Functional cascade molecules

CHEMICAL SOCIETY REVIEWS

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Cascade molecules/dendrimers are highly branched, regularly built molecules that have now been known for two decades. While efforts in the early stage of their investigation were directed towards the development of higher generation structures and new dendritic architectures, the design of functional dendrimers is more and more emphasized today. The latest literature in the field reflects the search for cascade molecules that accumulate certain functional groups resulting in novel properties—the first practical applications are in sight. Dendrimers that interact with, and can be manipulated with light, appear particularly attractive and hold promises for future developments.

1 Introduction

Cascade molecules/dendrimers, *i.e.* highly branched yet structurally perfect molecules, have now been known for two decades. The term ‘cascade molecule’ indicates that such compounds usually originate from a stepwise synthetic procedure whereas the word ‘dendrimer’ is a combination of the Greek ‘dendron’ (tree, branch) and ‘meros’ (part). Evolving around a core atom or molecule they possess repeating ‘generations’ of branches that branch again and again until an almost globular shape with a dense surface is reached. A manifold of different styles and designs of cascade molecules has so far been reported[1] and the yearly number of publications on this topic is ever increasing since the first cascade molecules were reported twenty years ago.[2] More than 2000 papers have now been published on the subject.

In 1979, Denkewalter *et al.* released a patent on branched structures based on amino acids.[3] Later, the US industrial chemist D. A. Tomalia revived the concept of highly branched, monodisperse molecules when he developed the family of so called polyamidoamine (PAMAM) dendrimers (Fig. 1).[4] Only in the early 1990s when research on dendritic molecules began to develop explosively did a great number of chemists all over the world eventually begin to explore the scope of this new concept.

2 Evolution of dendritic structures

When the dendrimer is build up synthetically from the core to the periphery, as in the first examples,[2–4] this is called a *divergent* synthetic strategy. When the dendritic branches are first built up and are then in a final step linked to the core molecule or atom, like a wedge, then this is known as a *convergent* synthesis.

The larger the dendrimer becomes, however, the larger the number of bond formations per molecule and thus the greater the probability of defects in the structure. In addition, as the dendrimers grow the terminal units move closer and steric hindrance becomes a problem in the ongoing synthesis. Calculations and the nature of exponentially increasing the number of terminal groups indicate that there is a limit to which the divergent strategy can be taken without significant deviations from the intended structure of the molecule. This is referred to as the ‘starburst effect’, a term coined by Tomalia for the upper generation limit above which only incomplete further conversion can be achieved due to steric crowding in the periphery.[5] Apart from PAMAM dendrimers, polyamine,[6–8] carbosilane,[9,10] and polyaryl ether[11] dendrimers are amongst the most investigated and commonly used dendritic structures. Polyamine (Fig. 2) and PAMAM dendrimers are now even commercially available.

Among others, it is through the work of Newkome, Fréchet, Meijer, Moore, and Majoral that more and more dendritic systems became known and the scope of their preparation was investigated. Newkome *et al.* have contributed a great number of new dendritic structures in the field, *e.g.* globular dendritic poly-alcohols that exhibit micellular behaviour.[12] Fréchet *et al.* developed a family of polyaryl ether dendrimers.[11] Meijer and coworkers have made available poly(propylene imine) den-

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Andreas Archut was born in Bonn in 1970. He obtained his education in chemistry in Bonn and Los Angeles. Working with Nobel laureate George A. Olah, he received the Master of Science degree from the University of Southern California in 1994. In 1997 he completed his PhD in the research group of Fritz Vögtle at the University of Bonn with a thesis on functional photoswitchable dendrimers.

Fritz Vögtle was born in Ehingen/Danube in 1939. He studied chemistry in Freiburg and chemistry and medicine in Heidelberg. In 1965 he received his PhD at the University of Heidelberg in the group of Heinz A. Staab. After his habilitation in 1969 in the same group, he became a professor of chemistry at the University of Würzburg. Since 1975 he has been professor and director at the Kekulé-Institut für Organische Chemie und Biochemie at the University of Bonn. Professor Vögtle’s research focusses on supramolecular chemistry, particularly on mechanically interlocked molecules like catenanes and rotaxanes, on dendrimers, and on host–guest chemistry.

Fritz Vögtle

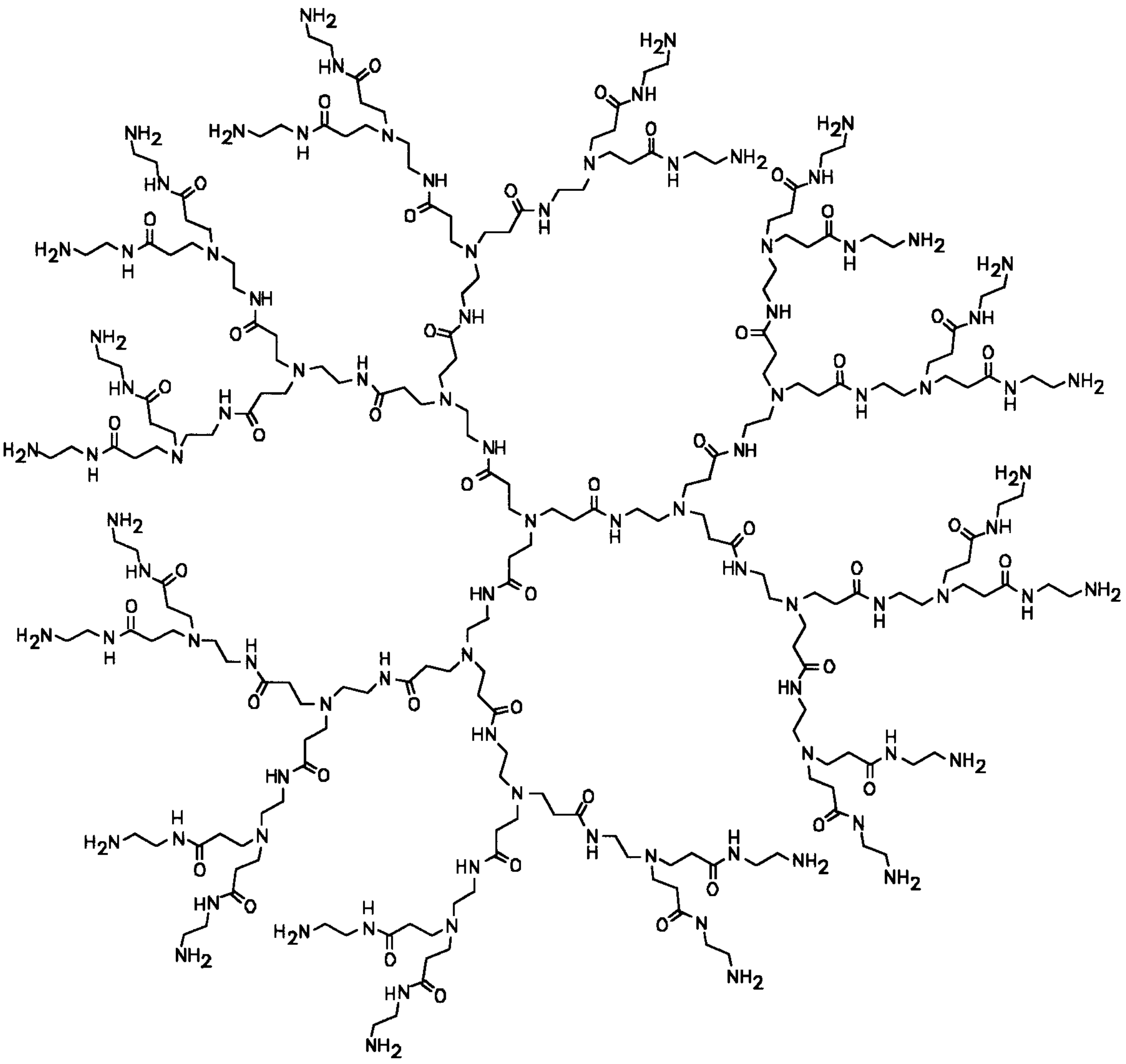

Fig. 1 PAMAM starburst dendrimers developed by Tomalia

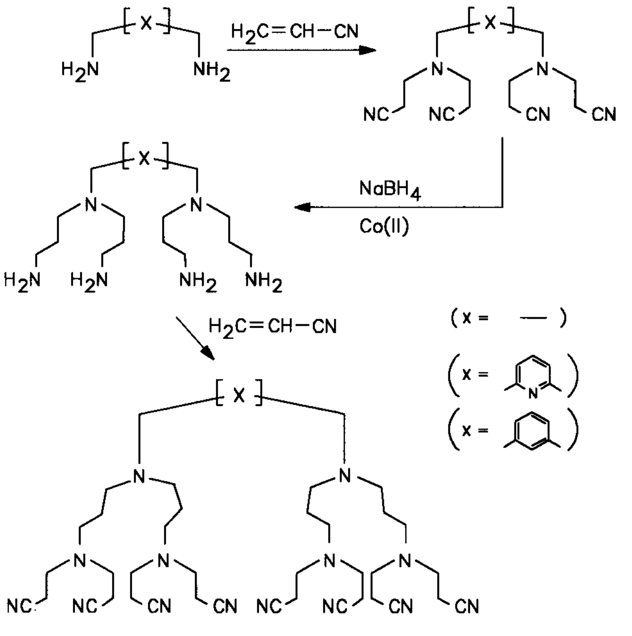

Fig. 2 The synthesis of polyamine dendrimers according to Vögtle's initial cascade molecules paper[2] follows a stepwise (repetitive) procedure of consecutive Michael addition–reduction steps

drimers to the scientific community that reach up to generation 5 with 64 amino groups in the periphery and they have used them for dendritic systems with promising abilities.[8] Moore succeeded in preparing pure hydrocarbon dendrimers of a previously unseen size and molecular weight (up to 30 000 emu) and yet still remaining soluble.[13] Phosphorus-containing dendrimers developed by Majoral *et al.* even surpass this weight record by far, the heaviest species reaching a molecular weight of more than 3 million emu today.[14]

3 Functional dendrimers

With a number of high generation 'skeletons' with multiple functional groups in the periphery, the general interest of dendrimer research has experienced a shift from generations to functions with the intention to approach applications in both the life and material sciences.[15,16] If one wants to introduce functionality to a dendrimer, *i.e.* attach a shaped functional group like a chromophore, ionophore, receptor, catalyst, or molecular switch to a dendrimer, there are two general ways to do so with readily available dendritic precursors (Fig. 3). Either such units can be connected to a dendritic skeleton with a number of reactive groups like amines, alcohols, or halides in the periphery, or one can use a functional core unit which is then functionalised by reaction with a 'dendreagent' with dendritic 'wedges' (also referred to as 'dendryl residues/substituents').[17]

Numerous periphery-functionalized dendrimers have been reported so far, *e.g.* those with ferrocene units, fatty acid moieties, or sugar units. The main feature of such compounds is the accumulation of a defined number (multiplication) of functional groups around a central dendritic core. Among functionalized dendrimers those species containing chiral

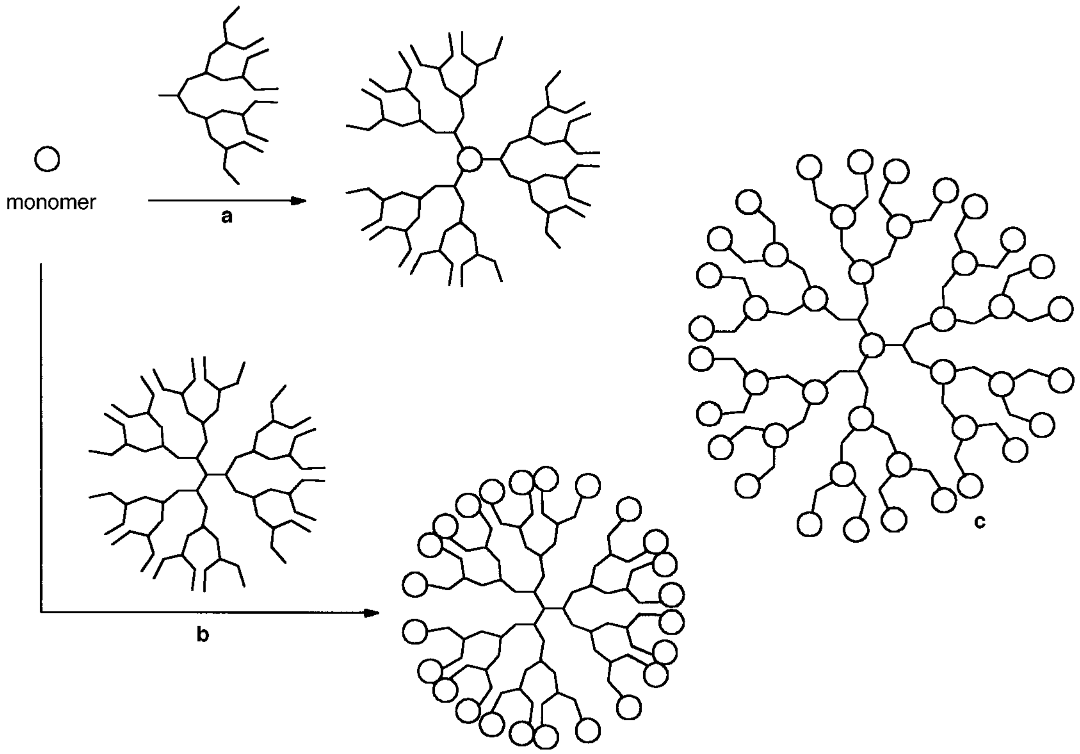

Fig. 3 Functionalization of dendrimers can be accomplished by three general approaches: functionalization of a dendrimer at the periphery (*b*), attachment of 'dendryl residues' to a functional core (*a*); when dendrimers with functional groups in all regions (core, branches, periphery, *c*) are desired a *de novo* synthesis is usually required

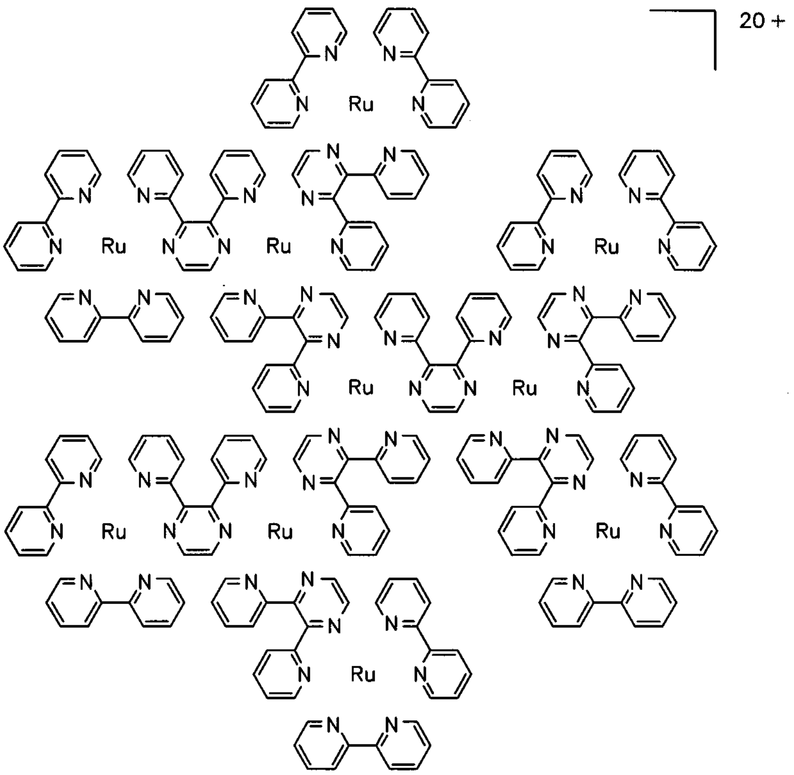

Fig. 4 Balzani *et al.* have contributed various metal-polypyridine dendrimers with interesting electrochemical properties

groups have become particularly important. Peerlings and Meijer have recently published a systematic approach to dendrimers possessing chirality.[18]

4 Photoactive metal-containing dendrimers

The metal–ligand–metal connectivity of ruthenium–bipyridine complexes and related coordination compounds has been used to assemble metal-containing dendrimers.[19] The resulting cascade molecules are interesting for both their electrochemical and their luminescence properties. The first dendrimer containing a ruthenium–bipyridine complex as the core unit was described by Balzani *et al.* in 1994 (Fig. 4).[20]

Core-functionalized dendrimers in turn take advantage of the spatial demand of their dendritic wedges that can serve as shields for the central unit. One example is the dendritic ruthenium–bipyridine complex depicted in Fig. 5: it was found that the lifetime of the excited state of the ruthenium ion is significantly prolonged compared to the non-dendritic complex since the dendritic periphery prevents quenching processes with the solvent or with dissolved oxygen.[21] Applications of this type of 'supramolecular dendrimer' in medical diagnostics are envisioned.[22]

Dendrimers with a metal porphyrin unit as the core have become interesting model compounds for heme-containing proteins and as sterically hindered oxidation catalysts. Inoue *et al.* were the first to describe a dendrimer with a metal porphyrin as its core (Fig. 6).[23] The convergent synthetic method of Fréchet was used to prepare the dendrimer in which the photoactive metal porphyrin center is sterically shielded, resulting in a size-dependent accessibility for quencher molecules.

Diederich *et al.* have prepared dendrimers with a zinc–porphyrin core and Newkome-type polyether amide branches with the aim to fine tune and control the redox potential of the chromophore.[24] Cyclovoltammograms of these dendrimers show that the first reduction potential of the zinc porphyrins decreases with increasing dendrimer generation and the authors rationalize this observation as being a result of the increasingly electron rich microenvironment created by the dendritic branches. The dendryl substituents 'shield' the porphyrin center and hence hinder the addition of electrons to it.

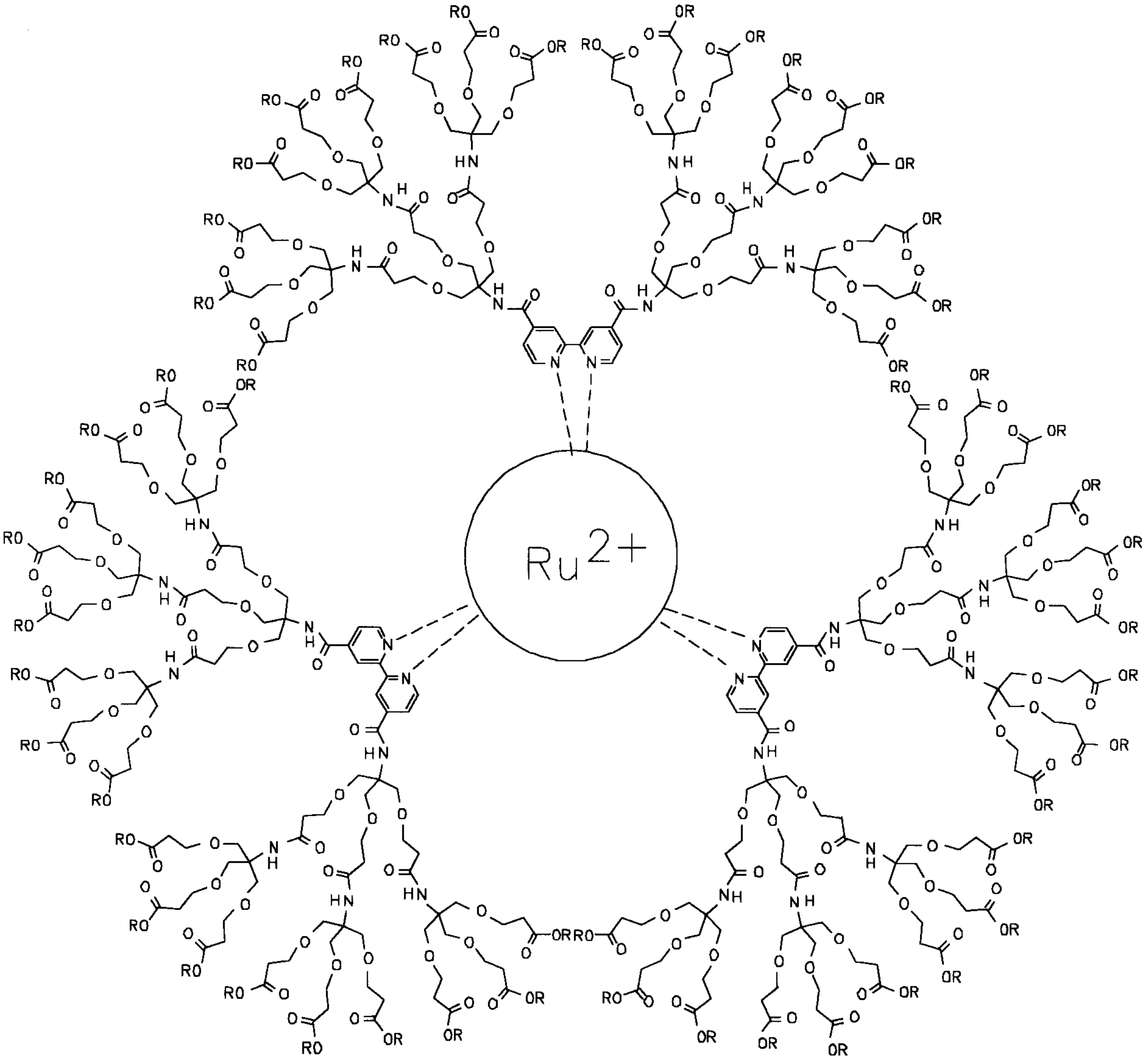

Fig. 5 'Dendrylation' of a ruthenium–bipyridine complex results in new properties. The shielding effect of the dendryl substituents renders the metal center less prone to quenching with solvent molecules and dissolved oxygen.

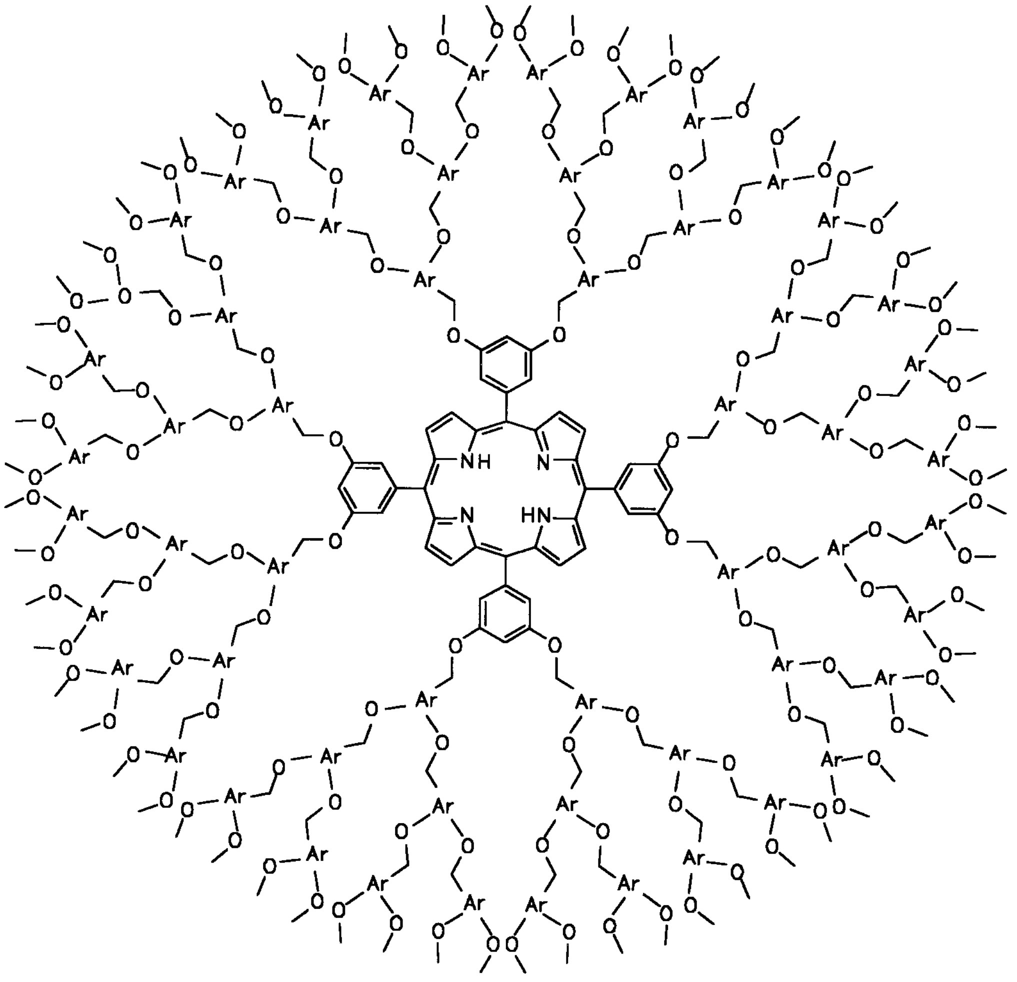

Fig. 6 Porphyrin dendrimers are model compounds for heme-containing proteins

5 Photoswitchable azobenzene dendrimers

Light is a useful way of manipulating molecular systems because its effect is fast, mild, and often reversible. Azobenzene derivatives have been used to construct photoswitchable devices for many years.[25] Azobenzene-type compounds, when they are not strongly sterically hindered, do not show any appreciable fluorescence or phosphorescence, but they can be easily and reversibly photoisomerized. The thermodynamically stable *E*-isomer can be photochemically converted to the *Z*-isomer, which is converted back to the *E*-isomer by light excitation and thermally in the dark (Fig. 7).[26,27] Azobenzene moieties have therefore been applied in the construction of photoresponsive molecular and supramolecular systems.

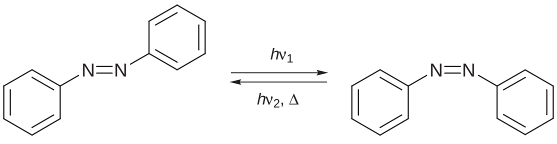

Fig. 7 The *E*/*Z* isomerization of azobenzene compounds can be brought about by means of light

A dendrimer bearing six peripheral azobenzene groups showing reversible switching behaviour was reported in 1993 (Fig. 8).[28] Recently, Junge and McGrath have reported the synthesis of a two-directional dendrimer with an azobenzene group in the center and have investigated its *E*/*Z* isomerization induced by ultraviolet light (Fig. 9).[29] Although the steric effect

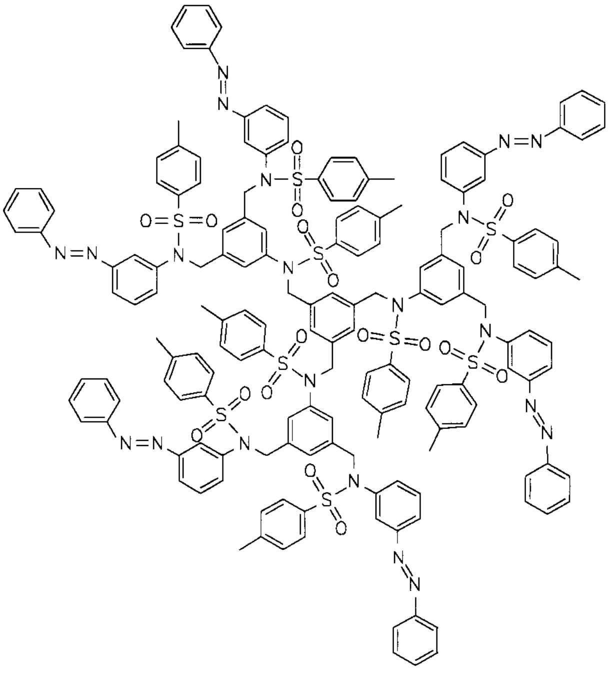

Fig. 8 The first photoswitchable dendrimer was reported by Vögtle *et al.*

of the isomerization of the chromophore is probably a minor one, the work has prompted speculation as to whether such molecules could be used to 'grab' molecules upon irradiation. It has been stated that in order to obtain such an effect there would have to be more switchable moieties present in the molecule.[30] Such molecules are now available (*vide infra*).

The *Z*/*E* photoisomerization of dendrimers with an azobenzene unit as the core has recently been claimed to occur by excitation with infrared radiation—with the dendrimer being able to harvest low-energy photons, channel the absorbed energy to the core, and bring about the chemical *E*/*Z* transformation.[31]

The latest report in the field of azobenzene dendrimers is a study by Vögtle, Balzani *et al.*: poly(propylene imine) dendrimers of the generations one through four, equipped with up to 32 azobenzene units in the periphery were investigated as to their photochemical switching behaviour (Fig. 10).[32] Interestingly, measurements of the quantum yields of the photoisomerization and of the changes in the absorption spectra of these dendrimers show no significant difference to the results obtained with the corresponding monomers. In other words, the azobenzene moieties behave independently even under increasingly close spatial proximity.

In addition, these periphery-functionalized dendrimers have been tested as materials for holographic data storage for the first time. Polymers with azobenzene moieties in the side chains are well known in holography. The structural rearrangement of the azo groups upon exposure to laser light is thought to be responsible for a change in the optical property of a holographic film. Although the results of these first experiments show that the dendrimers investigated are still less effective than the polymers commonly used, a further fine-tuning of the dendrimers' properties may lead to interesting optical applications for these dendrimers.[32]

6 Molecular dendritic antennae

Besides transition-metal sites other photo- and electro-chemically active organic functional groups have been introduced to dendritic structures. Xu and Moore have designed so-called 'molecular antennae' consisting of an electroluminescent luminophore equipped with dendryl residues capable of 'funneling' electrons to the focal point of the molecule.[33] In another study, the photoinduced electron transfer of a number of 'dendryl-substituted'[17] fluorophores was investigated.[34] It has been found that the fluorescence maxima in organic solvents of these dendritic compounds is strongly generation dependent. Whereas the fluorophore (*p*-dimethoxybenzene) behaves like the corresponding non-dendritic molecule up to generation {4} of the dendryl residue, an increasingly strong blue-shift was observed for generations {5} and {6}. It has been suggested that such compounds could be used for the design of electroluminescent diodes.[35]

7 Conclusion and outlook

Today, after several thousands of publications dealing with dendritic molecules, the chemistry of dendrimers is reaching maturity at a great pace. Branched, tree-like molecules are inspiring chemists from all fields and areas of chemistry since they open up routes to new materials, unique substance properties, and potential applications. Cascade molecules are the linking element between small (organic) molecules and high molecular weight macromolecules, and in times of great interest in nanometer-size molecular arrays, they are the ideal building blocks for nanoarchitecture. The first commercial applications have been realised, *e.g.* in medical diagnostics, and many more are presently envisaged. Photoactive dendrimers may play a prominent role in the future.

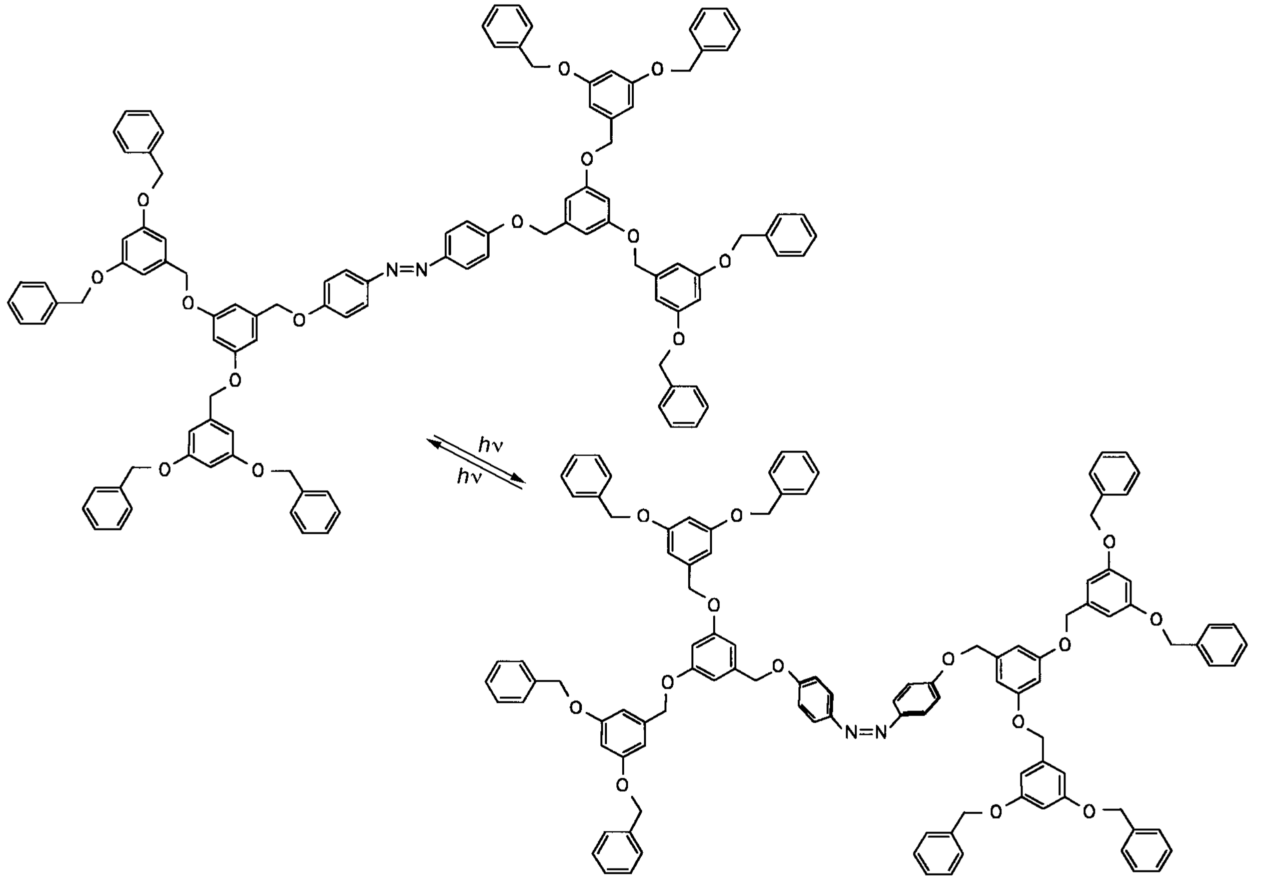

Fig. 9 Junge and McGrath have reported a dendrimer with an azobenzene core capable of undergoing photochemical isomerization

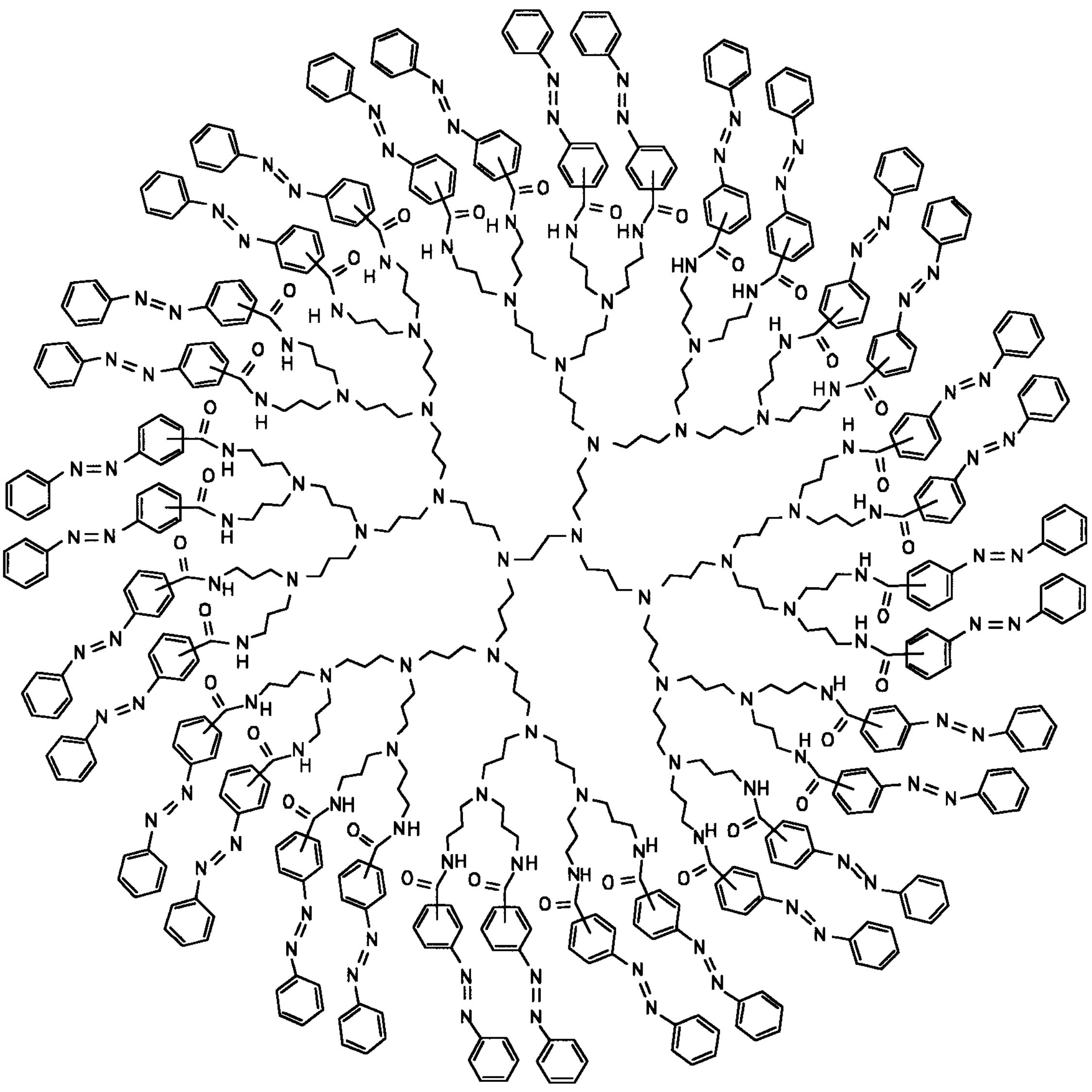

Fig. 10 Vögtle *et al.* have prepared dendrimers with up to 32 peripheral azobenzene groups that have been used as holography materials

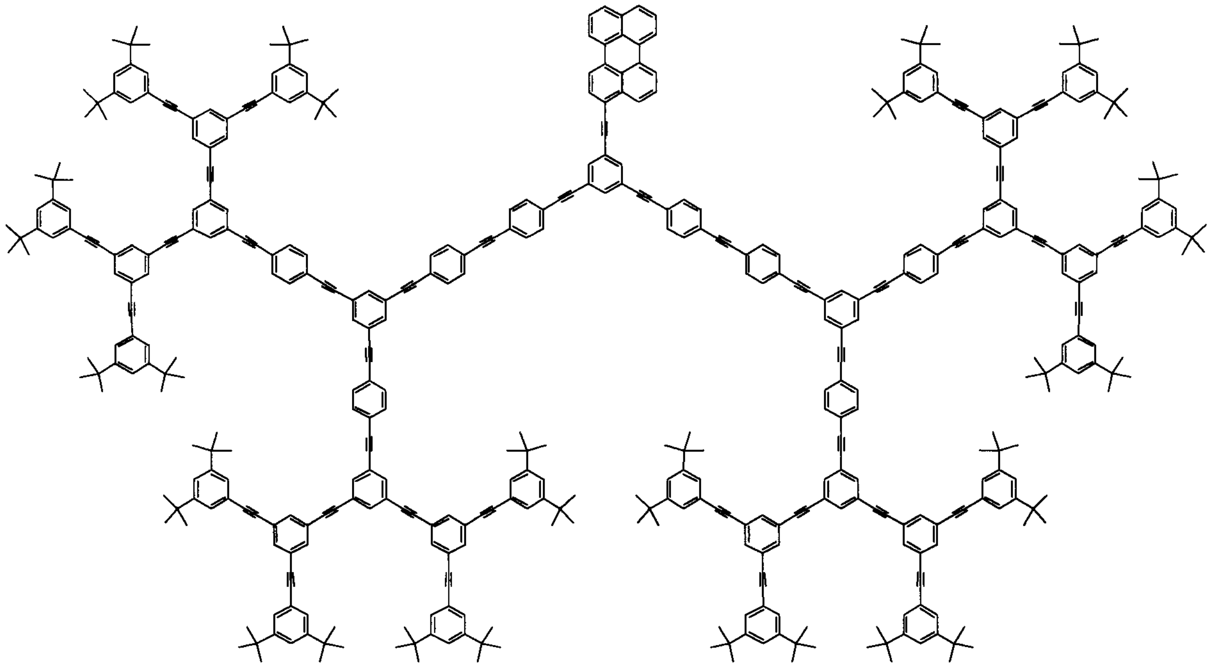

Fig. 11 Molecular antennae prepared by Moore *et al.* can funnel electrons to the focal point of the dendrimer

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