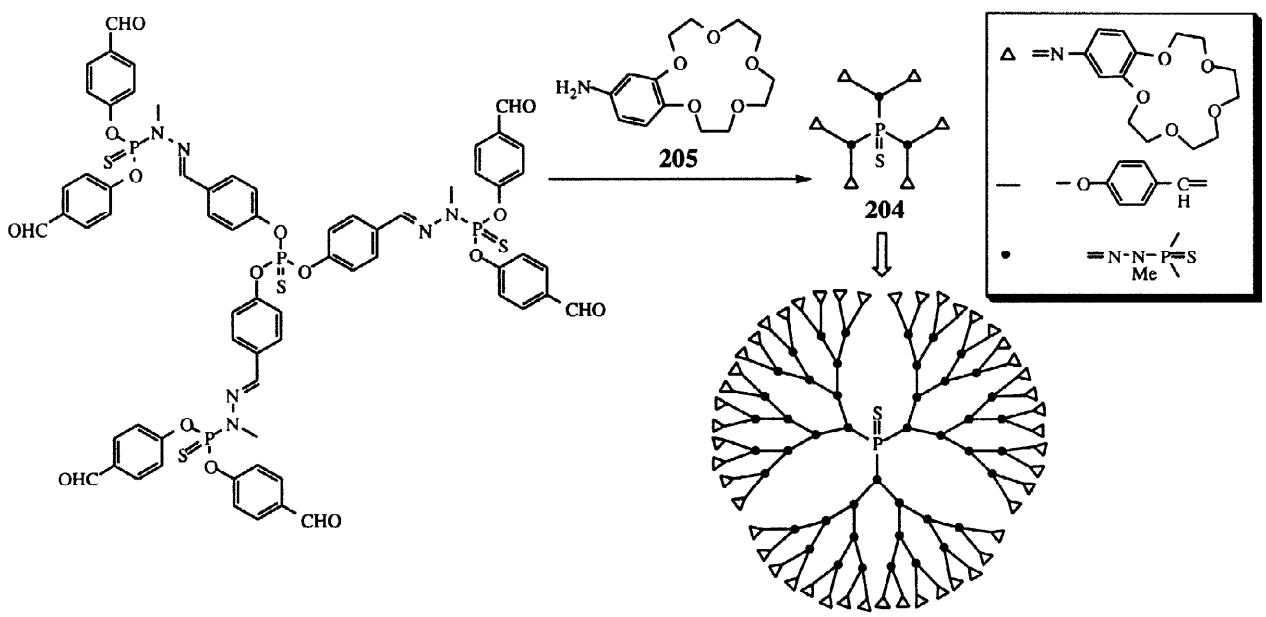
Dendritic receptors for cationic guests



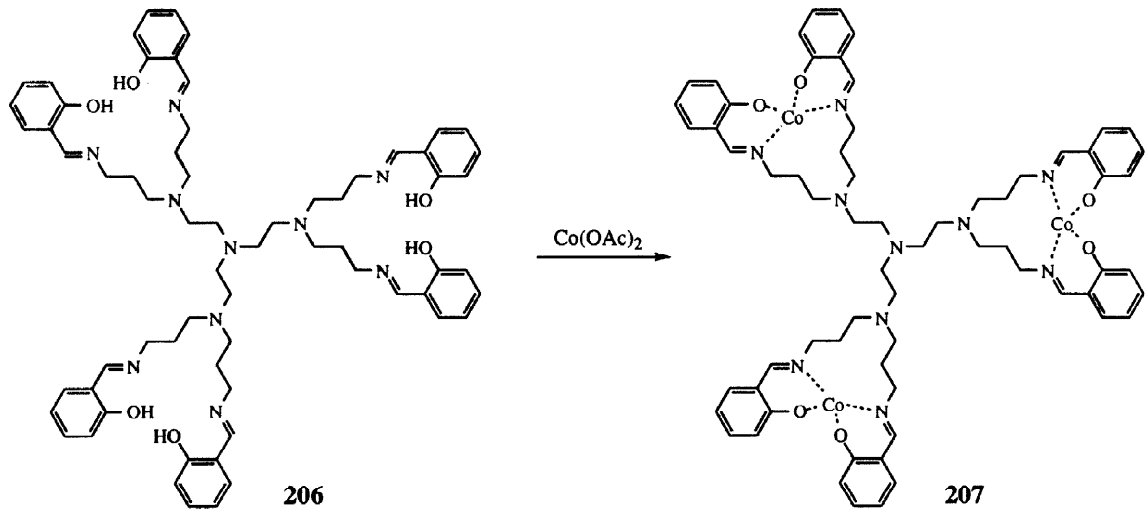
Metal ions belong to one of the most important class of cationic guests. Dendritic receptors **201** containing multiple crown ether receptor units for alkali metal ions were described by Shinkai.[149] Structurally they were made up of diaza-18-crown-6 branches and 3,5-dihydroxybenzamide junctures constructed by a convergent synthetic protocol. Due to the poor electron donating power of the amido nitrogens, these receptors showed poor extractability for alkali metal ions.[150] To improve the metal binding ability, a related series of crown dendrimers **202** and **203** with amino linkages were later prepared.[150] As expected, this polyamino dendritic series exerted good alkali metal binding ability, in particular to K^+ ion. Interestingly, the polyamino G1 crown dendrimer **202** was able to solubilize myoglobin more efficiently than the analogous higher generation dendrimers.



Phosphorous-based dendrimers **204** containing up to 48 crown ether moieties on the surface sector have also been reported by Majoral.[151] They were synthesised by divergent coupling of an excess of amino crown ether **205** to the surface aldehyde groups of a phosphoramide dendrimer. The metal binding properties of **204** were not however disclosed in this study.

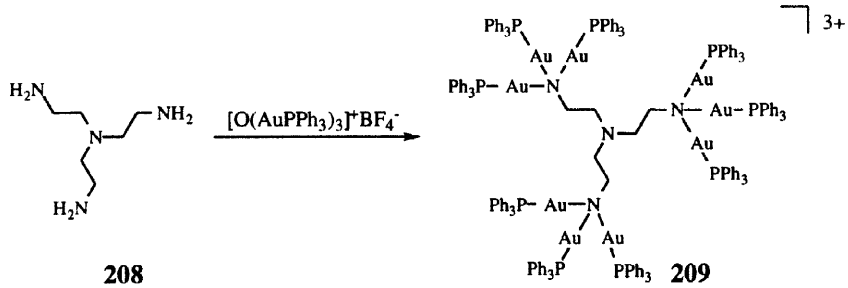


Nitrogen containing compounds, especially polyamino ligands, are known to form complexes with a variety of metal ions. The G1 polydentate ligand **206**, prepared *via* condensation of poly(propyleneimine) dendrimer[13] with 2-hydroxybenzaldehyde, could be converted to a tri-(cobalt-salen) complex **207** upon treatment with cobalt acetate.[7b] It was likely that the two hydroxyl imino ligands chelating to the Co(II) ion belonged to the same dendritic wedge, although this could not be confirmed in the study.



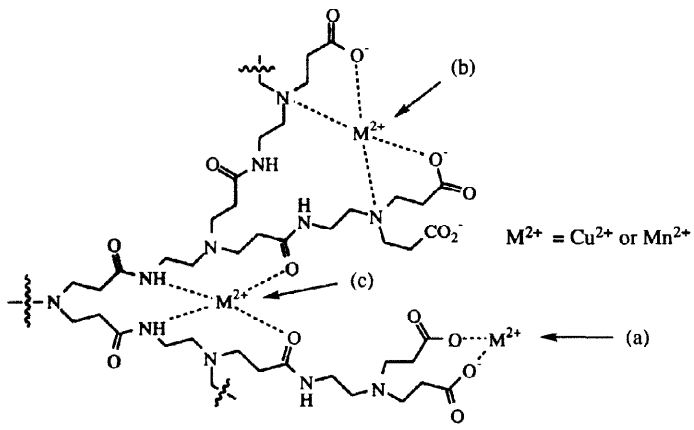
206 **207**

Similarly, reaction of tris(2-aminoethylamine) **208** with tris[(triphenylphosphine)aurio(I)]oxonium tetrafluoroborate afforded a crystalline polynuclear gold cluster **209**.[152] The compounds are stable to air, moisture and light, but their solutions slowly decompose at ambient temperature with separation of colloidal gold. Due to the high heavy metal content, this compound is expected to be useful in the areas of biochemical and medical diagnostics.



208 **209**

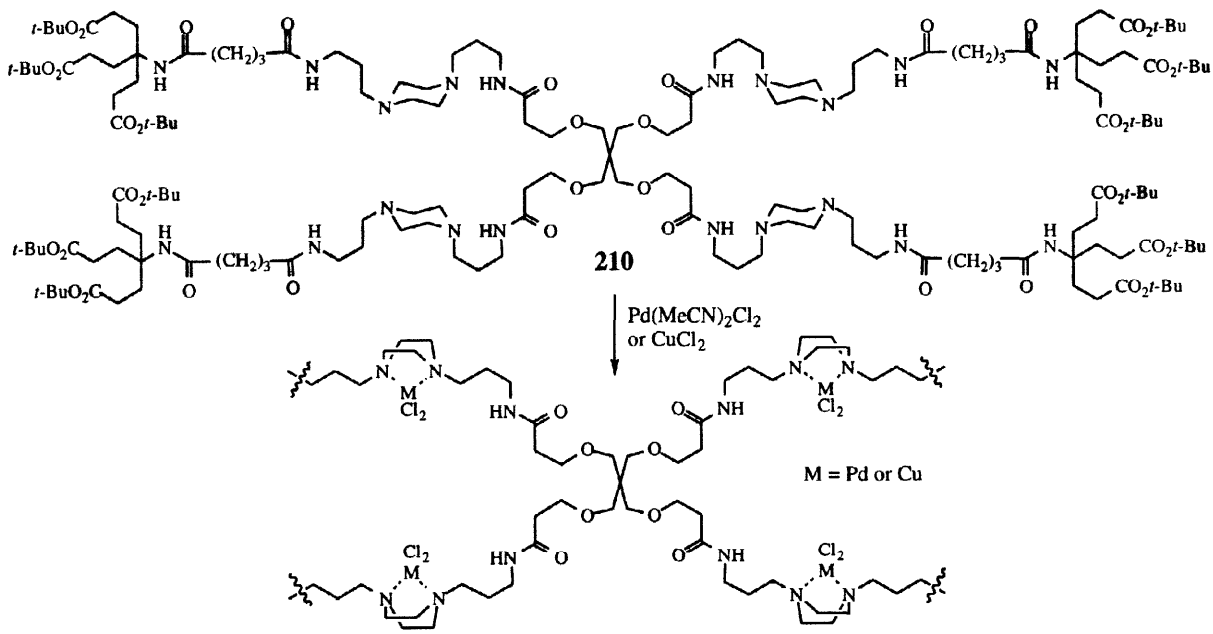
Carboxylate-terminated PAMAM dendrimers **163**, due to the availability of surface carboxylates and internal amido and amino functionalities for metal binding, have been used to prepare a number of copper(II)[153] and manganese(II) complexes.[4b] As a result of the multidentate nature of these dendrimers, several metal binding modes, characterised by different ligands and different structural disposition of the ligands, were found (Figure 14). These included the formation of (a) terminal bis(carboxylate) metal complex; (b) metal-N_2O_2 complex located at the periphery and (c) metal-N_2O_2 complex located at the interior of the dendrimer matrix. Furthermore, line shape studies of the EPR spectra of these complexes showed a distinction between earlier ($n < 3$) and later ($n > 3$) generations and were consistent with a change of the dendrimer shape across generations. Similarly, several metal binding modes were also detected with amino-terminated PAMAM dendrimers.[153b]



163

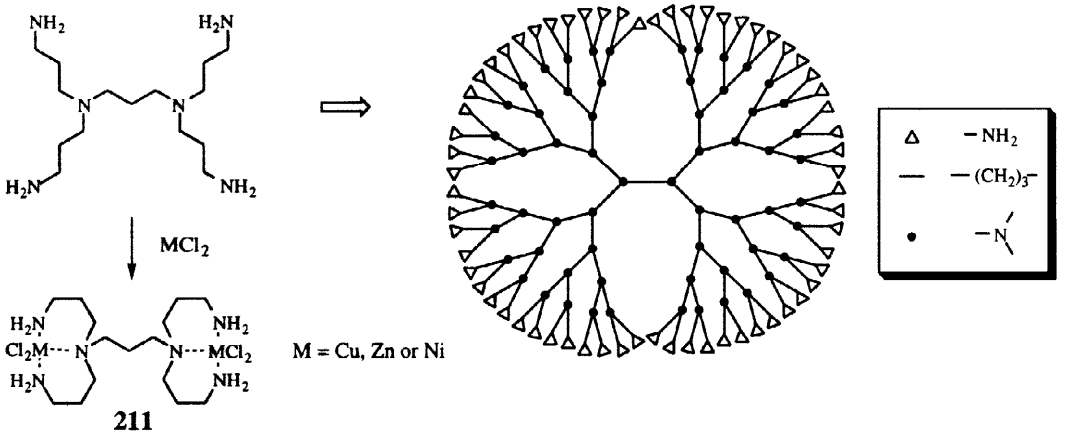
Figure 14. Possible modes of metal complexation by PANAM dendrimer.

Newkome also reported the synthesis of polyamino dendrimers **210** possessing four internally incorporated piperazine moieties, which readily formed complexes with metals.[154] Stable orange crystalline palladium(II) complexes were obtained upon stirring the dendrimer **210** with $Pd(MeCN)_2Cl_2$. Based on ^{13}C-NMR study, it was postulated that the binding ligand was the piperazine ring which adopted a boat conformation in order to facilitate metal chelation. The related copper(II) complexes were easily obtained by treating **210** with $CuCl_2$.



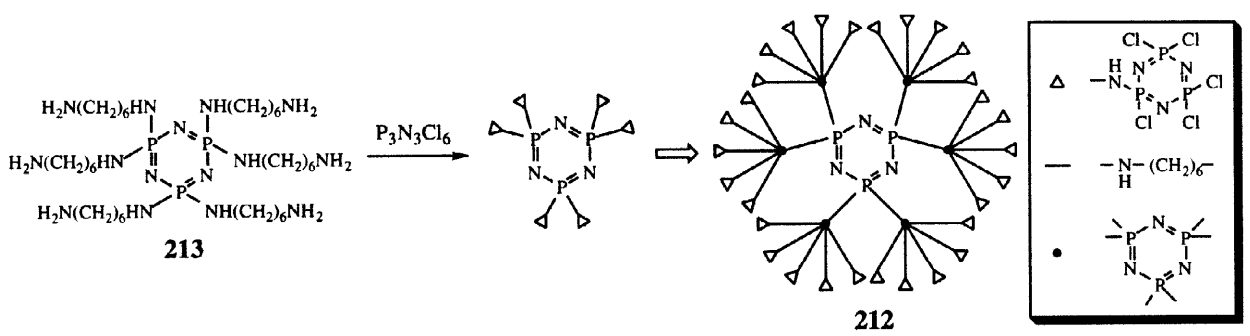
Very recently, well defined metallodendrimers **211** containing up to 32 metal ions deposited on the surface of poly(propyleneimine) dendrimers have been synthesised.[155] It was reported that the surface sector of this type of dendrimer, having a large number of bis-(3-aminopropyl)amine units, could form very stable complexes with various transition metal ions. Addition of $CuCl_2$ to different generations poly(propyleneimine) dendrimers in methanol resulted in the immediate formation of 1 : 2 complexes between the Cu(II) ions

and the terminal NH_2 groups. Multiple Cu(II) complexation with the G1 to G5 dendrimers gave metallo-dendrimers having 2, 4, 8, 16 and 32 copper nuclei, respectively. The copper(II) complex of the G5 dendrimer could be visualised under a transmission electron microscope as spheres with a radius of 3 ± 1 nm. All Cu(II) complexes exhibited one electrochemical irreversible reduction wave in aqueous solution. The reduction potential was noted to shift to higher values on moving toward the higher generations. This shift was likely caused by the increased density of Cu(II) on the dendrimer surface, resulting in a destablisation of the Cu(II)-states. Similar complexation patterns were observed for the corresponding Zn(II) complexes.

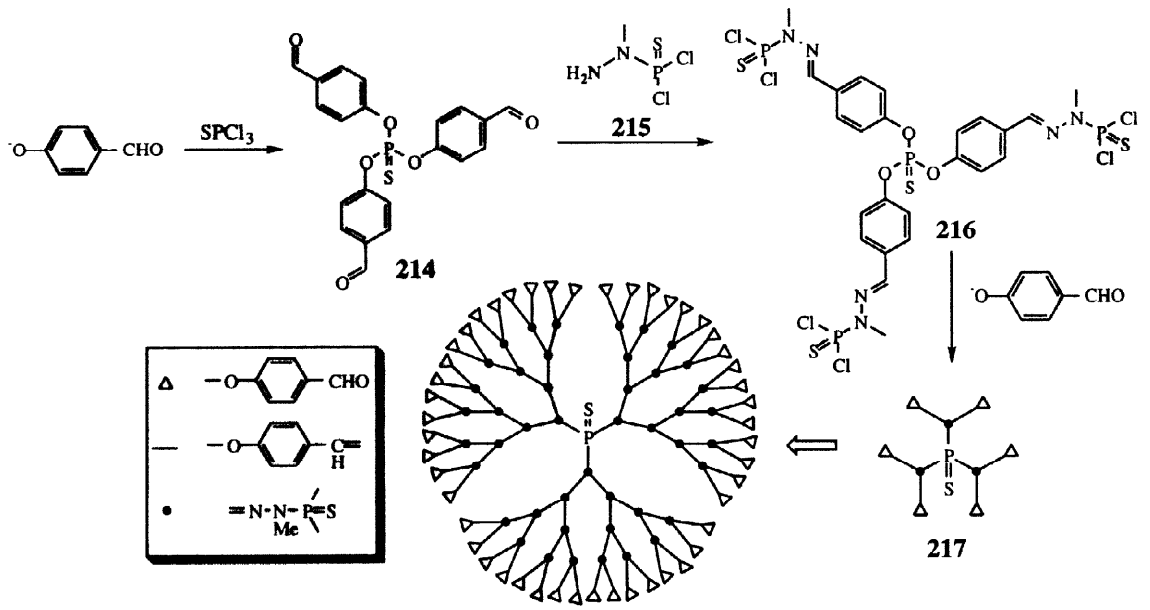


Another important group of metal-binding ligands are those containing neutral phosphorous atoms. Phosphorous containing dendrimers with different branching junctures, branching patterns, core structures and surface functionalities had been prepared mainly due to the work of Labarre[156] and Majoral.[157]

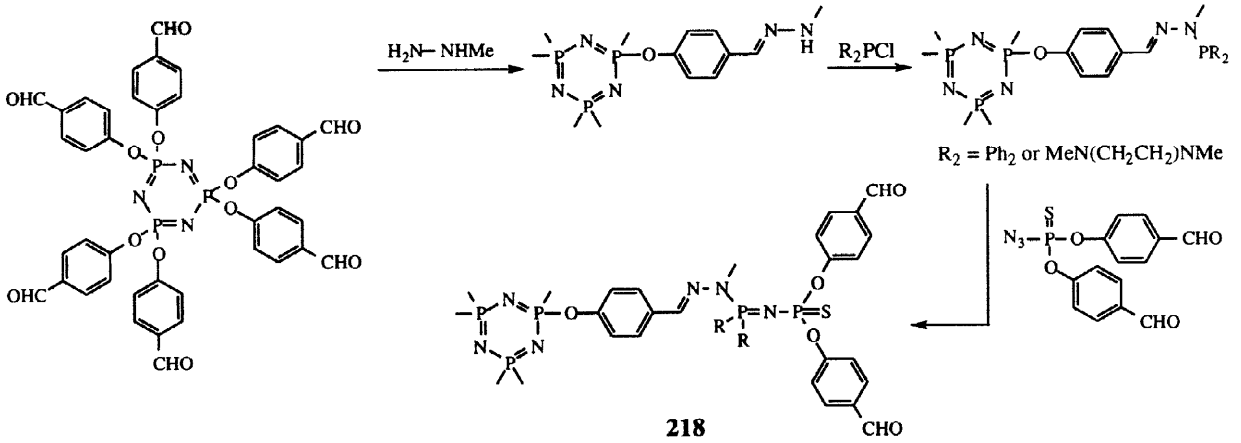
Labarre's work has been centred on the preparation of dandelion dendrimers **212** having six-fold cyclotriphosphazene branching junctures. The six chlorine atoms of hexachlorocyclotriphosphazene were regiospecifically replaced by 6 equiv. of hexadiamine to give a hexaamino intermediate **213** to which additional cyclotriphosphazene units were further added to give the G1 dendrimer. Using this divergent procedure, organophosphorous dendrimers up to G8 have been synthesised.[158] One of the unique features of this class of dendrimers is that the six diamino branches emanating from the cyclophosphazene core are stereospatially equivalent and hence the dendrimer itself is highly spherical. The metal complexing properties of these dendrimers were not documented.



Majoral's work has been focused on the preparation of neutral thiophosphoramide dendrimers.[157,159] Using a divergent synthetic strategy, the central core thiophosphoryl chloride was allowed to react with the sodium salt of 4-hydroxybenzaldehyde to give the G0 dendrimer **214**. Subsequent coupling of aldehyde **214**

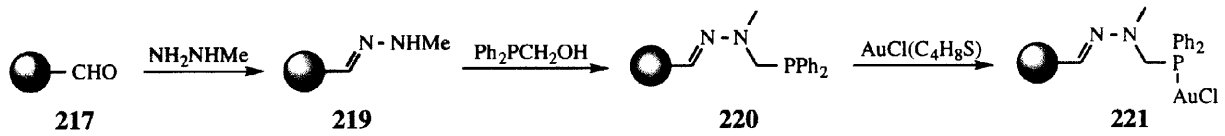


with a hydrazine derivative **215** afforded a tris(thiophosphoryl dichloride) **216**. Repetition of this reaction cycle gave the dendrimer of the next generation **217** containing multiple copies of aldehyde functionality on the surface. Neutral organophosphorous dendrimers up to G10 could be prepared by this facile divergent protocol. Because the functional groups employed in the synthesis were orthogonal to each other, no protecting groups were required. The aldehyde functional groups can be further elaborated into various functional moieties or ligands for complexation or catalysis purposes. Alternatively, functional group conversion can also take place on the thiophosphoryl dichloride ($S{=}PCl_2$) end groups to give different types of phosphine-terminated dendrimers.[160] This fascinating chemistry was later extended to the preparation of neutral phosphine dendrimers **218** having a sixfold cyclotriphosphazene core using a different branch structure.[39b]



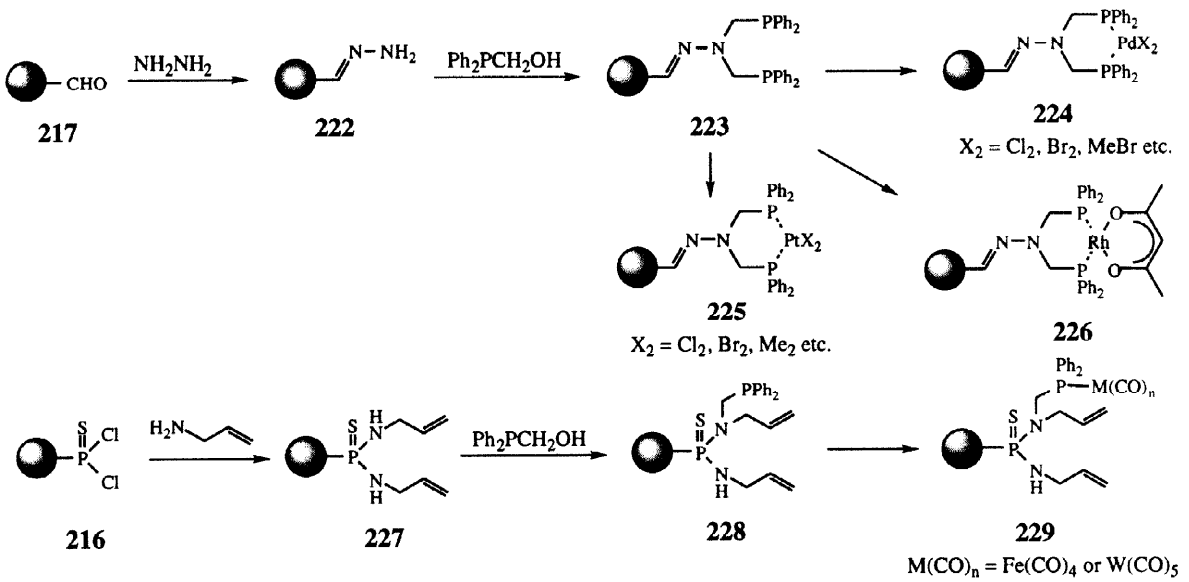
Treatment of the aldehyde-terminated organophosphorous dendrimer **217** or its higher generation analogs (up to G10) with methylhydrazine converted all the aldehyde end groups into the corresponding hydrazono derivatives **219**.[159] Additional functional group manipulation gave a phosphine-terminated dendrimer **220**

containing up to 3072 metal binding sites. Treatment of **220** with AuCl(tetrahydro-thiophene) afforded the corresponding metallodendrimer **221** in which the surface was covered with AuCl moieties. The higher generation gold-containing dendrimers could be imaged by high resolution electron microscopy and were shown to have a spherical structure.



217 **219** **220** **221**

Alternatively, grafting the surface of dendrimer **217** with bidentate diphosphino groups enabled the formation a variety of palladium, platinum and rhodium metal complexes.[161] Thus, treatment of the dendritic aldehyde **217** with hydrazine afforded hydrazone **222**, which underwent double alkylation to give the dendritic diphosphino ligand **223**. Upon metallation, dendritic palladium **224**, platinum **225** and rhodium complexes **226** could be obtained. On the other hand, treatment of the dendritic phosphoryl dichloride **216** with excess allylamine afforded a dendritic phosphoramide **227**.[162] Upon treatment with diphenylphosphinomethanol, compound **227** could be chain-extended to give a dendritic phosphine ligand **228**, which could form various iron and tungsten complexes **229**.



217 **222** **223** **224**

$X_2 = Cl_2, Br_2$, MeBr etc.

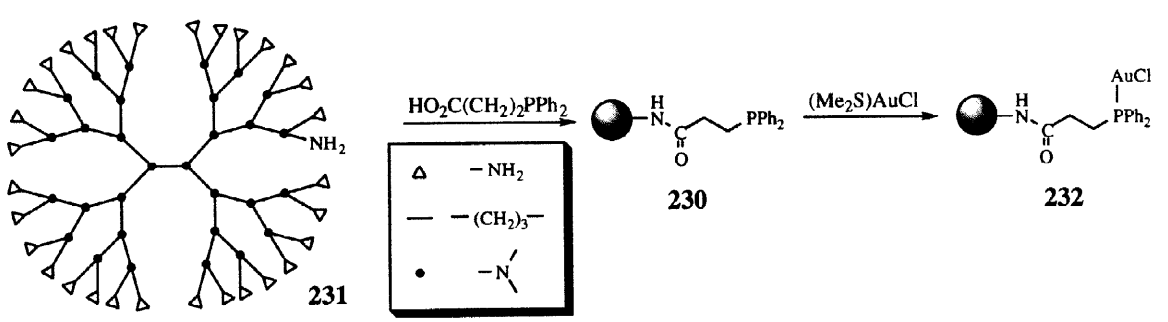
225

$X_2 = Cl_2, Br_2, Me_2$ etc.

226 **216** **227** **228** **229**

$M(CO)_n = Fe(CO)_4$ or $W(CO)_5$

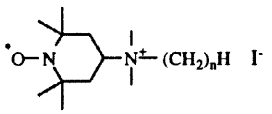
Schmidbaur also reported the preparation of phosphine-terminated polyamine dendrimers **230** and their complexation ability with gold(I).[163] Treatment of the amino-terminated poly(propyleneimine) dendrimer



230 **232**

231[13] with β-(diphenylphosphino)propionic acid afforded a diphenylphosphino-terminated product **230**, which could be converted into the corresponding gold(I) complex **232** on treatment with Me_2SAuCl.

Anionic carboxylate-terminated PAMAM dendrimers **163** were capable of forming macromolecular complexes with cationic poly(dimethylallylammonium chloride).[164] Acid-base titration experiments revealed that the complexation was stoichiometric and occurred most readily with the higher generation dendrimers. The lower generation analogs only complexed to the cationic polymer at high pH values or low ionic strength. This was attributed to the higher charge density of the higher generation dendrimers as compared to that of the lower ones. Similarly, positively charged nitroxide radicals **233** containing hydrocarbon chains of different lengths were known to bind the same receptor **163** *via* electrostatic interaction.[165] Analysis of the EPR spectra of the dendrimer-radical complex showed that radical probes with a longer hydrocarbon chain tended to have a reduced radical mobility. Such an observation could be ascribed to the stronger hydrophobic interaction between the longer hydrocarbon chain (n = 12) with the nonpolar interior branches of the dendrimer.

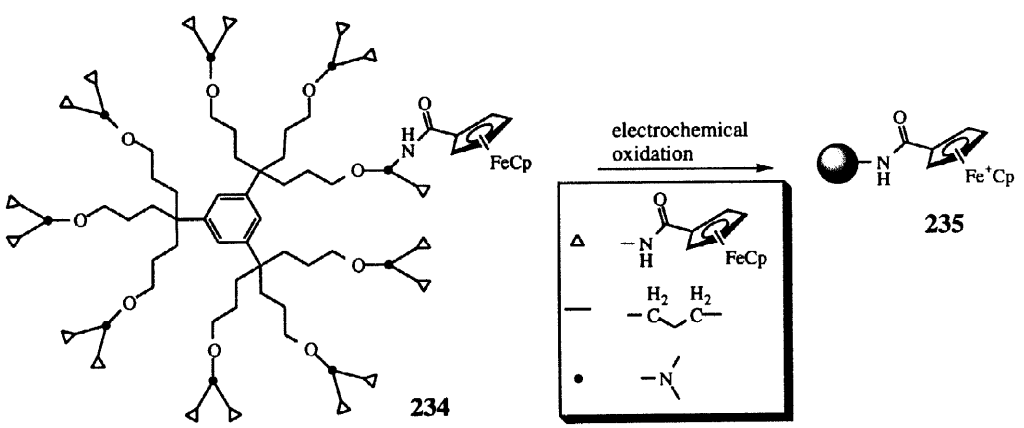


233 n = 1, 12 or 16

The cationic dye methylene blue also formed aggregates on the surface of anionic dendrimer **163**.[166] Such aggregation occurred most readily for the higher generation dendrimers. It was proposed that the flat dye molecules were stacked perpendicular to the dendrimer surface.

Dendritic receptors for anionic guests

The series of orange-red polyamido ferrocene-containing dendrimers **234** reported by Astruc were probably the only examples known to bind anionic guest molecules.[167] They were prepared by grafting the surface of a series of amino-terminated dendrimers with ferrocenyl acid chloride. These neutral metallo-dendrimers **234** were shown to possess strong binding ability toward small anionic species such as Cl^-, NO_3^-, HSO_4^- and $H_2PO_4^-$, as a result of the favorable H-bonding interaction originating from the amino protons embedded within the matrix. Upon electrochemical oxidation, dendrimer **234** was transformed into the corresponding cationic ferricinium species **235**. As a consequence of the synergistic effect of H-bonding and the Coulombic attractive force, the positively charged dendrimer **235** has a much stronger anion binding

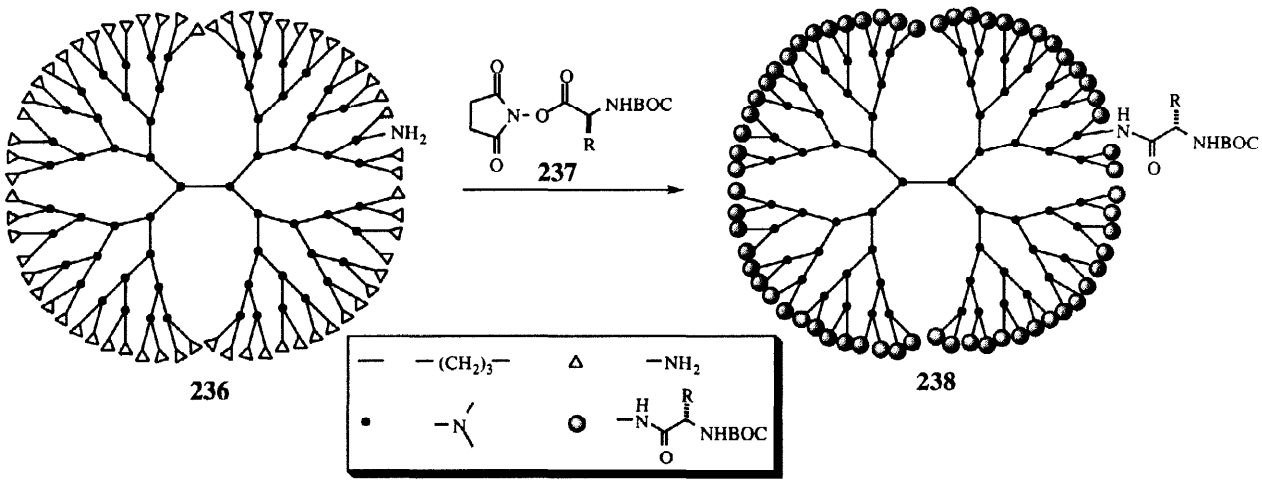


234 **235**

ability than the neutral species **234**. Such binding profiles could be followed by CV experiments as the $H_2PO_4^-$ bound species could be oxidised much more easily than the free dendritic species **234**. It was also found that the higher generation dendrimers possessed better binding ability to small inorganic anions than the lower ones.

Dendritic receptors as encapsulating agents

The various types of dendritic receptors described in previous sections exert their binding interactions to guest molecules mainly through electrostatic, coordination, H-bonding or van der Waals forces. Due to the presence of solvent-filled voids within the interior of dendrimers, they can also be used to irreversibly encapsulate guest molecules if the dendrimer surface can be subsequently end-capped to form a closed shell after guest entrapment.



The first example of guest encapsulation inside a dendritic box was realised by Meijer's elegant study on a series of amino acid-terminated dendrimers.[168] Structurally flexible amino-terminated poly(propyleneimine) dendrimers **236** up to G5 could be end-capped with various optically active amino acid residues **237** to yield enantiomerically pure chiral dendrimers **238**. Apart from the reaction between the G5 dendrimer and the tryptophane derivative, all surface amino groups reacted with amino acid residues in the expected stoichiometry. On the other hand, attempts to fully end-cap all of the 128 amino groups of the G6 dendrimer failed. ^{13}C-NMR relaxation measurements indicated that the higher generation macromolecules had a rigid surface structure. Such a notion was established by an increase in the T_1 value of the carbon atoms located near the surface sector toward the higher generations. When the capping reaction of the G5 dendrimer was conducted in the presence of 3-carboxyproxyl free radicals **239**, up to six guest molecules were contained within the dendritic matrix (Figure 15). However, dendrimers of lower generations such as G3 were not capable of trapping guest molecules. Their surface domains were not dense enough to form a closed shell in order to contain the guest molecules and prevent them from leaking into the environment. An ESR study indicated that the micro-environment of the dendritic voids was not uniform and at least two different trapping sites existed for the free radicals, one allowing relatively free motion and another restricting molecular motion.[169] It was also noted that the physical properties of guest molecules were modified after dendritic encapsulation. For examples, dye molecules such as eriochrome black T, when encapsulated within **238**,

exhibited solubility similar to that of host molecule **238**, but none at all to that of the dye itself. Upon trapping within a chiral G5 dendritic box, achiral rose bengal molecule exhibited Cotton effects in its CD spectra indicative of the asymmetric environment within the dendritic box.[170] Furthermore, the emission property of entrapped rose bengal was insensitive to solvent effects, a result which was consistent with the solvent impenetrable features of a dense packed dendrimer.

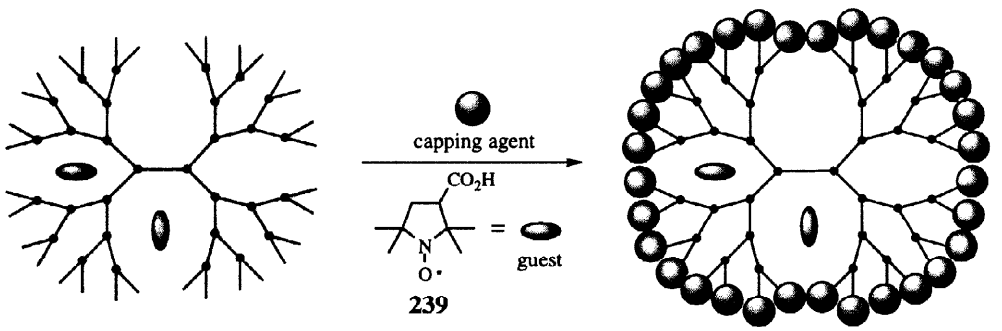
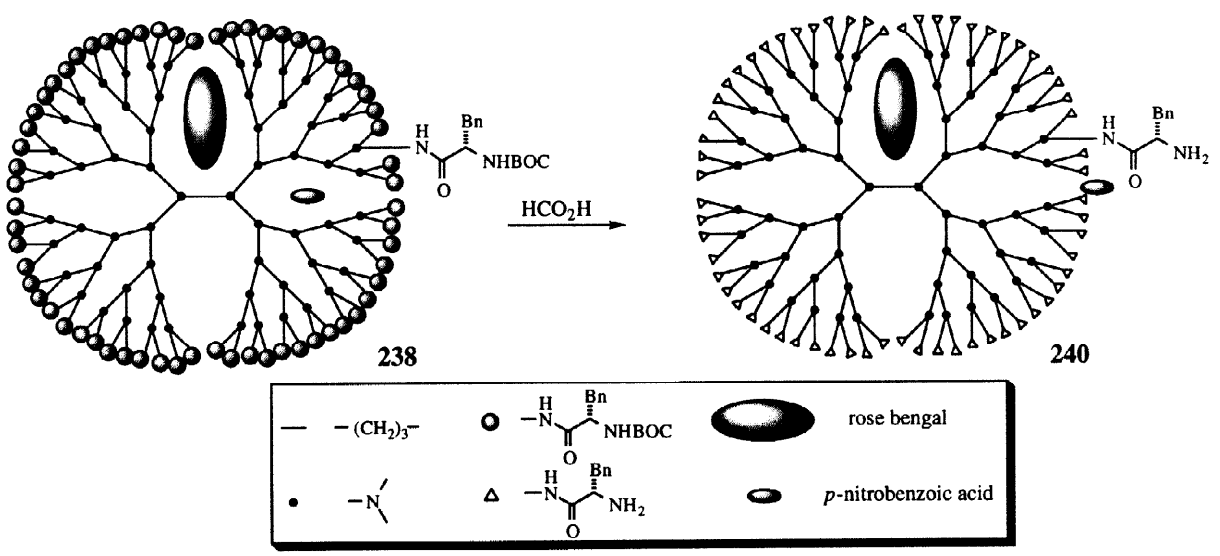


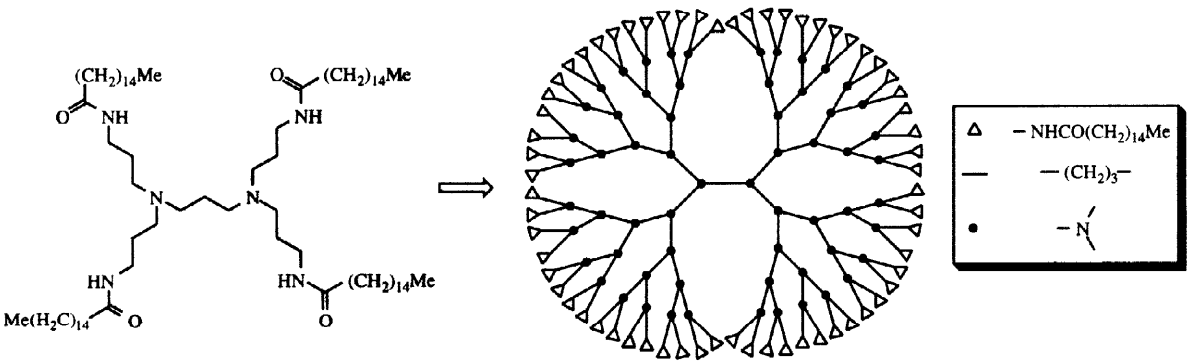
Figure 15. Schematic diagram showing the encapsulation of guest molecules into dendritic voids during end capping.

Meijer also demonstrated that guest molecules of different sizes and shapes could be selectively liberated after being encapsulated into a phenylalanine-capped poly(propyleneimine) dendritic box.[171] After entrapping 4 molecules of rose bengal and 1 - 8 molecules of *p*-nitrobenzoic acid into **238**, the BOC protective groups on the rigid dendritic shell were removed by acid hydrolysis. Subsequent dialysis of the reaction mixture gave a perforated dendritic box **240** within which the rose bengal molecules were still retained, whereas the smaller *p*-nitrobenzoic acid leaked out into the solution. By switching to other capping groups of different steric sizes, Meijer was able to show that the process of selective liberation of guest molecules could be fine-tuned.



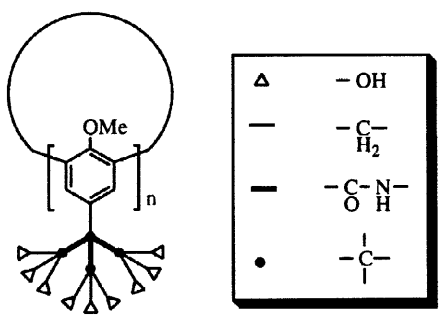
Apart from using capping agents to seal the dendritic box, it was also possible to change the rigidity of the dendritic shell by controlling the solvent polarity. A series of inverted unimolecular dendritic micelles **241** having a hydrophobic C_{16} hydrocarbon surface and a hydrophilic poly(propyleneimine) interior were prepared by Meijer.[172] In ethanol solutions, hydrophilic dyes such as rose bengal readily entered the dendritic core.

Under such solvent conditions all hydrophobic C_{16} hydrocarbon chains existed in a relaxed conformation and allowed the dye molecules to enter the dendritic matrix. The inverted micelle was then precipitated in acetonitrile and purified by dialysis in water. In aqueous conditions, the hydrophobic effect amongst the C_{16} chains came into play and the hydrocarbon chains tended to 'glue' together. As a result, the entrapped rose bengal molecules were unable to escape from the dendritic voids. The change of molecular dimension and swelling properties of dendritic macromolecules in different solvents was independently confirmed by Eimer through holographic relaxation spectroscopy.[173]

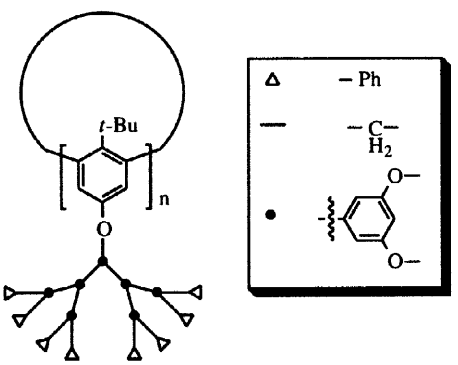


241

A number of potentially interesting dendritic hosts having a calixarene core have also been synthesised. For example, Newkome described the preparation of water soluble dendritic calix[4]- and calix[8]-arene **242** by adding hydrophilic polyols to the calixarene ring.[174] Ferguson also reported the attachment of polyether dendritic appendages to the phenolic handles of calix[4]- and calix[5]-arenes **243**.[175] However, the host properties of these dendritic receptors were not reported.



242 n = 4 or 8

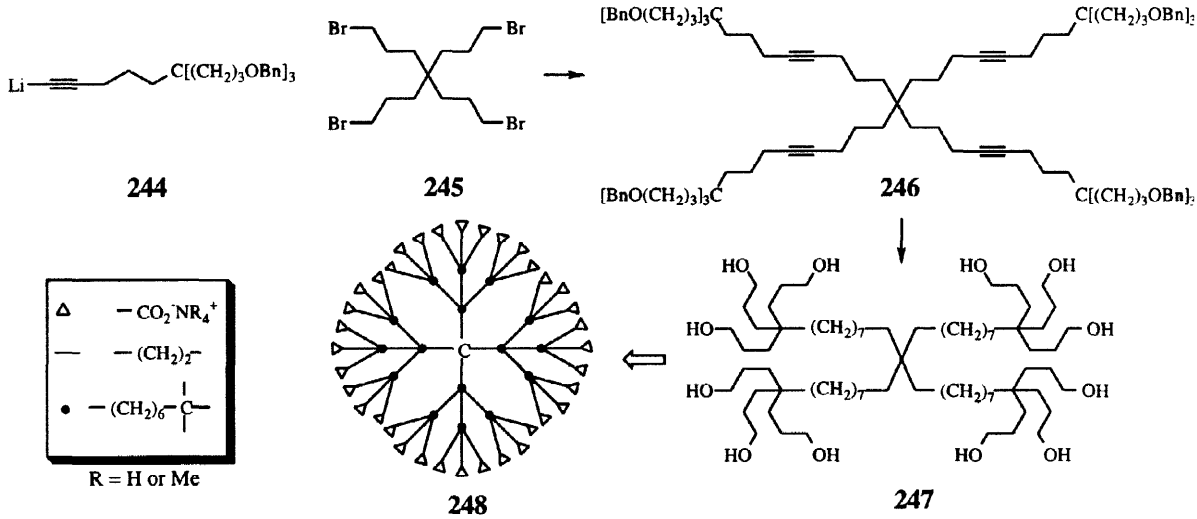


243 n = 4 or 5

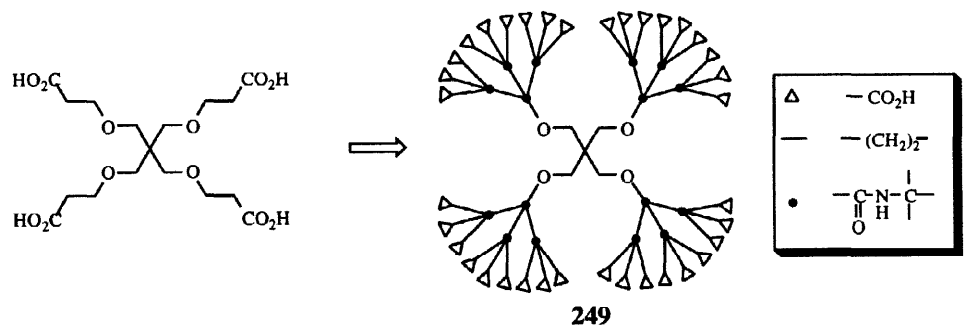
5.6 Ionic Dendrimers[176]

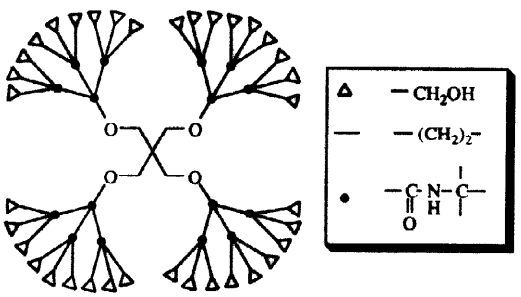
Categorically, ionic dendrimers can be divided into two classes: those having ionic centers throughout the network and those having ionic sites on the surface. Cationic organometallic dendrimers belonging to the former category have been reviewed earlier in terms of their electrochemical or photochemical properties. On the other hand, dendrimers with charged surface groups can be used as complexation agents and they have been discussed in Section 5.5. Here in this section we will focus on the physical and micellar properties of ionic dendrimers.

Dendritic micelles usually possess polar head groups on the dendrimer surface and a nonpolar interior core. These unimolecular micelles have been extensively investigated by Newkome. One such example was the carboxylate-terminated G2 dendrimer **248**.[177] The synthesis began with exhaustive alkylation of a hydrophobic branching core **245** by an acetylenic anion **244** to give a G1 intermediate **246**. Subsequent hydrogenation of the triple bonds and hydrogenolysis of the benzyl groups of compound **246** furnished the G1 polyol **247** which could be converted into a polybromide of the next generation. Iteration of this reaction protocol allowed the synthesis of polyols of higher generations. Finally the G2 polyol was transformed into the corresponding carboxylate derivatives **248** through standard functional group manipulations. The micellar properties of **248** were demonstrated by the formation of inclusion complexes with chlortetracycline, diphenylhexatriene, phenol blue and pinacyanol chloride in aqueous solutions.[178]



In a study of the pH effect on the hydrodynamic radii of charged dendritic macromolecules, Newkome reported the divergent preparation of carboxylic acid-terminated dendrimers **249**.[179a] Based on SEC and diffusion ordered 2D-NMR spectroscopy, it was established that the hydrodynamic radii of **249** was largest at pH 7, slightly shrunk at pH 13 and smallest at acidic pH. The molecular size variation was readily interpreted by the Coulombic repulsion between anionic carboxylated surface groups at neutral or basic pH. As anticipated, the radii of the corresponding electrically neutral alcohol-terminated dendrimers **250** showed little pH dependence.[179b] On the other hand, the amino-terminated dendrimers **251** had the largest radii at acidic pH and the smallest at basic pH values. In view of the dependence of dendrimer size on pH values, the use of dendrimers containing ionisable groups as molecular size standards in SEC[180] should take this factor into consideration.





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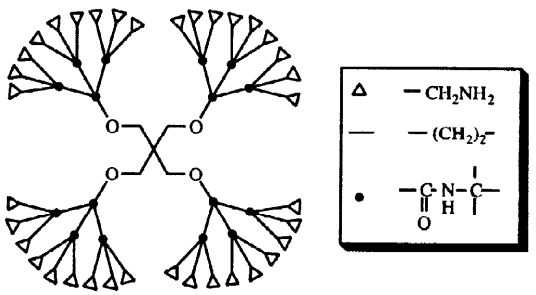
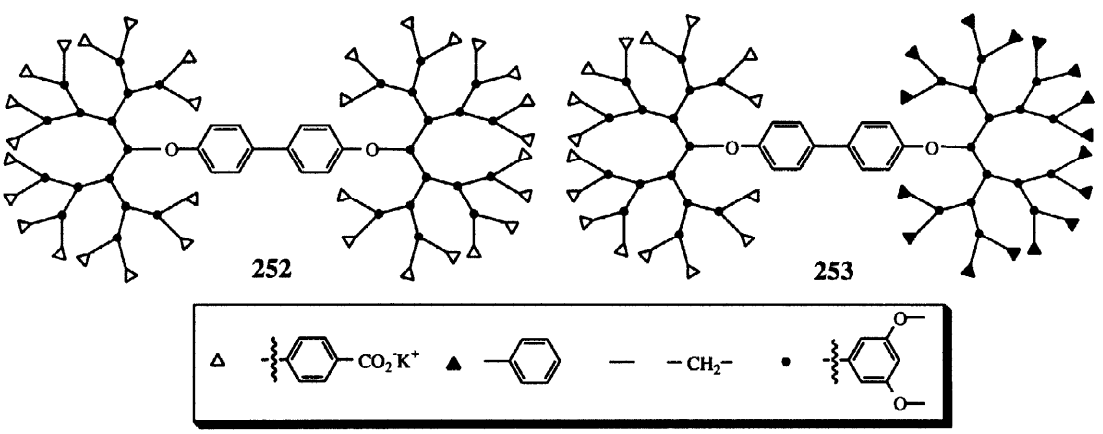


251

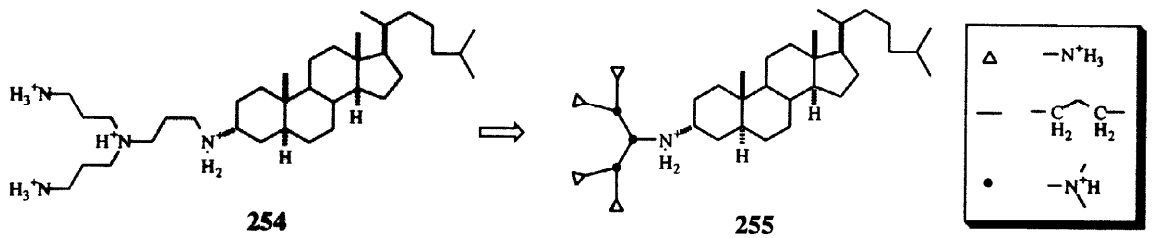
The separation of neutral molecules has been made possible by utilising the unimolecular micellar properties of anionic- or cationic-terminated dendrimers. For example, both the carboxylate-terminated PAMAM **163** and the polyamido dendrimer **249** could be used as stable carriers in the separation of uncharged solutes in electrokinetic chromatography (EKC).[181] The elution order of solute molecules from dendrimer-EKC was different from that of EKC using conventional ionic surfactants.[181a] Furthermore, higher generation PAMAM dendritic carriers tend to bind more strongly to solutes than lower generation ones, and thus lead to improved separation.

Ionic dendritic micelles can also be used as solubilisation agents. Fréchet reported the preparation of an anionic dendrimer **252** by attaching two carboxylate-terminated polyether dendritic sectors onto a central biphenyl core.[182] Thus, such an ionic micelle as **252** could improve the solubility of hydrophobic molecules like pyrene in water by 120 fold. Similar solubility enhancement was also noted for anthracene, 1,4-diamino-anthraquinone and 2,3,6,7-tetranitrofluorenone. Interestingly, the copolymer **253** having a hydrophilic western hemisphere and a hydrophobic eastern hemisphere is insoluble in both water and dichloromethane. This is in sharp contrast to the completely benzyl-terminated dendrimer and the negatively charged dendrimer **252**, which are extremely soluble in dichloromethane and water, respectively. Compound **253** was found to produce an emulsion which persisted for weeks when agitated in a mixture of water and dichloromethane.

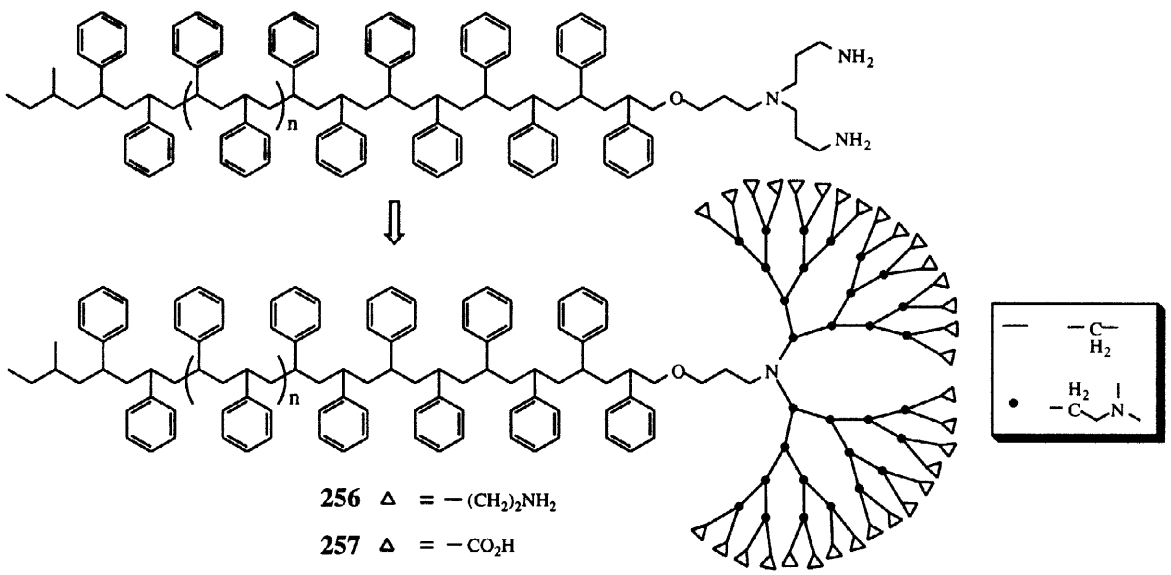


252 253

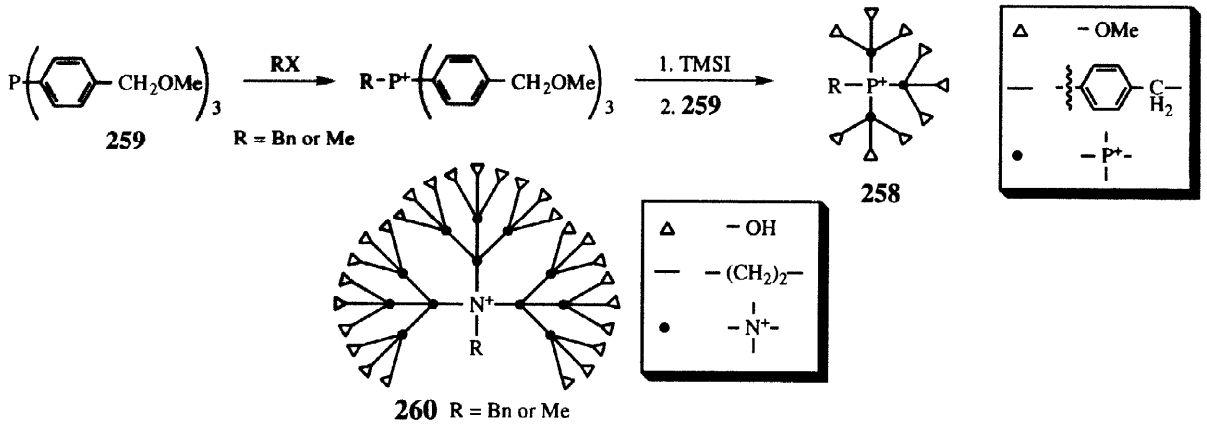
Inspired by the efficacy of using polyamine-based ionophores as mediators for transmembrane ion transport. Matile described the syntheses of amphiphilic polyamine dendrimers **254** and **255** having a cationic dendritic polyamine tail anchored to a hydrophobic steroid core.[183] Using 8-hydroxypyrene-1,3,6-trisulfonic acid as a fluorescent probe, the G1 analog **255** was shown to facilitate hydroxide ion transport across unilamellar vesicles. In contrast, the G0 analog **254** was inactive.



The grafting of linear polymer chains to ionic dendrimers offers a new avenue towards novel amphiphilic copolymers. In his first report, Meijer successfully attached a polystyrene chain to the central core of a series of amino-terminated poly(propyleneimine) dendrimers to produce dendritic amphiphiles **256**.[184] Based on the results of conductivity and monolayer pressure-area isotherm measurements, these dendrimers exhibited generation dependent amphiphilic behavior. The lower generation dendrimers, containing the polystyrene chain as the dominant structure, tended to stabilise an organic phase as the continuous phase. On the other hand, the higher generation amphiphiles, having a comparable hydrophilic dendritic sector to the hydrophobic polystyrene chain, were equally capable of stabilising both organic or aqueous dispersing phases. In a second study, carboxylic acid-terminated amphiphilic polyamino dendrimers **257** were prepared.[185] Conductivity studies showed that dendrimers **257** not only exhibited generation dependent, but also pH dependent amphiphilic character. Under strongly acidic or basic conditions, the dendritic sector existed as a highly charged species capable of stabilising an aqueous phase as the continuous phase.



The search for high capacity ion exchange materials for use in HPLC provides another impetus for the preparation of ionic dendrimers.[186] In this context, ionic dendrimers **258** based on a phosphonium branching juncture have been reported by Engel.[39a,187] These highly hygroscopic, cationic materials were constructed by a quaternisation reaction of tri(*p*-methoxymethylphenyl)phosphine **259** with an appropriate electrophile. The methoxy protective groups were then dismantled and converted into the corresponding iodo derivative which could then be further reacted with **259** to yield the cationic dendrimer of the next generation. The structurally related ammonium analogs **260** have also been synthesised.[188]

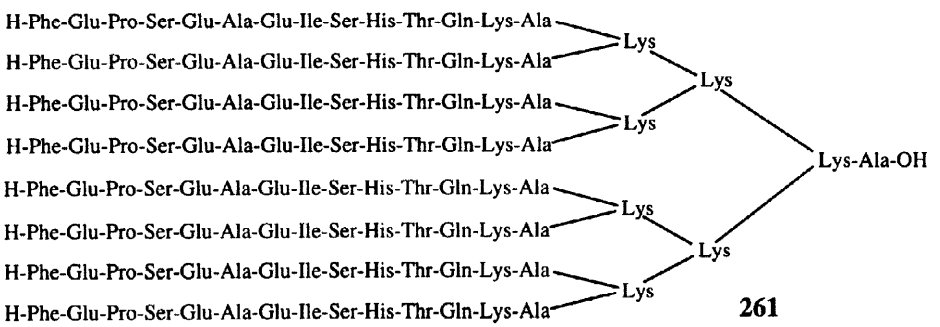


5.7 Biologically Active Dendrimers[189]

Dendrimers can in many ways be considered to resemble biological macromolecules such as proteins, enzymes, antibodies or polysaccharides. Their spherical shape and size are similar to those of globular proteins. Dendritic catalysts could also be engineered to possess properties akin to those of enzyme catalysts. The multivalent topology of dendrimers also paves the way for them to function as antibodies. Hence, a number of biologically-oriented dendrimers have been constructed by linking simple biological building blocks such as amino acids, nucleotides and monosaccharides together in a hyperbranched architecture. These macromolecules are constructed to mimick or model the biological functions of their natural counterparts.

Peptide dendrimers

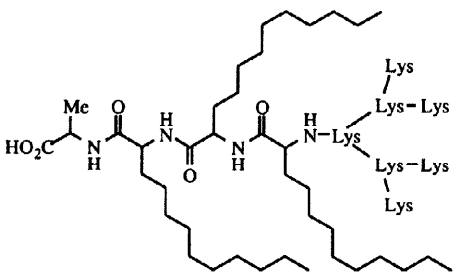
One of the earlier biological applications of dendrimers was the production of anti-peptide antibodies from peptide dendrimers. The traditional way of generating site-specific antibodies to peptides is to conjugate them to a carrier protein, which in turn can also be immunogenic and might cause undesirable effects. Tam reported a new approach to generate specific antibodies which obviated the use of a carrier.[190] This method relied on the solid phase preparation of a peptide dendrimer **261** having 8 copies of a 14-residue peptide anchored to a polylysine dendritic core. The resulting peptide dendrimer was sufficiently immunogenic to elicit specific antibodies in rabbits and mice which could interact with its corresponding native protein. This dendritic protocol had also been used to develop synthetic vaccines against hepatitis B[191] and human acquired immunodeficiency virus.[192]



The conjugation method described above involved the merger of several hydrophobic protected peptide fragments to a hydrophilic polylysine core. As a result, the coupling efficiency was low and product purification became a problem. Tam later developed a more direct approach which made use of nonpeptidyl

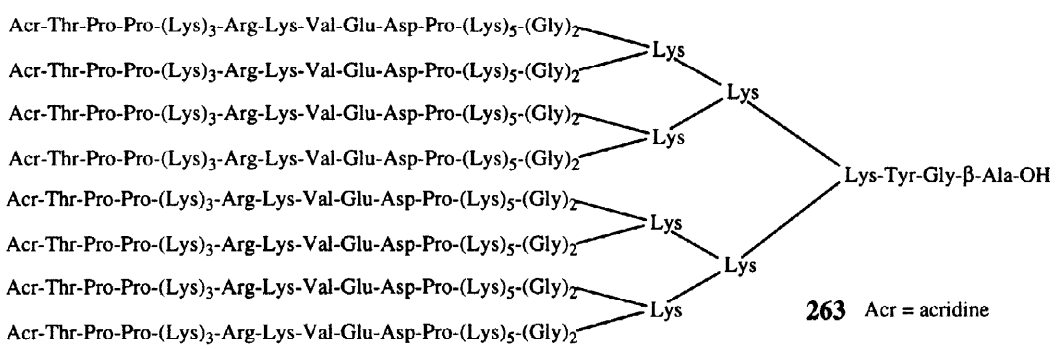
linkers such as a thiazolidine, oxime or phenyl hydrazone for the facile ligation between unprotected peptides and the dendritic core.[193] Such direct coupling methodology was successfully applied to the assembly of a number of cyclic peptides onto the polylysine core.[194]

To further improve the immunogenicity of a multiple antigenic peptide, Toth reported the attachment of several copies of lipophilic amino acids to a polylysine core to produce a lipidic peptide dendrimer **262**[30b] This modification was based on the finding that lipopeptides were effective low molecular weight carriers for immunogenicity. Lipidic modifications may facilitate the production of antibodies and vaccines and the long hydrocarbon chain can also protect the labile peptide bond from enzymatic degradation.



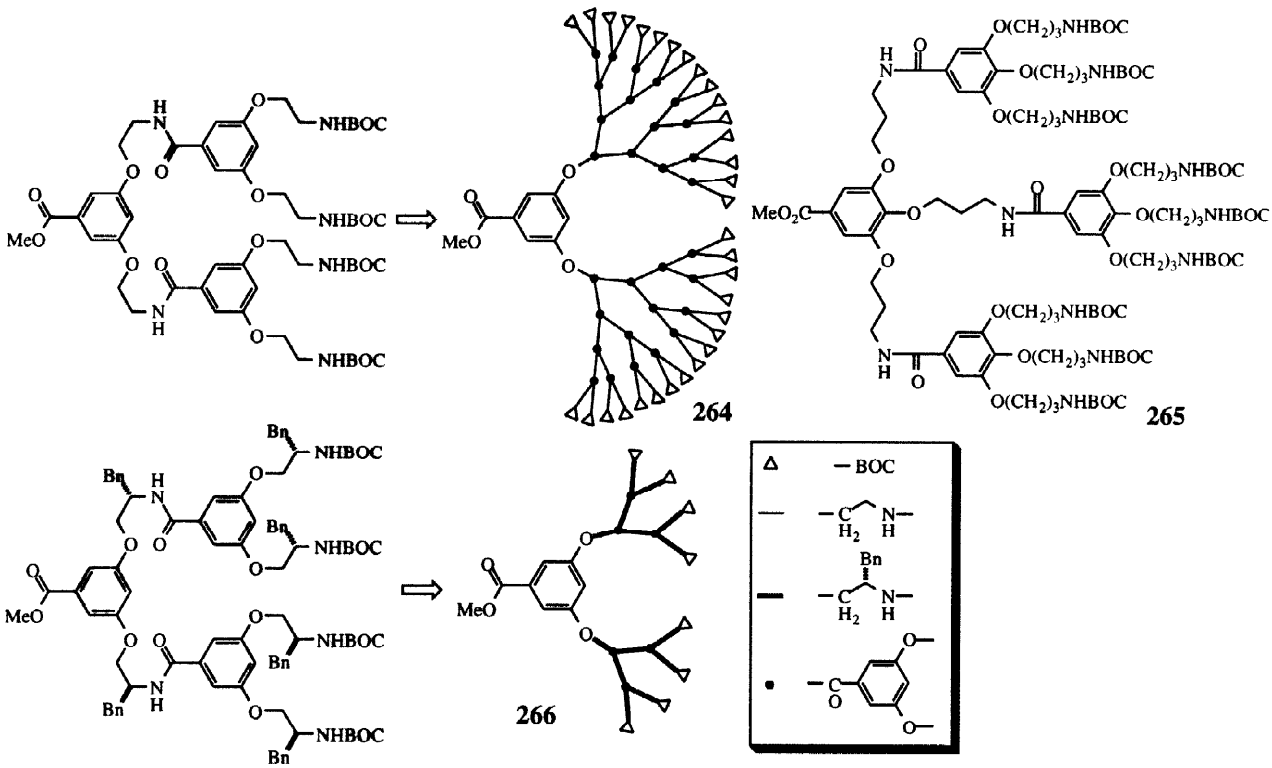
262

Peptide dendrimers such as **263** containing multiple copies of peptide fragments could function as intracellular vehicles.[195] Each peptide chain was encoded with three pieces of information. The acridine moiety located at the end served as a fluorescence tag to monitor the migration of the dendrimer inside cells by fluorescence microscopy. The penta(lysine) fragment near the dendritic domain was encrypted with a cytoplasmic translocation signal. Finally, the oligopeptide in between incorporated the nuclear localisation sequences. Dendrimer **263** was shown to be internalised by Chinese hamster ovary cells and accumulated in their nucleus. This type of peptide dendrimer has the potential for use as an intracellular delivery vector for targeting peptides to appropriate organelles and rerouting drugs destined to block biochemical pathways.



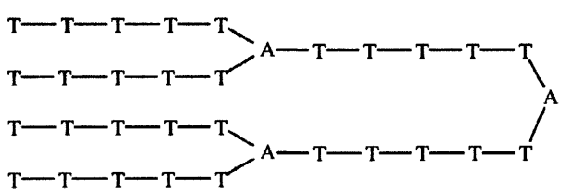
263 Acr = acridine

Liskamp recently reported a new class of amino acid-based dendrimers **264** having the surface decorated with amino acid-derived residues.[196] Using standard peptide coupling methods, dendrimers up to G5 with 3,5-dihydroxybenzamide junctures and ethanolamine branches were synthesised. In contrast to other peptide dendrimers described previously, dendrimers **264** were not expected to have good solubility in aqueous solution. The chemistry was later expanded to include the construction of peptide dendrimer **265** with gallic acid as the branching juncture and an optically active peptide dendrimer **266** having chiral amino alcohol branches derived from phenylalanine.[197]



Nucleic acid dendrimers

A branched nucleic acid having two oligonucleotide chains linked to a single nucleotide unit is structurally related to the biological intermediate during the splicing of DNA/RNA molecules. One of the pioneering works in the preparation of branched nucleic acid dendrimer is **267** which was reported by Damha.[31] The nucleic acid dendrimer used adenosine RNA units as branching junctures and penta(thymidine) DNA oligomers as branches. The preparation of **267** involved standard phosphoramidite chemistry, details of which have already been reviewed in Section 3.4. There were severe structural defects during ligation and this created a practical limit on the size of dendrimers which could be produced by this method.



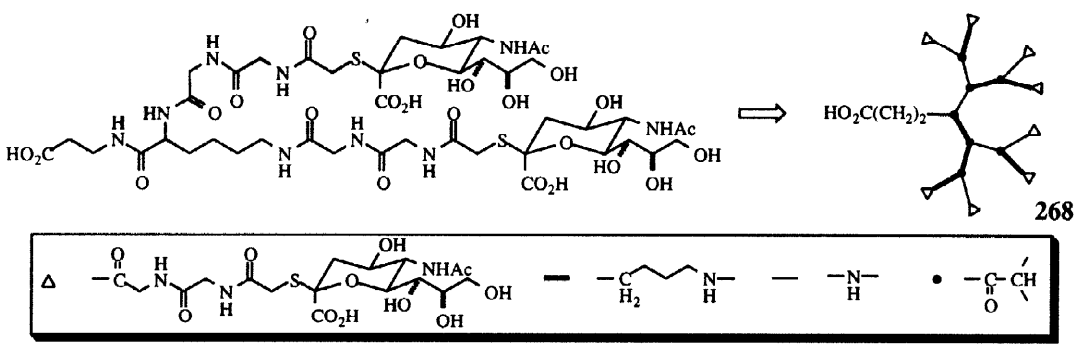
267

Glycodendrimers[198]

The importance of carbohydrates in mediating a number of biological responses such as cellular recognition and adhesion has become increasingly appreciated. While advances continue to be made in the development of novel synthetic methodologies for synthesising complex oligo- and polysaccharides, such molecules still pose a formidable synthetic challenge and, as such, are not widely viewed as feasible candidates for drug development. Glycodendrimers have therefore emerged as a new class of synthetically

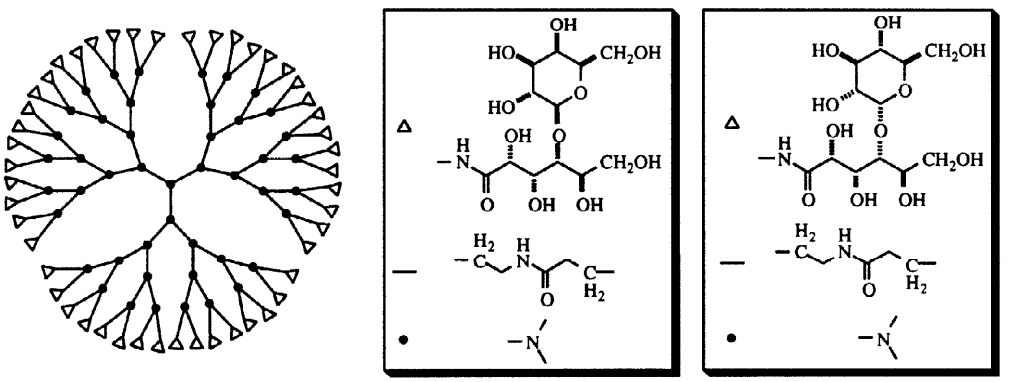
achievable compounds which bear a structural resemblance to polysaccharides and, as a result, may offer alternatives for therapeutic treatment.

The prime event in host cell infections by influenza virus is triggered by the recognition and binding of viral haemagglutinins (HAs) to α-sialosides present on the cell surface glycolipids and glycoproteins. In order to enhance the binding affinity of HA to α-sialosides, Roy described the preparation of a series of dendritic sialosides **268** for the inhibition of influenza A virus haemagglutination to erythrocytes.[199] Such glycodendrimers were prepared by a solid phase divergent anchorage of sugar units on a polylysine dendritic core supported on Wang resin. The binding properties of the sialylated dendrimers to wheat germ agglutinin were studied. Both the G0 and G1 dendrimers exhibited low affinity, but the higher generation ones showed good binding properties. Most importantly, all dendrimers exhibited 10^6 inhibitory capacities better than the monosialoside, thus demonstrating the cooperative cluster effects of these dendritic glycosides. In a similar manner, glycodendrimers with other mono- and di-saccharide surface dressing units were also prepared.[200] Other biologically active sugar dendrimers using polyhydroxybenzoic acids as the trivalent core and oligoethyleneglycols as hydrophilic spacers[201] and glycodendrimers having a polyamido matrix have likewise been synthesised.[202] Enzyme-linked lectin inhibition assays on these dendrimers revealed that their inhibitory potency increased with increasing dendrimer generation.



268

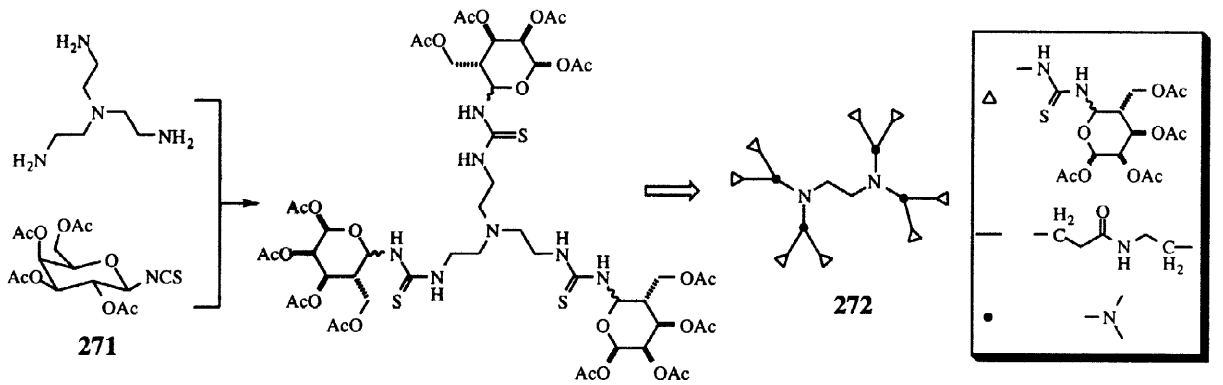
Based on a similar concept, Okada constructed a series of sugar balls by furnishing the surface of a PAMAM dendrimer with either *O*-β-D-galactopyranosyl-(1→4)-D-glucono-1,5-lactone or *O*-β-D-glucopyranosyl-(1→4)-D-glucono-1,5-lactone residues.[203] The resulting dendrimers **269** and **270** exhibited stereospecific binding properties. The galactose-derived dendrimer **269** did not co-precipitate with lectin concanavalin A (con A), which was known to bind specifically to glucosyl units; while the glucose-derived



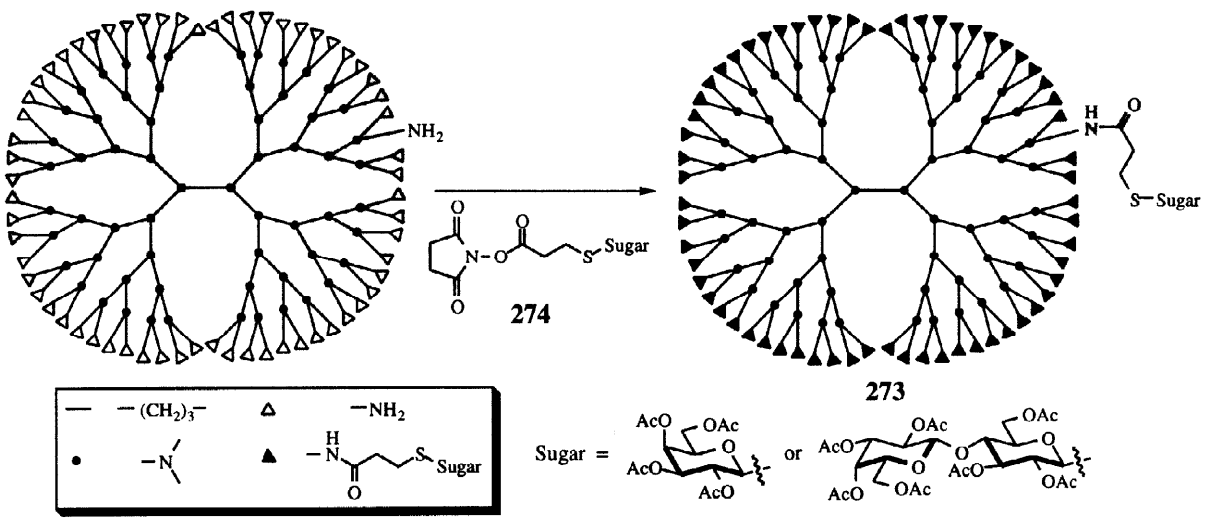
269 **270**

dendrimer **270** did. On the other hand, dendrimer **269** bound strongly to peanut agglutinin, which had a high specificity for terminal galactose residues, while **270** did not interact with peanut agglutinin.

Lindhorst reported the use of a thiourea linker to coat the surface of PAMAM dendrimers with sugar units.[204] Thus, treatment of PAMAM dendrimers with glycosyl isothiocyanate **271** afforded glycodendrimer **272** in good yields. The acetyl groups on the sugar moieties were then deprotected to give a water soluble dendrimer. It was later found that the coupling chemistry could be performed equally well on unprotected sugar isothiocyanate, thus eliminating the deprotection step.[204b]

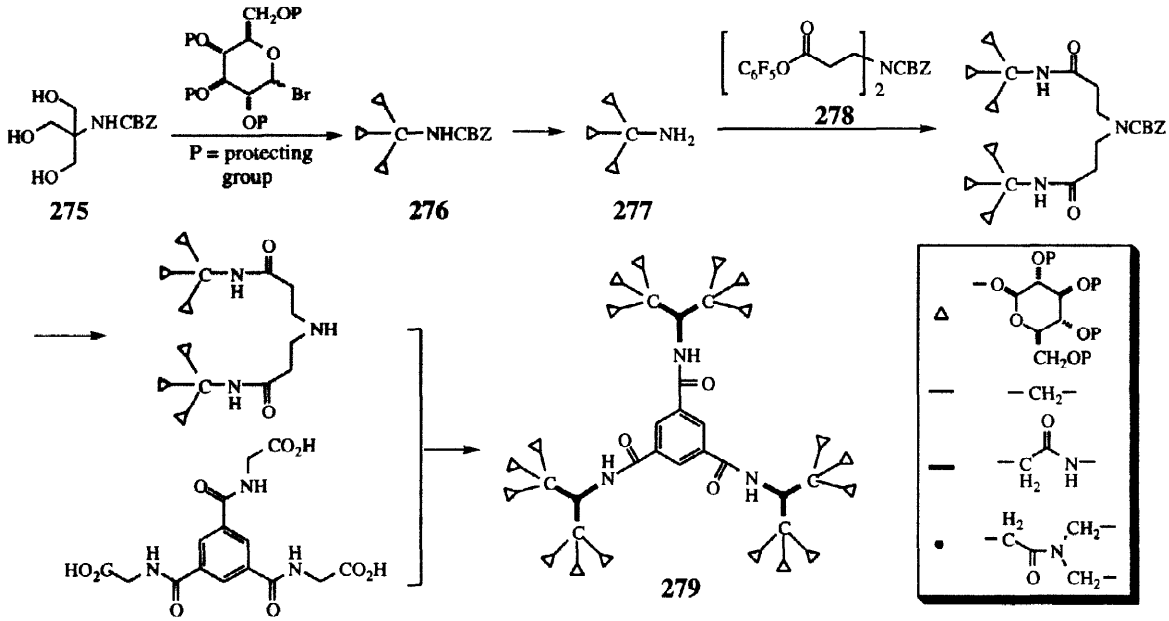


Stoddart and Meijer also disclosed their approach to carbohydrate dendrimers **273** by reacting activated sugar derivatives **274** with amino-terminated poly(propyleneimine) dendrimers.[205] The structural identities of these glycodendrimers were fully characterised by spectroscopic techniques. Based on mass spectroscopic evidence, all amino groups on the surface of G1 to G3 dendrimers were completely glycosidised.



Stoddart recently reported a convergent preparation of sugar dendrimers.[206] The synthesis began with the fixture of protected sugar units onto a [tris(hydroxymethyl)methyl]amine derivative **275** to give a dendritic sugar fragment **276** which was further elaborated to a glycine derivative **277**. This compound was then coupled to a polyamido branching juncture **278** to furnish sugar fragments of the next generation. Finally these glycodendritic wedges were ligated to a central core to afford glycodendrimers **279** of various generations. Molecular modelling indicated that there were extensive H-bonding interactions between

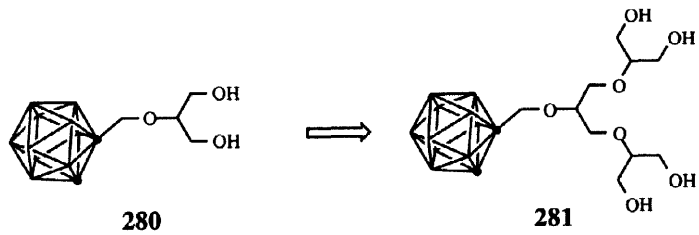
adjacent sugar residues and between amide groups in the fully deprotected higher generation dendrimers. A gradual change in morphology from an open to a more densely packed structure toward the higher generation was also noted.



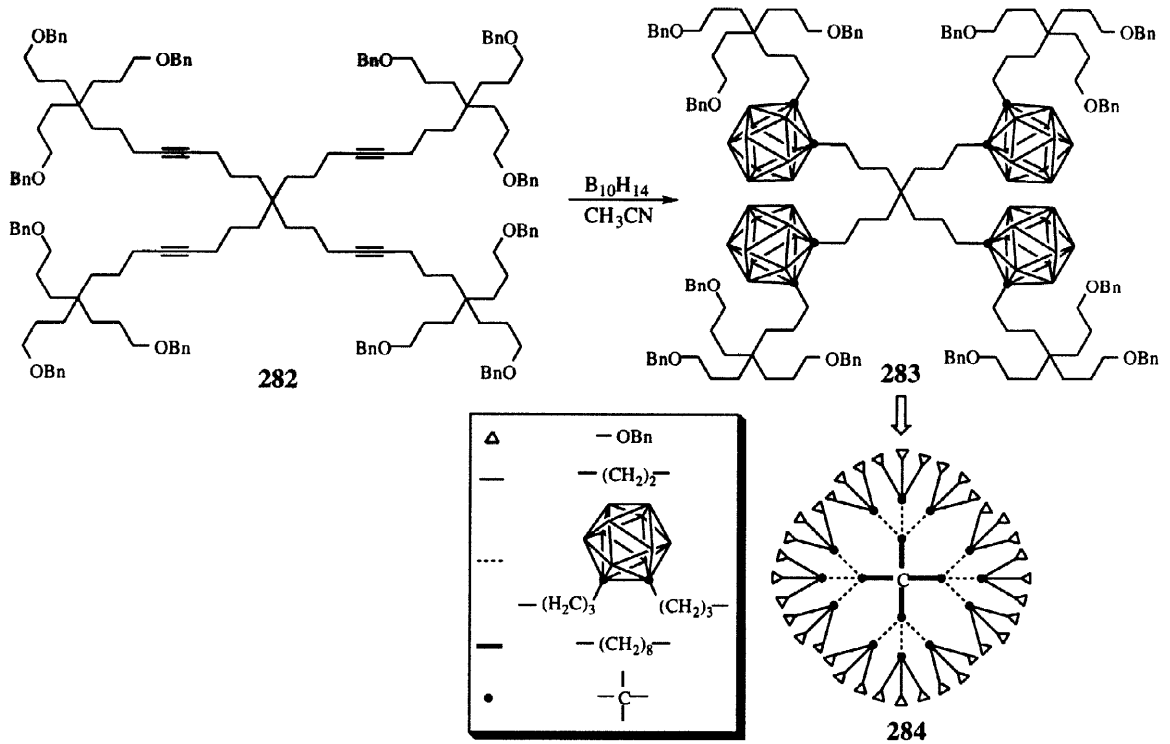
In a study toward the preparation of glycodendrimers of higher generations, Stoddart revealed the difficulties of producing structurally perfect dendrimers due to reduced core reactivity and steric inhibition.[206b] For example, the preparation of a G3 glycodendrimer containing 36 glucosyl residues employing a 6 × 6 coupling strategy involving 6 hexasaccharide wedges and a hexafunctional core failed to materialise. On the other hand, the same dendrimer could be obtained by a 12 × 3 coupling scheme involving 3 dodecasaccharide wedges and a trifunctional core.

Boron rich dendrimers

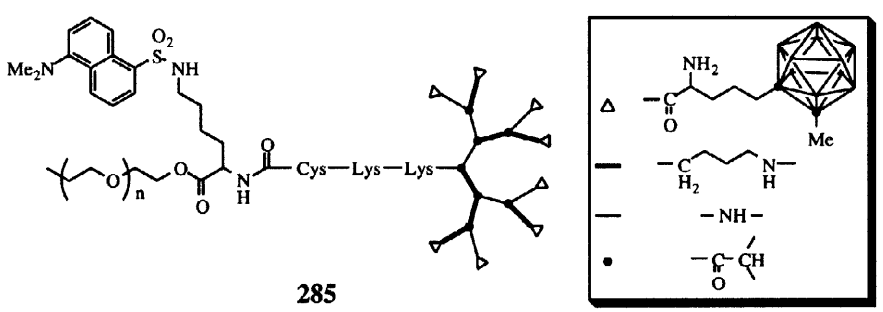
A number of dendrimer researchers have focused on the design and synthesis of boron-rich dendrimers suitable for boron neutron capture therapy of cancer. However, poor aqueous solubility has been an obstacle to the effective delivery of these compounds to a tumor site. This problem could be circumvented by adding water soluble dendritic appendages to a boron-rich cluster. Earlier in Section 5.3 we described the synthesis of a boron-rich dendrimer **98** by means of the facile addition of decaborane to carbon carbon triple bonds.[99] Using a similar reaction, Yamamoto reported the divergent synthesis of aqueous soluble boron-containing dendrimers **280** and **281** having a carborane core linked to a dendritic polyalcohol network.[207] With the extra hydroxy groups, the G1 dendrimer **281** was 8 times more soluble in water than the G0 analog **280**.



Newkome also disclosed the functionalisation of internal alkyne units of a protected dendritic polyol **282** with decaborane to afford the tetra- **283** and dodeca-*o*-carborane dendrimers **284**.[208] The benzyl groups were then deprotected and converted into the corresponding sulfates to improve their aqueous solubilities.



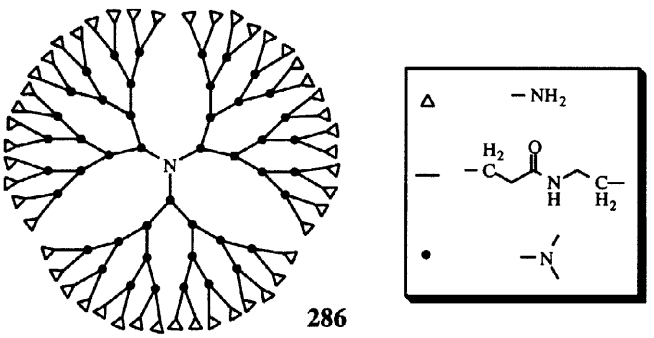
Qualmann and Kessels described the synthesis of a water soluble boron-rich dendrimer **285** having carborane clusters coated on the surface of a polylysine dendrimer core.[209] This copolymer also contains a thiol functionality for its attachment to target molecules, a fluorescent dansyl probe for spectroscopic monitoring of the coupling between the boron-rich marker to targeting molecules and a hydrophilic poly-ethyleneglycol chain to improve its water solubility. This dendrimer **285** was prepared by standard solid-phase peptide synthesis and the final step was the attachment of (*S*)-5-(2-methyl-1,2-dicarba-*closo*-dodeca-borane(12)-1-yl)-2-aminopentanoic acids to the α and ε-amino ends of the peripheral lysine residues.



Dendritic adjuvants for gene transfection

The introduction of genetic materials into cells is one of the major techniques to investigate gene function and the regulation of gene expression. While a variety of methods have been developed to

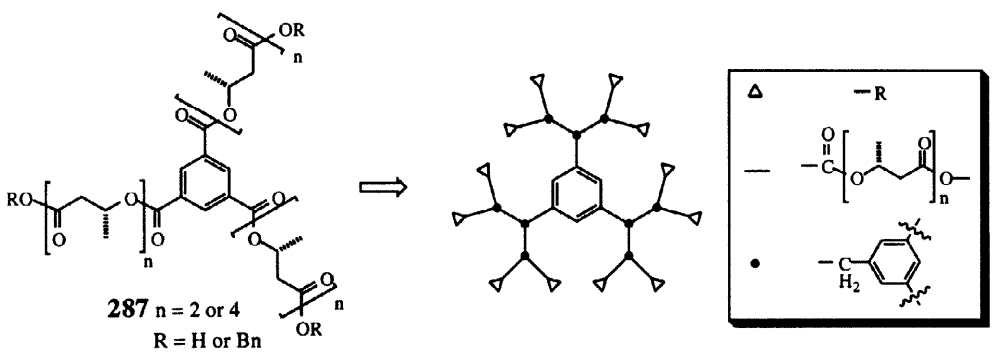
accomplish gene transfer into eukaryotic cells, they are often limited to certain target cell types and the transfection efficiency is low. Of the methods available, the formation of DNA complexes with inorganic salts, polycations or lipids appears to be the most efficient way for the transfer of genetic materials. Cationic dendrimers have also been used to facilitate gene transfection. For example, due to their good aqueous solubility and high positive charge densities at physiological pH, amino-terminated PAMAM dendrimers **286** were shown to be very efficient in achieving gene transfection in a wide variety of cell types.[210] Interestingly, the transfection efficiency turned out to be generation dependent. While the lower generations (G0 to G4) appeared to be poor adjuvants, good efficiency was seen with G5 to G10, with a plateau in activity after G8. The same dendrimers could also be used as delivery systems for antisense oligonucleotides to regulate *in vitro* gene expression.[211]



286

Miscellaneous applications

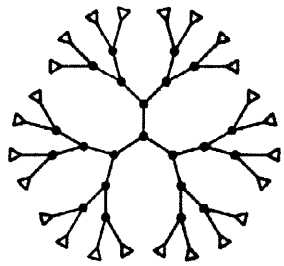
The first series of biodegradable dendrimers based on (*R*)-3-hydroxybutanoic acid (HB) and trimesic acid were reported by Seebach.[212] The polyester dendrimers **287** were prepared by coupling of either dimeric or tetrameric HB units onto a trimesic central core. These dendrimers were readily degraded into small fragments in the presence of polyHB-depolymerase. Dendrimers with repeating tetrameric HB units (n = 4) were hydrolysed 10^2 times more rapidly than the degradation of dendrimers with repeating dimeric HB units (n = 2). Such dendrimers could be used as biodegradable drug carriers.

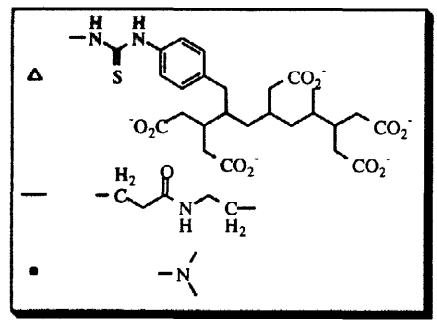


287 n = 2 or 4
R = H or Bn

Dendritic polydentate carboxylates such as **288** and **289**, when complexed with gadolinium, were useful magnetic resonance imaging (MRI) contrast agents.[213] These chelates were prepared by capping the surface of amino-terminated PAMAM dendrimers with the appropriate metal binding functionalities. These gadolinium-containing dendrimers have high proton relaxivities which reduce the dose required to produce

quality images. They also have a more prolonged biological half-life than other polymeric or monovalent MRI contrast agents.





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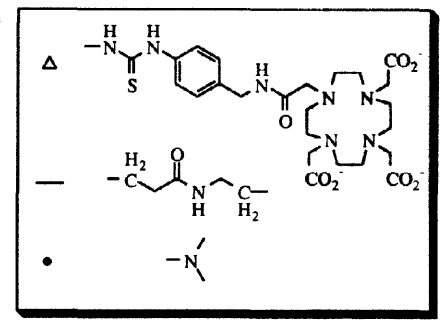


289

Dendrimers have also been employed as vehicles to facilitate the conjugation of antibodies and small molecules. For examples, Roberts reported the use of PAMAM dendrimers to link a porphyrin nucleus to an antibody.[214] The porphyrin unit was first anchored to a dendrimer surface and this intermediate was then conjugated to an antibody followed by incorporation of ^{67}Cu. Both the efficiency of the conjugation and the incorporation of ^{67}Cu were enhanced in the presence of PAMAM dendrimers. Similar observations were also noted by Wu during the preparation of a dendritic antibody-metal chelate conjugate.[215]

5.8 Liquid Crystalline Dendrimers

The design and preparation of novel macromolecular liquid crystals utilising dendritic building blocks is well documented. With few exceptions, most of these liquid crystalline materials are prepared by one pot polymerisation of AB_n monomers. Strictly speaking, these are hyperbranched liquid crystalline materials with severe structural defects and poor homogeneity.[6d,6e,216] In this section we will only concentrate on structurally defined dendrimeric liquid crystalline materials prepared by controlled, stepwise synthetic operations.

Two synthetic protocols have been used to engineer liquid crystalline dendrimers. The first approach is based on a convergent dendrimerisation of AB_n monomers which already possess certain mesogenic character. The second one involves the attachment of tapered shape dendritic fragments onto a functional core which has inherent self-assembly properties. Upon self-assembly, these taper-shaped fragments produce a supramolecular tubular architecture which possesses hexagonal columnar liquid crystalline properties. In this section we will focus our discussion on the first approach. Details of the self-assembly process will be reviewed in Section 5.9.

Recently Percec reported the convergent preparation of a series of structurally defined liquid crystalline dendrimers **290** starting from an AB_2 mesogenic monomer **291** containing two phenolic and one hydroxy functionalities.[217] The two phenolic groups were first alkylated with 1-bromo-10-undecene followed by functional group transformation of the remaining hydroxy moiety into the corresponding bromide. This bromide was then reacted with the monomer **291** to create the second level of branching. Finally these dendritic fragments were coupled to a trimesic acid core to give the target dendrimers. All dendritic intermediates and target molecules prepared by this method exhibited thermotropic cybotactic nematic, smectic, and crystalline phases which were generated from the *anti* conformation of the structural repeating

unit derived from monomer **291** (Figure 16). The higher generation dendritic compounds, in particular, have a higher tendency toward the formation of liquid crystalline phases.

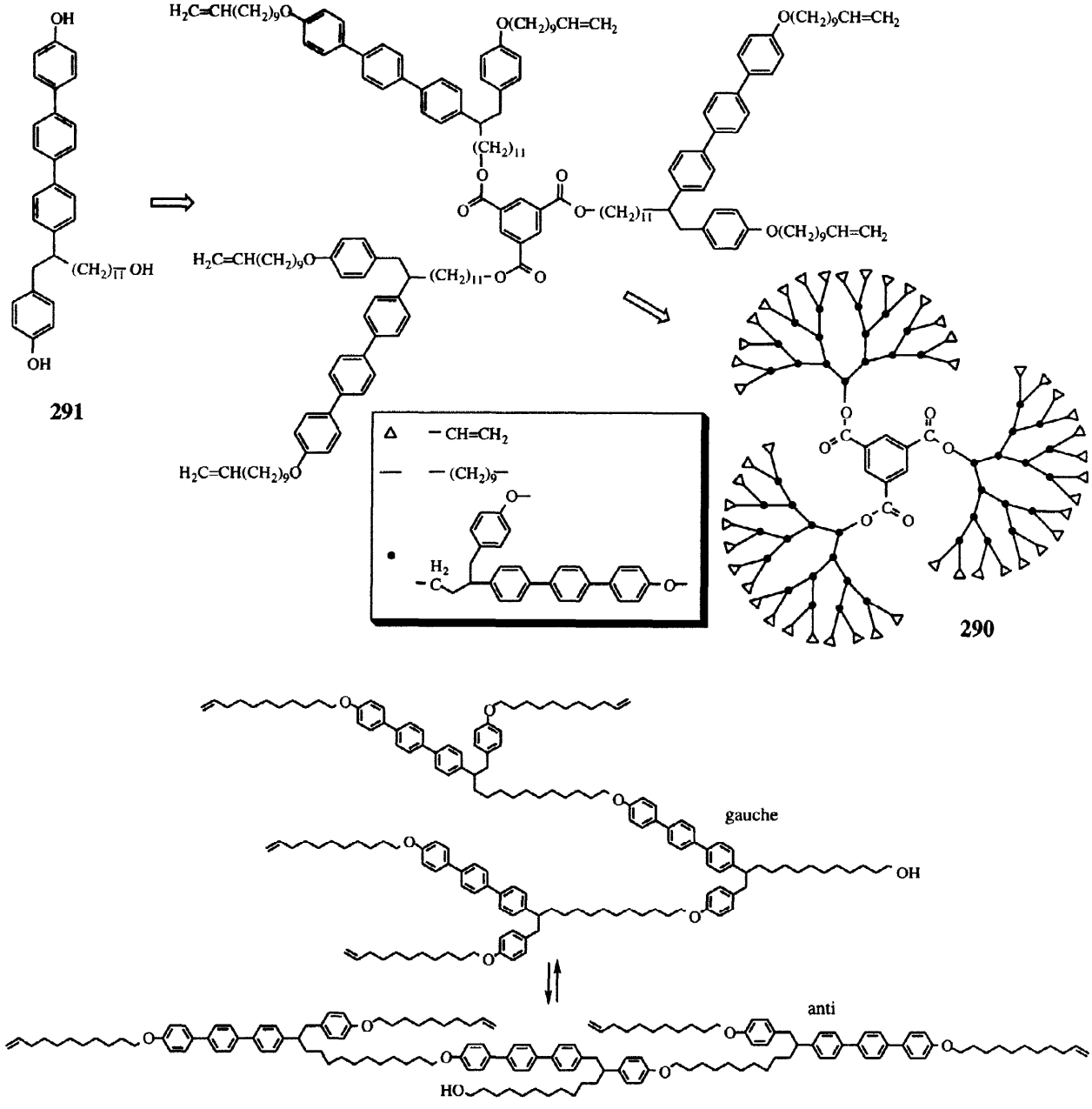
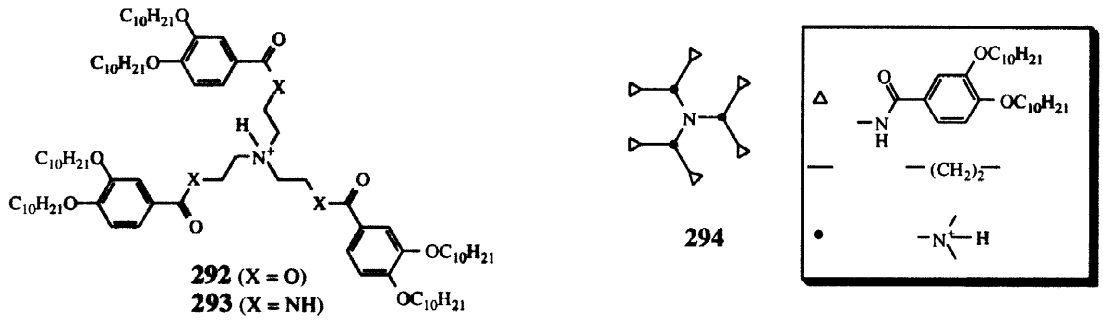
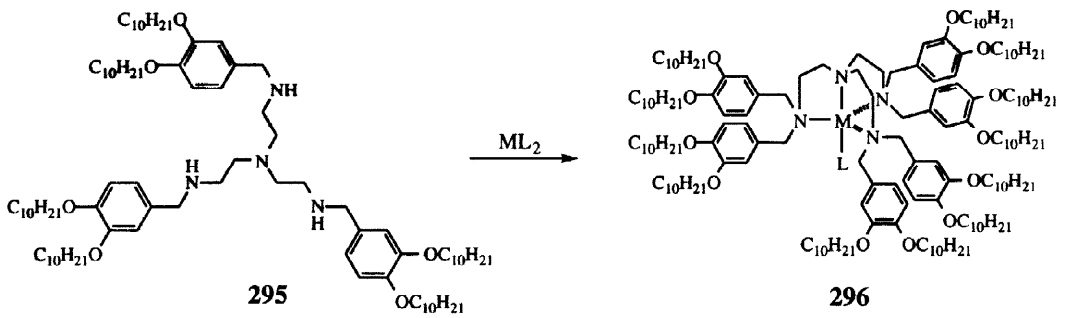


Figure 16. Conformational change between *gauche* and *anti* conformers of second generation dendritic alcohol

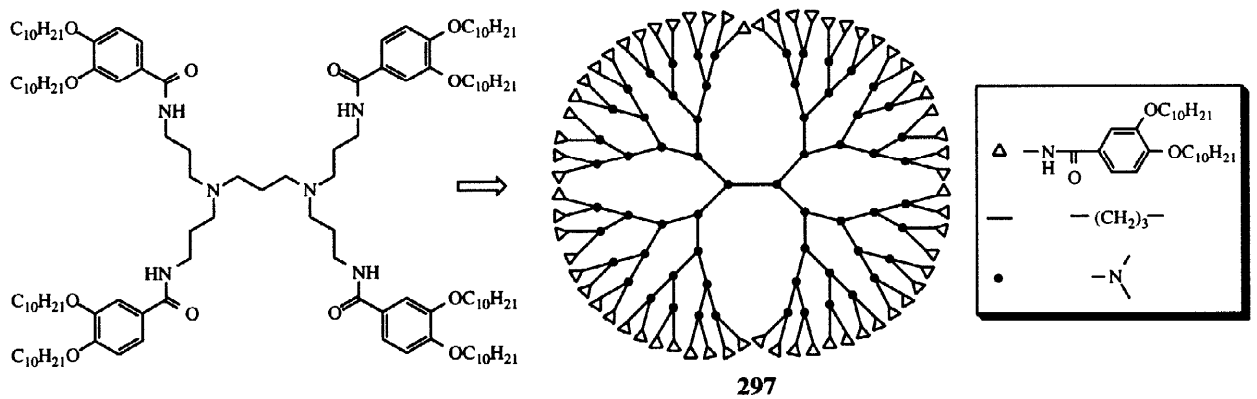
Lattermann also described the preparation of two G0 liquid crystalline dendrimers **292** and **293** having a positively charged ammonium core and three terminal aromatic groups each with two C_{10} hydrocarbon tails.[218] The mesophase of both dendrimers was considered to be smectic. Interestingly, the corresponding neutral amino dendrimers did not show any liquid crystallinity. A structurally related G1 cationic dendrimer **294**, having three periphery protonated nitrogen atoms and an electrically neutral core nitrogen, also exhibited an enantiotropic mesophase.



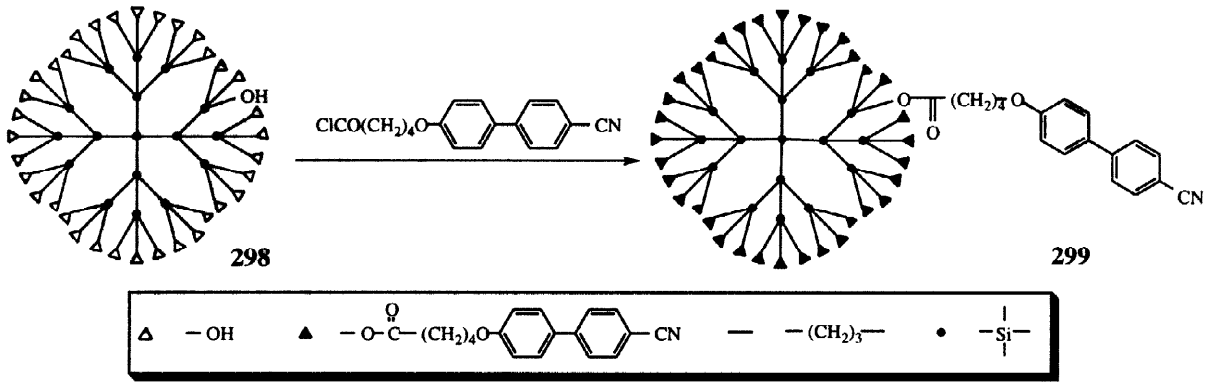
Treatment of the electrically neutral G0 ligand **295** with different metal ions resulted in the formation of metallomesogens **296**. All these metal complexes showed mesomorphic behavior with relatively low glass transition temperatures.[218b] The majorities of the metal complexes (M = Co, Cu, Zn) have a trigonal-bipyramidal structure except for the Ni complexes which are octahedral in shape.



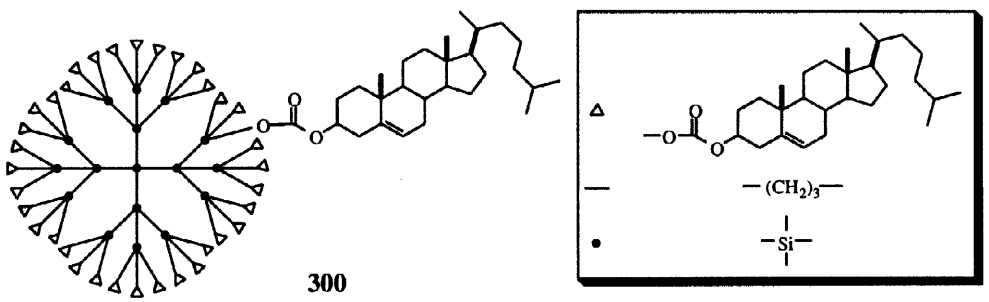
Lattermann also reported the capping of surface amino residues of poly(propyleneimine) dendrimers by 3,4-bis(decyloxy)benzoyl groups to give dendritic mesogens **297**.[219] Based on the results obtained from polarising microscopy and differential scanning calorimetry, **297** was shown to exhibit generation dependent thermal properties. While the G0 dendrimer exhibits a monotropic mesophase, the medium generation ones (G1 to G3) are enantiotropic and the largest G4 dendrimer is not liquid crystalline. X-ray investigations on the medium generation dendrimers indicated the presence of a hexagonal columnar structure. The columnar structure is probably due to the piling up of three dimensional cylindrical segments consisting of a polar poly-(propyleneimine) core as the cylindrical cross-sectional area and a nonpolar aromatic shell as the cylinder casing. The deformation of the dendritic structure from spherical geometry could be due to a favorable



mesogen-mesogen interaction leading to liquid crystalline phases. For the G4 dendrimer, due to steric congestion, the polar cylindrical cross-sectional area was buried under the nonpolar shell and this could be the reason for the lack of mesomorphism.



A G2 dendritic mesogen **299** based on an organosilane skeleton was reported by Frey.[220] The liquid crystalline dendrimer **299** was prepared by ligating cyanobiphenyl mesogens onto a silane-based polyol **298**, which was prepared by hydrosilylation/allylation reaction with tetraallylsilane, followed by hydration of all the surface allyl moieties.[221] Dendrimer **298** exhibits liquid crystalline properties, forming a broad smectic A phase in the temperature range of 17°C to 130°C. Furthermore, its low viscosity is advantageous for liquid crystalline applications. Frey also disclosed the results of an atomic force microscopic study on ultrathin films of a series of cholesterol-coated carbosilane dendrimers **300**.[222] These liquid crystalline dendritic structures were prepared by condensation of cholesteryl chloroformate with dendritic polyols **298**. Both G1 and G2 dendrimers are crystalline powders at ambient temperature and form smectic mesophases, with transition temperatures between 80°C to 90°C. Similar to Lattermann's result, the higher generation G3 does not form mesophases.



5.9 Self-assembled Dendrimers[223]

Thus far, most of the research effort in dendrimer chemistry has been concentrated on the construction of large molecular species *via* covalent bond formation. However, such a strategy is burdened with several inherent limitations when applied to the construction of extremely large dendritic molecules. For example, the large number of synthetic operations involved will inevitably lead to poor yields and possible structural defects, and will also place a practical limit to the dendrimer size which can be synthesised. The recent success of creating well defined, supramolecular architectures by self-organisation[224] of suitably designed

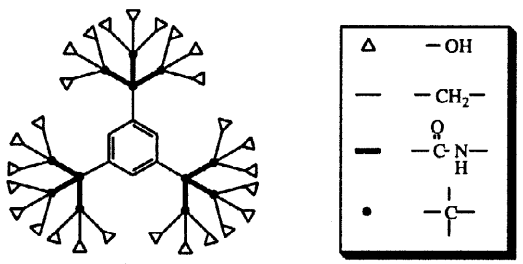
components through specific interactions suggested that self-assembly could be a more efficient and viable method for dendrimer synthesis. Here we will review the various self-assembly methods used to construct complex dendritic supramolecules.

Self-assembly mediated by hydrophobic interactions

The hydrophobic effect is one of the vital driving forces for self-organisation processes in nature. A number of important biological superstructures such as lipid bilayers, are formed *via* the hydrophobic interactions of nonpolar hydrocarbon tails of small amphiphilic lipid molecules.

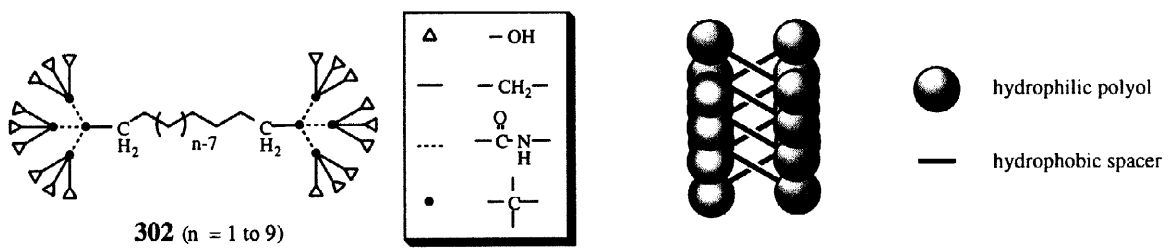
Amphiphilic dendrimers, having both hydrophobic and hydrophilic regions within one dendritic structure, tend to self assemble into micelles or bilayers under aqueous conditions. Similar to surfactant molecules, the hydrophilic head groups will expose themselves to the aqueous phase and the hydrophobic chains bury inside the interior. In contrast to surfactant molecules which have a linear structure, dendritic amphiphiles usually have a spherical structure. This is a critical packing parameter and can affect both the stability and packing pattern of these self-assembled dendritic aggregates.

One of the earlier examples of self-assembled dendritic systems was reported by Newkome.[225] During their earlier studies on the preparation of unimolecular micelles, it was discovered that hydrophilic polyols **301** readily associated to form aggregates containing about 40 molecules. Based on light scattering measurements, the critical micelle concentration of **301** is about 2 mM.



301

Similar studies on bolamphiphiles **302** having two polar dendritic groups franked by a hydrophobic spacer revealed the formation of a thermally reversible aqueous gel.[226] These molecules were prepared by coupling of triethyl sodiomethanetricarboxylate with α,ω-dibromoalkanes followed by dendrimerisation of the ester groups with tris(hydroxymethyl)aminomethane. The formation of an aqueous gel from a 2% aqueous solution of **302** was noted by optical and electron microscopy. Under transmission electron microscopy, the gel appeared as long fibrous rods having uniform diameter of 40 Å with variable lengths. Such an appearance

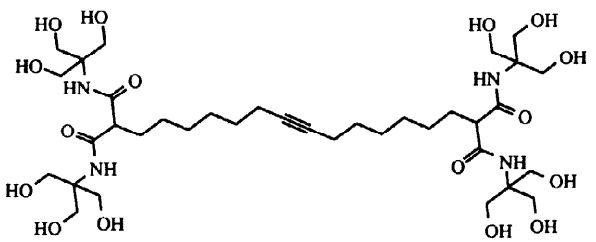


302 (n = 1 to 9)

Figure 17. The stacking of bolamphiphile **302** in aqueous solution

was rationalised by the packing of these dumbbell-shaped molecules in a cross-over fashion with the hydrophobic spacers stacking on top of each other in orthogonal fashion. Such packing could minimise the interactions between the hydrophobic spacers and the aqueous environment (Figure 17). The outer surface of these rods was covered with hydrophilic hydroxy groups which allowed the aqueous solution of **302** to cross-link *via* H-bonding through water molecules.

As a continuation of this work, Newkome reported the synthesis of a bolaamphiphile **303** containing a central triple bond.[81] Upon dissolution of **303** in water, the desired self-assembly resulted in gelation. Electron micrographs of the gelled dendrimer revealed the presence of single-stranded, rod-shaped structures. These single-stranded aggregates self-organised to form higher order aggregates possessing helical morphologies. Such helical superstructures were not observed for the corresponding saturated alkane analog **302**. Hence the linear alkyne spacer was responsible for inducing non-orthogonal stacking and resulted in the formation of helical structures. On the other hand, bolaamphiphile having a spirane **304** or biphenyl central spacer unit **305** did not form an aqueous gel.[227] This study indicated that the gelation property was strongly dependent on the length and rigidity of the spacer. The dendritic polyol **67** having an electrochemically active TTF spacer reported earlier also possesses gel-forming ability in aqueous ethanol or aqueous DMF solutions.[80]



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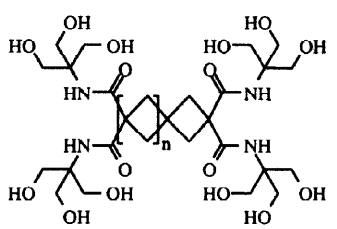
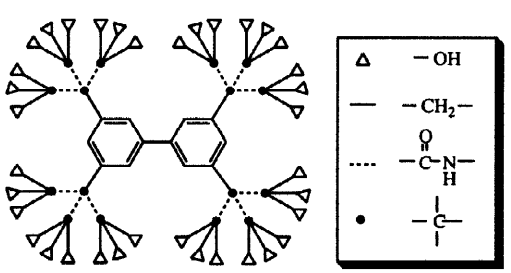


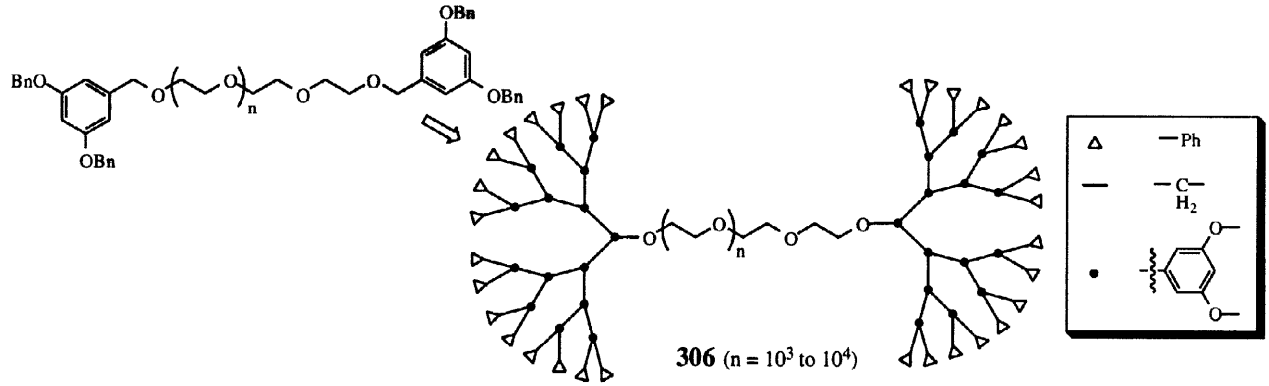
304 (n = 1, 3 or 5)



305

Fréchet described the preparation of novel hybrid linear-dendritic block copolymers **306** using either a hydrophilic polyethylene glycol (PEG) or a polyethylene oxide (PEO) chain to connect two hydrophobic polyether dendritic sectors.[228] Due to the differences in shape and solubility properties of the two blocks, these copolymers showed variable solution and solid state properties depending on the solvents used. According to ^{1}H-NMR analysis, the copolymer existed in an extended conformation in chloroform, which was a good solvent for both blocks. While in THF solution, which was a good solvent for the dendrimer block but not for the PEG block, the PEG block was tightly packed. In methanol, which was a good solvent for the PEG block but not for the dendrimer block, the dendrimer block was wrapped around by the extended PEG chain. The aggregation of these copolymers in solution was investigated by GPC/viscosity studies. In THF solution, the copolymers existed mainly as a monomeric species in solution. However, in aqueous methanol, some of

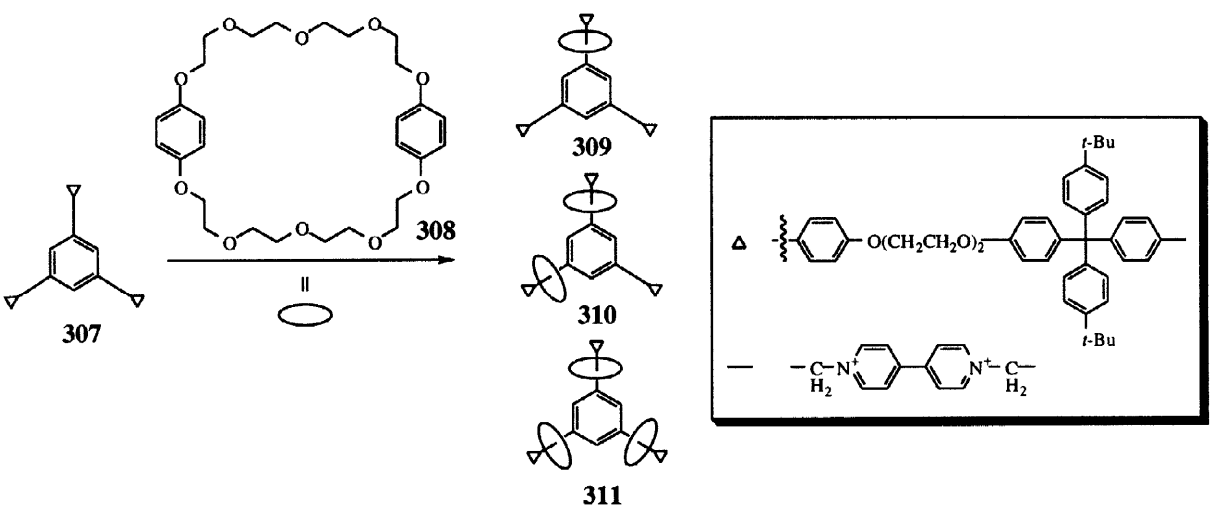
the copolymers were shown to form stable self-assembled multimolecular aggregates having large micellar structures depending on the dendrimer generation and concentration.



Light scattering and conductivity experiments performed on acetonitrile solutions of polypyridinyl Ru or Os organometallic dendrimers **120** and **125** also indicated the formation of aggregates with dimension of 100 nm at a concentration as low as 10^{-6} M.[229] The driving force behind this phenomena was due to the favorable hydrophobic interactions amongst the aromatic moieties.

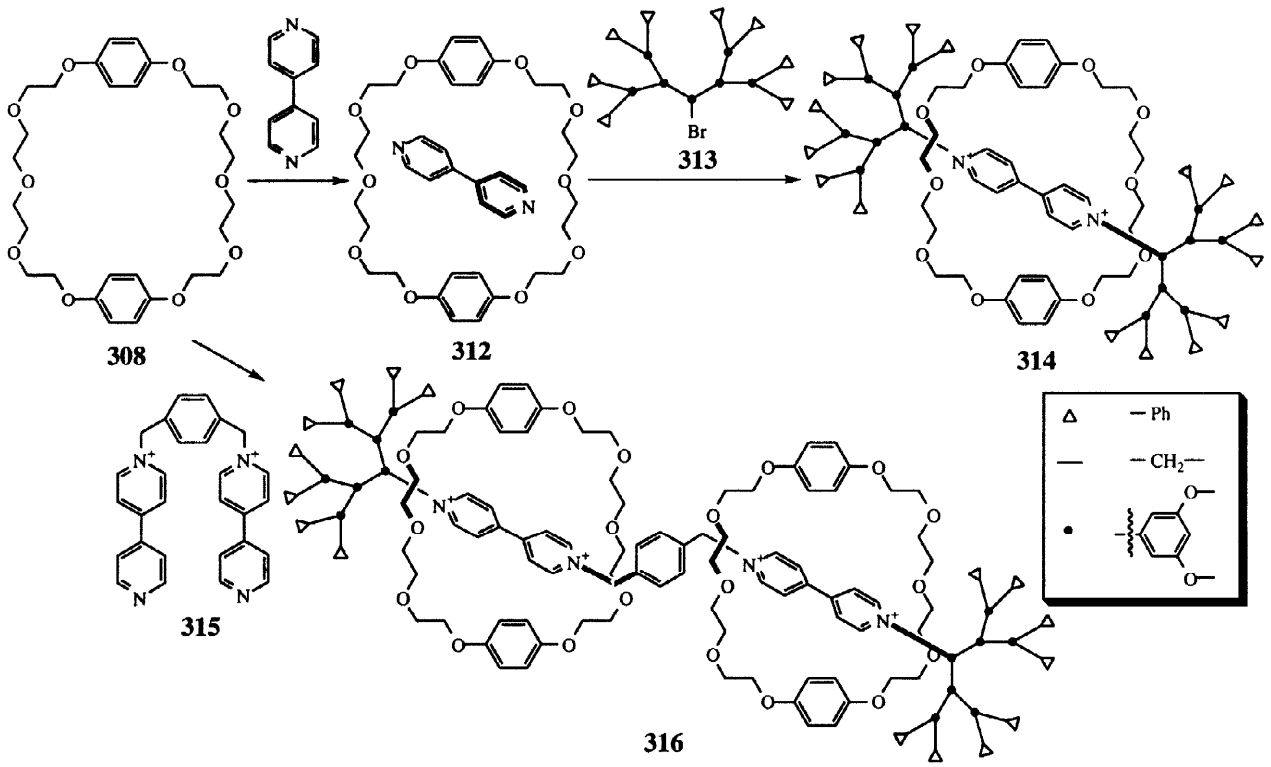
Self-assembly mediated by π-stacking interactions

The strong interaction between π-donor and π-acceptor molecules can be used to synthesise a variety of interesting self-assembling systems such as rotaxanes and catenanes. Stoddart recently reported the preparation of dendritic rotaxanes by a slipping method.[230] Thus, the G0 tris(bipyridinium) dendrimer **307** end-capped with three large blocking groups was treated with an excess of an aromatic crown ether **308** at a temperature high enough to allow the crowns to slip over the block groups. Obviously, a mixture of mono-, di- and tri-rotaxanes (**309** - **311** respectively) were formed under such reaction conditions.

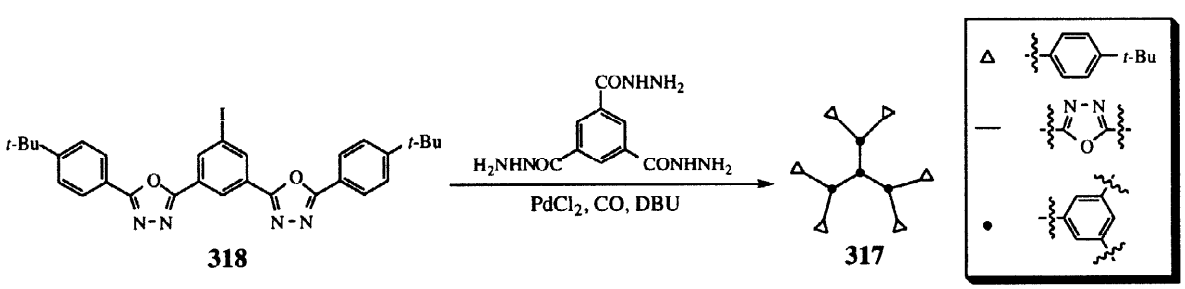


Dendritic rotaxanes could also be synthesised by a threading approach.[231] When 4,4'-bipyridine and the aromatic crown ether **308** were mixed in DMF, a pseudorotaxane-like complex **312** was formed with the rod-like bipyridine threading through the crown ether hole. In the presence of a polyether dendritic bromide **313**

under 12 kbar pressure, a [2]rotaxane **314** bearing two dendritic stoppers was formed. When an extended bis(bipyridine) **315** was used in place of 4,4'-bipyridine, a [3]rotaxane **316** was formed together with a [2]rotaxane containing only one crown unit. This chemistry could also be extended to the preparation of a [4]rotaxane. Despite their ionic character, these rotaxanes are soluble in a wide range of organic solvents.



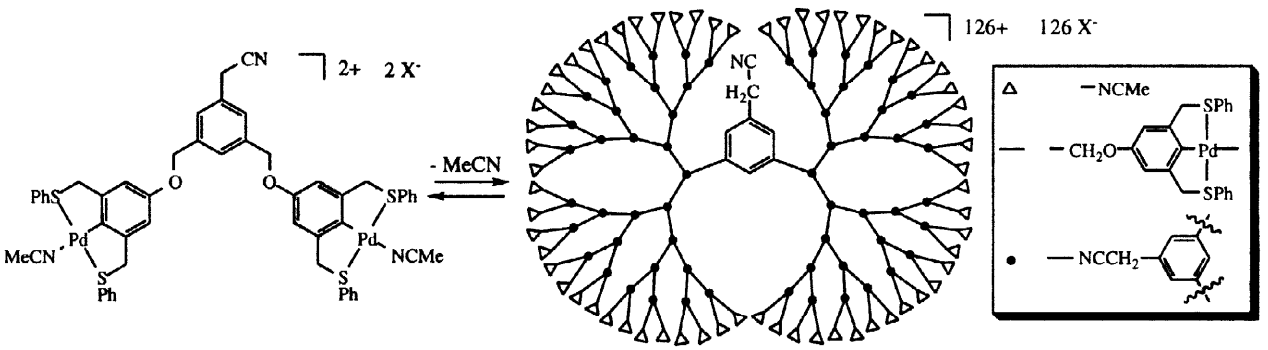
An oxadiazole-based G1 dendrimer **317**, prepared *via* palladium-catalysed carbonylation of an aryl iodide **318** in the presence of 1,3,5-benzenetricarboxylic acid trihydrazide, followed by an acid-catalysed triple cyclisation, was shown to form dimeric, trimeric and tetrameric π-stacks in chloroform solution.[232] However, the corresponding G0 dendrimer displayed negligible chemical shift dependence, implying little or no self association.



Self-assembly mediated by metal ions

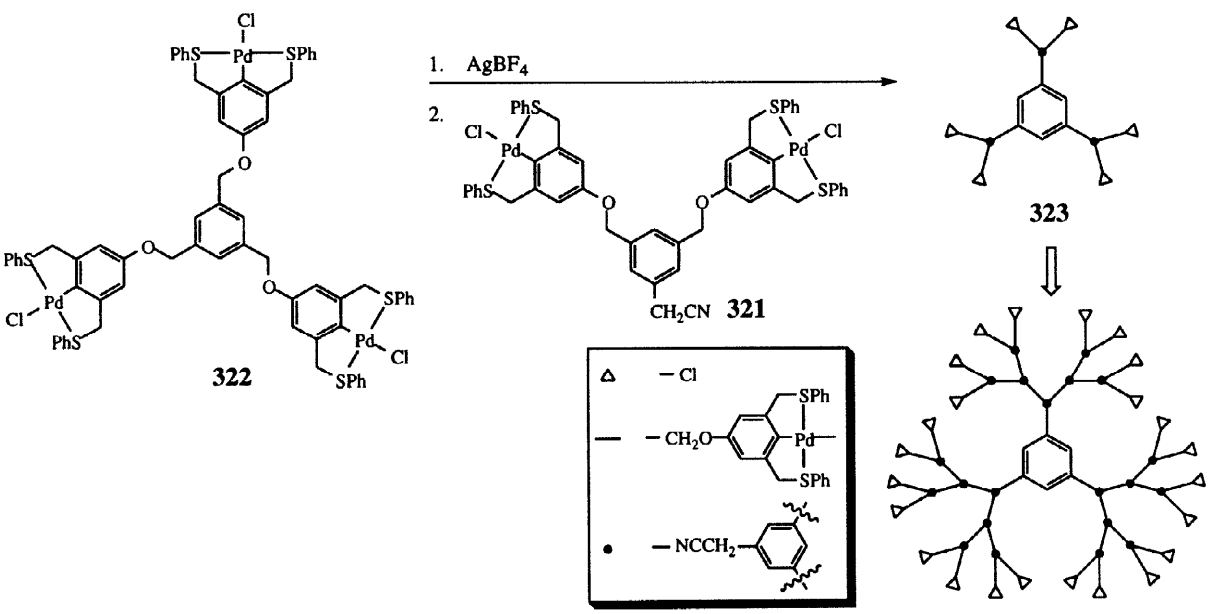
The use of metal ions and polydentate ligands to form well-defined self-assembly systems is well documented in supramolecular chemistry. Reinhoudt reported the self-assembly of an AB_2 monomer **319** having mutually interactive benzyl nitrile and aryl palladium(II) moieties.[233] The self-assembly process was based on substitution of the volatile acetonitrile molecule on the palladium centers by the benzyl nitrile group

of another monomer. When a solution of **319** was heated *in vacuo*, large spherical aggregates of **320** with diameter approaching 210 nm and a relatively narrow size distribution were formed. The self assembly process is fully reversible as the aggregates could be transformed back to the monomer on addition of acetonitrile. It was later found that the size of the self-assembly sphere was affected by the size of the substituent on the sulfur atom as well as that of the counter anion.[233b] In general, monomers with larger counteranions or bulkier thioethers gave smaller particle size. By varying the nature of the anions and the alkyl groups on the thioether, hyperbranched spheres of sizes ranging from 100 to 400 nm could be prepared.



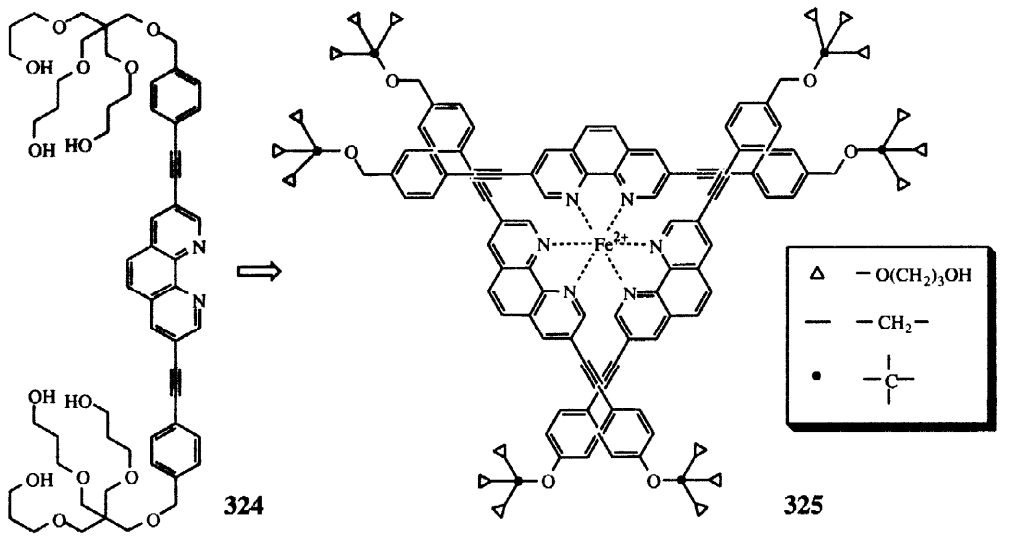
319 **320**

Reinhoudt subsequently described a controlled divergent self assembly of metallodendrimers.[42c] This method relied on the preparation of a protected AB_2 monomer **321**, which could be linked to a trivalent core **322** to form a G1 dendrimer **323**. In order to avoid self-coupling, the labile acetonitrile ligand was replaced by a kinetically inert Cl^- anion. The chloride anion in **322** was first displaced by a non-coordinating BF_4^- ion (by treatment with $AgBF_4$) to allow coordination of **321** to the palladium centers of the core molecule. The peripheral chloride anions of **323** were then replaced with BF_4^- to release the six palladium centers for the second round of metal-coordination to give dendrimers of higher generations.



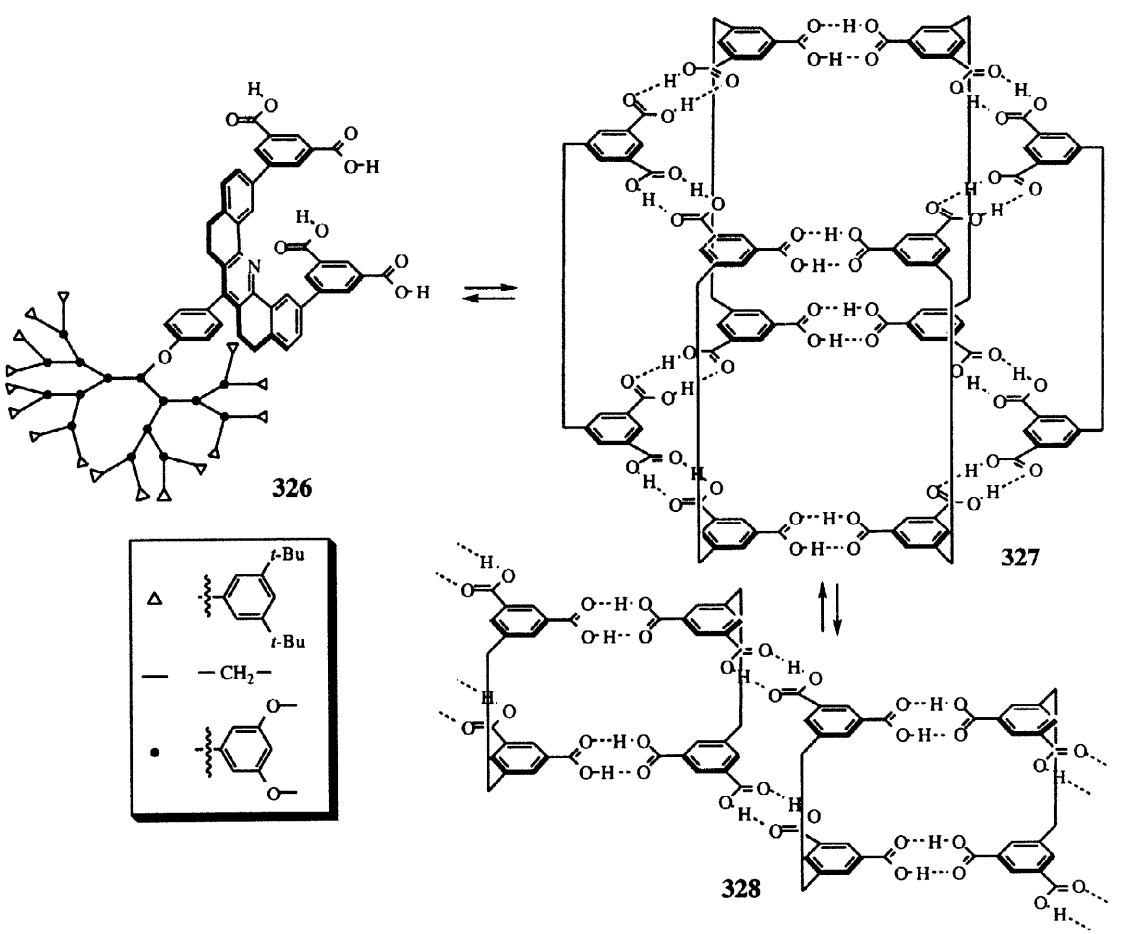
322 **321** **323**

The dendrimeric 1,10-phenanthroline ligand **324** also self-assembled in the presence of metal ions such as Fe(II) to give a red-purple octahedral complex **325** which contained 18 hydroxy groups and had a diameter of 40 Å.[234] This complex was fully characterised by ^{1}H-NMR and MS spectroscopy.



324 **325**

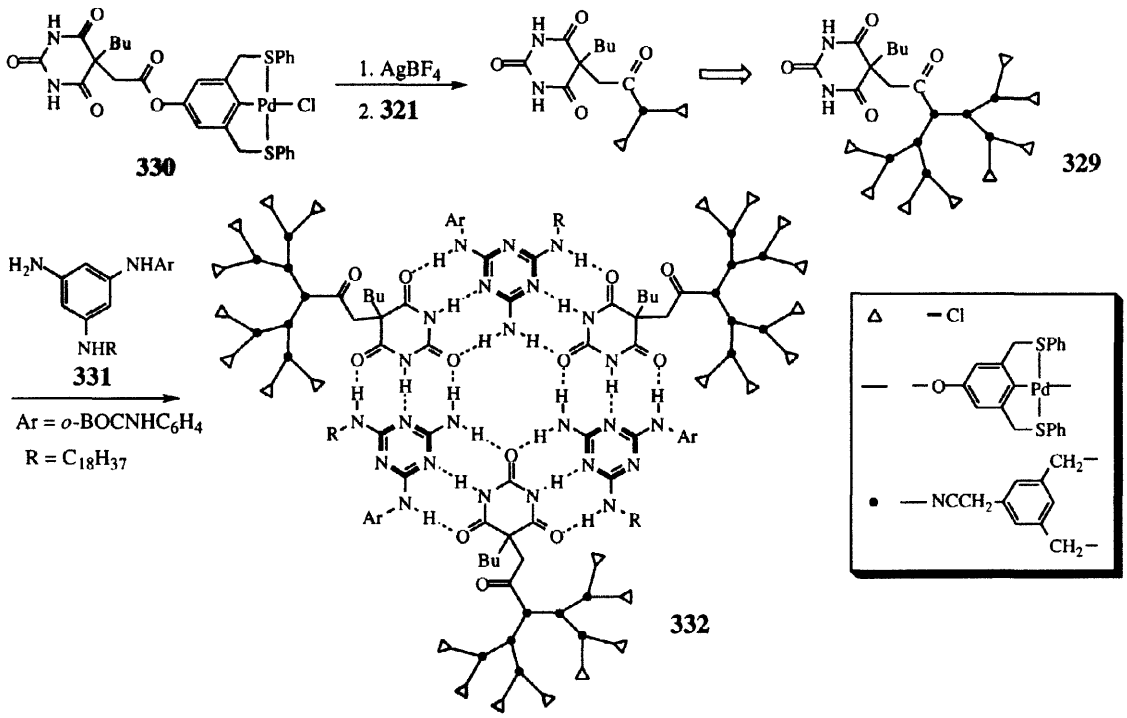
Self-assembly mediated by hydrogen bonds



326 **327** **328**

Zimmerman reported the preparation and self-assembling properties of a series of bis(isophthalic acid)-based dendrimers **326**.[235] Compound **326** self aggregated through H-bonding to form a hexamer **327** whose stability varied in a generation and solvent dependent manner. In weakly donating solvents such as chloroform or dichloromethane, the G2 to G4 dendrimeric species aggregated to form hexamers, as determined by SEC and laser light scattering studies. On the other hand, in strongly donating solvents such as DMSO and THF, compound **326** existed as a monomeric species. The hexameric aggregate derived from G1 tended to be less stable and was in equilibrium with a linear aggregate **328**. This is because the sterically bulkier dendritic appendages in the G2 to G4 dendrimers cannot be accommodated in a linear aggregate, and hexamer formation is hence favored.

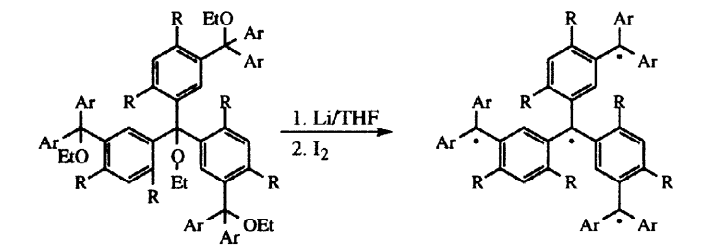
Reinhoudt and van Veggel further demonstrated the full potential of self-assembly construction by synthesising a complex dendritic system **332** using both H-bonding and metal complexation interactions.[236] A metal-assisted self assembled dendritic wedge **329** containing a barbituric acid core was prepared by an iterative convergent addition of the palladium-containing propagating unit **321** to a barbituric derivative **330**. The resulting dendritic wedge **329** was then self assembled in the presence of its H-bonding partner **331** to give a [3 + 3] hexamer **332** whose structure was confirmed by a ^{1}H-NMR study.



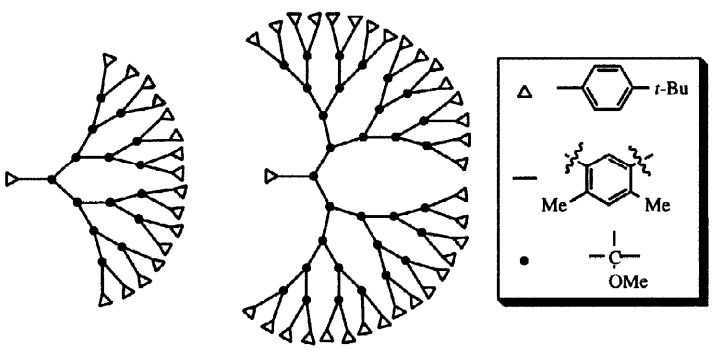
5.10 Dendritic Magnets[237]

One of the promising approaches to produce high spin paramagnetic or superparamagnetic systems depends on the placement of multiple spin systems connected by ferromagnetic coupling units on linear structures such as poly(*m*-phenylene)s. However, such architectures suffer from the problem of structural defect and poor solubility, and the possibility of radical recombinations due to the flexibility of the polymer chain. One possibility to circumvent these problems is to attach the spin systems to a dendrimer matrix. The matrix will provide a relatively rigid framework to reduce the chance of radical recombinations and will confer better solubility to the paramagnetic systems by the presence of solubilising groups located on the dendritic

domain. Adopting this idea, Rajca was able to generate a dendritic poly(arylmethyl) quintet tetraradical **333** from a tetraether derivative **334**.[238] Both ESR and magnetisation measurements confirmed that the dominant species for the tetraradical **333** was a high spin quintet. In particular, the sterically hindered tetraradical **333** (R = *i*-Pr) could be isolated as a stable solid and showed no detectable thermal population of the low-spin states at ambient temperature. Magnetic studies of **333** (R = *i*-Pr) in the solid state gave a magnetic moment of 3.9 μ_B, which was slightly lower than the expected average spin for a quintet. Later, Rajca reported the syntheses of dendritic polyethers **335** and **336** having the potential to generate 15 and 31 unpaired electron centers, respectively.[239] Magnetometry studies of these dendritic polyradicals gave spin values comparable to those for the homologs with 7 or 10 sites, respectively. This apparent lower spin value was caused by structural defects on the dendritic particle which were defined as failure to generate a radical site. The defective sites would interrupt or weaken the pathway for spin coupling.



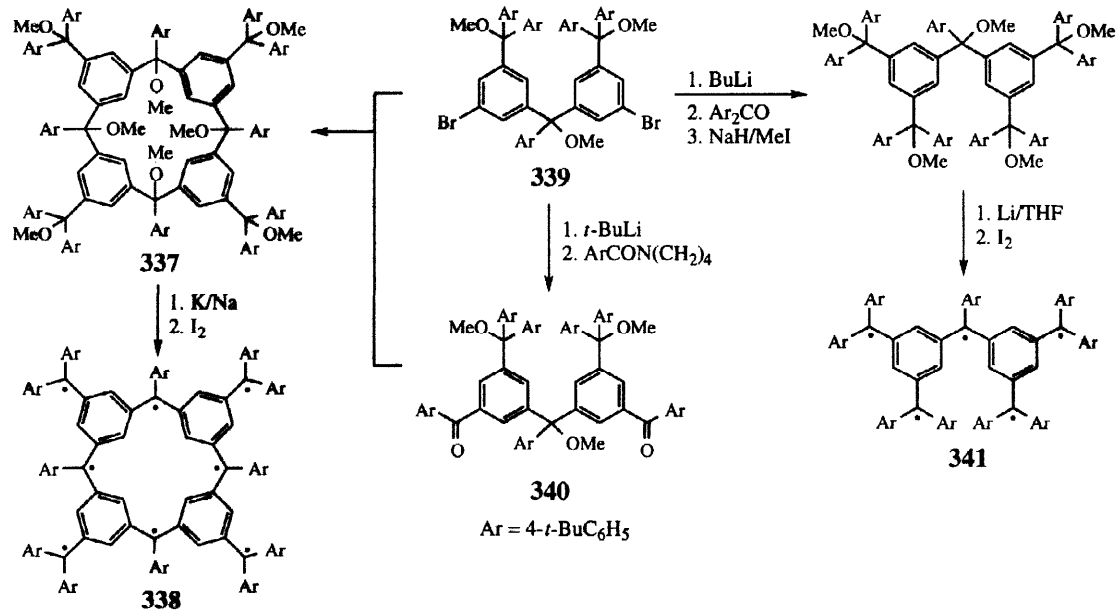
334 (Ar = 4-*t*-BuC$_6$H$_4$, R = H, Me, *i*-Pr) **333**



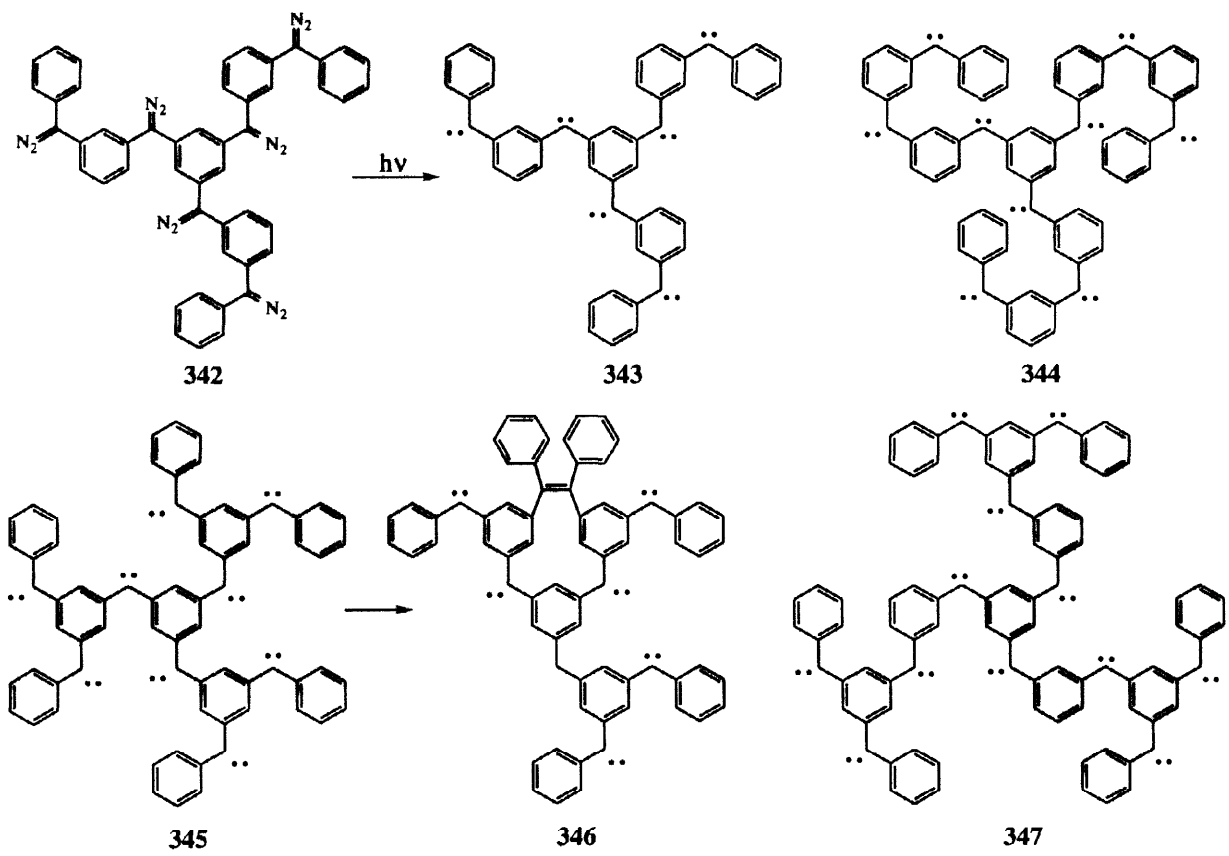
335 **336**

Rajca reasoned that if the spin centres were arranged in a cyclic array, then at least two structural defects must occur on the cyclic system in order to have substantial spin uncoupling. A calix[4]arene ring containing 8 ether linkages **337** was synthesised and converted into the corresponding high spin radical **338**.[240] This calixarene derivative **337** was prepared by macrocyclisation of a dianion generated from an aryl dibromide **339** and a diketone **340**. A magnetisation experiment established that **338** had the expected nonet ground state. Based on a similar argument, only a structural defect occurring at the solitary focal site of the acyclic dendritic G2 radical **341** will have a detrimental effect on the overall spin value. Again, a magnetisation experiment showed that **341** had the expected sextet ground state.

To maximise the spin values of organic molecules, Iwamura employed triplet carbenes as spin sources to generate superparamagnetic molecules.[241] A G0 hexadiazo compound **342** was prepared and photolysed to give the corresponding hexacarbene **343**. The magnetisation measurement indicated the ground state of **343** had a tridecet spin state. Due to the high efficiency of carbene formation, signals attribute to lower spin states



were very weak if not undetected. Likewise, the chain elongated nonacarbene **344** exhibited a nonadecet ground state.[241b] For both polycarbene species, the effective magnetic moment was lowered by about 15% if the concentration of the sample was higher than 1 mM. This was probably due to antiferro-magnetic intermolecular interactions.



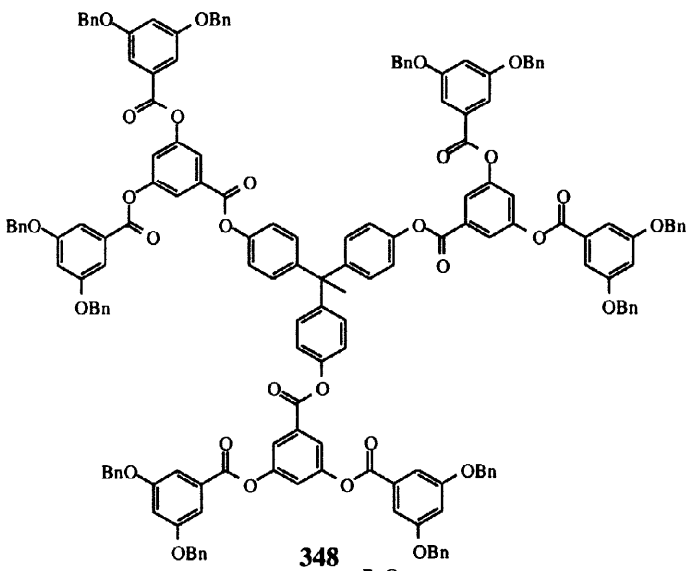
Rather unexpectedly, the G1 dendritic nonacarbene **345** which was also a structural isomer of **344**, exhibited a lower than expected spin multiplicity of ground state pentadecet.[242] The result was interpreted not to be due to incomplete photolysis of the starting nonadiazo compound, but rather to recombination of two triplet carbene centers into an ethylene unit to give **346** as the likely intermediate. The highly branched nature of **345** probably forced two carbene centers in close proximity and resulted in carbene recombination. Similar carbene recombination from the photolysis of an elongated G1 analog **347** was also noted.[242b]

So far all dendritic magnets have their spin sources covalently linked through ferromagnetic coupling units. However, Meijer recently reported that ferromagnetic exchange interactions could also occur intermolecularly when several free radicals were encapsulated within a dendritic box.[169] Thus, for the poly(propyleneimine) dendritic box **238** already encapsulated with two 3-carboxyl-proxyl radicals, intermolecular ferromagnetic alignment of the two encapsulated radicals into triplet state radical pairs was noted.

5.11 Dendritic Particles

Dendritic macromolecules can be considered as a special class of engineering nanoparticles from which complex architectural arrays can be built. There are also a number of unusual chemical and physical properties attributed to these dendritic particles that clearly differentiate them from classical linear polymeric systems.

One of the most informative investigations to compare the chemical and physical properties between spherical dendrimers and linear polymers was reported by Fréchet.[243] In this study, dendritic **348**, hyperbranched **349** and linear polyesters **350** were prepared and their chemical and physical properties investigated. Thermal property measurements such as glass transition temperature and thermogravimetric



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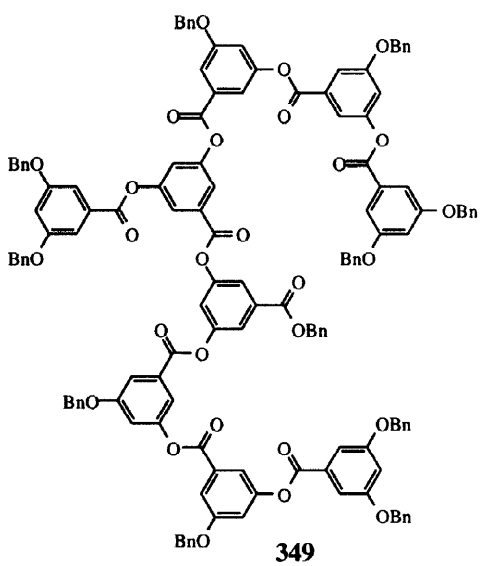

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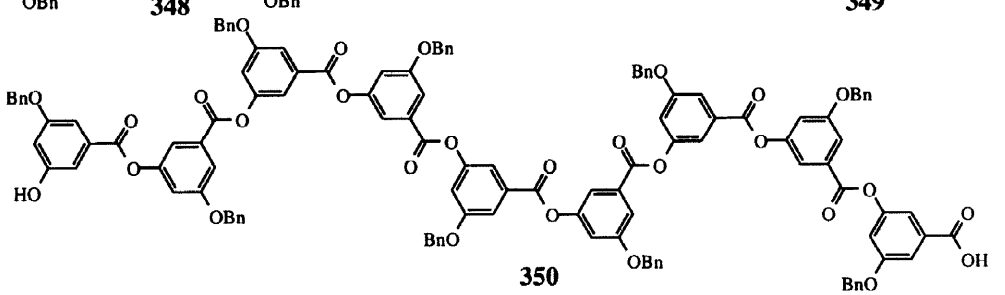

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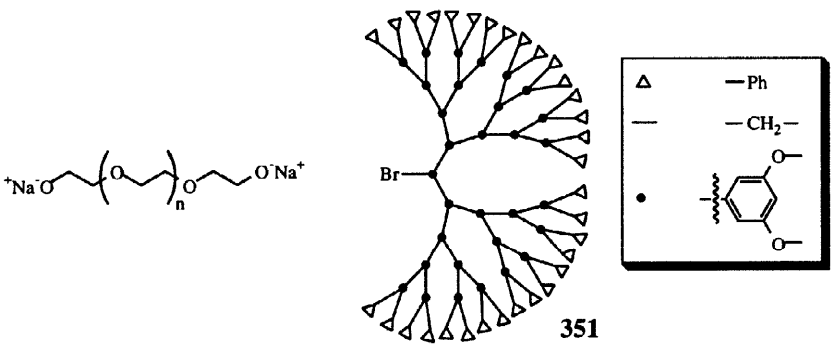
analysis showed little differences amongst the three different structural types. However, the dendritic and hyperbranched materials demonstrated far better solubility properties (50 times) in organic solvents (THF, acetone) than their linear counterpart. The three different polymers also showed differential chemical reactivity. It was noted that the benzyl ether groups of the hyperbranched and linear polyester showed little or no reactivity towards catalytic hydrogenolysis. In contrast, the benzyl ether groups in dendrimer **348** were readily cleaved under mild hydrogenolysis conditions.

The influence of the size of the dendritic sector on the reactivity of the focal point functionality is also of interest in dendrimer synthesis since a simple steric hindrance argument will predict a lowering of focal point reactivity. Such information would be extremely useful in probing the generality of the convergent synthesis strategy. In this regard, Fréchet has reported a kinetic study of the Williamson reactions of PEO or PEG with dendritic bromides **351** of various generations.[244] Contrary to most expectations, the reaction rate constant for the reaction increased with both the chain lengths of PEO and PEG fragments and the size of the dendritic sector. Thus, the pseudo second order rate constants in the Williamson ether synthesis of PEG (MW 1100) increased gradually from 0.44×10^{-3} to 1.01×10^{-3} $M^{-1}h^{-1}$ on moving from G1 to G4. This anomalous behavior was attributed to the increased solvation of the counteranion of the PEO and PEG by the linear and the dendritic polyether block.



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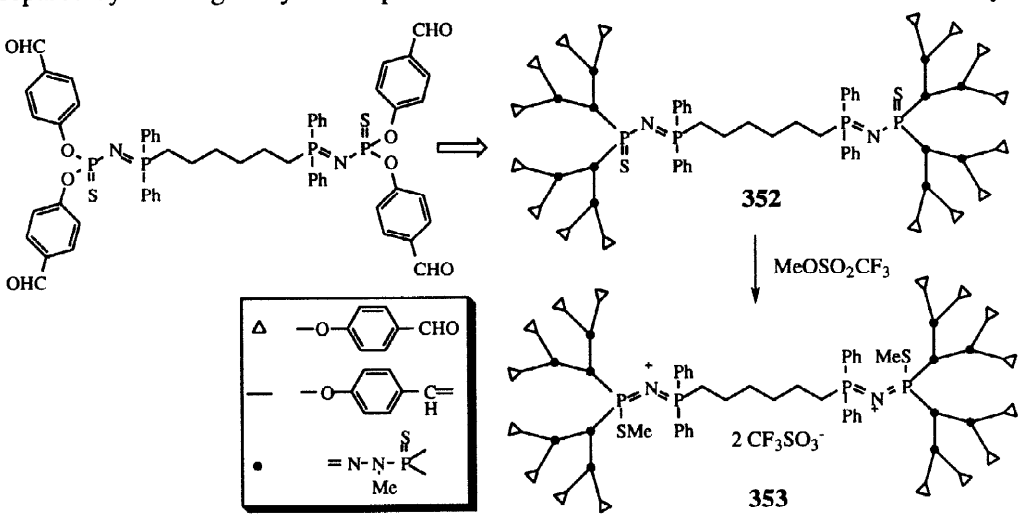
Another impressive study on the internal properties of dendrimers was also reported by Caminade and Majoral.[245] Layer block dendrimers containing different layers of ≡P=N-P(=S)= =N-N(Me)-P(=S)= such as **352** were prepared by a divergent synthetic procedure. Due to the differential chemical reactivity of these two



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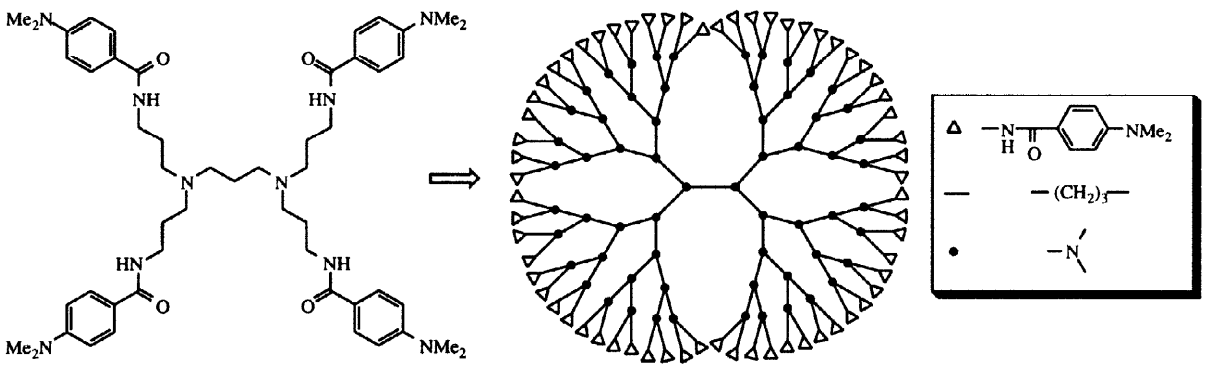
353

functional groups, the sulfur atom in the former functionality can be methylated with methyl triflate while that of the latter cannot. Hence, treatment of G2 dendrimer **352** having two core ≡P=N-P(=S)= functionalities enveloped within two layers of inert =N-N(Me)-P(=S)= shells with methyl triflate resulted in the chemoselective methylation to give the core-modified dendrimer **353**. Most remarkably, the same ≡P=N-P(=S)= functionality located in both the internal core and an intermediate layer of a structurally related G7 dendrimer could also be selectively methylated. This example showed that the interior core of a high generation dendrimer was still accessible for reaction, despite an unfavorable steric environment.

To probe the three dimensional structure of dendrimers as a function of generation, Meijer converted the amino end groups of poly(propyleneimine) dendrimers of different generations into 4-dimethylaminophenyl-carboxamides, a typical donor-acceptor second-order nonlinear optical chromophore.[246] The nonlinear optical properties of the resulting dendrimers **354** were investigated by hyper-Rayleigh scattering technique. The hyperpolarisability of the dendrimers increased linearly with the number of chromophores for the lower generations. However, at higher generations this increase in hyperpolarisability became smaller and eventually diminished. The results are in full agreement with the expectation that the structures of the dendrimers become more spherical at high generations.



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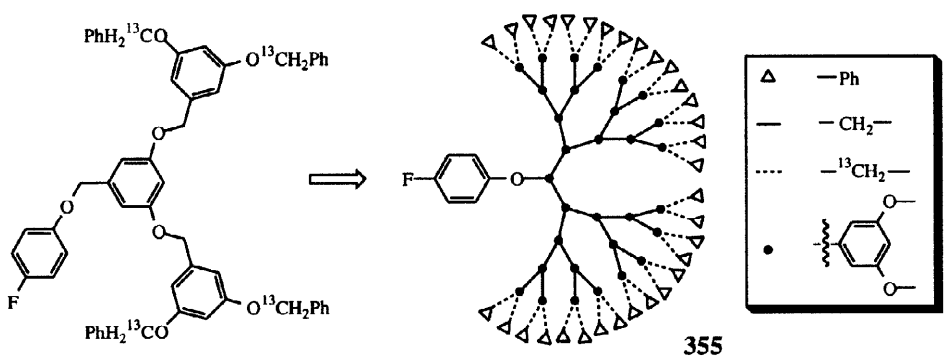
While the folding pattern of dendrimer chain ends has been the subject of theoretical investigations, the first experimental study on the solid state shape, size and chain end folding of a series of ^{13}C-labelled polyether dendrimers **355** was reported only recently by Wooley.[247] The dipolar couplings between ^{13}C nuclei located near the chain ends and an ^{19}F label placed at the dendritic core were determined by rotational-echo double-resonance NMR spectroscopy. Based on the experimental data, the average intramolecular ^{13}C-^{19}F distances (12 Å) were shown to be invariant for the higher generation dendrimers (G3 to G5). Such



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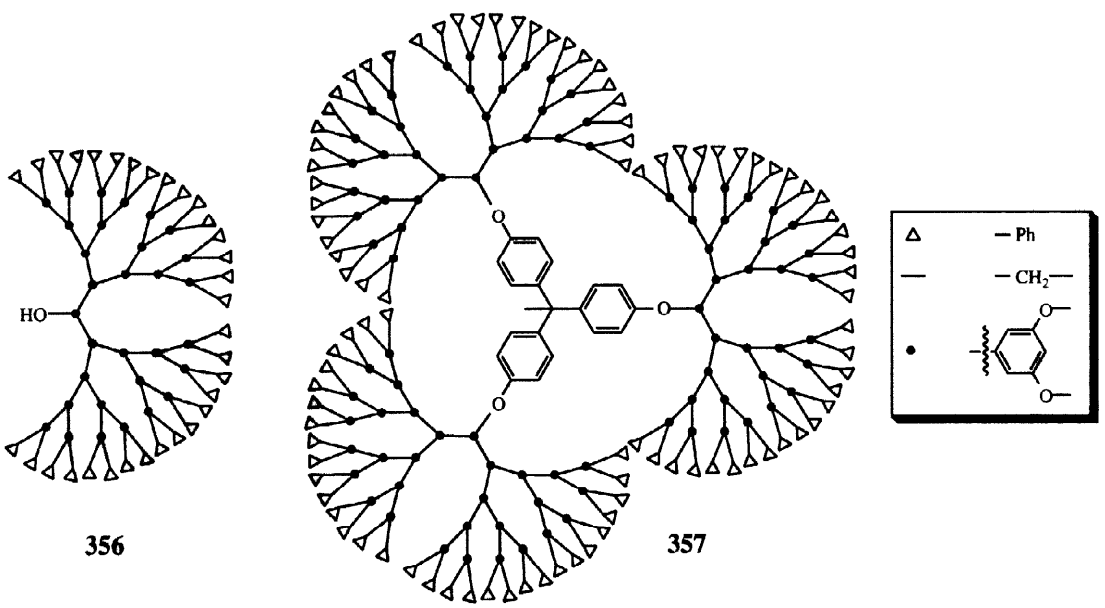
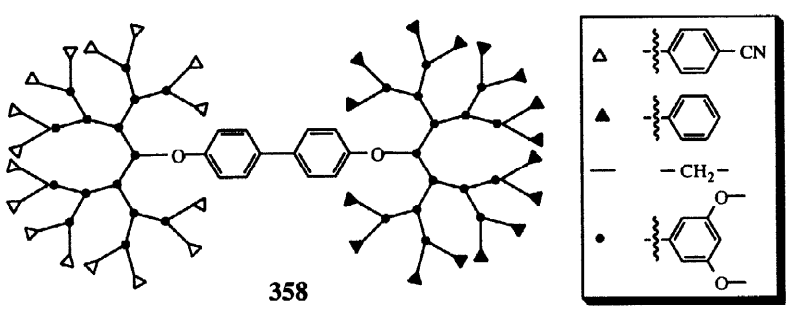
results could be interpreted by an inward folding of chain ends. On the other hand, the intermolecular ^{13}C-^{19}F distances decreased with increasing generation number, which was consistent with a decreased interpenetration between larger dendrimers. The folding back of chain ends toward the dendritic core had previously been predicted by molecular dynamic simulations.[248]

Although the intrinsic viscosity of a linear polymer increases with increasing polymer molecular weight, dendritic macromolecules have a unique viscosity profile. Several theoretical calculations on the intrinsic viscosity of model starburst dendrimers have appeared.[249] As it turned out, the intrinsic viscosity of polyether dendritic fragments **356** and polyether dendrimer **357** passed through a characteristic maximum as a function of generation,[250] this phenomenon was interpreted by the transition from an extended conformation to a globular structure as the molecular weight of the dendrimer increased. The melt viscosity behaviour of **356** and **357** were also investigated by a Rheometrics fluid spectrometer and the results obtained suggested that chain entanglements were not a dominant feature for these dendritic macromolecules.[251]



356 **357**

Unsymmetrical dendritic nanoparticles were synthesised by coupling of dendritic fragments containing electron withdrawing groups and fragments with electron donating groups at opposite ends of a central core.[252] Thus, cyano-terminated polyether dendritic wedges and benzyloxy-terminated polyether fragments of various generations were sequentially attached to 4,4'-dihydroxybiphenyl to give the macromolecular dipole **358**. The dipole moments of these molecules were very large and were shown to increase with increasing



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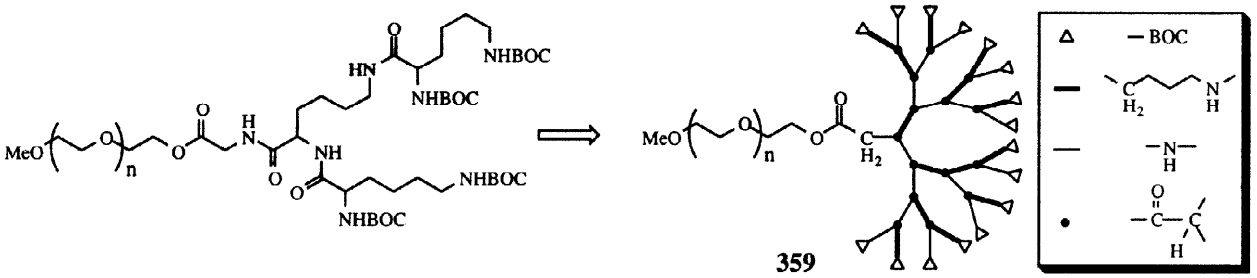
molecular weight. In contrast to linear polymers, the observed dipole moment exhibited a non-linear relationship with the molecular weight of the dendrimer. This was attributed to a change of molecular topology from a flexible lower generation structure to a less easily distorted higher generation rigid shell as a result of the applied electric field.

Hybrid linear-dendritic block copolymers capable of solubilising polar, water-insoluble molecules were described by Chapman.[253] These copolymers **359** were prepared by attaching a BOC-protected polylysine dendrimer to a hydrophilic tail of PEO using standard peptide coupling procedure. The G4 dendrimer was shown to be capable of solubilising the dye Orange-OT in aqueous solution. The discovery of such hydraamphiphiles may provide new directions for dendritic drug delivery systems.



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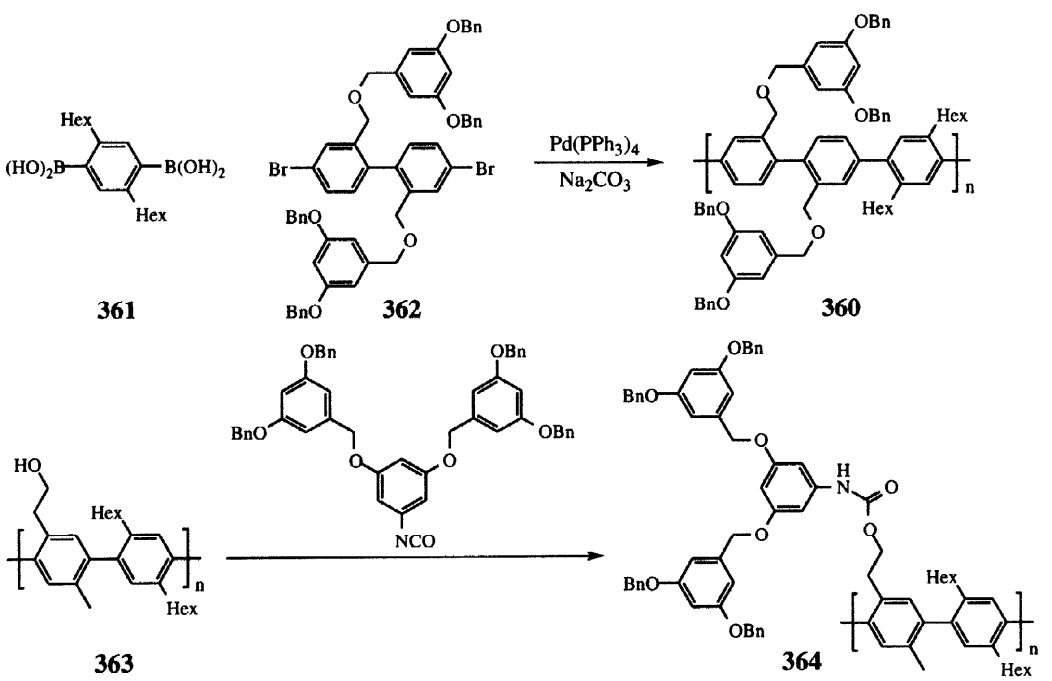
Rod-like conjugated polymers such as poly(*p*-phenylene)s are potentially useful organic conducting materials. Because of poor solubilities, they are extremely difficult to process. In an attempt to modify the properties of these linear polymers, Schlüter reported the attachment of polyether dendritic fragments on the rigid backbone of conjugated poly(*p*-phenylene)s.[254] It was anticipated that such hybrid molecules may adopt a cylindrical shape in solution. The dendrimer-coated poly(*p*-phenylene) **360** was prepared with a M_n of 17800 and M_w of 68000 by palladium(II)-catalysed polymerisation of a bis(boronic acid) **361** with a dendrimer-modified di(arylbromide) **362**. Alternatively, the coating could also be attached to an already

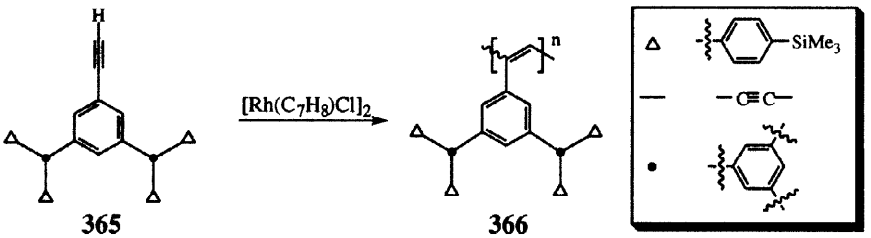


361 **362** **360**

363 **364**

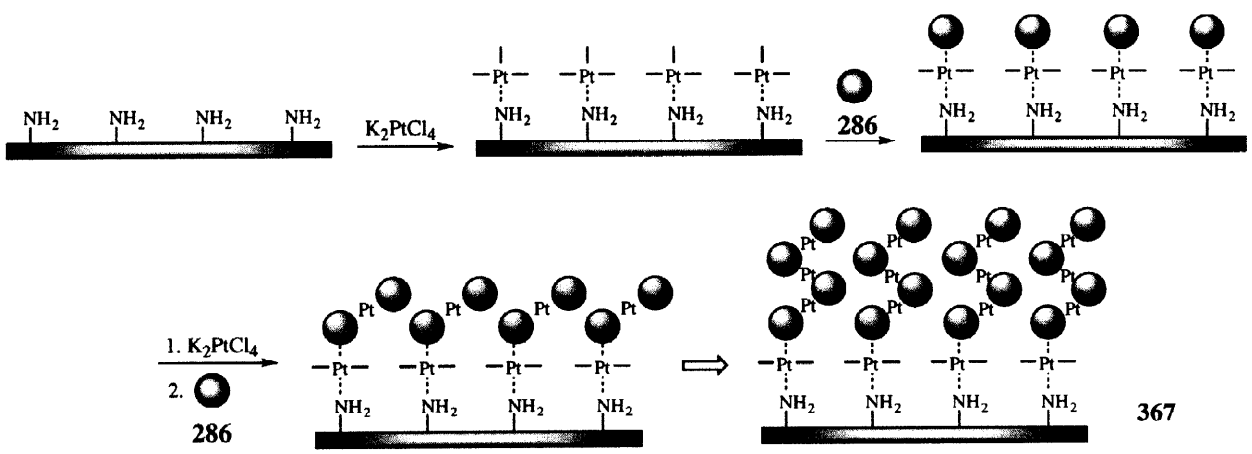
polymerised poly(*p*-phenylene) chain **363** to give the targeted polymer **364**.[254b] Styrene and acrylate derivatives carrying G1 and G2 dendritic wedges could also be polymerised in a similar manner.[255]

Dendritic phenylacetylene monomers **365** could be polymerised into polyacetylene **366** in the presence of a rhodium catalyst.[256] Based on ^{1}H-NMR data, the main chain was shown to possess a predominant *cis*-configuration and the energetically preferred conformation had a helical main-chain structure. This polymer could be processed to form thin films which were permeable to oxygen.



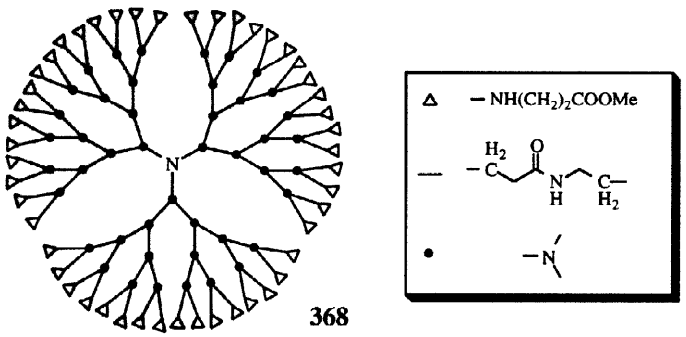
365 **366**

The use of dendrimers as spherical nanoscopic particles for growing multilayers was first demonstrated by Regen.[257] This process involved treatment of an amino-terminated silicon wafer with a solution of K_2PtCl_4, followed by the deposition of a layer of amino-terminated PAMAM dendrimer **286**. The layer was then washed with water and reactivated with a solution of K_2PtCl_4, followed by the deposition of a second layer of **286**. Repetition of this process yielded multilayer assemblies **367**. The function of Pt^{2+} is to serve as a binder for the amino groups of two PAMAM in adjoining monolayers. An ellipsometric film thickness study indicated a linear relationship between the film thickness and the number of deposition cycles. Amino-terminated PAMAM dendrimers **286** could also be covalently linked to a mercaptoundecanoic acid self-assembled monolayer *via* amide bond formation.[258] Such dendrimer-coated surfaces proved to be useful chemical sensitive interfaces for the detection of volatile organic compounds. Likewise, amino-terminated PAMAM dendrimer-modified silicon oxide surfaces were employed as platforms for the deposition of Au and Ag colloid monolayers.[259]



PAMAM dendrimers having ester end groups **368** could be used to control the pore size of porous silica during its preparation.[260] Organic-inorganic polymer hybrids were prepared by acid-catalysed sol-gel reaction of tetramethoxysilane in the presence of **368**. They were then subjected to pyrolysis at 600°C for 24 h to

eliminate all organic materials, leaving porous silica with a pore size which corresponded to the size of the dendrimer used in their preparation.



368

A number of dendritic particles with novel architecture have also been reported. Although little is known about their properties, nonetheless, they represent several important classes of dendrimer structure which have been used as basic building blocks for the construction of functional dendrimers. These include the siloxane,[14a,36] organosilane,[14b-d,261] polyphenylene,[37,262] phenyleneacetylene[18,33,126] and silsesquioxane dendrimers.[263]

6. Conclusions and Outlook

Dendrimers originally emerged as a new class of aesthetically pleasing macromolecules. However, initial experiments to investigate their physical and chemical properties were hampered by the lack of reliable and practical methods for their preparation. It was only after the development of the divergent and convergent synthetic strategies that large scale preparation of dendritic molecules then became a relatively easy task. A diverse array of dendrimers with organic, organometallic and inorganic architectures are now available for studies of their structural-property relationships, offering unlimited potential for fundamental discoveries and practical applications.

The field of dendrimer chemistry is rapidly expanding and new applications begin to appear in catalysis, material and biological chemistry. Dendrizyme,[70] already implicated in its name, has been shown to be an effective macromolecular catalyst which, amongst other properties, shows better substrate selectivity than conventional small molecular weight catalytic systems.[72] Due to the cooperativity effect, dendritic catalysts with multiple catalytic centers may sometimes offer superior reactivity than their monomeric analogs,[63] although most often the effectiveness of dendritic catalysts varies according to the intricate interactions amongst the catalytic functionalities, the nature of the environment and the substrate itself. Further investigations should be devoted to the design of catalytic systems with desirable surface characteristics and binding properties to allow rapid catalytic turnover, superior selectivities and easy catalyst recovery.

A dendrimer itself, as a polymeric particle, has been shown to possess unique properties which are different from conventional linear polymers. Depending on its functional constituent, a dendrimer may possess electrochemical, photochemical, liquid crystalline, magnetic and/or plastic properties. In terms of electrochemical properties, the dendritic framework provides a controllable stereochemical, topological, electronic and steric environment for the modulation of electrochemical behavior of electroactive functional groups. Most often the redox kinetics and redox potentials of the electrochemically active units are responsive

to their relative position within the dendrimer matrix. Multiple electron transfer can also be realised with dendrimers containing multiple redox centers residing either on the surface or in the interior of the dendrimer molecule. Electronic interactions amongst neighboring redox components have also been demonstrated. For dendritic macromolecules having multiple redox centers, each redox unit has been shown to exhibit its own characteristic redox pattern. Such multiple redox profiles could pave way for further research of molecular information storage materials and multielectron catalysis. The use of redox active dendrimers to modify electrode surfaces and to prepare amperometric and potentiometric biosensors also represent potential areas for industrial applications.[89] With regard to photochemical properties, structurally defined dendrimers with photoactive components have been demonstrated to channel light energy through specific pathways into a pre-determined unit within the dendrimer matrix.[125] Such photochemical molecular devices are very useful in solar energy conversion and information storage applications. To utilise their mechanical properties, dendritic particles have already been used as simple 'lego' components toward the construction of nanoscopic particles. The preparation of dendritic nanomechanics will be the next step along this direction.

Dendrimers can also be considered as mimics of biological macromolecules such as proteins and enzymes. The various kinds of functional groups within a dendrimer may function as receptors for host guest interactions *via endo-* or *exo*-recognition sites. For example, the *endo*-receptor properties had been applied to the preparation of novel encapsulating agents and as models for the study of electron transfer or enzymatic transformations in biological systems. On the other hand, the *exo*-receptor properties were exemplified in the design of magnetic resonance imaging agents, gene-delivery vectors, multiple antigenic agents and boron-rich compounds for cancer therapy. With these tremendous developments already in our grasp, it is therefore increasingly likely that dendrimers could find their first practical application in the medical arena.

The developments reviewed in this manuscript represent the diversity of research efforts devoted to the preparation of functionalised dendritic molecules during the past decade. Although the main focus of this manuscript is concerned with their diverse properties, it is necessary to re-emphasise the crucial role of synthesis in dendrimer research. There is still a pressing need to develop rapid, efficient and high yielding preparative methods for large scale dendrimer production before genuine applications can be realised. These and other achievements will undoubtedly broaden our understanding of the properties of this novel type of hyperbranched macromolecule.

Recent Works in Dendrimer Chemistry

A number of new developments in dendrimer chemistry have appeared since submission of this manuscript. The following is a list of recent references on the various sub-topics:

(a) New synthetic approaches to dendrimers.[264-267]

(b) Chiral dendrimers.[268-270]

(c) Catalytically active dendrimers.[271-276]

(d) Electrochemically active and conductive dendrimers.[277-285]

(e) Photoresponsive dendrimers.[286-293]

(f) Dendrimers as receptors or complexation agents.[294-298]

(g) Ionic dendrimers.[299]

(h) Biologically active dendrimers.[300-305]

(i) Liquid crystalline dendrimers.[306-308]

(j) Self-assembled dendrimers.[309-311]

(k) Dendritic magnets.[312]

(l) Dendritic particles.[313-320]

Acknowledgments

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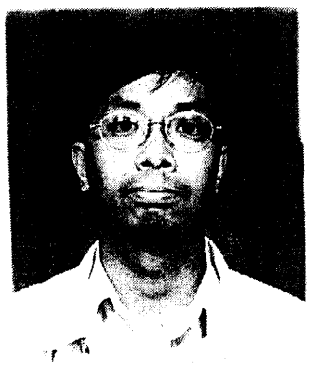
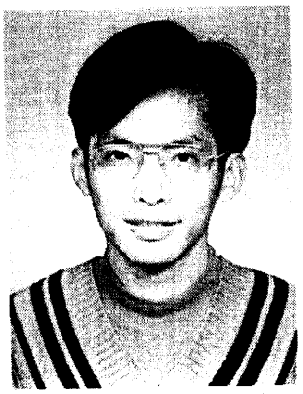
Biographical sketch



Hak-Fun Chow



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