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# Dendrimers and Supramolecular Chemistry

Peter J. Gittins[a]; Lance J. Twyman[a]
[a] Department of Chemistry, University of Sheffield, Sheffield, UK

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# Dendrimers and Supramolecular Chemistry

PETER J. GITTINS and LANCE J. TWYMAN*

*Department of Chemistry, University of Sheffield, Dainton Building, Brook Hill, Sheffield S3 7HF, UK*

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**This review details the combination of supramolecular chemistry and dendrimer chemistry. The use of supramolecular chemistry in the synthesis and modification of dendrimers, along with the application of dendrimers in supramolecular chemistry, is described. Many excellent examples exist within these areas; this review includes key examples intended to illustrate the main principles involved, and demonstrate the large number of possibilities presented through combining supramolecular and dendrimer chemistry.**

*Keywords*: Supramolecular chemistry; Dendrimer chemistry



## INTRODUCTION

The field of dendrimers is a rapidly expanding area. Since Tomalia synthesised the first polyamidoamine (PAMAM) dendrimer in 1985 [1], followed by Fréchet's convergent approach in 1989 [2], the growth in dendrimer research has increased almost exponentially. Initially efforts were concentrated on developing and adapting new and existing synthetic methods to provide the tools needed to expand this pioneering area of research. More recently attention has been directed toward the application and functional design of dendrimers. Ranging from drug and gene delivery systems [3–10] to catalysts and catalyst supports [11,12] dendrimers can be found in materials chemistry, synthetic chemistry as well as in biological [13] and physical [14] applications. This diversity can be attributed to the highly controlled iterative methodologies employed in dendrimeric syntheses [15]. The ability to control size and shape as well as factors such as hydrophobicity, coupled with ease of functionalisation allow dendrimers to be carefully engineered with the individual properties required for a given application. This is particularly useful in the field of supramolecular chemistry, allowing individual compounds to be tailored giving multifaceted control over interactions with specific molecules.

Many examples exist in which dendritic molecules are exploited to afford supramolecular complexes [16–22]. Dendrimers can be used as scaffolds for functionalised end groups in molecular recognition or as micelle-like containers that lock in guest molecules at the core or within the branched interior. Using non-covalent interactions, supramolecular dendrimers can be built up around a central core through self-assembly of a number of smaller dendrimer segments or dendrons. Other research has shown dendrimers to form supramolecular assemblies in the form of thin films, aggregates and molecular wires. This review is intended to give an overview of the literature and highlight the wide variety of possibilities available in supramolecular dendrimer chemistry.

## SYNTHESIS AND MODIFICATION OF DENDRIMERS BY SELF-ASSEMBLY

### Core Assembly

The first reports of self-assembled dendrimeric structures involved the association of several hydrophobic moieties in an aqueous solution [23]. More succinct examples of self-assembled dendrimers involve the congregation of a discrete number of like dendritic molecules in which non-covalent interactions form the dendrimer core. The formation of such dendrimers has been achieved using a variety of different approaches, and the diverse nature of this particular application of supramolecular interactions

*Corresponding author.

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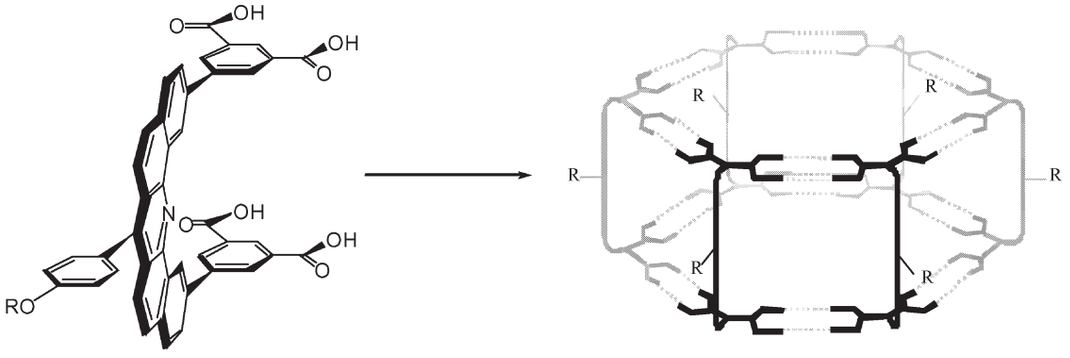



**1**

FIGURE 1 Schematic representation of the hexameric self-assembly achieved by Zimmerman *et al.*



in the field of dendrimer chemistry merits separation into a number of distinct categories.

### *Hydrogen Bonding*

Zimmerman *et al.* produced a hexameric assembly of polyarylether dendrons held together by hydrogen bonding [24]. The polyether dendrons were functionalised with isophthalic acid groups at the core. The self-assembled species was formed as a result of interaction between these carboxylic acid groups. In an isolated state, isophthalic acid forms dimers with itself. In order to increase the strength of the hydrogen bonding interactions, two isophthalic acid groups were attached *syn* to each other by a rigid spacer to give the tetraacid **1**. This tetraacid group was attached at the core of a number of different generation polyether dendrons and self-assembled dendrimers were achieved. SEC studies showed that the nature of the self-assembly varied depending on the size of the dendron as well as sample concentration. For smaller dendrons the aggregate was unstable. This is thought to be a result of the ability of the dendrons to adopt a linear arrangement. As the size of the dendritic wedge is increased greater stability is observed. Linear aggregation becomes more and more difficult and steric factors steer association toward the hexamer (Fig. 1). By varying the size of the dendrimer it is therefore possible to exert a degree of control over the orientation of the assembly.

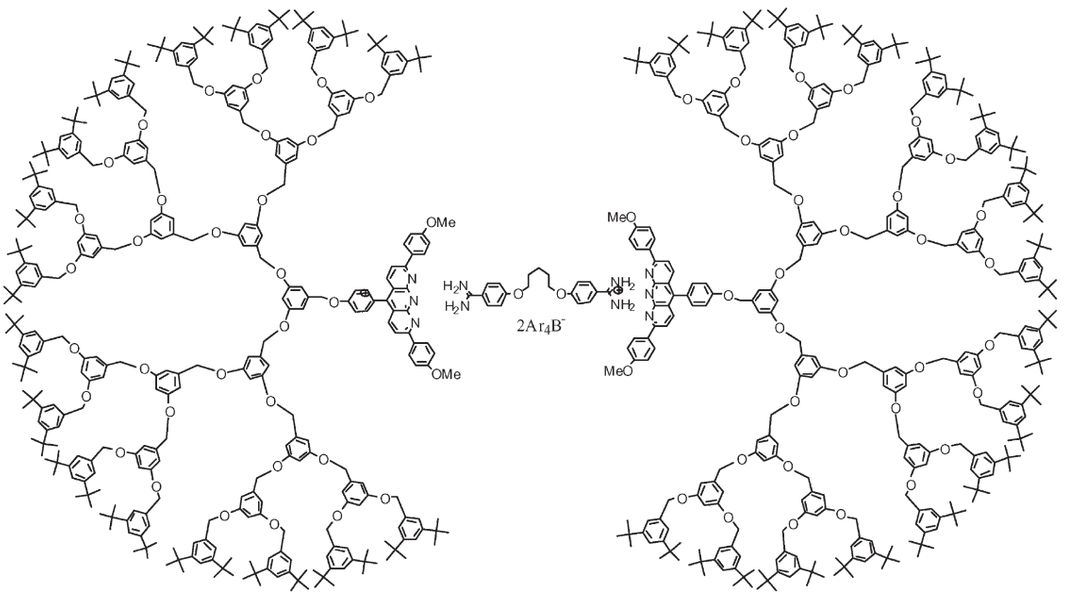
Again using hydrogen bonding interactions, Zimmerman and *et al.* formed a heteromeric bis-dendritic complex [25]. Adopting a Donor–Acceptor approach in which the dendritic building blocks act as the hydrogen bonding acceptors with a pentamidine salt donor species providing a centre for self-assembly.

Polyether dendrimers were attached to a 1,9,10-anthyridine core by alkylation of a phenol-modified anthyridine with generation 1-4 Fréchet-type dendritic bromides. The resulting dendritic anthyridines were then used in the subsequent self-assembly, with the anthyridine cores providing a "triple acceptor" (AAA) motif. Initially 2,6-diamino-1,4-dihydropyridine, which presents a perfectly complementary "triple donor" (DDD) hydrogen bonding motif, was suggested as a possible core for self-assembly. Unfortunately this compound is susceptible to oxidation. Binding studies using a model compound showed that the benzamidine group, a "double donor" (DD), exhibited strong binding with the dendritic acceptor species. Thus a ditopic pentamidine salt, containing two benzamidine groups, was used as a core. This compound was shown to self-assemble effectively with the dendritic anthyridines. The third generation dendron afforded a self-assembled complex, **2** (Fig. 2), of 2:1 stoichiometry with the pentamidine in 1% acetonitrile-$d_3$/$CDCl_3$.

Aside from the different functional groups used, the major difference in this methodology, compared to the previous example, is the introduction of a second complementarily functionalised group. Without this second group the self-assembly does not occur. The use of a two-component system also allows for a more tailored approach, rather than relying on stoichiometry and steric factors to determine the precise arrangement of the self-assembled species.

### *Electrostatic*

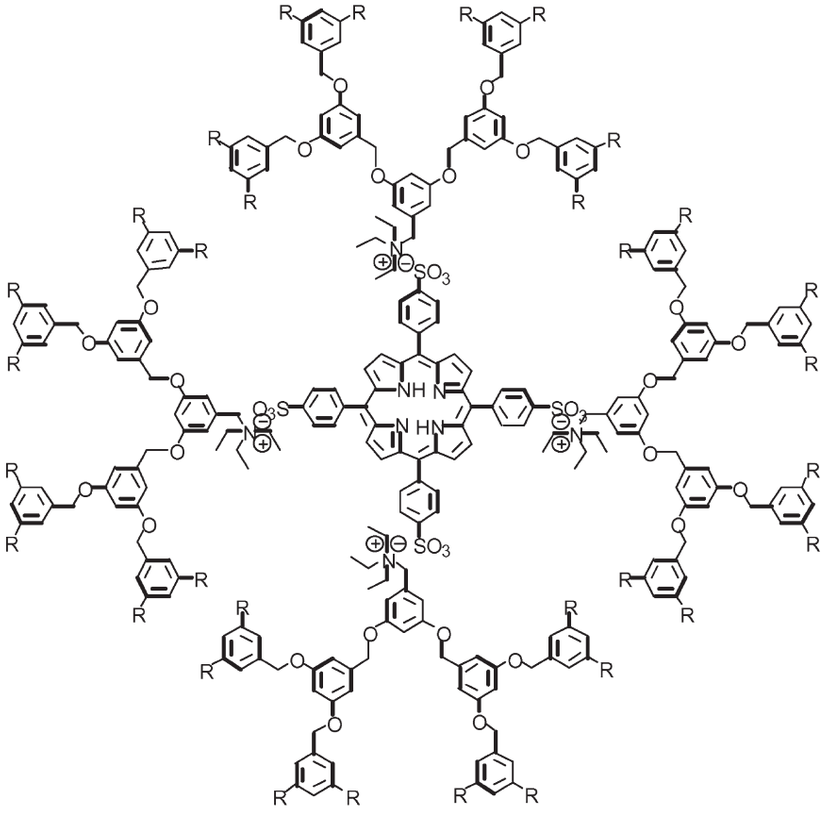
In addition to hydrogen bonding, electrostatic interactions can also be employed to afford two-component supramolecular dendrimers self-assembled at the core. Self-assembly of quaternary ammonium bromide-cored dendrons around a sulfonated porphyrin, **3**, has been achieved by Bo *et al.* [26] (Fig. 3). This was accomplished using the same principles applied to the synthesis and




**2**

FIGURE 2 Anthyridine-cored polyether dendrimers self-assembled around a pentamidine salt.






**3**

FIGURE 3 Porphyrin-centred polyether dendrimer reported by Bo *et al.*

assembly of polyelectrolyte-surfactant complexes in the manufacture of ordered thin films [26]. In the search for a potential synthetic model for a globular protein, a porphyrin-centred dendrimer is an ideal starting point. The ability to produce such a self-assembled arrangement is one step closer to mimicking biological systems than a covalent approach. The method employed by Bo *et al.* centres around coulombic interactions between sodium tetrakis(4-sulfonatophenyl)porphyrin anions and quaternary bromide cored polyether dendritic cations.

Second and third generation dendritic quaternary bromides were synthesised from bromide cored Fréchet type dendrons and triethylamine. The quaternary bromide dendrons were then used as building blocks to give the larger self-assembled dendrimer. The self-assembled $(G\text{-}2)_4$ porphyrin complex was achieved by addition of an aqueous solution of porphyrin to a solution of the G-2 quaternary bromide in ethanol. The G-3 complex was afforded through a slightly different method; being insoluble in ethanol, the dendron was dissolved in $CH_2Cl_2$ and a slight excess of the porphyrin was added. A stoichiometric complex was formed and the excess porphyrin was washed away with water.



### *Organometallic—Metal Ligand Coordination*

Well-defined discrete structures can be formed using metal-based complexation. Metal–ligand coordinate bonds are somewhat stronger than hydrogen bonds and other forms of weak interaction, such as $\pi-\pi$ stacking, hydrophobic/hydrophilic and electrostatic interactions, which are less precise in terms of directionality. This makes metal–ligand interactions ideal for use in controlled self-assembly [27] and has been widely used in the formation of self-assembled dendrimers [28]. Fréchet and Kawa developed a system based on the interaction of a number of cationic lanthanides and the carboxylate anion group present at the focal point of convergently prepared polyether dendrons [29]. Self-assembly of the dendritic wedges around the lanthanide (Ln) core to give **4** (Fig. 4), is of particular interest due to the distinctive luminescent properties of the lanthanides.

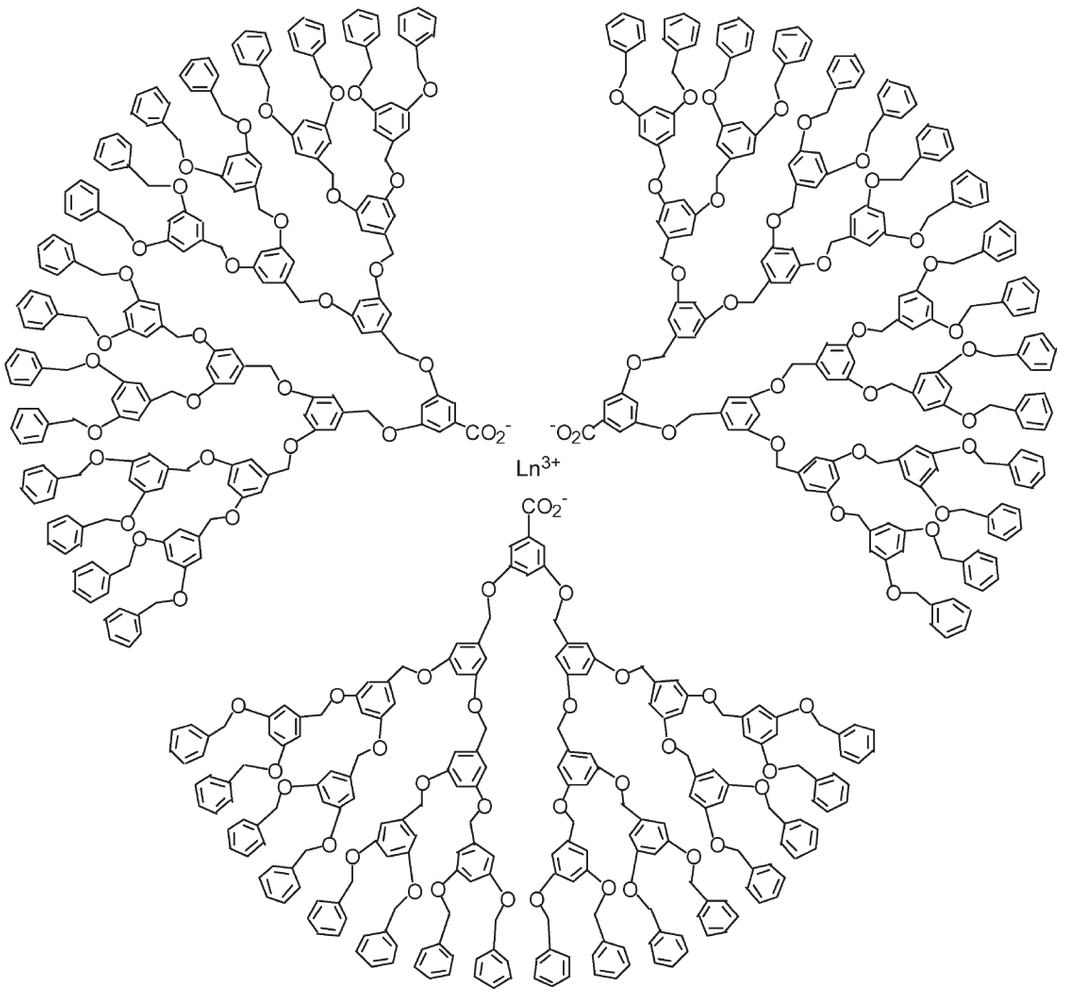
The characteristic narrow width emission and long lifetimes of lanthanides makes them especially useful in fibre optic application for use as signal amplifiers. The formation of these self-assembled dendrimers is not only desirable due to the antenna effects imparted by the dendron components, but also because of the shielding provided by the "dendrimeric shell". In existing inorganic substrates, the clustering of the lanthanide species leads to a significant degree of self-quenching. By shielding the core with dendrimeric groups, such problems are greatly reduced.

Ruthenium/pyridinyl metal–ligand interactions have been widely used in the construction of supramolecular dendrimers [30]. Newkome's "Lock and Key" complex, **5** (Fig. 5), led the way in the application of ruthenium-based coordination chemistry in the context of supramolecular dendrimers [31]. In similar more recent research, a naphthalene terminated dendritic complex self-assembled around a ruthenium core was developed by Plevoets *et al.* [32], with the intention of developing a species containing photoactive groups with two distinct and well defined energy levels; $[Ru(bipy)_3]$ at the core and naphthyl units at the periphery.

Using a modification of the convergent synthesis published by Hawker and Fréchet to give naphthalene-terminated dendritic polyethers, Balzani, Vögtle *et al.* prepared a "dendritic ligand", with a bipyridine core. The method followed was identical until the last step, where instead of 3,5-dihydroxybenzyl alcohol, a dilithio bipyridine species was used. This compound was obtained by taking 4,4′-dimethyl-2,2′-bipyridine and treating with an excess of LDA in dry THF. Reaction with the dendritic benzyl bromides afforded the 4,4′-disubstituted dendritic bipyridine ligands.

Self-assembly around Ru(II) to give **6** (Fig. 6) was achieved by refluxing a 3:1 mixture of the dendritic bipyridine ligand and ruthenium trichloride in a 2:1 chloroform/ethanol solution. This was accompanied by a colour change from dark violet to bright orange indicating the formation of the trisbipyridine ruthenium complex. Column chromatography was used in the initial purification of the products, although in order to purify the product further the $Cl^-$ ions were exchanged for $PF_6^-$. The complex is not soluble in water as a result of the organic nature of the dendritic wedges.

Luminescence experiments showed that the "free" dendritic ligands exhibit a large emission band attributed to the dimethoxybenzene and naphthalene groups. This emission is practically eliminated in the self-assembled species and is, regardless of excitation wavelength, replaced by a visible emission characteristic of the $[Ru(bipy)_3]$ type chromophore. Excitation of the self-assembled species at 270 nm, is absorbed almost exclusively by the ligand chromophores. The resulting naphthalene/dimethoxybenzene emission is quenched by 90% compared with the free ligands. There is still, however, a large emission band attributable to the $[Ru(bipy)_3]$ core with almost the same intensity as for excitation at 450 nm, the wavelength at which only the $[Ru(bipy)_3]$ group absorbs. This shows that there is an efficient transfer of energy from the periphery to the core; a characteristic of the antenna effect.




**4**

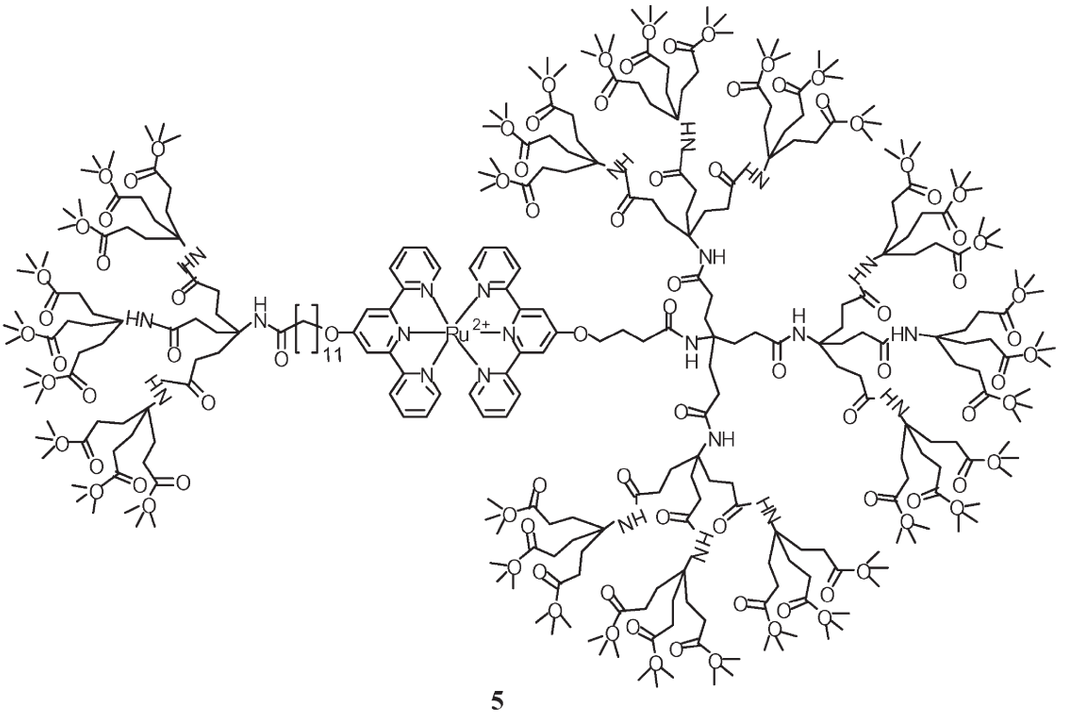
FIGURE 4 Lanthanide-cored dendrimer self-assembled through metal–ligand interactions.

Self-assembled fullerene functionalised dendrimers have also been synthesised, designed to include self-assembled species incorporating an energy transfer system. Nierengarten, Felder and Nicoud took polyether/ester dendritic wedges functionalised with $C_{60}$ fullerenes at the periphery and attached them to 1,10-phenanthroline diol [33]. These ligands were then used to form self-assembled copper(I) complexes, **7** (Fig. 7), from $Cu(CH_3CN)_4$-$BF_4$. The photoinduced energy transfer processes of the resulting dendrimers were investigated by Armaroli [34]. It was concluded that the fullerene groups absorbed the majority of incident light, however, energy from any light that did reach the copper core was transferred back to the fullerenes. In effect the molecule served as a dendritic black box.

Weiner and Narayanan report the synthesis of a cobalt cored self-assembled dendrimer complex, **8** (Fig. 8), formed through coordination dendrimeric ligands around a Co(III) centre [35]. They present this type of assembly as a possible tool for the study of tumour cells *in vivo*, due to their potential biocompatibility. Using a convergent approach, a six-armed dendritic unit, with an ethylenediamine based backbone was prepared giving a dendron capable of behaving as a bidentate ligand. Self-assembly of these ligands around a central metal core was achieved upon heating with $CoCl_2{\cdot}6H_2O$ in methanol.

### *Host–Guest Interactions*

β-Cyclodextrin modified dendritic molecules have been employed by Newkome *et al.* to afford self-assembled dendrimeric complexes with a potentially diverse and highly specific array of different cores [36]. Having a well-defined cavity capable of housing a variety of guests, as well as being water



**5**

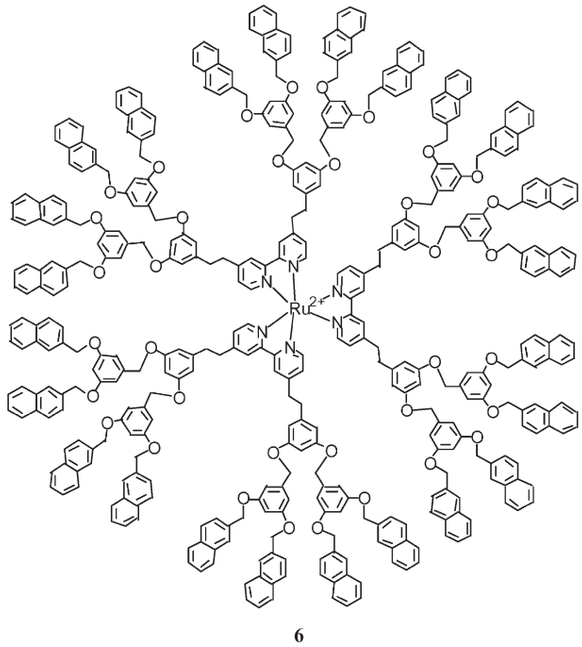
FIGURE 5 Newkome's lock and key dendrimer.



soluble, cyclodextrins (CDs) have been the subject of a significant amount of research in the area of molecular recognition [37,38]. The methods developed in these investigations can be exploited to give a non-covalent centred dendrimer formed by the convergent self-assembly of cyclodextrin-cored dendrons around a bis(adamantane ester), **9** (Fig. 9).

After first synthesising two water-soluble dendritic β-CD dendrons, phenolphthalein was used as a UV/Vis active probe to confirm that encapsulation by CD was retained. First generation polyester terminated dendrons were synthesised from 6-heptaamino-β-CD heptahydrochloride and an $AB_3$ isocyanate functionalised triester. The resulting ester terminated dendron was subjected to formic acid hydrolysis and dialysis to give the carboxylic acid terminated dendron. Finally the carboxylic acid terminated dendron was treated with Behera's amine, $H_2NC(CH_2CH_2CO_2CMe_3)_3$, before repeating the acid hydrolysis to give the carboxylic acid terminated dendritic CD. By addition of a bis(adamantane) ester of tetraethylene glycol, a self-assembled dendrimer complex was achieved with two dendrimer segments arranged around a single bis(adamantane) ester.

Pseudorotaxanes based supramolecular interactions have also been employed by Gibson *et al.* to form dendrimers self-assembled at the core [39]. The approach taken by Gibson, does, however, differ slightly from that taken by Newkome. Whereas Newkome used a cyclodextrin "host" at the core, Gibson developed a strategy incorporating a single tritopic "guest", self-assembled with three "host" dendrons. Drawing from work initially



**6**

FIGURE 6 Bipyridine-cored dendrons self-assembled around a ruthenium(II) ion.

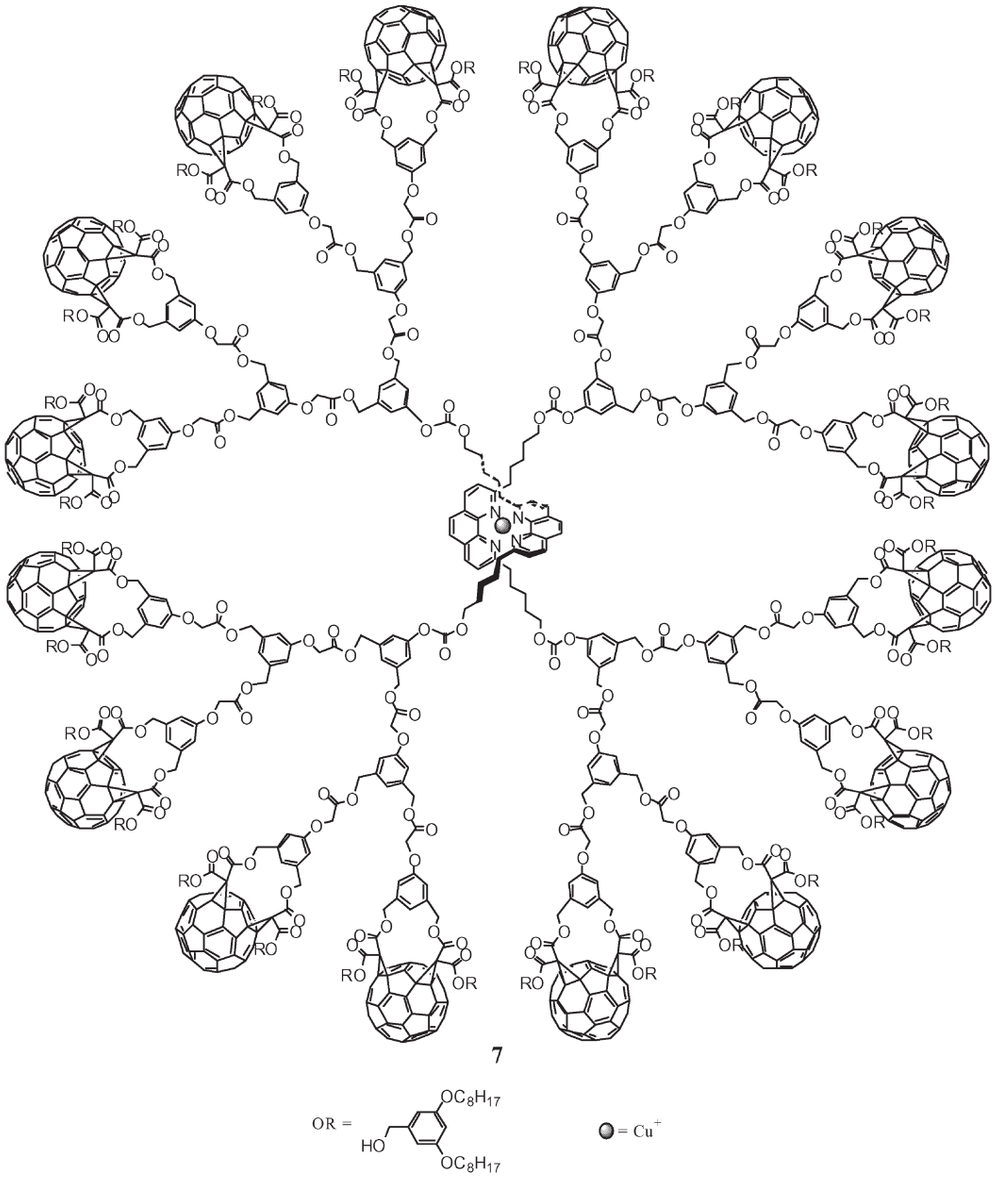



FIGURE 7 A third generation fullerenodendrimer with a bis(phenanthriline)$Cu^+$ core and 16 peripheral $C_{60}$ units.

published by Stoddart *et al.* [39], which reported pseudorotaxane formation between secondary ammonium salts and dendrons containing dibenzo-24-crown-8 at the focal point; Gibson employed 1,3,5-tris(*p*-benzyl-ammoniomethylphenyl)benzene tri(hexafluorophosphate) **10** as the guest core, and polybenzylether dendrons with 2-carboxydibenzo-24-crown-8 at the focal point **11** as the host molecules. This is shown schematically in Fig. 10.

### Branched Assembly

Supramolecular chemistry has been employed more fully, by a number of groups, to construct dendrimers with non-covalent interactions throughout the branched structure of the molecule. The significance of metal–ligand interactions in the preparation of supramolecular dendrimers is demonstrated elegantly by Balzani *et al.* [40]. Both divergent and convergent syntheses have been reported, whereby a complete dendritic array is systematically built up using self-assembly of pyridinyl groups coordinated around ruthenium and osmium metal centres. As with all iterative dendrimer syntheses, the system developed centres around the ability to protect and deprotect easily and efficiently. The difference from conventional methodology arises in the growth steps of the synthesis. Instead of deprotecting to allow a covalent reaction to take place, deprotection makes

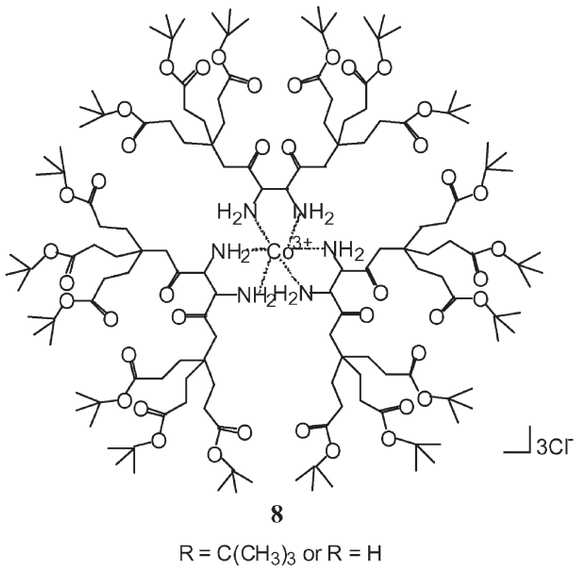



FIGURE 8 First generation ethylenediamine based dendrons arranged around a cobalt centre.

ligand groups available for further metal–ligand interaction.

Using the familiar $[Ru(bipy)_3]^{2+}$ as a model, three ligand types were employed. *B*ridging *L*igands (BL), *T*erminal *L*igands (TL), and the third type a *P*rotected Branching *L*igand (PL). Two schemes were developed, one based on 2,3-bis(2-pyridyl)pyrazine (2,3-dpp) as the branching ligand, and 2,2′-bipyridine (bipy) as the terminal ligand and a second using 2,5-dpp BL and 2,2′-biquinoline (biq) TL. Protection was facilitated by the ease with which single nitrogen on 2,3- and 2,5-dpp can be (de)methylated [41]. This simple reaction reduces the capacity of the ligands to chelate, blocking one of the bidentate faces.

First reported by Petersen *et al.* [42], $[Ru(2,3\text{-}dpp)_3]^{2+}$ was shown to be a *Complex Ligand*, i.e. a previously formed complex which has available chelating sites allowing it to behave as a ligand. Taking this concept one step further, Balzani *et al.* introduced the idea of a *Complex Metal*, i.e. a previously formed complex which can go on to behave as the "metal" and act as a centre for ligands to coordinate around.

$[Ru(2,3\text{-}Medpp)_2Cl_2]^{2+}$ **12c** is an example of a complex metal. The key feature being that the 2,3-Medpp (PL) component can be deprotected to unblock a further ligand. Thus, once $[Ru(2,3\text{-}Medpp)_2Cl_2]^{2+}$ has acted as a complex metal, it can be deprotected allowing it to behave as a complex ligand, in the same way that **12a** is deprotected to give **12b**, a complex ligand. This ability to easily convert from complex metal to complex ligand is the key factor in the overall synthesis. Dendrimers are built up using this process in an iterative manner. Terminal ligands can be used to prevent further growth of the dendrimer at the periphery, an invaluable property when using a convergent process. These closed structures are referred to as *sterile*. Using osmium as well as ruthenium in addition to the two ligand systems, a variety of different species can be achieved with both metals and ligands incorporated in a controlled manner. With further research, the potential exists for highly specific artificial light harvesting arrays to be developed (Fig. 11).

Reinhoudt *et al.* developed a similar strategy for both convergent and divergent assembly of supramolecular dendrimers [43]. Again the methodology centres around the concept of using a component as a ligand, followed by deprotection of the resulting complex, allowing it to behave as a "metal". Initially the coordination was mediated by interaction of nitrile terminated ligand groups with palladium ion centres, however, a stronger more versatile system was developed using pyridine functionalised groups to afford the ligand. A particularly noteworthy addition to the methodologies developed by Balzani *et al.*, lies in Reinhoudt's use of non-covalent coordination chemistry to "block" future complexation sites compared to the covalent (de)protection employed by Balzani. This further reduces the reliance on covalent chemistry in the construction of macromolecules.

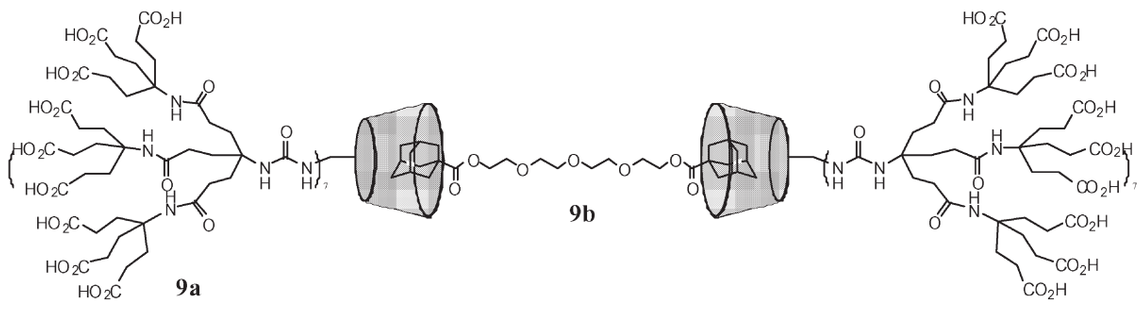



FIGURE 9 Cylclodextrin-cored dendrons self-assembled around a bis(adamantane ester).

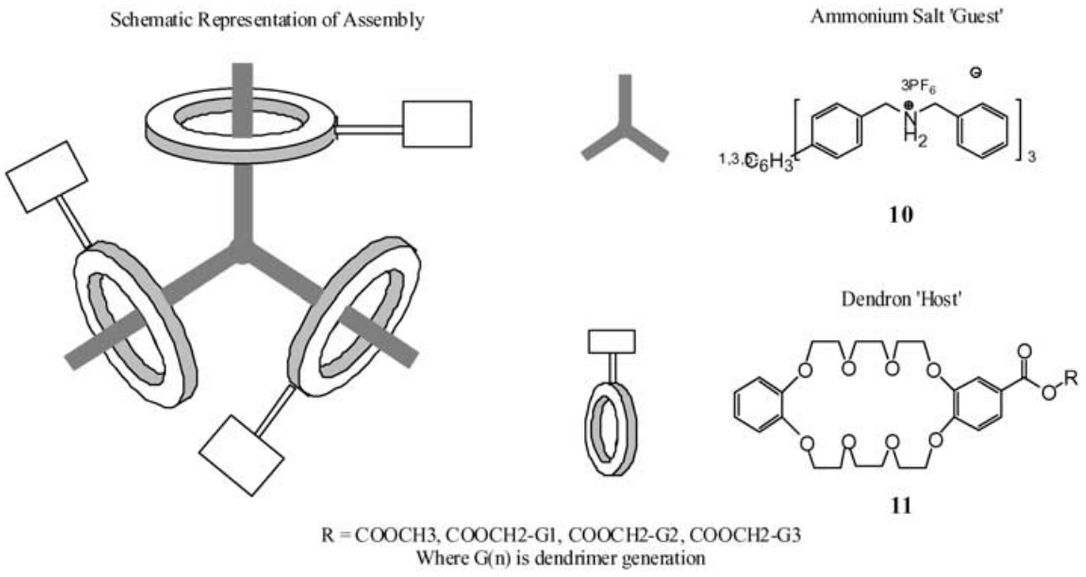



FIGURE 10 Pseudorotaxane based assembly used by Gibson *et al.* to form the dendrimer core.



**Peripheral Assembly**

Periphery functionalisation is one of the largest areas of research associated with dendrimer chemistry. In addition to the wealth of research into covalently modified dendritic molecules, there are a significant number of dendrimeric species reported in the literature, where periphery functionalisation has been achieved through self-assembly. Dendrimers, which are conducive to electrostatic interactions at the periphery, have been used to prepare inverse micellar structures or dendritic boxes. Crooks *et al.* report the spontaneous assembly of dodecanoic acid around an amine terminated PAMAM dendrimer [44]. The resulting dendrimer/acid complex **13** (Fig. 12) is soluble in non-polar organic solvents, due to the long alkyl chains surrounding the dendrimer.

The acid/base assembly can be reversibly controlled by adjustment of the pH. This allows the dendrimer to be used as a macromolecular phase transfer agent. Guest molecules contained within the interior voids of the "dendriplex" can therefore be shuttled from hydrophobic to hydrophilic phases and vice versa. This was shown effectively by the transfer of methyl orange into toluene. The hydrophilic dye binds to the amine groups within the dendrimer interior, and is successfully transported between phases. An interesting application of this system is the transfer of palladium/dendrimer nanocomposites from the aqueous phase into toluene. These materials exhibited catalytic activity in toluene toward hydrogenation reactions. Compared to similar OH terminated nanocomposites in water, catalytic activity is higher for the self-assembled species.

In addition to the large number of dendrimers prepared by coordination around ruthenium, to form the core, a number of studies have been published in which pyridinyl groups coordinated to ruthenium ions have been used to afford modified dendrimers with self-assembled peripheral groups. Newkome *et al.* have prepared dendrimers with terpyridinyl ruthenium chloride groups at the periphery [45]. More recently, Zhou *et al.* [46], have reported an additional application of this type of ruthenium complex. In this study a carbosilane dendrimer platform was synthesised, with covalently attached bipyridine groups at the periphery. By refluxing this compound in ethanol for $\sim$72 h with 11.4 equivalents of $Ru(bipy)_2Cl_2$, the desired self-assembled compound, containing eight periphery $[Ru(bipy)_3]^{2+}$ was achieved **14** (Fig. 13).

The self-assembled complex exhibits enhanced oxidative-reduction electrochemiluminescence (ECL), compared to monomeric $[Ru(bipy)_3]^{2+}$ species. $[Ru(bipy)_3]^{2+}$ compounds are of importance in immunoassay and DNA probing where they can be used as ECL labels. This provides a possible application for these self-assembled dendrimeric compounds where a single site could be labelled, but with an increased signal intensity due to the greater number of $[Ru(bipy)_3]^{2+}$ in each complex.

Whereas Newkome made use of cyclodextrin based pseudorotaxane to form the core of a self-assembled dendrimer [36], Kim *et al.* developed a pseudorotaxane methodology for modifying the periphery of a polypropyleneimine/DAB

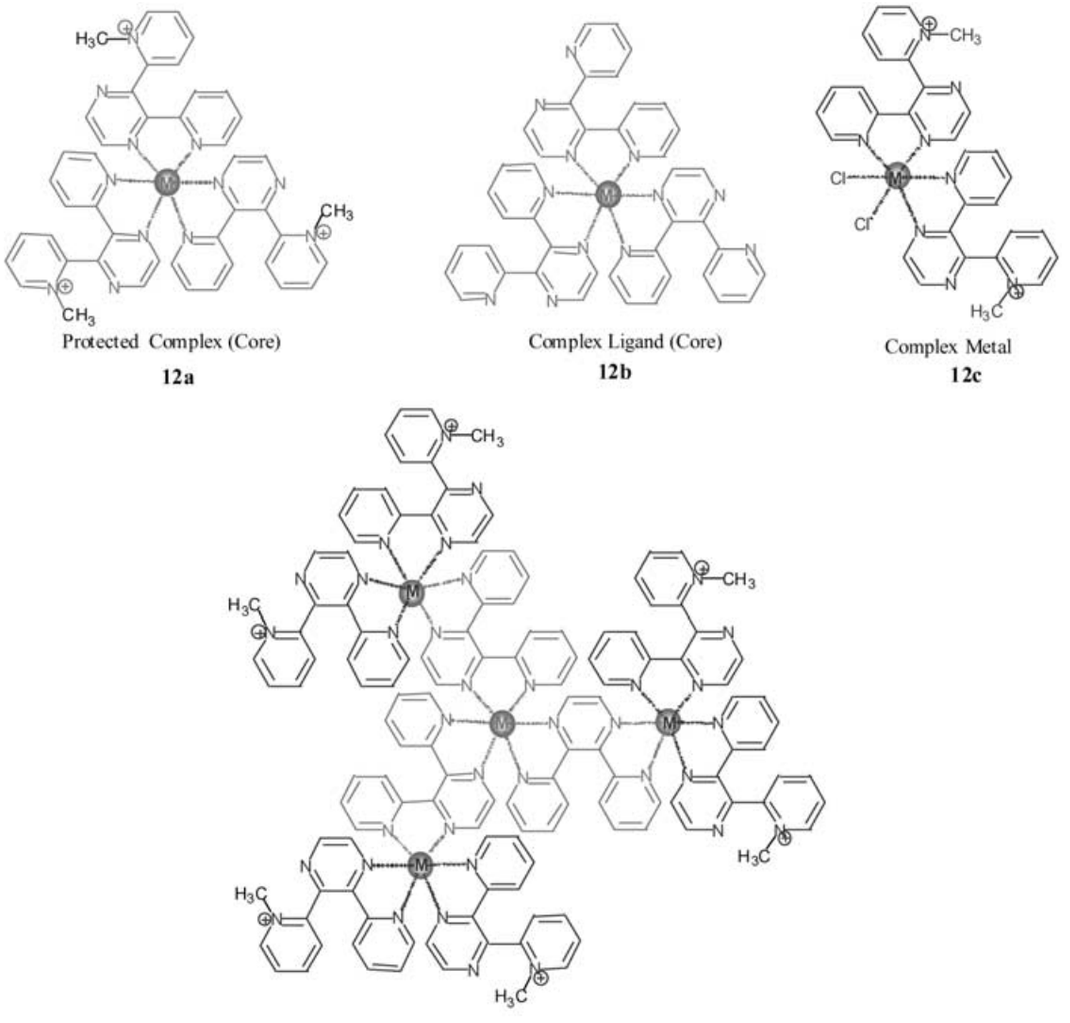
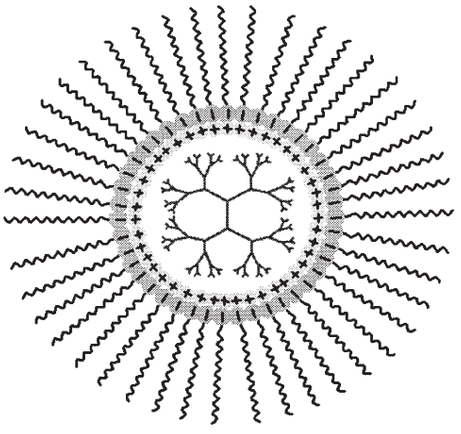



FIGURE 11 Complex metal/complex ligand methodology by Balzani *et al.*

dendrimer [47]. In the first stage, G1–G4 dendrimers were functionalised with protected diaminobutane groups. After deprotection of the diaminobutane units, the dendrimer was then treated with cucurbituril (CB [6]) in water, affording dendrimers with quantitative self-assembly of the cucurbituril around the diaminobutane groups, **15** (Fig. 14).

## SUPRAMOLECULAR CHEMISTRY USING DENDRIMERS

Thus far, the focus of this review has been concentrated upon on the use of supramolecular interactions in the self-assembled formation and modification of dendrimers. There is, however, a substantial amount of research devoted to the study of supramolecular interactions between covalently formed dendrimers. This area of research includes dendrimers employed in the construction of nanoscale aggregates [48,49], monolayers, and films [50,51], as well as dendrimers used in the formation of such self-assembled species as nanorods and other nanostructures [52,53]. In addition to this, there are many accounts of dendrimers used as liquid crystals [54–61], and numerous examples of supramolecular interactions between covalent dendrimers and guest molecules bound within the branched interior or at the surface of the dendrimer [62].



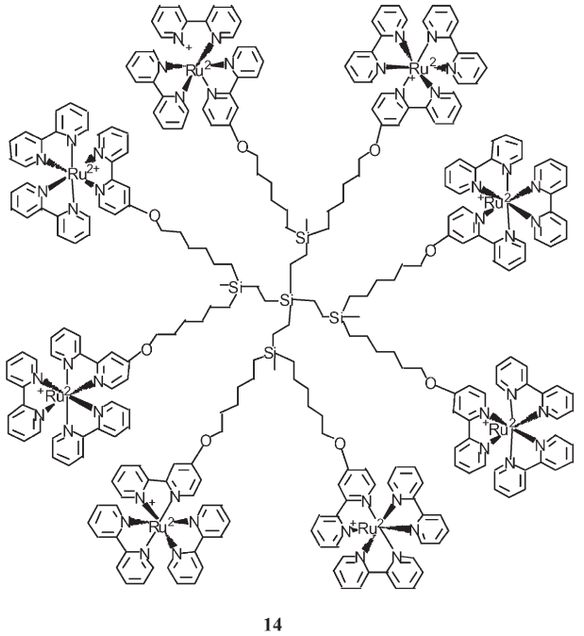
**13**

FIGURE 12 Schematic representation of the dodecanoic acid peripherally functionalised dendrimer reported by Crooks *et al.*



### Host–Guest Chemistry of Dendrimers

In the field of dendrimer host–guest chemistry PAMAM dendrimers have been extensively exploited [63]. In the correct solvent conditions, hydrophobic guest molecules can be induced to reside in the hydrophobic interior of the dendrimer. This process is reversible on changing to a hydrophobic solvent. The core-shell molecular behaviour that dendrimers possess was initially put forward by Maciejewski in 1982 [64], although it was not until later that experimental evidence was reported. Goddard and Tomalia [65] were among the first to apply dendrimers in the field of host–guest chemistry. T1 NMR experiments led them to propose that guest molecules might not necessarily be fully encapsulated within the interior but could alternatively be partially incorporated at the dendrimer surface.



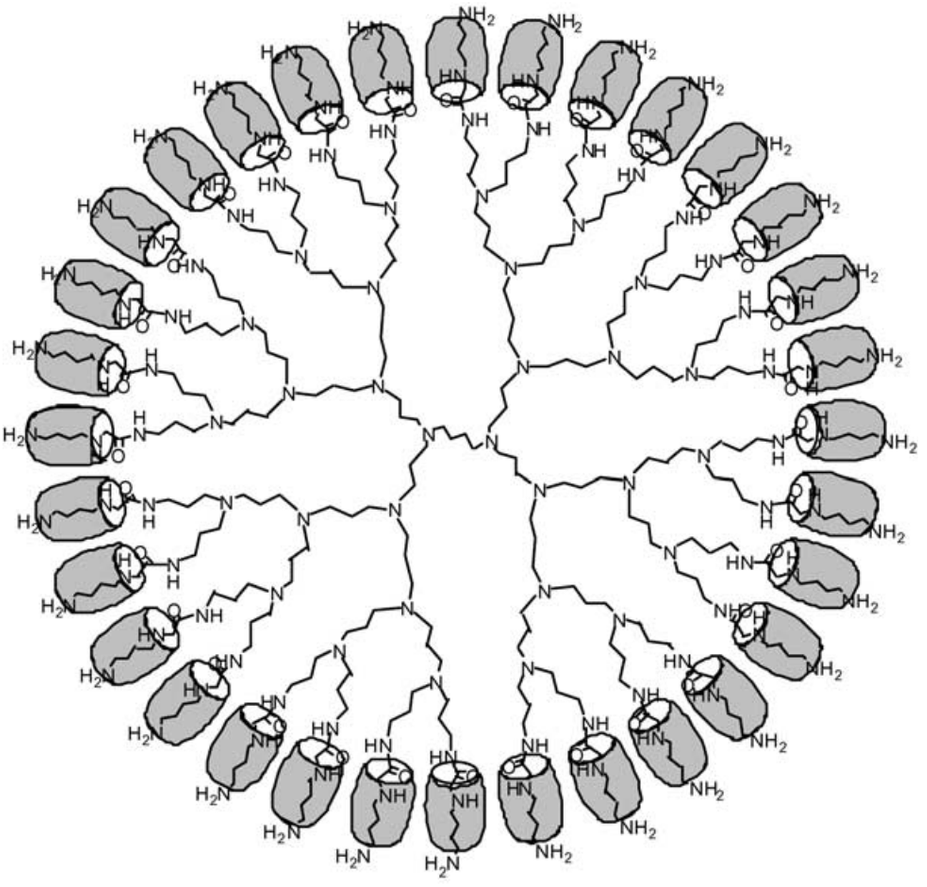
**14**

FIGURE 13 Carbosilane-cored dendrimer with non-covalently attached $[Ru(bipy)_3]^{2+}$ groups.

The micelle-like properties of such host–guest interactions were identified by Newkome *et al.* and reported in the synthesis of a "Unimolecular Micelle" from a non-polar dendrimer with charged peripheral groups [66]. The concentration independent nature of such "static micelles" is a particular interesting feature. Fréchet *et al.* also prepared unimolecular micelles, in this case using polyaryl ether dendrimers [67]. The high solubility in aqueous solution imparted by the carboxylate groups, together with the hydrophobic nature of the dendrimer interior, presents a structure capable of solubilising non-polar organic molecules in aqueous solution via encapsulation within the interior of the dendrimer.

It is evident that a large amount of work has been conducted in the study of dendrimers for use in host–guest chemistry. The useful application of such systems is, however, more limited. Shinkai *et al.* have demonstrated the use of dendrimer-like "Crown Arborols" for use in the extraction of alkali metals [68], and several examples do exist of catalysis mediated by non-covalent interactions with dendrimers. In our group, we have developed a specific application of this simple form of molecular recognition. The use of water-soluble PAMAM dendrimers as static, covalent micelles, to increase the rate of aminolysis reaction, is reported in recently published work [69,70]. As shown in Fig. 15, the guest species is bound hydrophobically in the outer region of the dendrimer **16a** concurrent with evidence reported by Tomalia [48]. This increases the rate of aminolysis reaction. Hydrogen bonding interactions with the amine groups of the dendrimer's specific interior environment hold the guest molecules in a conformation that stabilises the tetrahedral transition state **16b**. The rate of aminolysis reaction was increased 25-fold compared to that when using the equivalent amine concentration of *N*-acetylethylenediamine. This increase in reaction rate was observed for dendrimer generations up to G-4 (32 amines). For the larger G-5 (64 amines) dendrimer, reaction was slower than that observed for the smaller G-4 (32 amines) dendrimer. This is due to increased steric crowding at the dendrimer surface, a characteristic of higher generation dendrimers.

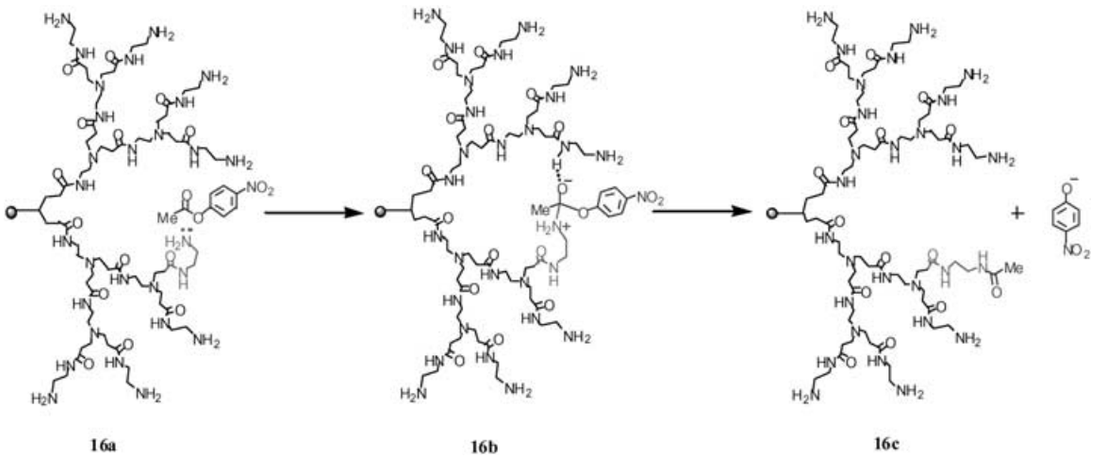
Further, more complex systems have been developed. These involve more precise interactions with greater directionality and increased molecular specificity. Newkome *et al.* presented a series of dendrimers, capable of binding host molecules



**15**

FIGURE 14 DAB dendrimer, functionalised at the periphery with pseudorotaxane formed from cucurbituril.

through hydrogen bonding with covalently incorporated (diacylamino)pyridine groups [71]. These binding units have been shown to bind such guests as imides and barbituric acids. Diederich *et al.* report the incorporation of a cyclophane group at the core of a polyether/amide dendrimer [72]. NMR studies showed the molecule to be capable of binding guest molecules within the cyclophane cavity, rather than within the branched interior of the dendrimer. Larger "dendrophanes" have been shown to be



**16a** **16b** **16c**

FIGURE 15 The three proposed steps involved in a dendrimer-assisted aminolysis reaction.

capable of binding complicated structures such as steroids [73]. Diederich has also reported the synthesis of a "dendrocleft" capable of binding sugars at the core of the molecule [74,75].

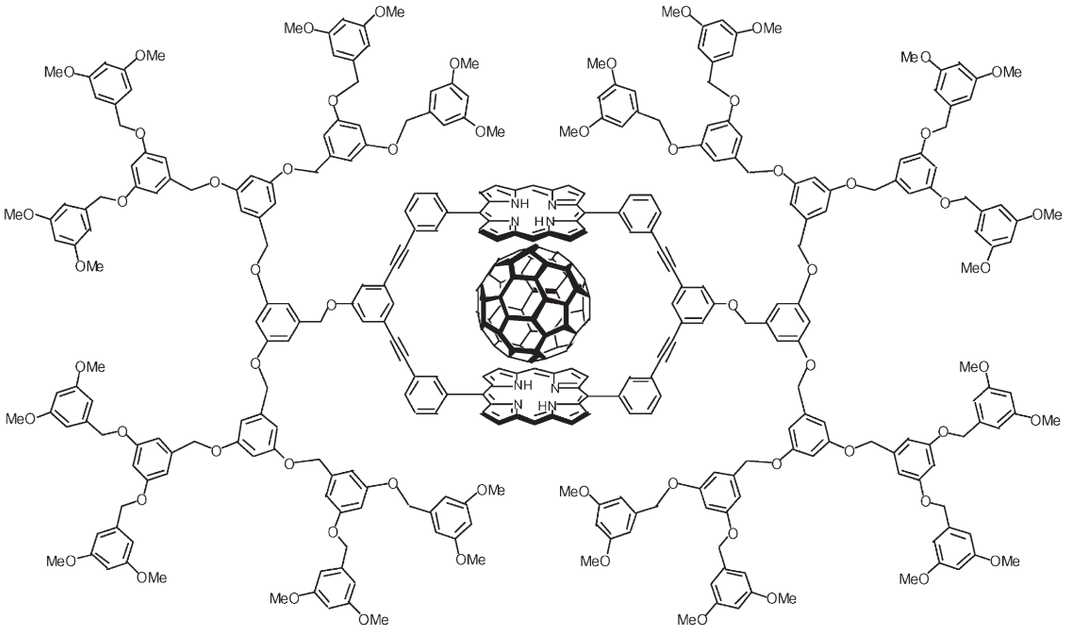
In other related work, the strong binding ability of porphyrins has been exploited in dendrimer-based host systems. Aida *et al.* report the synthesis of di-porphyrin-centred dendrimers capable of binding fullerenes. The dendrimers were prepared by condensation reaction of two core functionalised polybenzylether dendrons. The incorporation of two benzaldehyde groups at the focal point of each dendron allowed for reaction with dipyrromethane under acidic conditions forming the di-porphyrin core. The resulting dendrimer **17** was shown to be conducive to binding fullerenes. Fig. 16 depicts the inclusion of a $C_{60}$ fullerene between the two porphyrin groups. The use of these compounds in the production of photo- and electro-active materials is highlighted by the authors as a promising area for further research.



## Drug and Gene Delivery

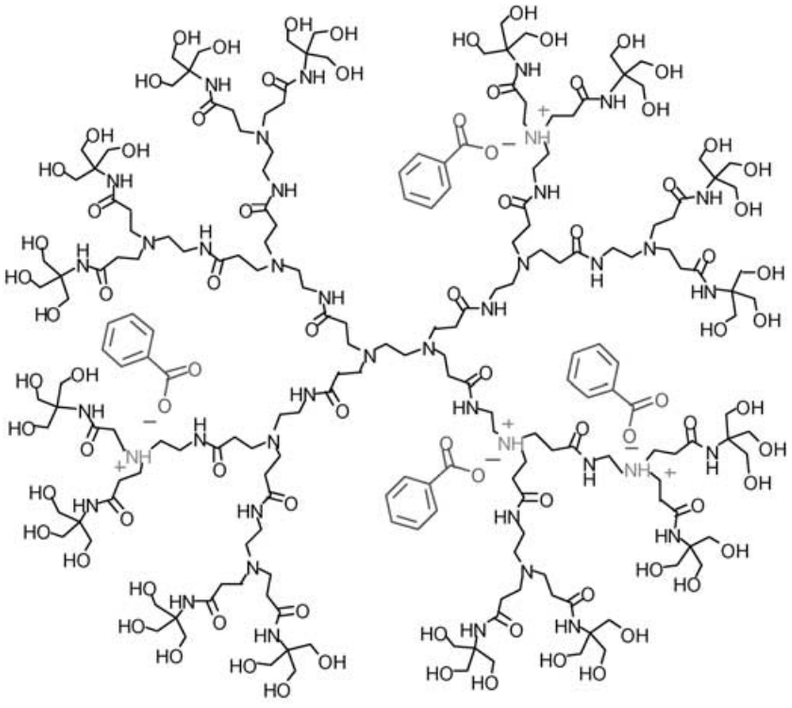
The potential of dendrimer host molecules for use as drug delivery systems has been shown by a number of research groups [76]. Using dendrimers to form static micelles, Twyman *et al.* [6] demonstrated that acidic guest molecules could be selectively bound within the internal voids of a modified PAMAM dendrimer **18** (Fig. 17), via a simple ion pairing interaction. This results in a water-soluble dendrimer/"drug" complex. Flow calorimetry experiments were carried out using yeast in an aqueous medium [77]. Exposure to the dendrimer encapsulated anti-fungal drug molecules showed the drug to be efficiently released in an active form, behaving as a fungicide toward the yeast cells. A number of dendrimers capable of solubilising organic molecules have been reported, including the account of Smith *et al.* who produced a dendritic peptide capable of binding proflavine, a hydrophilic dye [78].

Other direct applications of dendrimer supramolecular chemistry include the binding of polyanionic DNA molecules to cationic species, such as PAMAM and DAB dendrimers. Haensler and Szoka [79] first demonstrated the use of PAMAM dendrimers as gene vectors in 1993. Transfection of genes using dendrimers is made possible by the complexation between DNA and the dendrimer surface. With PAMAM dendrimers, a stable DNA/dendrimer complex is formed as a result of electrostatic interactions between negatively charged phosphate groups on the nucleic acid, and protonated primary amine groups on the dendrimer surface, which are positively charged. The resulting complexes possess an increased net positive charge compared to the discrete DNA. This property is essential if efficient cellular uptake is to be achieved and is also beneficial in guarding against DNA-ase, thus extending the length of time that the DNA will remain intact. Results obtained by Baker *et al.* suggest that transfection using DNA/dendrimer complexes




**17**

FIGURE 16 Porphyrin-cored polyether dendrimer/fullerene complex.



**18**

FIGURE 17 Incorporation of benzoic acid within the branched interior of an OH terminated PAMAM dendrimer.



becomes more efficient with increasing excess of positive charge [80].

DAB or polypropyleneimine dendrimers have also been used in transfection studies, and in protonated form, are capable of interacting desirably with DNA, to afford complexes suitable for use as gene vectors. Other research includes the use of cationic phosphorus-containing dendrimers as transfecting agents. Supramolecular assemblies of these dendrimers were shown to be highly efficient at transfecting luciferase genes during *in vitro* studies.

## Dendrimer Assembly

The self-assembly of covalently formed dendrimers into larger supramolecular structures is also experiencing significant investigation. Studies have been carried out into the formation of films and the deposition of monolayers on surfaces, as well as aggregation of dendrimers to form liquid crystals, fibrous assemblies [81], and other interesting supramolecular nanostructures. Mong *et al.* have investigated the self-assembly of β-analine based dendritic β-peptides dendrimers into nanoscale aggregates [82]. Driven by intermolecular H-bonding interactions, these dendrimers display a tendency to aggregate in non-polar and polar aprotic solvents. This is substantiated by the breaking up of aggregates on the addition of a small amount of protic solvent to the solution; the H-bond donor solvent causes interference with intermolecular H-bonding.

Dendrimer aggregates have been prepared by self-assembly through electrostatic interactions. The concept of forming such an array is attributed to Tomalia and Esfand [48], however, the first reported study on the electrostatic assembly of dendrimer electrolytes was published by Aida *et al.* [49]. Using complementary porphyrin-cored polybenylether dendrimers with either negatively or positively charged surface groups, Aida *et al.* prepared an infinite dendrimer assembly. By changing the relative concentrations of each species they were able to control the aggregation process. This is illustrated schematically in Fig. 18. The resulting assemblies are of particular interest due to the energy transfer properties imparted by the porphyrin cores.

## Interfaces, Surfaces and Films

A number of studies have been conducted into the behaviour of dendrimers on surfaces and interfaces, especially the air–water interface [50,51]. The preparation of such dendrimeric Langmuir films was initially reported by Saville *et al.* [83], using polyether dendrimers with hydrophilic hydroxy groups at their focal points. For a homologous series of dendrimers it was noticed that for larger generations, surfactant behaviour was not observed. This is attributed to crowding of the focal group, and

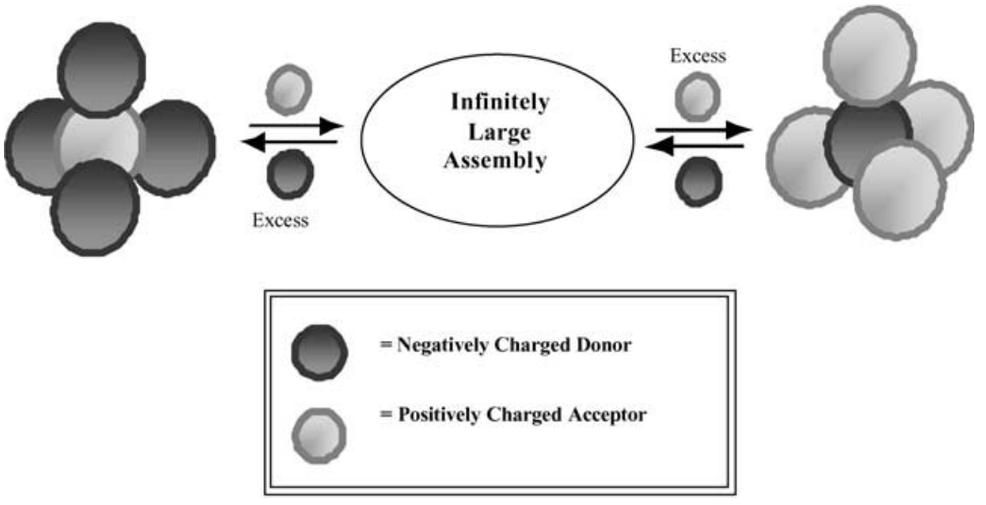



FIGURE 18 Schematic representation of the electrostatic interaction between negatively charged and positively charged dendrimer electrolytes.



steric shielding caused by the increased number of dendritic branches. Use of solvatochromatic dyes at the focal point has been made to confirm this perception [84]. In addition to this work, several variations on the system have also been studied.

Hawker, White *et al.* [85] investigated similar polyether dendrimers containing either nitrile or methyl ester peripheral groups. The more hydrophilic nature of the functionalised periphery, and subsequent greater affinity for the water surface, caused the dendrimers to spread out more, forming thinner layers. The dendrimers were seen to adopt a flatter conformation as opposed to the more elliptical configuration in the un-functionalised polyether dendrimers. Other modifications include changing the functionality of the focal group to incorporate oligo(ethylene glycol) chains with different lengths [86]. As the relative size of the hydrophilic chains was increased, with respect to dendrimer generation, the stability of the monolayers was also seen to increase. Similar work by Percec *et al.* [87] reports periphery functionalisation of the same Fréchet type polybenzylether dendrons with hydrophobic dodecyl chains. With crown ether focal points these dendrimers arrange themselves so as to extend the alkyl chains upwards, whilst positioning the hydrophilic crown ether moiety at or below the water surface. This type of self-assembly has also been achieved using both PAMAM dendrimers [88], and DAB/polyethyleneimine dendrimers [89,90] containing both hydrophilic and hydrophobic sections.

Meijer *et al.* prepared polypropylenimine dendrimers functionalised with palmitoyl chains, alkyl chains with azobenzene chromophores and adamantine groups. These were intended, respectively, to provide an amphiphilic dendrimer, one lending itself to UV analysis and a reference dendrimer with a consistently globular structure. After comparing these three different dendrimers, they concluded that amphiphilic dendrimers such as these possess the ability to change their conformation depending on their environment. The dendrimers take on the globular configuration most commonly associated with dendrimers in hydrophobic/organic solvents, however, at a water–air interface, the dendrimers adopt a cylindrical conformation, presenting the flattened hydrophilic interior of the dendrimer to the water surface and directing the hydrophobic chains perpendicular to the interface (Fig. 19).

Further studies on amphiphilic dendrimers have been conducted by Fréchet *et al.* Using a convergent method and in the final step combining two polyether dendrimer "hemispheres" with different terminal functionalisation, Fréchet *et al.* generated an unsymmetric dendrimer with both hydrophobic and hydrophilic portions [91]. The amphiphilic nature of these molecules predisposes them to self-assemble at surfaces and interfaces. Figure 20 shows this schematically.

These properties have been exploited in the stabilisation of organic/aqueous emulsions and in the formation of interfacial membranes. Dendrimers similar to these have been synthesised containing

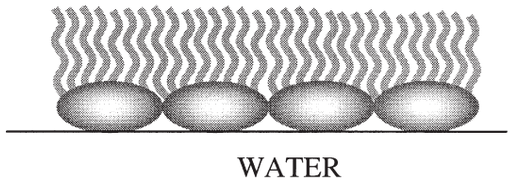



FIGURE 19 Schematic representation of amphiphilic dendrimers assembled on a water surface.

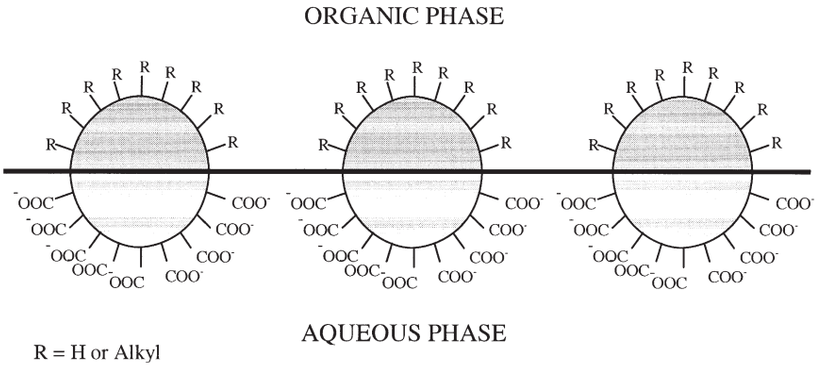



FIGURE 20 Unsymmetric amphiphilic dendrimers assembled at an organic/aqueous interface represented schematically.



electron-donating and electron-withdrawing groups instead of hydrophilic/hydrophobic portions [92]. These dendrimers were shown to orient themselves in an electric field.

## Nanostructures

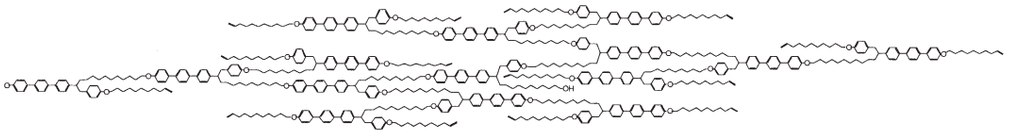
The highly specific iterative synthesis used to construct dendrimers not only provides for ease of functionalisation, useful in preparing the amphiphilic species mentioned above, but also allows for the synthesis of relatively large molecules with well-defined size and shape. These features make dendrimers particular valuable in the self-assembly of more complex nanostructures. Loi *et al.* prepared disc-like and tetrahedral shaped polyphenylene dendrimers [52], based on a divergent Diels–Alder cycloaddition method [93]. Peripheral functionalisation with dodecyl groups was carried out in the final stages. Dendrimer layers were prepared using spin coating on highly oriented pyrolitic graphite. On subsequent analysis using Atomic Force Microscopy, rod-like structures made up from the polyphenylene dendrimers were observed. These nanorods arranged themselves further into parallel rows and in some cases two-dimensional crystal structures were observed.

In similar work, self-assembly of pseudo-dendrimer "Dendron Rodcoil" molecules into supramolecular nanoribbons is reported by Stupp *et al.* [53]. Consisting of linear alkyl portions, linear biphenyl ester segments, and hydroxyl terminated dendron groups, the architecture of the building blocks is such that they possess structural similarities not only with dendrimers, but also with both rods and coils. Electron microscopy showed self-assembly, resulting in nanoribbon structures of consistently 10 nm in width and only one molecule deep, suggesting a head to head packing of molecules. The length of the ribbons was surprisingly large, with some strands as long as 10 μm, and on further investigation, it was found that these nanoribbons arrange into molecular networks capable of gelling solvents at concentrations as low as 0.2 wt%

The authors suggest that the self-assembly of these molecules is mediated through a combination of $\pi-\pi$ stacking and hydrogen bonding interactions. Evidence is provided to support this in the form of a number of analogous compounds. It was found that at least four terminal hydroxyl groups were required on the dendron segment if the formation of nanoribbons was to be observed. Analogues were also prepared to test the role of the aromatic biphenyl groups. These showed that at least two biphenyl groups were needed for self-assembly to occur, however, networks with greater mechanical stability were observed when more than two units were incorporated. Together these two series of compounds demonstrate the synergistic nature of the self-assembly with both characteristic groups required for assembly to occur.

## Liquid Crystal Structures

Due to their well-defined structures, dendrimers have been applied to the construction of liquid crystals. Exploiting the tailored synthesis of dendrimers allows the supramolecular interactions between them to be fine-tuned. Meijers *et al.* report the formation of liquid crystalline dendrimers through peripheral functionalisation of polypropyleneimine dendrimers with pentyloxycyanobiphenyl and decyloxycyanobiphenyl mesogenic units [54]. A significant number of papers on the self-assembly of dendrimers into liquid crystal arrangements have been published by Percec *et al.* [55–61]. After initial investigations into the self-assembly of hyperbranched polymers into liquid crystalline phases, problems with high polydispersities and specificity led the research toward development of analogous dendrimer structures. Based on the convergent strategy developed by Fréchet, to give polybenzylether dendrimers, Percec *et al.* were able to synthesise similar dendrimers containing both



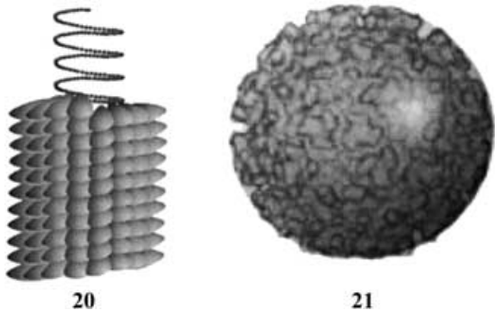
**19**

FIGURE 21 Proposed *anti* dendrimer conformation in the nematic liquid crystal phase.

longer alkyl groups and larger aromatic components. By adopting an *anti* conformation, **19** (Fig. 21), rather than the more usual *gauche* arrangement, these dendrimers form liquid crystalline mesophases.

Following on from predictions by Tomalia [65] concerning the relationship between dendrimer generation and morphology, Percec among others [94] developed numerous self-assembled systems based on liquid crystal type assembly of several different dendrimer mesogens. Particular attention was directed toward controlling the mode of assembly through variation of dendrimer structure, especially dendrimer generation. Not only does this research provide novel self-assembled systems, but it also allows X-ray diffraction techniques to be used in determining the size and shape of both the supramolecular array and hence the individual building blocks. Previously, the long range order needed to perform X-ray analysis on dendrimers, was not presented, and instead changes in the dendrimer structure were inferred through changes in observed physical properties, such as hydrodynamic volume, hydrodynamic radius, viscosity measurements, and refraction index, as well as various photophysical parameters [94].

By synthesising a series of liquid crystal dendrimers, Percec was able to confirm predictions made by Tomalia *et al*. As the dendrimer size increases with each generation, the shape of the molecules changes from a disc-like segment to a more conical structure or spherical segment, and finally adopting a spherical shape at larger generations. Supramolecular structures such as these are particularly interesting due to their biological significance.



**20** **21**

FIGURE 22 Schematic representation of the tobacco mosaic virus **20** and the icosahedral virus **21**.

The self-assembled cylindrical structure of the dendromesogens developed by Percec resembles strongly that of the tobacco mosaic virus **20** and the spherical assembly of the larger generation dendrons is comparable to that of the icosahedral virus **21**. These biological structures are represented schematically in Fig. 22.

First generation 3,4,5-tris[*p*-(*n*-dodecan-1-yloxy)-benzyloxy]benzoic acid monodendrons possess a multifunctional core group and are synthesised using a convergent approach [95]. These molecules are of the disc-like segment shape **22a** shown in Fig. 23.

Firstly, these molecules self-assemble themselves into discs which stack to form a supramolecular cylinder **22b**. These cylinders arrange themselves in a hexagonal columnar fashion **22c**. The same is observed for the second generation, however, these segments are obviously larger and fewer are needed to form the disc. For third and fourth generation dendrons, there is a marked change in both the monodendron and the resulting supramolecular assembly. Both dendrons are more three-dimensional and conical in shape **22d**, the third generation making up one sixth of a sphere and the fourth generation making one half of a sphere. These come together to form spherical arrangements **22e**. This changes the wider crystal structure, from the hexagonal columnar (p6mm) structure already seen, to a three dimensional cubic (Pm3n) lattice **22f**. Further studies have been carried out involving the functionalisation of dendrons with terminal aliphatic groups and also thermally triggered changes in assembly [96]. It was shown that by increasing either the temperature or the size of the aliphatic groups, assembly could be steered from columnar to spherical.

## CONCLUSION

As can be seen from the examples described in this review, the field of research devoted to the study of dendrimers *and* supramolecular chemistry is both wide and varied. The combination of these two branches of chemistry provides the basis for a sizeable amount of interesting and innovative research, spanning a number of different disciplines.

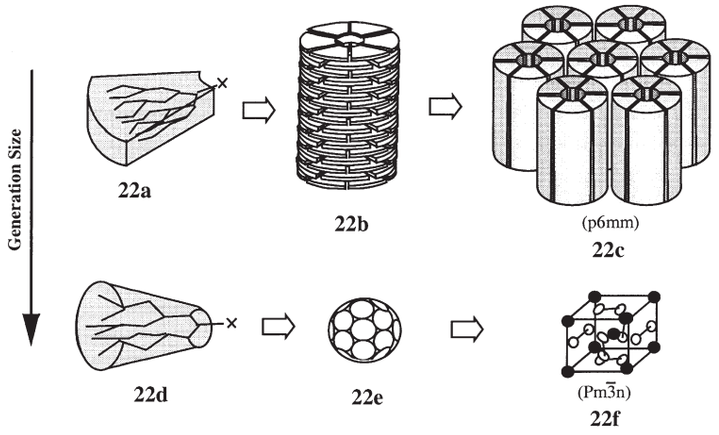



FIGURE 23 Schematic representation of the effect of generation size on self-assembly of dendrimers into liquid crystal arrays.



The construction of dendrimers via supramolecular interactions accounts for a large part of this research and in this area alone there are numerous examples of dendrimers, which not only incorporate exotic molecules, but also are of significant value due to the increased understanding of biological and physical systems that they bring, and the applications in which they can be employed. Much research has concentrated on the incorporation of photoactive moieties and the development of self-assembled molecules that incorporate energy transfer systems, mimicking the biological systems seen in nature.

Whilst a significant portion of the literature concerns the formation of dendrimers through non-covalent interactions, an equally important, although less widely prospected area, exists where supramolecular interactions are exploited together with covalently formed dendrimers. This area of host–guest chemistry has been studied by many groups and is beginning to find useful applications in drug and gene delivery, as well as more modest applications in the area of synthesis and catalysis. Self-assembled dendrimeric arrays have been investigated, providing interesting insights into the way in which biological systems such as viruses arrange themselves. Other research contributes further to the realisation of nanoscale devices. The precisely controlled topological and functional properties of dendrimers combined with the use of chemistry which is predisposed to interact in a particular way, can be used effectively to produce numerous different structures. Using supramolecular chemistry over harsher chemistry (i.e. as opposed to covalent chemistry requiring "forcing" conditions) often results in cleaner and more efficient synthesis. Altogether the field of dendrimeric supramolecular chemistry is set to provide an important contribution to many areas of science and technology.

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