Functional Dendrimers: Unique Biological Mimics

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Dedicated to Professor Jack D. Dunitz on the occasion of his 75th birthday

Abstract: In the last five years, there has been increasing interest in the development of dendritic architectures which model specific aspects of biological function. This Concepts article describes how the shapes and structures of dendrimers with their three distinct environments (core, branched shell, and external surface) have been elegantly utilized to replicate or modulate processes known from biological systems. We describe how the dendritic shell can produce localized microenvironments analogous to those found at the active sites of enzymes, and we evaluate the progress made in the development of dendrimers for recognition and catalysis. Examples of controlled energy transfer through dendritic branches and of the construction of large supramolecular systems by self-assembly of dendritic subunits are presented. In particular, the article focuses on those dendrimers for which it has been clearly established that the branching plays an essential role in the creation and modulation of function.

Keywords: catalysis · dendrimers · energy transfer · molecular recognition · self-assembly

Introduction

Molecular architecture has always held a deep fascination for chemists, and this is perhaps one of the reasons why, in the past ten years, dendrimer chemistry has risen so rapidly to a position of international prominence.[1, 2] Initially, dendrimer chemistry was concerned with the development of suitable synthetic protocols to produce cascade molecules with a well-defined number of generations[1–3] and, in particular, with the problems associated with the isolation and characterization of these monodisperse macromolecules. In the last five years, however, the search for functional dendrimers has truly begun.[4] Of particular current interest is the discovery of specific functions and properties that are a direct consequence of the dendritic architecture. Dendrimers make unique biological models owing to their three-dimensional nanoscale structures, which can be synthesized in a controllable manner. They contain three topologically different regions (core, branches, and surface), each of which can exhibit functional properties modulated by the dendrimer as a whole.[5] This Concepts article focuses on dendrimers that model specific biological functions and in which the cascade architecture plays a truly active role in creating or modulating the desired property.

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Discussion

Modification of properties at the dendrimer core: In a key paper in 1993, Fréchet and co-workers first showed that dendritic branching could modulate physical properties at the dendrimer core.[6] They synthesized dendritic wedges of varying generational sizes, such as the generation 5 ([G-5]) derivative **1** (Figure 1), containing at the focal point a solvatochromic probe (a *p*-nitroaniline derivative), the UV/Vis absorption wavelength of which is dependent on solvent polarity. With increasing generation number and size of the dendritic wedge, the UV/Vis absorption band of the central chromophore in CCl_4 shifted to longer wavelengths. As the dendritic wedge expands, the solvatochromic probe is increasingly shielded from the bulk apolar solvent and the effective polarity in its surroundings increases, causing the observed bathochromic absorption shift. Such an effect was not observed when the bulk solvent was more polar, for example when Me_2SO was used. The authors also noted a discontinuity in the absorption band shift between third- and fourth-generation dendritic branching and argued that at this point the structure of their wedge became more globular, encapsulating the probe even more effectively, a proposal in agreement with previous viscosity measurements.[7] This result is of considerable importance as it indicates the existence of a distinct microenvironment inside a dendrimer, resembling those found in proteins. It is conceivable that large changes in pK_a of functional groups located inside dendrimers will eventually be measured, in analogy to the dramatically

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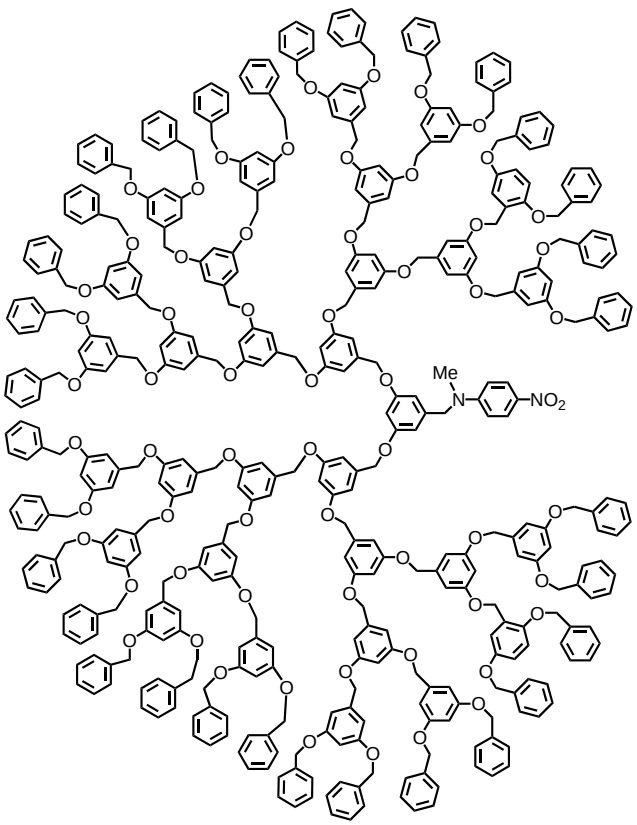

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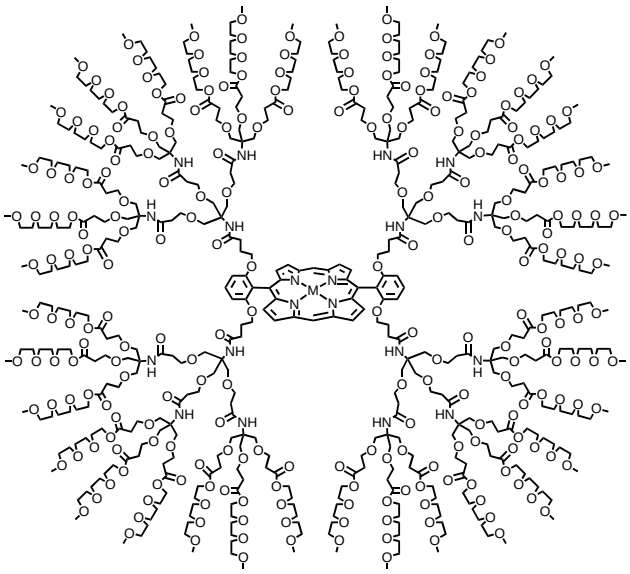
Figure 1. Fifth-generation ([G-5]) dendritic wedge (**1**) with a solvatochromic probe at the focus.[6]

altered pK_a values of amino acid side chains depending on their exact location inside proteins.[8]

Another remarkable example of the modulation of physical properties by an enzyme superstructure is provided by the electron-transfer proteins based on the heme Fe^{III}/Fe^{II} redox couple. The metal center in cytochrome *c*, for example, has an oxidation potential 300 – 400 mV more positive than that of heme model systems with similar metal ion ligation.[9] It is proposed that the hydrophobic polypeptide shell plays a critical role in controlling the redox behavior of the heme-bound metal ion. Diederich and coworkers have reported the water-soluble second-generation dendritic Fe^{III} porphyrin **2a** (Figure 2) as a cytochrome *c* model.[10] They investigated the electrochemical properties of **2a** and the corresponding smaller first-generation dendrimer in both CH_2Cl_2 and H_2O. Progressing from the [G-1] to the [G-2] derivative in CH_2Cl_2, the redox potential of the biologically relevant Fe^{III}/Fe^{II} couple remained virtually unchanged, whereas in aqueous solution, the [G-2] derivative **2a** exhibited a potential 420 mV more positive than the lower generation compound. The large difference between these potentials in H_2O was attributed to differences in solvation of the core electrophore. The relatively open dendritic branches in the [G-1] compound do not impede access of bulk solvent to the central core, whereas the densely packed dendritic superstructure of **2a** significantly reduces contact between the heme and external solvent. As a result, the more charged Fe^{III} state is destabilized



2a M = $Fe^{III}Cl$
2b M = Fe^{II}

Figure 2. The dendritic Fe^{III} porphyrin **2a** acts as a model system for cytochrome *c*[10] and the Fe^{II} derivative **2b** for hemoglobin.[37]

relative to Fe^{II} and the redox potential is strongly shifted to a more positive value. The dendritic model system **2a** is limited by uncertainty about the nature of axial ligation; work is currently in progress to synthesize a dendritic Fe^{III} porphyrin with covalently attached axial ligands.[11]

Other dendrimers with encapsulated redox-active metal centers have been reported.[12] Gorman et al. prepared dendritic iron – sulfur clusters such as the [G-2] derivative **3** (Figure 3).[13] As the dendritic generation increased, the core reduction potential in dimethylformanide solution became increasingly negative, an effect attributed to the increasing insulating effect of the dendritic shell. As was also observed for dendritic Zn^{II} porphyrins,[10a,c] the electrochemical reduction at larger cascade generations became less and less reversible on the cyclic voltammetric time scale, owing to the increasing kinetic difficulty of transferring electrons from the electrode to the core electrophore. Similar kinetic effects due to burial of the redox-active group are well established for cytochrome *c*[14] and other electron-transfer proteins.[15]

Tris(bipyridine) ruthenium(II)[16] has also been incorporated at the core of dendritic superstructures and investigated photochemically. The excited-state lifetimes of the higher generation compounds were found to be longer than those of their smaller analogues in aerated acetonitrile. It was proposed that the luminescence of the larger dendrimers was less efficiently quenched by O_2 because of either a) a decrease in diffusion rate constant of O_2 with increasing molecular volume, b) lower solubility of O_2 in the dendritic interior, or c) preferential solvation of the metal complex core by the dendritic branching.

These examples clearly demonstrate that the dendritic architecture can modulate physical properties at the core, and this effect can be considered as the creation of a dendritic

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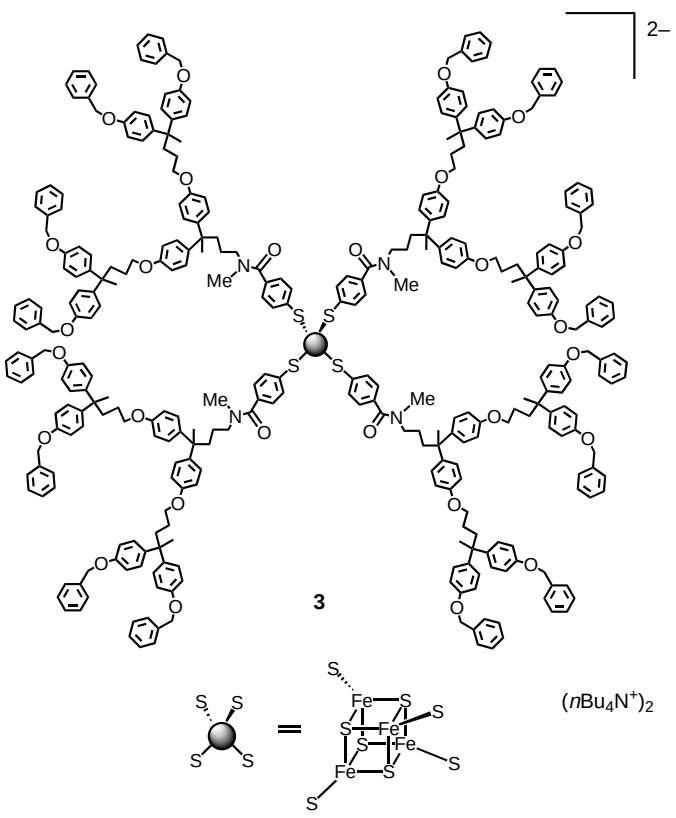

Figure 3. The cascade branching controls the redox properties of dendritically encapsulated iron–sulfur clusters such as **3**.[13]

microenvironment. The results indicate a versatile new approach to modulating and optimizing the reduction potential of redox catalysts by controlling the polarity of their environment using dendrimer technology. Attachment of dendritic shells, in particular by convergent growth methods, should find increasing future application in tuning the potential of electrophores for use as redox mediators in electrocatalysis or for performing specific tasks in advanced materials design. Such worthwhile developments would be encouraged on a broad basis if vendors of fine chemicals started selling tailor-made dendrons of various generations and polarity for attachment to electroactive cores. On the fundamental research side, the exact operating factors which are most important in controlling and shaping dendritic microenvironments must be rigorously clarified. Although significant changes in redox potential were measured in the examples discussed above, the potentials of other redox-active transition metals inside dendritic superstructures were hardly changed and the only observation was increased irreversibility of the electron-transfer processes at higher generations.[17] A more careful tailoring of the properties of dendritic wedges and the topology of the resultant dendrimers seems highly desirable in order to create still more specific environmental effects for use in electrochemical and photochemical devices.

Recognition with dendritic structures:[18] Ever since the inception of dendrimer chemistry, there has been considerable excitement about using such architectures for complexation with guest molecules.[19] All three topologically distinct regions (core, branching shell, and surface) of dendrimers can associate with suitable substrates, and the first examples of these distinctively different recognition events have emerged. Newkome et al. showed early on that water-soluble hydrophobic dendrimers act analogously to micelles and that these "unimolecular micelles" can encapsulate hydrophobic guests within their branches.[20] In a reversal of this strategy, a hydrophilic dendritic core with a fluorinated surface was recently used to extract hydrophilic dye molecules such as methyl orange from water into supercritical CO_2 by encapsulation.[21]

Meijer and co-workers prepared the fifth generation poly(propyleneimine) dendrimer **4** (Figure 4) and demonstrated its function as a "dendritic box" capable of retaining substrates trapped during synthesis and preventing them from diffusing outwards.[22] Molecules of different sizes, such as 7,7,8,8-tetracyano-*para*-quinodimethane (TCNQ) or the dye rose bengal were trapped during dendrimer synthesis; UV/Vis spectroscopy showed that rose bengal was encapsulated with an average of one molecule per dendritic box.[23, 24] Guest

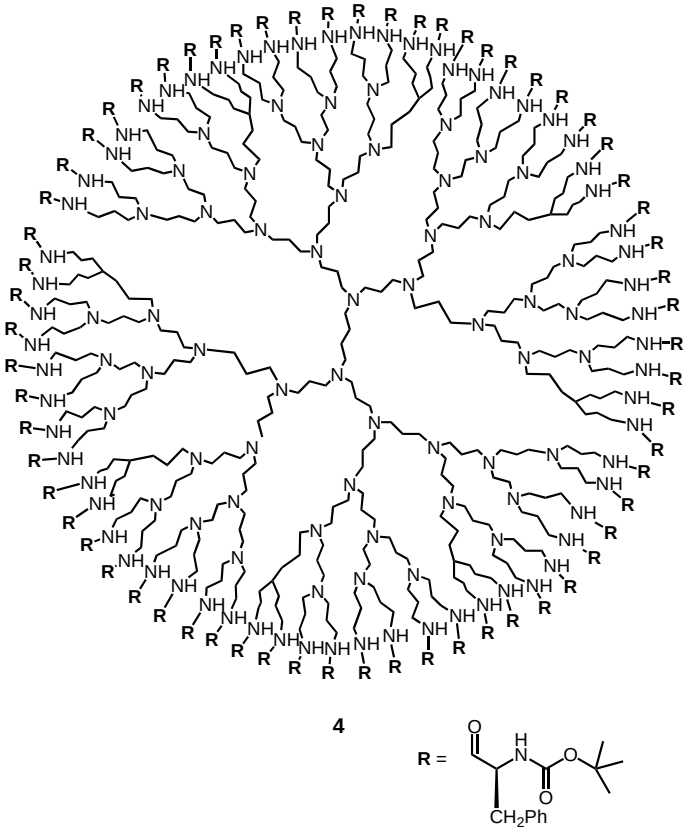

Figure 4. A dendritic box capable of trapping and encapsulating guest molecules during construction.[22, 23]

diffusion out of the box was slow since the dendrimer is closely packed with the branches spreading from a small initiator core; furthermore, the bulky, H-bonding surface groups pack tightly, preventing guest escape. If the *tert*-butyl surface groups were removed, guest molecules could diffuse out of the box, but only if they were sufficiently small.[23] Thus,

rose bengal remained in the box while *p*-nitrobenzoic acid leaked out. An appropriate dendritic surface can therefore control guest binding within a cascade molecule, which acts as a mimic for biological container and transport systems such as vesicles. Prospective uses of this fascinating research include transport and slow-release systems for drug delivery,[25] encapsulation of fluorescence markers for pores in the nanometer range, and control of the photochemistry and photophysics of single molecules isolated in dendritic containers.

It should be made clear, however, that the systems described above have no clearly defined binding unit within the dendritic structure such as would exist at the recognition site of an enzyme. One approach to dendrimers with defined recognition sites is to functionalize the dendritic surface or branches with multiple recognition sites, enhancing binding efficiency through simultaneous association with several substrates.[26] Research by the groups of Shinkai[27] and Astruc[28] has shown increased sensory responses to guest binding on a dendritic surface.

More relevant to enzyme mimicry are the water-soluble dendritic cyclophanes (dendrophanes) of Diederich and coworkers, which contain well-defined cyclophane recognition sites as initiator cores for the complexation of steroids[29, 30] or flat arenes.[29b, 31] Systems such as the [G-3] dendrophanes **5a** with a cyclophane core suitable for complexation of benzene and naphthalene derivatives or **5b** with a steroid-complexing cyclophane core mimic apolar binding sites buried within globular protein superstructures (Figure 5). They display the following characteristics:

a) The structurally well-defined cyclophane recognition sites at the centers of the dendrophanes remain open and effective at all dendritic generations ([G-1] to [G-3]). Thus, the dendrophanes form inclusion complexes of similar stability to those formed by the isolated initiator core cyclophanes. In all complexes, the substrates are located exclusively in the central cyclophane cavities and nonspecific incorporation into fluctuating voids in the dendritic shell is negligible.

b) Fluorescence titrations with the fluorescent probe 6-(*p*-toluidino)naphthalene-2-sulfonate (TNS) demonstrated that the micropolarity around the binding cavity was significantly reduced with increasing dendritic size. The micropolarity at the center of **5a** in water is comparable to that of ethanol.

c) The host–guest exchange kinetics observed for all dendrophanes are remarkably fast: ^{1}H NMR binding titrations, which rely on fast host–guest exchange ($k_{decompl} > 10^2$ to 10^3 s^{-1}), were possible with **5b**, whereas complexation by **5a** occurred on the NMR time scale. The fast host–guest exchange kinetics with **5b** were confirmed by fluorescence relaxation measurements with fluorescent steroidal substrates.[32] This contrasts with the findings for Meijer's dendritic box, but Meijer's system has a tight, densely packed superstructure diverging from a small initiator core, whereas the dendritic wedges in **5a** and **5b** are attached to large, nanometer-sized cyclophane cores producing apertures through which substrates can rapidly enter or leave the binding cavity. Furthermore, the Meijer dendrimer possesses H-bonding and sterically encumbering surface groups, whereas the carboxylates at the dendrophane surfaces will not densely pack for electrostatic reasons.

The reduced micropolarity at the cyclophane core and fast host–guest exchange kinetics make water-soluble dendrophanes attractive targets as catalytically active mimics of globular enzymes. Catalytic dendrophanes with active cyclophane initiator cores[33] shielded from the aqueous solution by the dendritic superstructure are now under construction; the target is the acceleration of reactions which benefit from a reduced environmental polarity. We are currently preparing a thiazolium-appended cyclophane for use as an initiator core in catalytic dendrophanes.[34] Reactions catalyzed by the cofactor thiamine diphosphate or thiazolium model systems are favored in media of reduced polarity, since the transition states are less polar than the ground states and are therefore stabilized in such environments.[35] We hope that such catalytic dendrophanes will illustrate the ability of the dendritic superstructure to enhance supramolecular catalysis by reducing the core micropolarity.

The axial ligation of small ligands to dendritic heme metal centers has also attracted significant interest.[36, 37] In particular, dendritic iron porphyrins have been successfully studied as hemoglobin mimics by the groups of Aida[37] and Collman and Diederich.[38] In systems such as **2b** (Figure 2), the dendritic cage prevents the formation of porphyrin μ-oxo dimers,[38] and highly efficient reversible O_2 complexation occurs in the presence of imidazole ligands in toluene solution. Both hemoglobin and picket-fence porphyrin[39] complex CO in preference to O_2, but the reverse is true for the dendritic system **2b** which, in the presence of 1,2-dimethylimidazole, exhibits an affinity for O_2 12 times higher than that for CO. The affinity of **2b** for O_2 is exceptionally high, and it was suggested that a proximate amide NH group in the dendritic shell may form a hydrogen bond to the terminal atom of the dioxygen molecule bound in a bent fashion to the Fe^{II} center. The low affinity for CO, on the other hand, was explained by steric hindrance by the dendritic branches, which prevent CO from binding to Fe^{II} in the energetically most favorable linear fashion. Additional work is now under way to test these hypotheses further and to clarify the origin of the exceptionally high O_2 affinity. Therefore, dendrimers similar to **2b** but lacking amides or other H-bond donors are being prepared; they should display a much reduced O_2 affinity if hydrogen bonding contributes substantially to the stabilization of the O_2 complex formed by **2b**.[40] Another prospect for the future is the exploration of the NO-binding capacity of dendritic Fe^{II} porphyrins.

An area in which we foresee important developments in the future is the dendritic modulation of hydrogen-bonding receptors[26b, 41] to bind polar substrates in competitive solvents such as water. Whereas hydrogen-bond recognition of small molecules in water by synthetic receptors has been remarkably inefficient in the past, it can be expected that the reduced polarity inside water-soluble dendrimers will strengthen hydrogen bonding enough to allow complexation to occur. Water-soluble dendritic receptors incorporating well-defined H-bonding sites at the core for amino acids[42a] or carbohydrates[42b] are currently under preparation in our laboratory; we expect not only that they will promote host–

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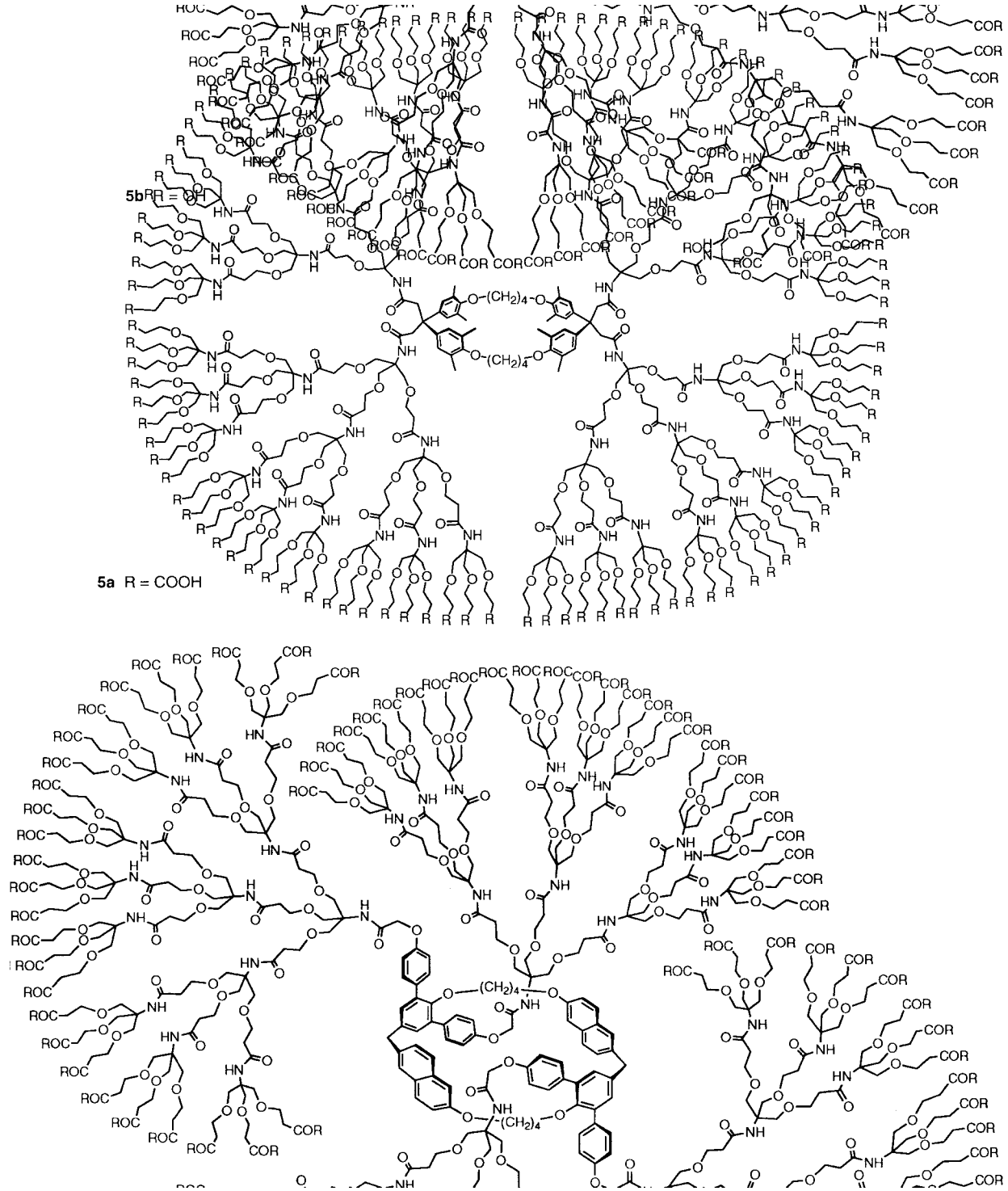

Figure 5. The [G-3] dendrophanes **5a** and **5b** contain buried cyclophane cores suitable for the recognition of flat arenes[31] and steroids,[29] respectively.

guest complexation through stable H-bonds, but also that the dendritic shell should provide energetically favorable hydrophobic desolvation in addition to numerous van der Waals contacts. Subsequent developments will target the construction of optically active dendrimers for chiral molecular recognition. Chirality in dendritic architecture has already excited considerable interest[43] and has been the subject of a previous Concepts article.[44]

Another area of current and future activity concerns the recognition of dendritic surfaces by large biomolecules. Attractive candidates for such developments are dendrimers coated with carbohydrates on their exterior surfaces. The synthesis and properties of carbohydrate-containing dendrimers have been discussed in a recent Concepts article by Stoddart and co-workers[45a] and in other reviews.[45b,c] Glycodendrimers could be recognized by adhesion proteins such as selectins and ultimately provide antiadhesive drugs; they could also find application in the production of carbohydrate-based vaccines.[45]

Dendritic catalysts: There are two justifications for the synthesis of dendritic catalysts. Firstly, there is the possibility of creating large dendrimers with many active sites. Such systems may be intermediate between heterogenous and homogenous catalysts, with ready removal of the catalyst by filtration.[46] Secondly, there is the possibility of encapsulating a single catalytic site whose activity and selectivity becomes modulated or enhanced by the dendritic superstructure.[47] If the dendritic catalytic site also provides for reversible substrate binding prior to reaction, supramolecular enzyme-like catalysis will result; this is the aim of the catalytic dendrophanes discussed above.

There have been a number of reports on representatives of the former class of dendritic catalysts.[48] Ongoing research is aimed at providing a convincing practical demonstration of the obvious advantages that such catalysts containing multiple active sites could possess. Careful design is required, however, to yield dendritic catalysts with distinct advantages such as facile recycling or cooperativity between catalytic centers.

The "dendrizymes" reported by Brunner were among the first dendritic catalysts to model enzymes, with an organometallic active site buried in the branching.[47] Generally, rates were decreased by dendritic branching and enantioselectivities in asymmetric catalysis were very low. In one case, however, a modest favorable effect of the branching on catalytic activity was observed. In the enantioselective cyclopropanation of styrene with ethyl diazoacetate to give *cis*-ethyl 2-phenylcyclopropanecarboxylate, the catalyst was Cu^{I} triflate modified by optically active pyridinealdimines.[47, 49] In the absence of branching on the pyridinealdimine derived from (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol, asymmetric induction was close to zero (2% enantiomeric excess (*ee*)). The same transformation in the presence of dendritic pyridinealdimine **6** (Figure 6), with branches derived from (1*R*,2*S*)-ephedrine, however, gave an enantioselectivity of 10% *ee*, which can be rationalized in terms of differential steric effects from the chiral branches.

Dendritic steric effects were also observed by Suslick and co-workers in epoxidations catalyzed by dendritic manganese porphyrins as models for cytochrome P-450 enzymes.[50] In analogy to bulky groups in proximity to the catalytic center, the dendritic branching inhibited the epoxidation of sterically demanding alkenes and enhanced the selectivity of the catalyst. Mak and Chow reported cleft-type dendritic bis(oxazoline)metal complexes such as **7** (Figure 7) for use as catalysts in the Diels–Alder reaction.[51] The reaction of two differently sized dienophiles was investigated, and the dendritic catalyst showed a slightly enhanced ratio of initial reaction velocities, with reaction of the smaller dienophile being less hindered by the branching.

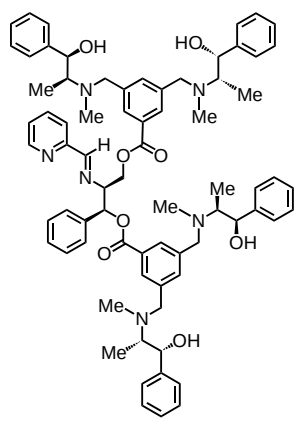

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Figure 6. Dendrizyme **6** shows a small, dendritically enhanced enantioselectivity in the cyclopropanation of styrene with ethyl diazoacetate catalyzed by Cu^{I} triflate.[49]

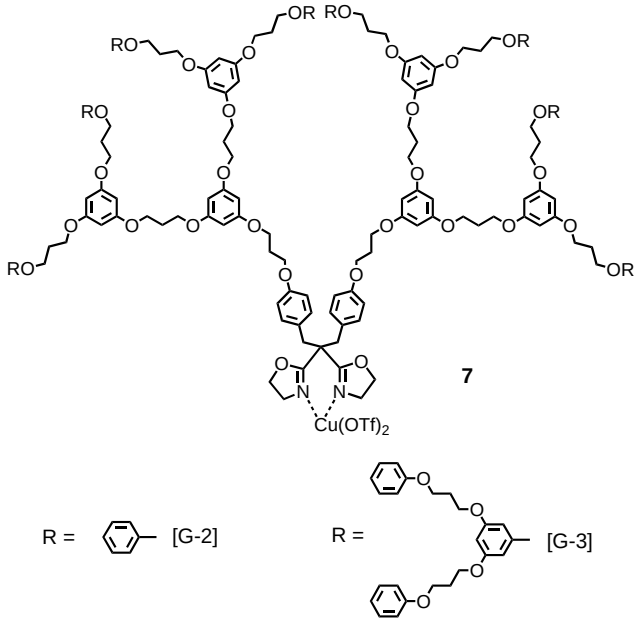

Figure 7. A dendritic catalyst for the Diels–Alder reaction.[51]

Other dendritic catalysts have been reported[52] but it is proving difficult to clearly establish any role for the dendritic branching other than purely steric effects. It is clear that the next generations of dendritic catalysts require careful design in order to endow them with additional positive attributes such as electronic activation and transition state stabilization by the specific branching environment around the catalytic center.

Energy transfer through dendritic structures: The treelike structure of a dendritic wedge naturally suggests itself as a

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molecular antenna suitable for transfering energy or electrons from the multitopic surface to the dendron focus. Excitation energy plays an important role in natural phenomena such as photosynthesis, in which carotenoids act as antennae and absorb solar radiation in a spectral region where chlorophyll only absorbs weakly, subsequently transferring this energy to chlorophyll by singlet–singlet energy transfer.[53] Using dendrimers to model such energy transfer processes may yield a better physical understanding of this crucial biological event.[54]

The research of Moore and co-workers has been particularly elegant. They reported a series of rigid polyaromatic ethyne-linked dendritic wedges with a fluorescent perylene chromophore at the focus.[55] When the dendrons were irradiated at 310 nm (absorption band of the dendritic branching), the perylene chromophore emitted at 484 and 518 nm with quantum yields up to 98%. This indicates that singlet–singlet energy transfer occurs in the wedge. The light-harvesting ability increased with increasing generation, while the efficiency of the energy transfer decreased. Dendron **8** (Figure 8) was especially interesting; it contained an inbuilt energy gradient obtained by using phenylacetylene spacers increasing by one repeat unit proceeding from the periphery to the core. This design means that the levels of the localized electronic states decrease smoothly in energy from the exterior to the interior, creating a directional energy flow. This dendron was compared with analogous systems without an energy gradient, and its rate of energy transfer was two orders of magnitude faster.

The research groups of Balzani[56] and Constable[57] have used a metal-based approach to the problem of dendritic light-harvesting systems, based on Ru^{II} and Os^{II} bi- (and ter-)pyridine subunits. In particular, Balzani and co-workers stress the tunability of their dendritic structures, with the incorporation of different metal ions and ligands in unique environments being possible.[56]

Polyaromatic ether wedges have also been used to transfer energy and electrons.[58, 59] Thus, Jiang and Aida used a dendritic superstructure to harvest low-energy photons and provided evidence that this energy converted a *cis*-azobenzene at the dendritic core to its *trans* form.[60, 61] It seems clear that this last study shows the way forward for efficient energy-harvesting dendritic superstructures. The antennae must be coupled to functional units and the energy used to drive chemical processes, perhaps even catalysis. In this way, these novel dendritic systems will form useful, light-driven molecular machines.

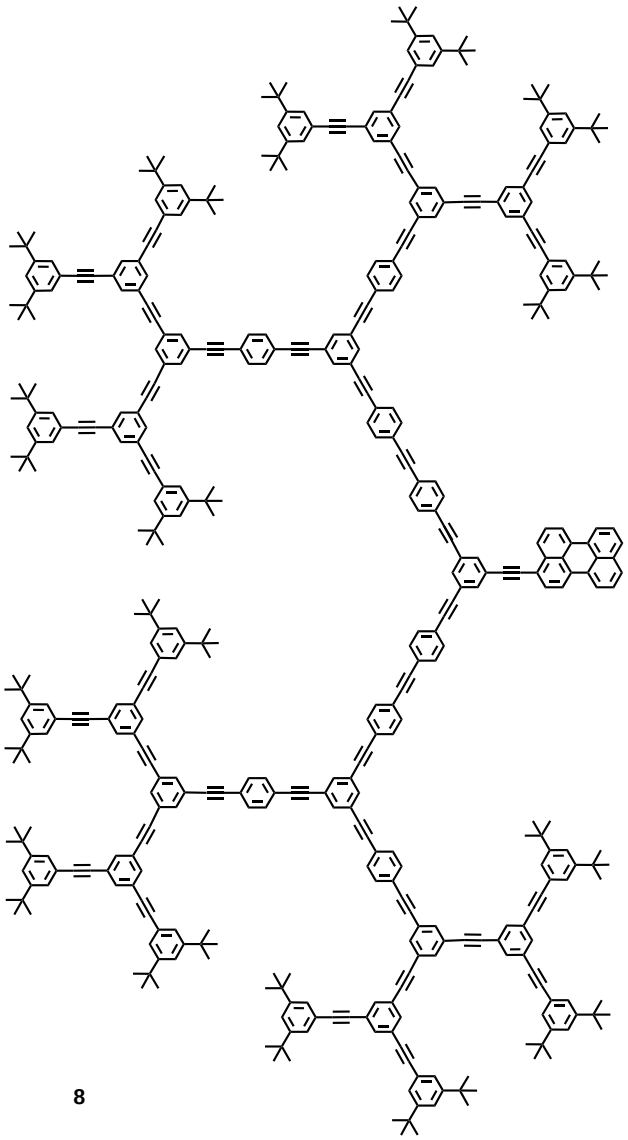
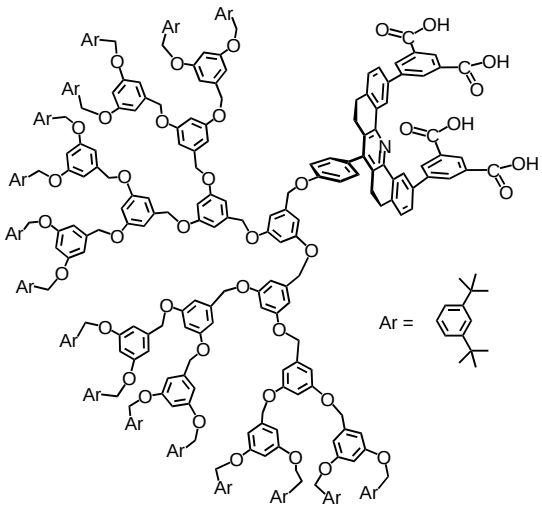


Figure 8. In dendritic wedge **8** with an inbuilt energy gradient, energy is efficiently transfered from the peripheral branches to the perylene group at the focus.[55b]

Assembly of dendrimers to form higher molecular architecture:[18] One function of biological systems arousing substantial current interest is self-assembly.[62] It is therefore a natural development that dendrimer chemists should begin to turn to self-assembled arrays of dendrimers to address new properties and functions.

The first reports of self-assembled dendritic structures generally focused on the association of hydrophobic subunits in aqueous solution.[63, 64] Zimmerman and co-workers, however, described a discrete hexameric structured assembly of dendritic wedges (**9**, Figure 9) which was held together by directional COOH···COOH hydrogen-bonding interactions.[65] The stability of this dendritic supramolecular aggregate was dependent on the generation of dendrimer used to form the assembly. For the smallest dendritic wedge, the hexameric array was unstable and it was argued that this was due to its ability to form linear aggregates instead. Such linear aggregation is not possible once the dendritic wedges become larger, because of buttressing effects, and the hexamer becomes the more stable aggregate. In this way, the dendrimer controls the assembly process.

One application of assembled structures is the exploitation of their liquid crystalline properties. Initially, the approach to dendritic liquid crystals was either to functionalize a dendritic surface with multiple mesogens[66] or to incorporate long mesogenic branching groups into the dendritic structure.[67] Recently, however, Pesak and Moore prepared columnar liquid crystals from a planar shape-persistent dendritic molecule containing a phenylacetylenic core.[68] In contrast



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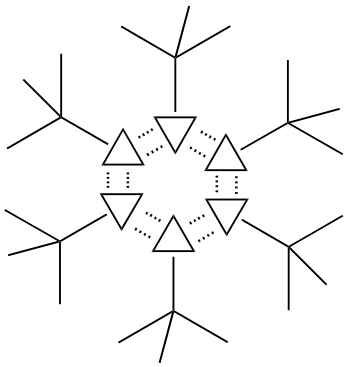

Hexameric aggregate

Figure 9. The dendritic wedge **9** self-assembles by H-bonding in noncompetitive solvents to form a hexameric adduct.[65]

to previous systems, these planar dendrimers are intrinsically mesogenic, that is, they do not depend on the incorporation of discrete mesogenic units for their liquid crystallinity.

It seems certain that many fascinating dendritic assemblies will be reported in the coming years. Such assembled systems may eventually incorporate functional groups suitable for molecular recognition and catalysis. As in biology, supramolecular dendritic assemblies will display distinct functions and properties that are absent in the individual molecular building blocks. The assembly of complementary dendritic subunits with different structures and functions, similar to membrane-bound protein arrays, represents another frontier of these developments.

Conclusions

The difficulty of keeping this Concepts article short is testimony to the huge interest in the use of dendritic architectures as biological mimics. The rapid progress made by dendrimer technology during the past years is impressive. In particular, the various specific effects which the dendritic architecture can bring to bear on function are becoming ever clearer, and it is to be expected that in the near future dendrimers will become increasingly prized for their intriguing and unique properties.

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