1
Introduction

1.1
Historical – Cascade molecules and dendrimers

In 1978 Vögtle *et al.* [1] described a series of synthetic "cascade molecules" [2–4] as the first tangible representatives of compounds exhibiting potentially perpetual branching. Starting from diverse primary monoamines and diamines, "cascade synthesis" was performed to attach spacer units of propylenamine structure whose N atoms served as a $1 \rightarrow 2$ branching point (formal branching of a bond into two new ones) during each subsequent repetitive step [5].

In the simplest case, reaction of a primary *mono*amine *via* a two-fold Michael reaction with acrylonitrile (bis-cyanoethylation) led to the *dinitrile* (Fig. 1.1). Subsequent reduction of the two nitrile functions – by hydrogenation with sodium borohydride in the presence of cobalt(II) ions – afforded the corresponding terminal *diamine*. Repetition (iteration) of this synthetic sequence, consisting in Michael addition followed by reduction, provided the first – structurally variable – access to regularly branched, many-armed molecules.

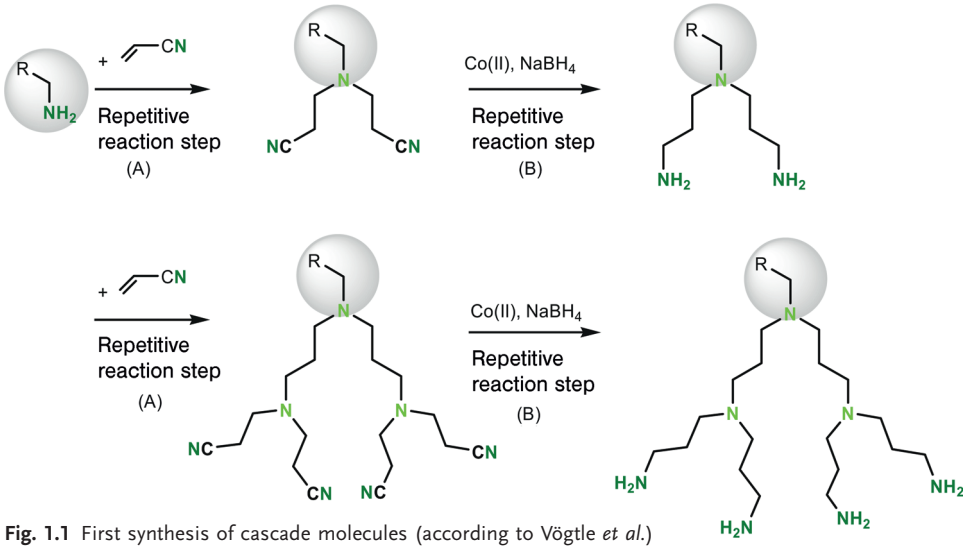


Fig. 1.1 First synthesis of cascade molecules (according to Vögtle *et al.*)

Dendrimer Chemistry. Fritz Vögtle, Gabriele Richardt and Nicole Werner

ISBN: 978-3-527-32066-0

Several years earlier (1974), the same group had already described many-armed, albeit non-branched, molecules as *octopus molecules* [6], whose numerous arms were used for complexation with metal ions (Fig. 1.2). These octopus molecules can be regarded as forerunners of nitrogen-containing propylenamine cascade molecules since they already demonstrated the utility of many adjacent functional arms – all the more readily attainable by branching – for example for host-guest interactions [6].

Initially, further development of highly branched (cascade-type, dendritic) molecules proceeded slowly for many years, probably due to the synthetic and analytical obstacles to be overcome at the time with these species, which occupy an intermediate position at the boundary between low-molecular weight and high-molecular weight compounds.

Denkewalter *et al.* described a pathway to polylysine dendrimers (Fig. 1.3) *via* divergent synthesis in 1981 patents (see Section 2.1) [7].

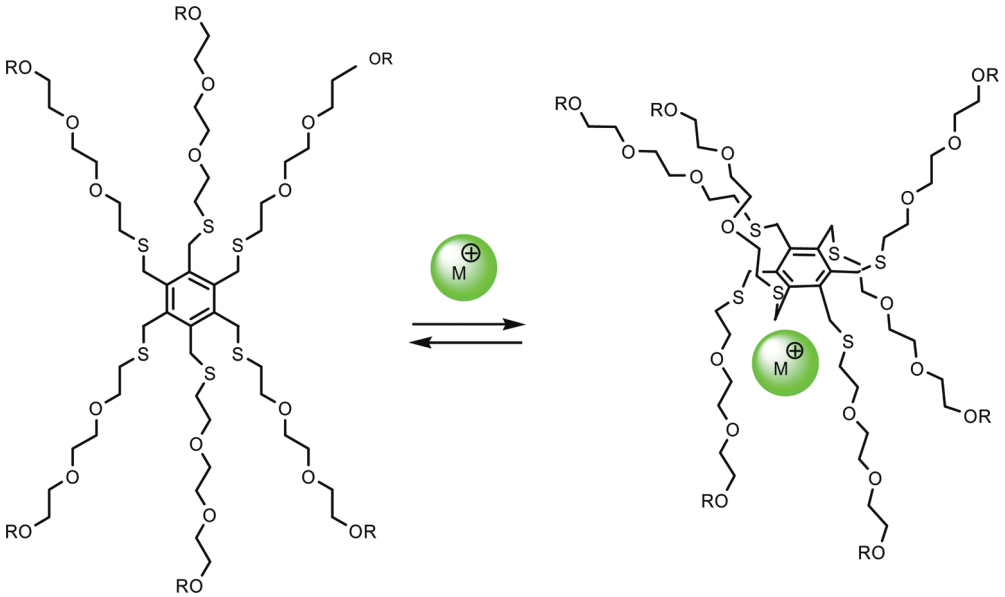


Fig. 1.2 Octopus molecule (left): host-guest interaction with metal ions (schematic; according to Vögtle, Weber)

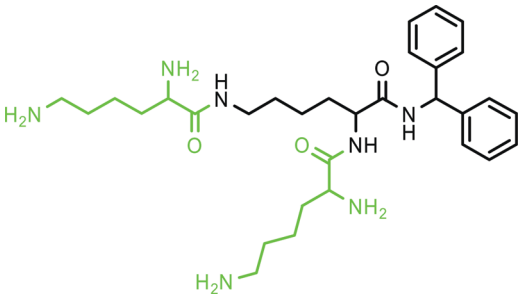


Fig. 1.3 Polylysine dendrimer (according to Denkewalter *et al.*); the two peripheral lysine units are shown in green

In 1982 Maciejewski developed a densest packing concept for polymers having a cascade-like structure [8]. On the basis of statistical considerations, in 1983 de Gennes (1991 Nobel laureate for physics) and Hervet presented limits to the growth of branched molecules (*starburst-limited generation*), paying due attention to the influence of steric hindrance [9]. Further statistical model calculations were combined with the "cascade theory" [10]. According to de Gennes, highly branched molecules are considered as "soft material" [11].

In 1985 Tomalia developed branched *poly*(*ami*do*ami*nes) (PAMAM), which he also designated as "starburst dendrimers" (Fig. 1.4) and generally propagated the name "dendrimer" (from the Greek *dendron* = tree and *meros* = part) [12]. Like the first cascade synthesis, the synthetic route again involved Michael addition (of methyl acrylate to ammonia). The resulting ester was converted into the primary triamine by reaction with an excess of ethylenediamine. Repetition of the reaction sequence (iteration) by analogy with the cascade synthesis led to dendrimers of up to the tenth generation – with decreasing purity and perfec-

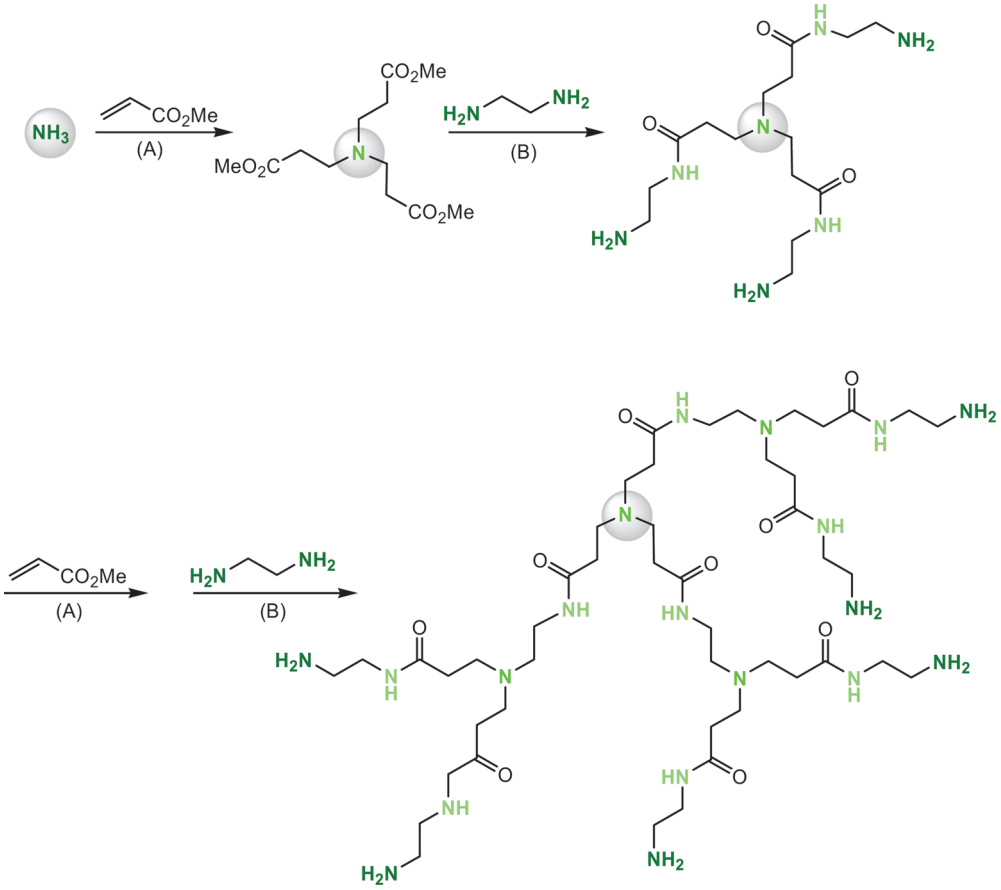


Fig. 1.4 Synthesis of poly(amidoamine) dendrimers (PAMAM; according to Tomalia *et al.*)

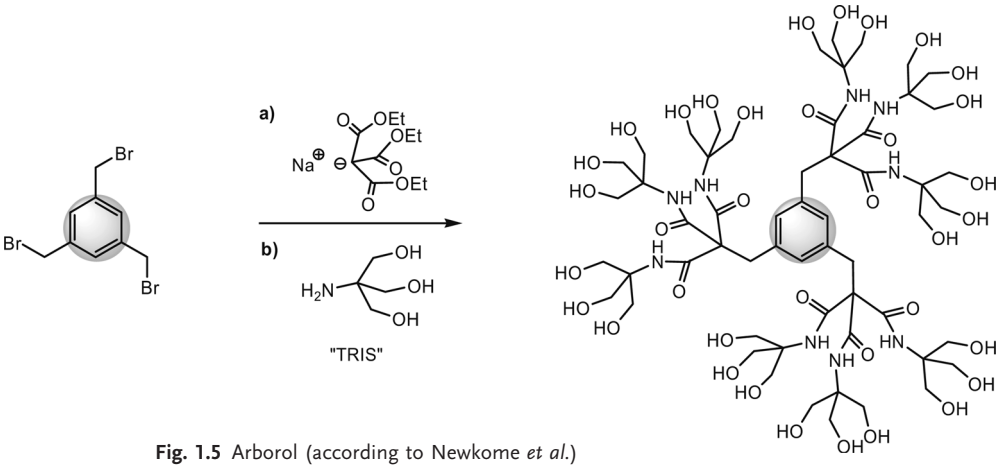


Fig. 1.5 Arborol (according to Newkome *et al.*)

tion (see Section 1.3). Tomalia referred to the individual ester stages as half generations (0.5, 1.5, 2.5) [13].

Also in 1985, Newkome *et al.* presented a divergent synthetic route to water-soluble, highly branched "arborol systems" (Fig. 1.5) with terminal hydroxyl groups, whose name is derived from the Latin *arbor* = tree [14].

Tomalia's exhaustive review paper with coloured illustrations [10] did much to popularise the highly branched compounds and to ensure broad general acceptance of the family name "dendrimers". In the same year, Fréchet and Hawker described the first convergent synthesis of dendrimers. They constructed poly(aryl ether) architectures "from the outside inwards" (Fig. 1.6; see Section 2.2) [15].

Miller and Neenan succeeded in the very same year in producing the first hydrocarbon dendrimers based exclusively on arene units, also using a convergent synthetic strategy [16] (Fig. 1.7).

In this introduction, the history of dendritic molecules is limited to initial developments. It also warrants mention that theoretical considerations of infinite (polymer) networks by Flory can be traced back to 1941 [17].

Further pioneering work and workers in the field of dendrimers will be mentioned in Chapters 2 and 4, which also consider more recent developments relating to synthetic methods and types of dendrimers.

The exponential growth and topicality of research into dendritic molecules almost thirty years after their first synthesis (1978) is apparent not only from the large number of publications (presently totalling more than 10 000, and increasing by more that 1000 per annum, plus about 150 patents), but also from the mere fact that more than 8000 researchers are currently active in this area and more than 150 companies have already applied for patents relating to dendritic compounds (source: IDS-5 Programme).

The Dendrimer Symposia which have been held biannually since 1999 also reflect this development: The first *I*nternational *D*endrimer *S*ymposium (*IDS-*

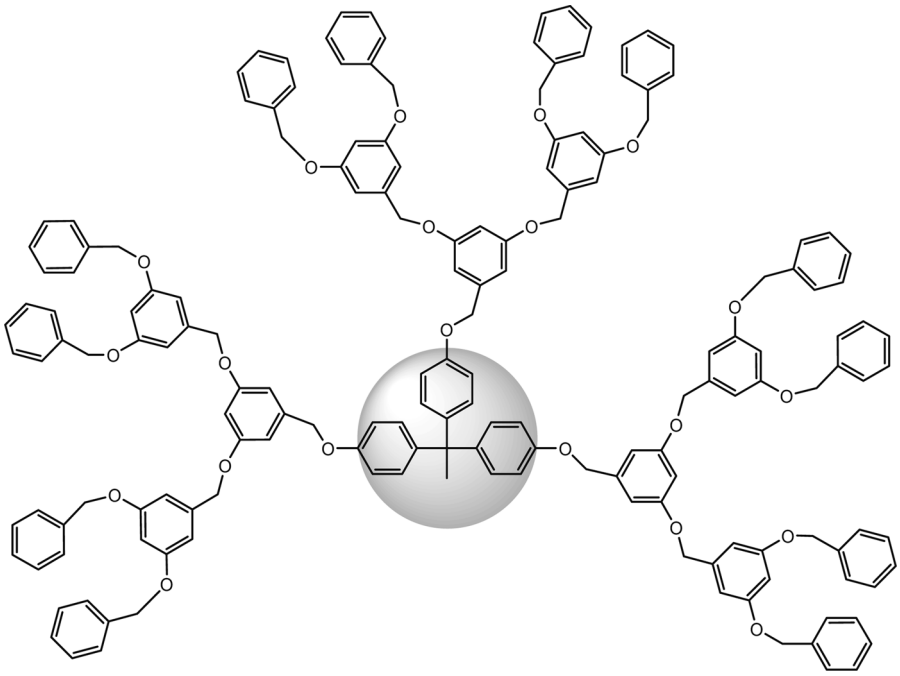


Fig. 1.6 Fréchet dendrimer

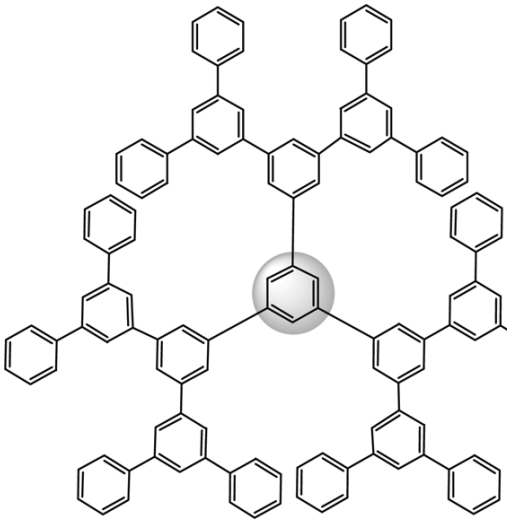


Fig. 1.7 Hydrocarbon dendrimers (according to Miller and Neenan)

Fig. 1.8 Flyers and logos of the first four Dendrimer Symposia held at: *Frankfurt*, 1999 (Organisation: F. Vögtle, K. Müllen, DECHEMA); *Tokio*, 2001 (Organisation: T. Aida, M. Ueda, DECHEMA); *Berlin*, 2003 (Organisation: A. Schlüter, F. Vögtle, E. W. Meijer, A. Hult, DECHEMA); *Michigan*, 2005 (Organisation: D. Tomalia, J.-F. Stoddart, F. Swenson, J. F. Fréchet); (*IDS-5: Toulouse*, 2007 (Organisation: J.-P. Majoral, A.-M. Caminade))

1), initiated by Vögtle and Müllen, was held in 1999 at Frankfurt/Main under the auspices of DECHEMA (Fig. 1.8). 183 participants from 21 countries gathered together to discuss the design, synthesis, structures, analysis, and applications of dendritic molecules [18].

At the second International Dendrimer Symposium emphasis was placed, among other topics, on the multiplication of functional groups on the periphery of dendritic molecules with a view to enhancing physical and chemical effects. Moreover, the inclusion of guest species was also discussed from the standpoint of supramolecular chemistry. The guests considered also included active substances (*e.g.* cytostatics), which can be specifically released from the "embrace" of the dendrimer at certain target sites in the organism (*drug targeting; drug release;* see Chapter 8).

The third International Dendrimer Symposium took place at Berlin Technical University in 2003. Interdisciplinary lectures demonstrated the extent to which dendritic molecules "branch out" into other areas of science, such as physics, biology, medicine, and engineering. The possibilities of functionalisation and resulting applications in industry were at the focus of this symposium. For example, nano-dimensioned dendrimer-based contrast agents were presented as *multilabels* for visualisation of blood vessels (see Chapter 8). Potential applications of dendritic materials as luminescence markers in diagnostics attracted lively interest (see Chapter 8). Consideration of the differences between dendrimers and hyperbranched polymers from the viewpoint of their cost-favourable application was also a topic of discussion [18].

At the fourth International Dendrimer Symposium held in 2005 at Mount Pleasant, Michigan/USA with 81 international speakers, the main emphasis was placed on the potential applications of dendritic molecules. This was apparent not least from the strict categorisation of the lectures according to possible

commercial applications as (nano)materials (displays, optical sensors) or in medicine (see Chapter 8). The fifth International Dendrimer Symposium in 2007 at Toulouse was dominated by the topics synthesis, nanomaterials and in particular by the development of dendritic therapeutics [18 b].

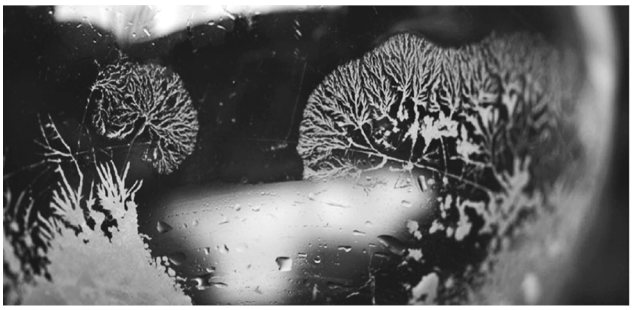
1.2 Dendritic architectures

The name dendrimers, which has meanwhile largely displaced the original designation of *cascade molecules*, is derived from the Greek words *dendron* and *meros*, and is meant to underscore the tree-like branched structure of this class of compounds (see Section 1.1).

Multiply branched (dendritic) structures are frequently encountered in nature, science, technology, art, and everyday life. Examples of naturally occurring dendritic structures are seen in the branching of trees and roots (Fig. 1.9), blood vessels, nerve cells, rivers, lightning, corals, and snowflakes [19 a]. Metals deposited on electrodes or on noble metals [19b] often exhibit branching, as do fibres and gels [20] The bottoms of geckos' feet bear millions of multiply split thin hair ends, permitting them to climb up walls and cross absolutely smooth ceilings [21 a, b]. On the basis of this model – and that of flies, spiders, and other animals – a peelable adhesive was developed at the Max Planck Institute for Metals Research in Stuttgart, which could replace refrigerator magnets, for example [21 c]. Evolution itself can be depicted dendritically [21 b, 22–23]. Many-armed deities play a special role in some religions. A room divider that can be individually shaped and joined up to form a network structure has been launched on the market [24]. Zone maps of underground railways show dendritic patterns.

Fractals are mathematically defined self-similar structures (Fig. 1.11) [26]. The *scaffold* of cascade or dendritic molecules is fractal if the atoms are considered to be points and the bonds to be strictly one-dimensional lines. Self-similarity

Fig. 1.9 Dendritic structures in nature: Branching of trees, before and after hosting of "guests" (mistletoe) in the intermediate spaces [25 a]



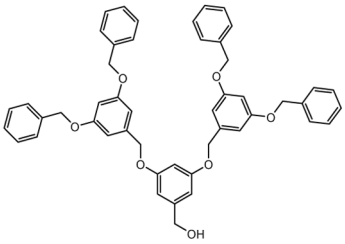


Fig. 1.10 Substance crystallising in dendritic patterns [25 b] (Fréchet dendron of the second generation)

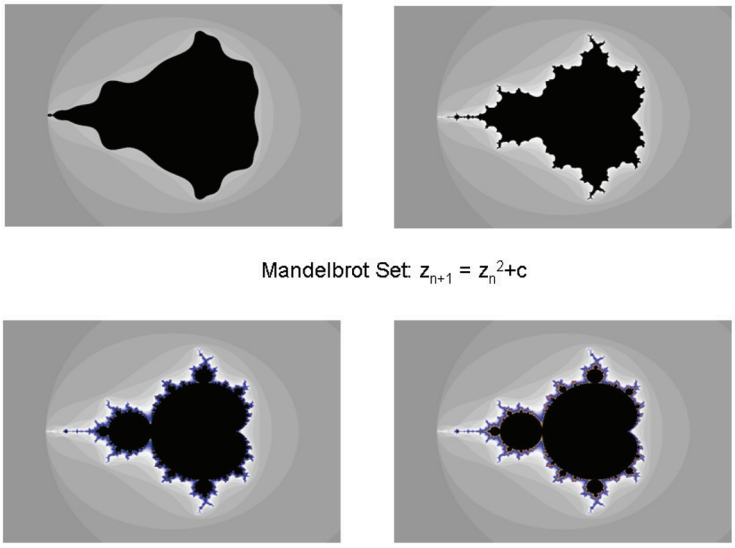


Fig. 1.11 Fractal structures (computer generated) [28]: The four parts of the figure (from left to right) show a series of Mandelbrot sets [26] after 5, 10, 50, and 150 iterations. The intermediate result serves as the starting point for each iteration. (The individual images were produced in colour, but could only be presented in modified form here)

means that structural elements are repeated on different scales. While the self-similarity of the mathematically calculated constructions in Fig. 1.11 may not be immediately apparent, the principle is readily illustrated with the aid of the Sierpinski triangle [27]. Joining the mid-points of the three sides of the equilateral triangle shown on the left of Fig. 1.12 produces another equilateral triangle reduced in size by a factor of 1/4 compared to the original triangle. Removal of this new triangle leaves the middle figure of Fig. 1.12. Application of this procedure to the middle figure affords the right-hand figure. Each repetition of the procedure results in a new generation of the Sierpinski triangle. The starting figure is called the first generation.

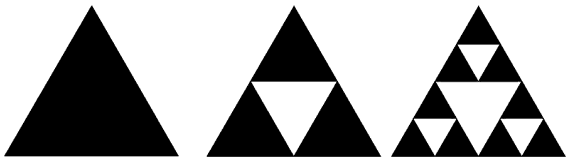


Fig. 1.12 Principle of self-similarity, demonstrated by the first three generations of the Sierpinski triangle

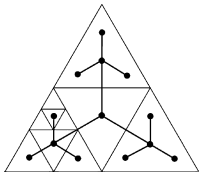


Fig. 1.13 Modified (dendritic) representation of Sierpinski triangle

If the graphical representation of the Sierpinski triangle is modified by drawing the triangles not as geometric bodies but only as lines joining the centroids of the triangles removed, then Fig. 1.13 results. The dendritic branching is now readily recognised and it is apparent that the total length of the branches increases with each new generation.

If a three-dimensional body such as a tetrahedron is substituted for the two-dimensional triangle, the branching sites lie on the surface of an imaginary sphere. This accounts for the shell-like structure of dendrimers.

Dendrimers are molecular (nano)architectures of well-defined size and number of terminal groups. Starting from a multi-functional core unit, the structure branches – often in regular layers (shells) resembling onion skins – in three dimensions from the inside outwards. These *generations* can serve to characterise the molecular size – within a given type of dendrimer. The branched structures linked in the form of segments to the central unit are termed *dendrons*. The end groups, which may in turn be "terminal functional groups", are located on the – formal – surface of the dendrimers, which is often designated as the periphery (Fig. 1.14). Given a conformationally flexible dendrimer with largely aliphatic skeleton, these terminal groups will, however, often be folded back into the interior of the molecule and therefore form neither a homogeneous outer shell nor well-defined free pores (see Section 7.6.3.2).

Depending upon the nature of the terminal groups, the dendrimers will vary in shape, stability, solubility, conformational rigidity/flexibility, and viscosity. The number of end groups of desired functionality increases with increasing number of generations. This can lead to reinforcement of certain phenomena, such as light-harvesting effects (Chapter 5), or also – as described in Chapter 8 – to an *amplification effect*. Within certain limits, appropriate design and synthesis of a dendrimer thus permits certain properties to be modified or possibly tailored to requirements.

Owing to their self-similar (fractal) structure, the number of terminal groups of a dendrimer of any generation can be calculated with the aid of the following equation:

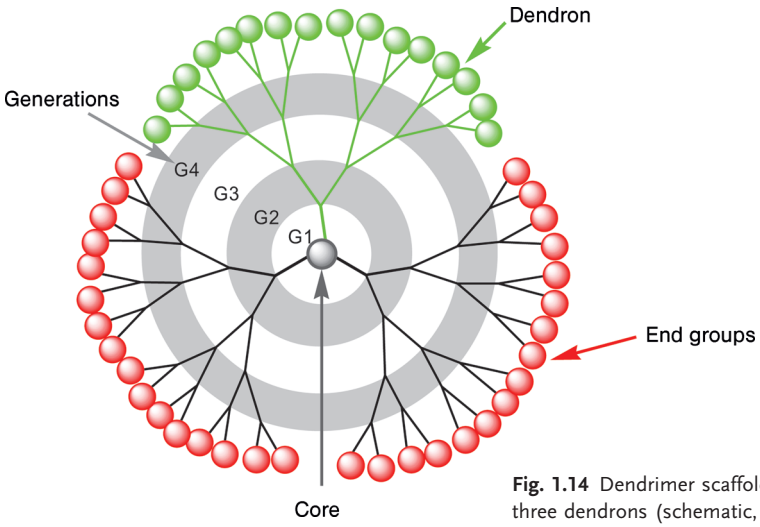


Fig. 1.14 Dendrimer scaffold – with three dendrons (schematic, idealised)

$$n_G = F_k(F_v - 1)^G \tag{1.1}$$

n_G: number of end groups in the G-th generation
F_k: functionality of the core (= number of bonds emanating from the core)
F_v: functionality of branching unit (number of bonds emanating from a branching point)
G: generation of the dendrimer

This equation ultimately expresses no more than the fact that the number of terminal groups increases as a function of the number of (former) functional groups of the core (core multiplicity) and that of the branching units (branching multiplicity) rises exponentially with the number of generations.

The mechanical stability of a dendrimer depends upon the conformational flexibility/rigidity of the branching units and the end groups. Modification of the branching units leads to a change of density in the interior of the dendrimer molecule. This is important for the host/guest chemistry considered in detail in Section 6.2, which makes use of areas of lower density to accommodate guests. The dendrimer skeleton acts here as a kind of – reversible – "dendritic box". Appropriate choice of the branching modules permits selective inclusion of guest molecules – apart from solvent – in a dendrimer, without any need for preformed *vacant* cavities or niches.

The oligo- or multi-functional core unit also plays a role in determining the space occupied by a dendrimer. The core itself can exercise a function, as demonstrated by metallodendrimers (see Section 4.1.11), in which the metal ion core in a supramolecular or coordinatively constructed architecture coordinates with the surrounding branching units – and in this way can influence catalytic and photochemical processes.

The ways in which the individual structural units of a dendrimer can affect its properties are compiled in Table 1.1.

A specific feature of dendritic molecules is that they show a lower viscosity in solution than corresponding compounds with a lower degree of branching. This behaviour is characterised by the Staudinger index η (dimensions mL/g) determined by recording the change of viscosity of a solution with different dendrimer (or polymer) concentrations and then extrapolating to zero concentration with the aid of empirical equations. The molecular mass dependence of the Staudinger index, known as the *intrinsic viscosity* or also as the *limiting viscosity*, is given by the Mark–Houwink relation:

$$[\eta] = KM^{\alpha} \tag{1.2}$$

η: Staudinger index
K: system-dependent constant
M: molecular mass
α: Exponential index which depends upon the shape of the dissolved dendrimer; it can lie between 0 and 2

Unlike that of linear polymers, the *intrinsic viscosity* of dendrimers does not increase linearly (Fig. 1.15) with molar mass, but reaches a maximum at a certain generation (limiting generation), only to decrease again at high generations

Table 1.1 Influence of the various components of dendrimers

Core	Branching unit	Surface	End group
	Influences		
Shape	Shape	Shape	Shape
Size	Size	Size	Stability
Multiplicity	Density/niches	Flexibility	Solubility
Functions	Guest inclusion	Properties	Viscosity

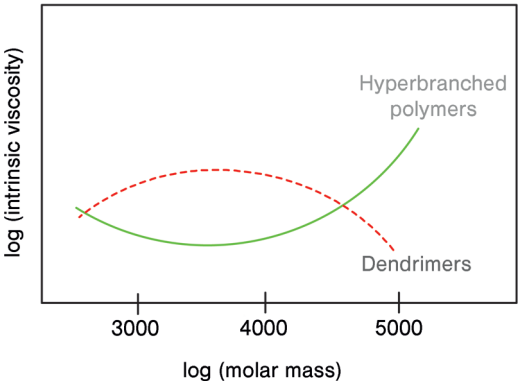


Fig. 1.15 Intrinsic viscosity of dendrimers – compared with that of polymers (schematic) [10, 30]

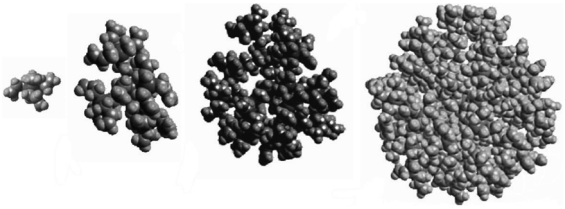


Fig. 1.16 Progressively globular form adopted with increasing number of generations illustrated for carbosilane dendrimers of zeroth to third generation (from left to right; according to Frey *et al.* [31b])

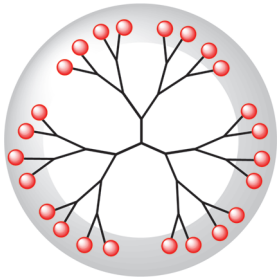


Fig. 1.17 Segment density distribution of a dendrimer molecule according to the "dense-shell model" (schematic)

(*dendrimer effect*). The intrinsic viscosity of hyperbranched polymers (Sections 4.1.5.4 und 2.7) likewise increases with increasing molecular mass [29].

This phenomenon can be explained by the gradual transition from a practically open structure of lower generations of dendrimers to an almost globular form of the higher generations (Fig. 1.16) [31].

This is why dendrimers of higher generations also have a smaller volume than corresponding linear polymers. Moreover, they also show better solubility in organic solvents and generally crystallise only with difficulty.

Depending upon their molecular structure, dendrimers can be classified as tendentially more rigid (*e.g.* "polyphenylene dendrimers"; Section 4.1.5) and tendentially more flexible (*e.g.* POPAM, PAMAM dendrimers; Sections 4.1.1 and 4.1.2).

In their theoretical considerations of molecular structure, de Gennes and Hervet assumed an ideal dendrimer with extended branches with all terminal groups arranged at its periphery in a kind of "outer ring" around the dendrimer core [9]. According to this model, dendrimers should exhibit a lower segment density at the core, which increases to a maximum value on moving to the periphery. This concept is known as the "dense-shell model" (Fig. 1.17).

In their postulated "dense-core model", Lescanec and Muthukumar advocated an opposing segment density profile [32]. Thus a maximum density is postulated at the core of the dendrimer and a decrease in segment density proportional to the distance from the core. The decrease in segment density towards

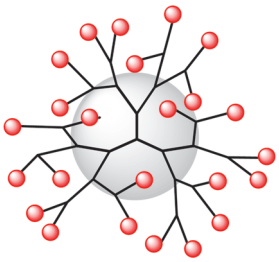


Fig. 1.18 Segment density distribution in the "dense-core model" (schematic)

the periphery is caused by a partial *backfolding* of end groups into the interior of the dendrimer (Fig. 1.18).

Most studies performed partly on molecular models [33] but also on real POPAM and PAMAM dendrimers support the latter model concept [34]. Careful studies on the three-dimensional structure of flexible dendrimers in solution were performed by Ballauff *et al.* by means of *SANS* (*S*mall *A*ngle *N*eutron *S*cattering) [35] (see Section 7.6).

1.3 Perfection, defects, dispersity

The *degree of branching DB* defined by Fréchet *et al.* provides a criterion for the classification of dendritic molecules with regard to their perfection [36].

$$DB = (I_T + I_D)/(I_T + I_D + I_L) \tag{1.3}$$

I_T: number of terminal monomer units
I_D: number of dendritic monomer units
I_L: number of linear monomer units

In contrast to perfect dendrimers with a degree of branching of 100%, hyperbranched polymers (Sections 2.7 and 4.1.5.4) will have degrees of branching between 50 and 85%, depending upon the monomer – for example, whether AB_2 or AB_8 monomers were used as starting materials [37].

Above a certain dendrimer size, a limiting generation is reached beyond which a dendrimer of perfect structure is no longer possible. If dendrimer construction takes place from the inside outwards (divergent; see Section 2.1), the space needed for the terminal groups increases with the square of the dendrimer radius *r*. However, the number of terminal groups increases exponentially with $(F_v–1)^G$ (see Eq. 1.1). This means that with each new generation there is a – formal – increase in the occupancy of the surface with terminal groups, leading to an increased density of the outer shell(s) of the dendrimer.

$$\text{Area per end group} = (\text{dendrimer surface area})/(\text{number of end groups}) \approx 4\pi r^2/(F_k \times F_v^G) \quad (1.4)$$

F_k: functionality of the core
F_v: functionality of the branching unit
G: generation of the dendrimer

Even if the above-mentioned backfolding of peripheral groups is taken into consideration, beyond a certain limiting generation (Fig. 1.19) further reaction – *e.g.* a quantitative chemical reaction of terminal groups – will be hindered by steric effects, resulting in growth defects. This phenomenon is also known as the *starburst limit effect* [9]. According to Tomalia, ideally branched 5th generation polyethyleneimine dendrimers (PEI) [38] are ruled out by "*starburst dense packing*" [10].

The *polydispersity* of dendritic molecules, expressed in the form of their *polydispersity index* (PDI), is directly related to their structural perfection. The PDI is a measure of molecular weight distribution.

$$\text{PDI} = M_w/M_n \quad (1.5)$$

M_w corresponds to the average molar mass (*e.g.* by sedimentation equilibrium measurements)
M_n represents the number average of the molar mass (*e.g.* by determination of terminal groups) [14 b, 39].

If the polydispersity index (PDI) has a value of unity, the substance is designated as *monodisperse*. *Monodispersity* is considered to be a property of the *cascadanes* (defect-free dendritic molecules; cf. Section 1.4) and almost perfect dendrimers. Since these compounds are synthesised *via* an iterative approach, monodispersity has so far generally been limited to lower generations. Should it prove possible to repeatedly remove all reactants and by-products of the individual synthetic steps during the construction of a dendrimer, then structurally perfect dendrimers will result.

In contrast, *polydispersity* is a characteristic property of hyperbranched dendritic polymers, and results from the formation of by-products as a result of cycli-

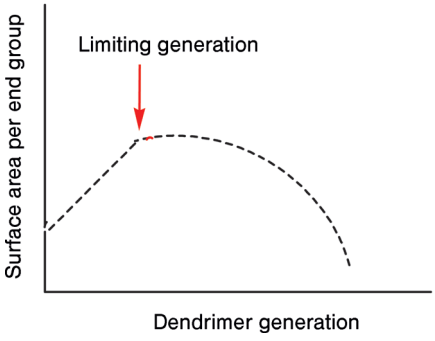


Fig. 1.19 Attainment of the limiting generation in dendrimer growth as a result of the starburst limit effect (schematic; idealised)

sation and steric hindrance during polymerisation. A *monodisperse* substance always consists of molecules of homogeneous size, whereas in *polydisperse* compounds the individual molecules have different (heterogeneous) masses. Branching defects make a minor contribution to polydispersity, which arises mainly from coiling, bridging (ring formation), and irregular growth.

1.4 Definition and classification of dendritic molecules

The first correctly dendritically branched molecules were termed *cascade molecules* and could be prepared divergently by a *cascade synthesis* (Section 1.1).

Dendritic molecules (*cascade molecules*) are repetitively branched compounds. This collective term embraces the various *dendrimers*. The latter generally exhibit "almost perfect" structures and display properties characteristic of monodisperse compounds (see also Section 1.3). With regard to their molecular masses, dendrimers range from low-molecular to high-molecular chemistry.

Cascadanes consist exclusively of molecules of the same kind and the same weight with correct, regularly branched, or perfect, defect-free structure [40].

In contrast, *hyperbranched* compounds, which do not have perfect structures owing to their method of synthesis, show polydisperse properties because they contain molecules of different masses.

If parts of dendrimers and cascadanes acts as substituents or functional groups of molecules, then they are called *dendrons,* or – if defect-free – *cascadons*.

If cascadanes form host/guest complexes, for example by inclusion of smaller guest molecules, then they are designated as *cascadaplexes*; corresponding dendrimer-based complexes are known as *dendriplexes* (Fig. 1.20) [40].

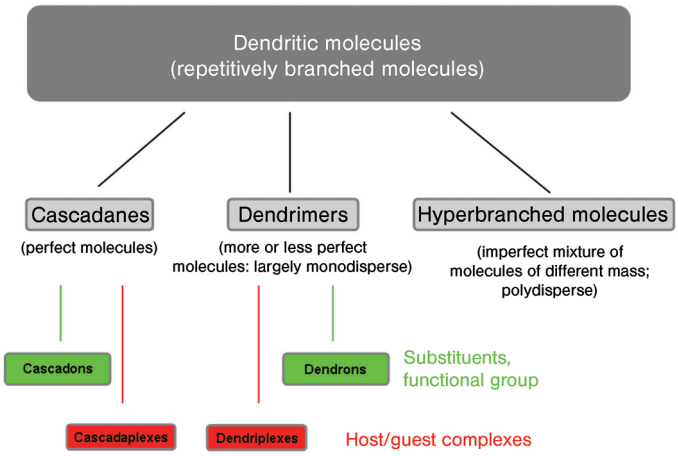


Fig. 1.20 Classification of dendritic molecules [40, 45]

1.5 Nomenclature of dendritic molecules

Like other known (macro)molecules (*e.g.* molecular knots [41], catenanes, rotaxanes [42]), dendritic molecules can be named in accordance with the *IUPAC Rules of Nomenclature*. However, these rules are not always sufficiently comprehensive to adequately, unequivocally, and clearly name such complex structures as dendritic molecules [43].

1.5.1 Newkome nomenclature

In 1993 Newkome [44] constructed a dendrimer nomenclature on the basis of the family names of the cascade molecules. This modular naming procedure for dendritic molecules and their fragments (dendrons, dendryl-/cascadyl substituents) begins with a statement of the number of peripheral terminal groups, so that the multiplicity is already clear from the beginning of the name. After the class designation "cascade", the individual branches are enumerated ("divergently") starting from the core (carbon and hetero atoms; number of branches as superscript), with the individual generations separated by colons. The terminal groups are then characterised. The names constructed thus take the form:

$$Z \text{ cascade: core building block } [N_{core}]\text{: (branching unit)}^{G}\text{: end groups} \qquad (1.6)$$

Z: number of terminal groups
N_{core}: core multiplicity
G: number of generations with branching building blocks

By way of illustration, Fig. 1.21 shows a POPAM dendrimer of the 2nd generation (cf. Fig. 1.14), which, according to Newkome, bears the name 16-Cascade:1,4-diaminobutane[4-*N*,*N*,*N*′,*N*′]:(1-azabutylidene)^2:aminopropane.

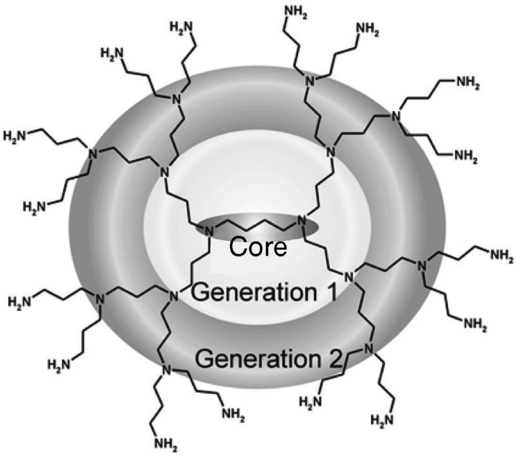


Fig. 1.21 POPAM dendrimer according to the Newkome nomenclature: 16-Cascade:1,4-diaminobutane[4-*N*,*N*,*N*′,*N*′]:(1-azabutylidene)^2:aminopropane [45]

1.5.2 Cascadane nomenclature

In the case of complex dendrimers with differing branches or differing dendryl substituents on a non-dendritic scaffold it is necessary to include further details in the name. For this reason, a more detailed "*cascadane nomenclature*" [45] has been developed, according to which the above POPAM would be called:

1,4-Diaminobutane[*N,N,N′,N′*]:{4-azabutyl(4,4)}$^{G_1,G_2}{}_{4n,8n}$
:3-aminopropyl$_{16}$-cascadane.

Here the generations (G_1 and G_2) with the corresponding number of branchings (4 and 8) are clearly indicated as superscripts and subscripts. The number of terminal groups (16) is also given as a subscript. The class designation cascadane appears at the end of the name. The numbers (locants 4,4) of the two branching atoms are given in parentheses.

As a consequence of the complex molecular structures, such nomenclatures are not without complications and require numerous rules. However – unlike the *IUPAC* [46] or *nodal nomenclature* [47] – owing to their modular structure they quickly reveal important individual characteristics (number of generations, number of terminal groups), which is of benefit in the laboratory and also in computer searches.

The individual rules are reduced here to their bare essentials; more detailed information will be found in the original literature [45].

Rule 1 Dendritic structures consist of self-similar units (*fractals*).

Rule 2 A dendritic structure consists of a core unit and a dendritic unit.

Rule 3 If a molecule contains one dendritic structure part or only different ones, the dendritic structures (=dendrons) are treated as substituents and are assigned the suffix *-cascadyl*. If at least two dendrons in a molecule are of the same kind, then the name is given the suffix *-cascadane* (Fig. 1.22).

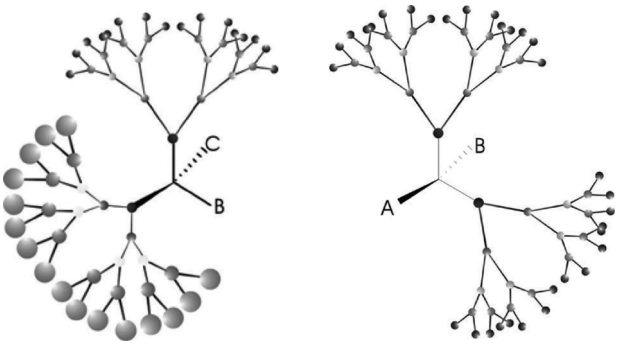


Fig. 1.22 *Cascadyl* (left), *cascadane* (right) [45]

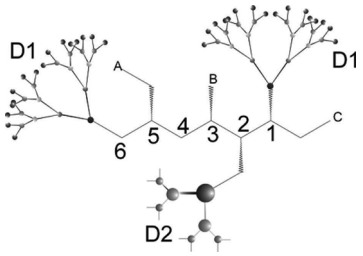


Fig. 1.23 5-(A-methyl)-3-B-1-(C-methyl)-2-(D2-cascadyl)-hexane(1,6) [45]

Rule 4 The enumeration of several different dendrons begins with that dendron which has the longest chain in the first generation. If the chain lengths are the same, then the order is decided by the next generation.

Rule 5 The name of the core unit in dendrimers is derived from the shortest unbranched chain connecting dendrons of the same kind. The positions at which the dendrons are bound to the core unit are placed in parentheses after the name of the core unit (Fig. 1.23).

Rule 6 The atoms in the branches of the scaffold are numbered from the inside outwards, excluding inner branching. The length of the chain represents the shortest connection between the branching points.

Rule 7 Every bifurcation represents the end of a generation. The terminal groups [suffix (end)] do not form a generation.

Rule 8 The name of the core unit is followed by the names of the scaffold units. These are placed in curly brackets. The term in curly brackets precedes a superscript indicating the ordinal number of the generation, and a subscript giving the total number of framework units in the pertinent generation followed by an "*n*". The individual generations are separated from one another and from the end groups by colons. The number of end groups is indicated by a subscript.

The name of this example (Fig. 1.24) is thus (in general):

"Core(1,1):{branch A (A,A)}$^{G_1}{}_{2n}$:{branch B (B,B)}$^{G_2}{}_{4n}$:end$_8$-cascadane"

Rule 9 If units are repeated in several generations, they are listed in the superscript after the *curly brackets* and separated by commas. The number of framework units in the corresponding generations is written in analogous order.

Rule 10 If repetitions of units occur in generations which do not immediately follow each other they are indicated as described in rule 9. The term listing the generation completing the dendritic structure immediately precedes the end groups.

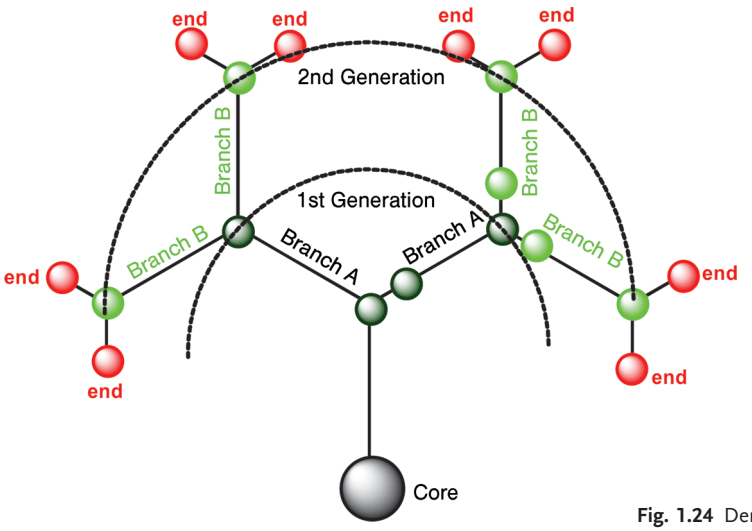


Fig. 1.24 Dendritic unit

Rule 11 If different scaffold units are distributed symmetrically in a generation, the term in curly brackets gives their names placed in angle brackets. They are ordered according to increasing chain length. After the angle brackets a subscript shows the number of repetitions followed by an "*n*". The subscript after the curly brackets gives the total number of scaffold units in the generation. If the framework units are distributed non-symmetrically in the scaffold, the scaffold has to be divided into smaller dendrons. If it is necessary to know the exact location of the scaffold unit, superscripts are added to the branching positions. Equal branching units are separated by obliques. These branching positions are placed in front of the names of the framework units of the next generation to which they are joined. If the same branching unit occurs several times, all branching positions to the preceding generation are listed in front of the name. The number of repetitions followed by an "*n*" is added as a subscript after the angle brackets.

Rule 12 Arene units are counted as a chain member by analogy with *nodal nomenclature* [47]. Ring atoms are numbered according to the *IUPAC rules*.

The names thus have the following appearance:

$$\begin{aligned}\text{Core(a,b)}:&\{\langle\text{branch A(c,d)}\rangle\langle\text{branch B(e,f)}\rangle\}^{G_1}{}_{2n}\\ &:\{\text{c,d,e}\langle\text{branch C(g,h)}\rangle_{3n}\ \text{f}\langle\text{branch D(x,x)}\rangle\}^{G_2}{}_{4n}:\text{end}_8\text{-cascadane}\end{aligned}$$

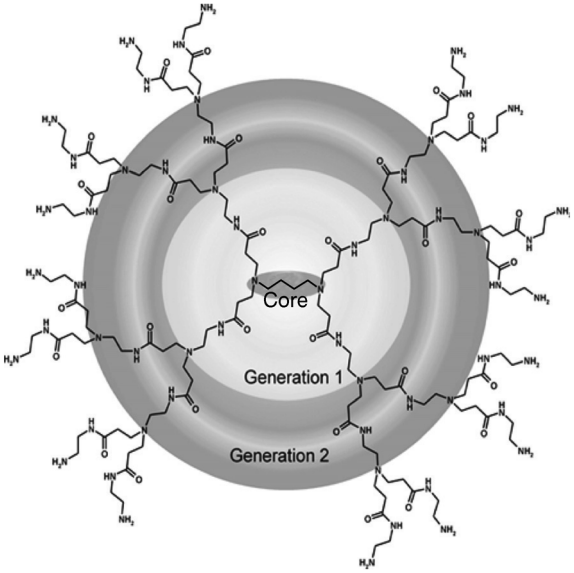


Fig. 1.25 Second generation of a PAMAM dendrimer [45]

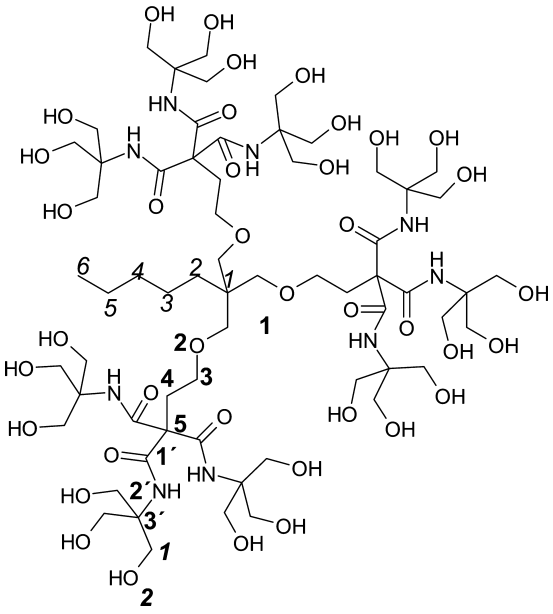


Fig. 1.26 Hexane(1,1,1):{2-oxapentyl(3,3,3)}$^{G_1}{}_{3n}$: {1-oxo-2-azapropyl(3,3,3)}$^{G_2}{}_{9n}$: hydroxymethyl$_{27}$-cascadane [45]

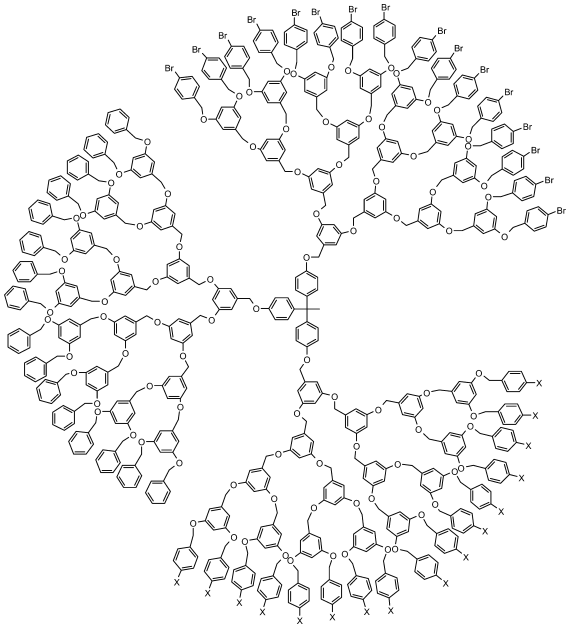


Fig. 1.27 For X = H: 1-(Phenyl (4′):{1-oxa-3-(phenyl-3′,5′-diyl) propyl(3′,5′)}$^{G_1,G_2,G_3,G_4}{}_{1n,2n,4n,8n}$: (1-oxa-4′-brombenzyl)$_{16}$-cascadyl) ethane-1,1-dibenzenol(4″,4‴):{1-oxa-3-(phenyl-3′,5′-diyl) propyl(3′,5′)}$^{G_1,G_2,G_3,G_4}{}_{2n,4n,8n,16n}$: (1-oxabenzyl)$_{32}$-cascadane [45]

Further examples of cascadane nomenclature are given below for the sake of illustration. The reader is referred to the original literature for further explanations and rules [45].

According to cascadane nomenclature, the second-generation PAMAM dendrimer shown in Fig. 1.25 has the name:

1,4-Diaminobutane[*N,N,N′,N′*]: {4,7-diaza-3-oxoheptyl(7,7)}$^{G_1,G_2}{}_{4n,8n}$: 3-aminoethyl$_{16}$-cascadane

Bibliography and Notes for Chapter 1 "Introduction"

Review articles are indicated by the words "Review(s)" or "Book/Books" in bold-faced type.

1 E. Buhleier, W. Wehner, F. Vögtle, *Synthesis* **1978**, 155–158.

2 The term "cascade" was chosen because it evokes analogies to the repetitive branching of the arms, for example the water cascade of a fountain, in which the number of "waterfalls" increases on proceeding from the top small basin to the progressively larger ones below to an extent determinable by the designer.

3 With some justification, this type of molecule could have been called dendritic at the time (see the title of this book), in allusion to corresponding nerve cells whose branching is, however, somewhat more random in nature. Several years later Tomalia coined the term "dendrimers" from the branching of trees [12]. We later used the new designation synonymously with "cascade molecules", because it had been popularised by the review published in *Angewandte Chemie* [10]. Although there is a tendency to reserve the name dendrimers preferentially for high-molecular substances [39a], we use the two terms interchangeably: In our opinion dendritic molecules are by no means limited to polymer chemistry, as the last syllable of the name dendrimer might suggest, but play an important role in lower-molecular chemistry which will undoubtedly increase in the future when synthesis and analysis have advanced further. Nevertheless, Newkome 1993 [44] and we 2006 [45] use the more suitable root "cascade" for construction of a nomenclature for all dendritic compounds.

4 Remarkably, this publication attracted little attention and generated little response at the time and for several years afterwards, nor were any priority claims made. The macrocyclic iterative variant "*non-skid-chain like molecules*" also mentioned in reference [1] shares this fate to the present day.

5 ***Review*** of repetitive/iterative syntheses: N. Feuerbacher, F. Vögtle, *Top. Curr. Chem.* **1998**, *197*, 2–18; Y. Zhao, R. R. Tykwinski, *J. Am. Chem. Soc.* **1999**, *121*, 458–459; P. A. Jacobi, H. Liu, *J. Am. Chem. Soc.* **1999**, *121*, 1958–1959; A. Boydston, Y. Yin, B. L. Pagenkopf, *J. Am. Chem. Soc.* **2004**, *126*, 10350–10354.

6 F. Vögtle, E. Weber, *Angew. Chem.* **1974**, *86*, 896–898; *Angew. Chem. Int. Ed.* **1974**, *13*, 814–816; F. Vögtle, H. Sieger, W. M. Müller, *J. Chem. Research (S)* **1978**, 398–399; ***Review***: F. M. Menger, *Top. Curr. Chem.* 1986, *136*, 1–16.

7 R. G. Denkewalter, J. F. Kolc, W. J. Lukasavage, in *US Pat. 4.360.646*, **1979**; R. G. Denkewalter, J. F. Kolc, W. J. Lukasavage, in *US Pat. 4.289.872*, **1981**; R. G. Denkewalter, J. F. Kolc, W. J. Lukasavage, in *US Pat. 4.410.688*, **1983**.

8 M. Maciejewski, *Macromol. Sci. Chem.* **1982**, *A17*, 689–703.

9 P.-G. de Gennes, H. Hervet, *J. Phys. Lett. Fr.* **1983**, *44*, L351–L361.

10 ***Review***: D. A. Tomalia, A. Naylor, W. A. Goddard III, *Angew. Chem.* **1990**, *102*, 119–157; *Angew. Chem. Int. Ed.* **1990**, *29*, 138–175.

11 P.-G. de Gennes, *Angew. Chem.* **1992**, *104*, 856–857, *Angew. Chem. Int. Ed.* **1992**, *31*, 842–845.

12 D. A. Tomalia H. Baker, J. Dewald, M. Hall, G. Kallos, S. Martin, J. Roeck, J. Ryder, P. Smith, *Macromolecules* **1986**, *19*, 2466–2468.

13 D. A. Tomalia, H. Baker, J. R. Dewald, M. Hall, G. Kallos, S. Martin, J. Roeck, J. Ryder, P. Smith, *Polym. J.* **1985**, *17*, 117–132.

14 a) G. R. Newkome, Z.-Q. Yao, G. R. Baker, V. K. Gupta, *J. Org. Chem.* **1985**, *50*, 2003–2004; b) ***Book***: G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendrimers and Dendrons*, Wiley-VCH, Weinheim 2001, 1st Edit.

15 C. Hawker, J. M. J. Fréchet, *J. Chem. Soc., Chem. Commun.* **1990**, 1010–1013.

16 T. M. Miller, T. X. Neenan, *Chem. Mater.* **1990**, *2*, 346–349.

17 P. J. Flory, *J. Am. Chem. Soc.* **1941**, *63*, 3091–3100; **1952**, *74*, 2718–2723.

18 a) ***Short review***: M. Freemantle, *Science/Technology* **1999**, *77*, 27–35;

b) J. P. Majoral, A.-M. Caminade (eds.), *Book of Abstracts*, 5th International Dendrimer Symposium, Tolouse **2007**.

19 ***Books***: a) For further examples of branching in nature, see also G. Pölking, *Schöpfungsdesign*, Tecklenburg, Steinfurt **2006**; b) B. H. Kaye, *A Random Walk through Dimensions*, VCH-Verlagsgesellschaft, Weinheim **1994**.

20 ***Reviews***: M. Žinić, F. Vögtle, F. Fages, *Top. Curr. Chem.* **2005**, *256*, 39–76; F. Fages, F. Vögtle, M. Žinić, *Top. Curr. Chem.* **2005**, *256*, 77–131, and further literature cited therein.

21 a) K. Autumn, V. A. Liang, S. T. Hsieh, W. P. Chan, T. W. Kenny, R. Fearing, R. J. Full, *Nature* **2000**, *405*, 681–685; b) E. Pennisi, *Science* **2000**, *288*, 1717–1718; c) S. Gorb, *J. Royal Soc. Interface* (DOI: 10.1098/rsif.2006.0164); c) ***Short overview***: *GIT Labor-Fachzeitschrift* **2008**, *7*, 629; d) K. Takahashi, J. O. L. Berengueres, K. J. Obata, S. Saito, *Int. J. of Adhesion and Adhesives* **2006**, *26*, 639–643; cf. *Nachr. Chem.* **2008**, *56*, 406.

22 R. Haag, F. Vögtle, *Angew. Chem.* **2004**, *116*, 274–275; *Angew. Chem. Int. Ed.* **2004**, *43*, 272–273.

23 K. Hien, *Laborjournal 1–2*/**2004**, 32–34; K. Autumn, R. Full, *GEO Magazin* 10/**2000**; J. Kahn, M. Thiessen, K. Eward, *National Geographic Deutschland*, June **2006**.

24 Design: Roman & Erwan Bouroullec.

25 a) Photo taken by F. Vögtle; see also *Generalanzeiger*, Bonn, 12. 03. 2007; b) U. Hahn, G. Pawlitzki, F. Vögtle, June **2001**; DFG Calendar, published by Deutsche Forschungsgemeinschaft, Bonn **2003**; c) ***Overview***: D. Singh, G. Fernandes, R. Sinha, A. Jerath, M. Lindsay, *Bäume der Welt*, Dorling Kindersley, Starnberg **2006**.

26 ***Books***: B. B. Mandelbrot, *The Fractal Geometry of Nature*, W. H. Freeman and Company, New York, **1982**; G. Binnig, *Aus dem Nichts*. Piper, München, 4th Edit. **1992**; H.-O. Peitgen, P. H. Richter, *The Beauty of Fractals*. Springer, Berlin **1986**; H.-O. Peitgen, H. Jürgens, D. Saupe, *Chaos and Fractals*. Springer, Berlin **1992**; B. Kaye, *Chaos and Complexity*. VCH, Weinheim **1993**.

27 W. Sierpinski, *C. R. Acad. Paris* **1915**, *160*, 302–305; J.-L. Giavitto, S. Spicher, in N. Krasnogor, S. Gustafson, D. A. Pelta, J. L. Verdegay (eds.), *Systems Self-Assembly*: Multidisciplinary Snapshots. *Studies in Multidisciplinarity*, Elsevier, Amsterdam **2008**, *5*, 199–243.

28 We thank Dr. Jörg Friedhofen, Kekulé Institute of the University of Bonn, for these graphics.

29 ***Review***: C. J. Hawker, J. M. J. Fréchet, *Step-Growth-Polymers for High Performance Materials* (Eds. J. L. Hedrick, J. W. Labadie), Oxford Press, Oxford **1996**, Chapter 7; M. Seiler, *Chem. Eng. Technol.* **2002**, *3*, 237–253; comparison of thermosensitivity properties of POPAM dendrimers and linear analogues: Y. Haba, C. Kojima, A. Harada, K. Kono, *Angew. Chem.* **2007**, *119*, 238–241; *Angew. Chem. Int. Ed.* **2007**, *46*, 234–237.

30 E. M. M. de Brabander-van den Berg, E. W. Meijer, *Angew. Chem.* **1993**, *105*, 1370–1372; *Angew. Chem. Int. Ed.* **1993**, *32*, 1308–1311; T. H. Mourey, S. R. Turner, M. Rubinstein, J. M. J. Fréchet, C. J. Hawker, K. L. Wooley, *Macromolecules* **1992**, *25*, 2401–2406.

31 a) ***Reviews***: A. W. Bosman, H. M. Janssen, E. W. Meijer, *Chem. Rev.* **1999**, *99*, 1665–1688; R. Hourani, A. Kakkar, M. A. Whitehead, *J. Mater. Chem.* **2005**, *15*, 2106–2113; b) H. Frey, K. Lorenz, C. Lach, *Chem. unserer Zeit* **1996**, 75–85.

32 L. Lescanec, M. Muthukumar, *Macromolecules* **1990**, *23*, 2280–2288.

33 M. L. Mansfield, L. I. Klushin, *Macromolecules* **1993**, *26*, 4262–4268; M. L. Mansfield, *Polymer* **1994**, *35*, 1827–1830; D. Boris, M. Rubinstein, *Macromolecules* **1996**, *29*, 7251–7260; N. W. Suek, M. H. Lamm, *Macromolecules* **2006**, *39*, 4247–4255.

34 A. M. Naylor, W. A. Goddard III, G. E. Kiefer, D. A. Tomalia, *J. Am. Chem. Soc.* **1989**, *111*, 2339–2341; R. Scherrenberg, B. Coussens, P. van Vlief, G. Edouard, J. Brackmann, E. de Brabander, K. Mortensen, *Macromolecules* **1998**, *31*, 5892–5897.

35 M. Ballauff, C. N. Likos, *Angew. Chem.* **2004**, *116*, 3060–3082; *Angew. Chem. Int. Ed.* **2004**, *43*, 2998–3020; ***Review***: M. Ballauff, (Volume editor F. Vögtle), *Top.*

Curr. Chem. **2001**, *212*, 177–194; C. N. Likos, M. Schmidt, H. Löwen, M. Ballauff, D. Pötschke, P. Lindner, *Macromolecules* **2001**, *34*, 2914–2920; S. Rosenfeldt, N. Dingenouts, M. Ballauff, P. Lindner, N. Wemer, F. Vögtle, *Macromolecules* **2002**, *35*, 8098–8105, reference to work by other authors cited therein; S. Rosenfeldt, E. Karpuk, M. Lehmann, H. Meier, P. Lindner, L. Harnau, M. Ballauff, *ChemPhysChem.* **2006**, *7*, 2097–2104.

36 C. J. Hawker, R. Lee, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1991**, *113*, 4583–4588.

37 E. Malmström, M. Johansson, A. Hult, *Macromolecules* **1995**, *28*, 1698–1703; Y. Ishida, A. C. F. Sun, M. Jikai, M. Kakimoto, *Macromolecules* **2000**, *33*, 2832–2838; P. Bharathi, J. S. Moore, *Macromolecules* **2000**, *33*, 3212–3218.

38 Cf. PPI in Chapter 4, Fig. 4.1; replacement of propano by ethano groups in the latter formula yields the corresponding third-generation PEI.

39 ***Books***: a) J. M. J. Fréchet, D. A. Tomalia, *Dendrimers and Other Dendritic Polymers,* Wiley, Chichester **2001**; b) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendrimers and Dendrons: Concepts, Syntheses, Applications,* Wiley-VCH, New York, Weinheim **2001**.

40 In our opinion an adequate distinction between ideal, defect-free dendritic molecules, for which we propose the term "cascad*anes*", and the more or less defect-free (monodisperse) "dendrimers", and polydisperse, imperfect "hyperbranched compounds" has so far been lacking in the area between polymer chemistry and small-molecule chemistry. Other reasons for such a distinction are because highly pure compounds have always been especially important in small-molecule chemistry, and because of the need to name an individual molecule.

41 O. Safarowsky, B. Windisch, A. Mohry, F. Vögtle, *J. Prakt. Chem.* **2000**, *342*, 337–342; ***Review***: F. Vögtle, O. Lukin, *Angew. Chem.* **2005**, *117*, 2–23; *Angew. Chem. Int. Ed.* **2005**, *44*, 2–23.

42 New IUPC recommendations for rotaxanes: A. Harada, W. V. Metanomski, G. P. Moss, E. S. Wilks, A. Yerin, "*Nomenclature of Rotaxanes*", International Union of Pure and Applied Chemistry, Project 2002-007-1-800.

43 It would be beyond the scope of this textbook to dive further into the details of dendrimer nomenclature. Instead, basic rules are given to create an awareness of the problems and complexity. Nevertheless, with the aid of the literature cited (see ref. [45]) it is possible to develop names for certain formulae – and *vice versa*.

44 G. R. Newkome, G. R. Baker, J. K. Young, J. G. Traynham, *J. Polym. Sci. A., Polym. Chem.* **1993**, *31*, 641–651; G. R. Newkome, G. R. Baker, *Polym. Preprints* **1994**, *35*, 6–9.

45 J. H. Friedhofen, F. Vögtle, *New J. Chem.* **2006**, *30*, 32–42.

46 ***Review***: *International Union for Pure and Applied Chemistry, Nomenclature of Organic Chemistry Sections A, B & C*, Butterworth, London **1971**.

47 ***Review***: N. Lozac'h, A. L. Goodson, W. H. Powell, *Angew. Chem.* **1979**, *91*, 951–1032; *Angew. Chem. Int. Ed.* **1979**, *18*, 887–899, N. Lozac'h, A. L. Goodson, *Angew. Chem.* **1984**, *96*, 1–15; *Angew. Chem. Int. Ed.* **1984**, *23*, 33–46.