# Synthesis of Nanomaterials

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**Dendrimer Chemistry,** *Concepts, Synthesis, Properties, Applications* By *F. Vögtle, G. Richardt, N. Werner*, Wiley-VCH Verlag, 2009

## **4. Dendrimers**

In 1978 Vögtle et al. described a series of synthetic "cascade molecules" exhibiting potentially perpetual branching. Starting from diverse primary monoamines and diamines, "cascade synthesis" was performed to attach spacer units of propylenamine whose N atoms served as a 1 to 2 branching point (formal branching of a bond into two new ones) during each subsequent repetitive step.

In the simplest case, reaction of a primary monoamine via a two-fold Michael reaction with acrylonitrile (bis-cyanoethylation) led to the dinitrile. 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 provided the first access to regularly branched, many-armed molecules.



Several years earlier (1974), the same group had already described many armed, albeit non-branched, molecules as octopus molecules, whose numerous arms were used for complexation with metal ions (host-guest interactions).

Denkewalter et al. described a pathway to polylysine dendrimers via divergent synthesis in 1981 patents.



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



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. According to de Gennes, highly branched molecules are considered as "soft material".

In 1985 Tomalia developed branched poly(amidoamines) (PAMAM), which he also designated as "starburst dendrimers" and generally propagated the name "dendrimer" (from the Greek dendron = tree and meros = part).

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.



In 1985, Newkome et al. presented a **divergent synthetic** route to water soluble, highly branched "arborol systems" with terminal hydroxyl groups, whose name is derived from the Latin arbor = tree.





In 1985, Fréchet and Hawker described the first **convergent synthesis** of dendrimers. They constructed poly(aryl ether) architectures "from the outside inwards".

Miller and Neenan succeeded in producing the first hydrocarbon dendrimers based exclusively on arene units, also using a convergent synthetic strategy.



The exponential growth of research into dendritic molecules, thirty years after their first synthesis (1978) is apparent: large number of publications (more than 10 000, 1000 per annum, plus about 150 patents), and more than 8000 researchers are currently active in this area and more than 150 companies have already applied for patents relating to dendritic compounds.

## **Dendritic architectures**

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, blood vessels, nerve cells, rivers, lightning, corals, and snowflakes. Metals deposited on electrodes or on noble metals often exhibit branching, as do fibers and gels.

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.

Evolution itself can be depicted dendritically. 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. Zone maps of underground railways show dendritic patterns.

Fractals are mathematically defined self-similar structures. 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 means that structural elements are repeated on different scales.

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 characterize 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 surface of the dendrimers, which is often designated as the periphery.



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 or 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:

$$n_{\rm G} = F_{\rm k} (F_{\rm v} - 1)^{\rm G} \tag{1.1}$$

 $n_{\rm G}$ : number of end groups in the G-th generation

- $F_k$ : functionality of the core (= number of bonds emanating from the core)
- *F*<sub>v</sub>: 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, 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, 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 individual structural units of a dendrimer can affect its properties.

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  |  |

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 behavior is characterized by the **Staudinger index** (dimensions mL/g) determined by recording the change of viscosity of a solution with different dendrimer 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, is given by the **Mark–Houwink** relation:

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

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

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Unlike that of linear polymers, the intrinsic viscosity of dendrimers does not increase linearly with molar mass, but reaches a maximum at a certain generation (limiting generation), only to decrease again at high generations (dendrimer effect). The intrinsic viscosity of hyperbranched polymers likewise increases with increasing molecular mass.



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.

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 crystallize only with difficulty. Depending upon their molecular structure, dendrimers can be classified as tendentially more rigid (e.g. polyphenylene dendrimers) and tendentially more flexible (e.g. POPAM, PAMAM dendrimers).

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. 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 Segment density distribution of a dendrimer molecule according to the "dense-shell model" (schematic) In their postulated "dense-core model", Lescanec and Muthukumar advocated an opposing segment density profile. 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 the periphery is caused by a partial backfolding of end groups into the interior of the dendrimer.

Most studies performed partly on molecular models, but also on real POPAM and PAMAM dendrimers support the latter model concept. Careful studies on the three-dimensional structure of flexible dendrimers in solution were performed by Ballauff et al. by means of SANS (Small Angle Neutron Scattering).



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

## 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.

 $DB = (I_{\rm T} + I_{\rm D})/(I_{\rm T} + I_{\rm D} + I_{\rm L})$ (1.3)

 $I_{T}$ : number of terminal monomer units

- *I*<sub>D</sub>: number of dendritic monomer units
- $I_{\rm L}$ : number of linear monomer units

In contrast to perfect dendrimers with a degree of branching of 100%, hyper-branched polymers will have degrees of branching between 50 and 85%, depending upon the monomer e.g., whether  $AB_2$  or  $AB_8$  monomers were used as starting materials.

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), 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 an increase in the occupancy of the surface with terminal groups, leading to an increased density of the outer shell(s) of the dendrimer.

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

- $F_{\mathbf{k}}$ : 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, further reaction will be hindered by steric effects, resulting in growth defects. This phenomenon is also known as the **starburst limit effect**. According to Tomalia, ideally branched 5<sup>th</sup> generation polyethyleneimine dendrimers (PEI) are ruled out by "**starburst dense packing**".

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.

 $PDI = M_w/M_n$ 

(1.5)

- $M_{\rm w}$  corresponds to the average molar mass (e.g. by sedimentation equilibrium measurements)
- M<sub>n</sub> 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) and almost perfect dendrimers.

Since these compounds are synthesized 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 cyclization and steric hindrance during polymerization. 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.

## **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.

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. 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.

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**.



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

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**. 19

## Nomenclature of dendritic molecules

Like other known (macro)molecules (e.g. molecular knots, catenanes, rotaxanes), 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.

#### Newkome nomenclature

In 1993 Newkome 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 heteroatoms; number of branches as superscript), with the individual generations separated by colons. The terminal groups are then characterized.

Z cascade: core building block  $[N_{core}]$ : (branching unit)<sup>G</sup>: end groups (1.6)

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

POPAM dendrimer of the 2<sup>nd</sup> generation bears the name:

16-Cascade: 1,4-diaminobutane[4-N,N,N',N']:(1-azabutylidene)<sup>2</sup>:aminopropane.



Z cascade: core building block  $[N_{core}]$ : (branching unit)<sup>G</sup>: end groups

Z: number of terminal groups

 $N_{\rm core}$ : core multiplicity

G: number of generations with branching building blocks

## **Cascadane nomenclature**

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

1,4-Diaminobutane[N,N,N',N'] : {4-azabutyl(4,4)}<sup>G1,G2</sup> <sub>4n,8n</sub>: 3-aminopropyl<sub>16</sub>-cascadane.

Here the generations (G1 and G2) 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, 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.

## Synthetic methods for dendritic molecules

Dendrimer architectures can be constructed in a wide variety of ways. Principal goals in the past were to assure general availability of routine methods for readily accessible dendrimer structures, as has been accomplished with POPAM and PAMAM dendrimers as well as Fréchet dendrons.

On the other hand, it is both important and desirable to construct new branching generations on such readily accessible and in part commercially available dendrons, to endow them with new functionalities, with pores, or with specific properties (solubility, aggregation behavior, philicity, luminescence, rigidity, backfolding, chirality, guest inclusion, gel formation, etc.).

The majority of the syntheses considered will be discussed in terms of a general "CFP concept": The coupling sites are designated by a C (in a red sphere), the functional end groups by F (in a green sphere). If the relevant groups are made to react in their protected form, the corresponding color coding is retained and the protected functionality subsequently marked with a P.

## **Divergent synthesis**

Synthesis of a dendrimer according to the divergent method proceeds stepwise starting from a multifunctionalized core building block, to whose reactive coupling sites C new branching units in the form of dendritic branches are attached via a reactive terminal functionality F. During reaction, other functional groups of the branching unit are protected as indicated by the letter P.

After the first reaction step, the protected functional groups P are deprotected (activated) and then serve as new reactive coupling sites C for further branching units. A new dendrimer generation arises with each branching unit. The repetitive (iterative) synthetic sequence, consisting of both the construction step, in which coupling of a branching unit to two further units (12 branching) takes place, as well as the activation step, progressively yields higher generations and permits the dendrimer to grow from the inside outwards.

An advantage of the divergent method is the attainable high-molecular (nano)scaffold architecture as well as the possibility of automation of the repetitive steps. The divergent method is therefore the method of choice for commercially available POPAM and PAMAM dendrimers.

One disadvantage of this synthetic methodology is seen in the exponentially increasing number of functional terminal groups, since they cannot always be made to react quantitatively and thus give rise to structural defects. Such defects cannot always be avoided, even on addition of large excesses of reactants.

Moreover, purification and separation of structurally perfect from defective dendrimers are problematic because the compounds have very similar properties. The first known syntheses of dendritic molecules were divergent and were used by the working groups of Vögtle, Denkewalter, Tomalia, and Newkome.





mer is shown as a black central point. Steps a) coupling and b) activation stand for a repetitive pair of steps for construction of the next generation

## **Convergent synthesis**

The convergent synthesis strategy proceeds in the opposite direction, from the periphery to the core, that is from the outside inwards. (Functionalized) dendrimer components ("dendrons") are bonded to the reactive terminal groups linked to a focal point of a multifunctional core unit. Coupling of an active (unprotected) functional terminal group F, bearing two further protected linkage sites P (in a red sphere), with a branching unit, consisting of two active coupling sites C as well as an inactive (protected) functional group P (in a green sphere), leads to a first-generation dendrimer/dendron (step a). For further build-up of the next dendron generation, the inactive group of this G1 dendron can be activated (step b), and a further branching unit formed with two active sites C and an inactive functional group P. The steps can be repeated until all segment-shaped dendrons of the desired generation react with an oligo-functional core module (e.g. "C3") to form the desired higher-generation dendrimer.

Because of the small number of reactive terminal groups involved, this type of synthesis has the advantage that it does not produce the structural defects (e.g. missing branches in higher generations) often observed in the case of the divergent synthetic route. Moreover, this synthetic method can be performed with equimolar quantities (without any need for large excesses) thus facilitating preparative work-up. The by-products formed (owing to incomplete reaction of bulky dendrons with the branching unit) differ drastically in molecular mass and can be removed more easily after each step than in the case of divergent synthesis.

The dimensions of dendrimer growth are subject to limitations set by steric hindrance during reaction of the dendrons at the periphery. This is the reason why this synthetic strategy is used mainly for the preparation of lower-generation dendrimer. Hence divergent and convergent syntheses are in a way complementary.



tional group; P=protective group)

The convergent synthetic strategy is well suited for the production of macromolecular architectures such as segmented-block dendrimers, which bear either the same or different generations of dendrons, but with different molecular scaffolds linked to a core unit. This type of dendrimer is of interest owing to its multifunctionality. In the case of surface-block dendrimers, the dendrimer periphery exhibits different functionalities in specific molecular segments. They are formed by coupling of dendrons differing in the nature of their terminal functionalities to a common core unit.

## **Recent synthetic methods**

## **Orthogonal synthesis**

In an orthogonal synthesis, two different branching units with complementary coupling functions are used alternatingly and no activation step is employed. The selected reactants as well as the resulting coupling product must be inert towards the subsequent reaction conditions. The term orthogonal means that the functionalities are initially inert towards the coupling conditions, but can be activated in situ for the desired subsequent reaction or coupling. If this condition is met, the dendrimer can be constructed divergently or convergently in just a few steps.

The method of orthogonal coupling has still not been very widely adopted because the building blocks used have to meet very stringent structural requirements. Spindler and Fréchet were the first to prepare a third-generation polyether carbamate dendron (starting from 3,5-diisocyanatobenzyl chloride and 3,5-dihydroxybenzyl alcohol) in a one-pot synthesis.



#### **Double-stage convergent method**

This new variant is a combination of the convergent and the divergent method. Its significant step consists in the coupling of a small dendron with an active functional group F at the focal point, produced by convergent synthesis, to a low-generation multifunctional dendrimer with peripheral coupling sites C, the hypercore, produced by divergent synthesis.

Compared to conventional convergent synthesis, the two-stage method promises fast access to highergeneration monodisperse dendrimers, combined with a jump in terminal functionalities, since the surface functionalities of the hypercore are subject to less steric hindrance than in the case of simple nondendritic core building blocks of conventional convergent synthesis.

Moreover, this approach permits the formation of dendrimers with different inner and outer branching units (layer-block dendrimers).



Fig. 2.4 Double-stage convergent method (C=coupling group, F=functional group)

#### **Double-exponential method**

The double-exponential method can basically be regarded as a convergent growth strategy for a dendron. It involves synthesis in two directions, towards the periphery and towards the focal point: Starting from a completely protected branching unit, consisting of two protected coupling sites C and a protected functionality F, selective deprotection is performed such that the functional group F is activated in one of the branching units and the two coupling units are activated in the other. If two branching units with active groups F (marked green) now react with such a group having two coupling sites C (marked red), a second-generation dendron is formed.

Iteration of the synthetic sequence leads to the corresponding fourth-generation dendron. Access to a fourth-generation Fréchet dendron can thus be shortened by one stage, since no first-generation dendron can be formed by this method – i.e. by doubling of the numbers of generations.



**Fig. 2.5** Double-exponential method (*C*=coupling group, *F*=functional group; *P*=protected group)

#### Hypermonomer method

Compared to conventional FC2 or FC3 monomers, the number of terminal groups increases faster (14 branching) with monomeric FC4 synthetic building blocks (i.e. hypermonomers). However, the number of synthetic steps required for construction of a dendrimer remains the same as in the case of preparation by conventional methods. On reduction to the simple CFP scheme, the course of synthesis can be described as follows: Four branching units with an active functional group F are made to react with active coupling groups C of the hypermonomer FC4, where the functional group F in the hypermonomer itself is deactivated and therefore labelled P for "protected".



## **Click chemistry**

In 2001 Sharpless proposed this method – in which smaller units are joined together by way of heteroatom bonds (C–X–C; X=heteroatom) – as a fast track route to compounds. The criteria for a "click reaction" were recently summarized: broad applicability with high yields; readily accessible starting compounds; readily separable by-products or none at all; straightforward reaction conditions; easy product isolation; stereospecific.

Typical reactions applied are 1,3-dipolar cycloadditions, nucleophilic substitutions for ring opening of strained electrophilic heterocycles, as well as additions to carbon-carbon multiple bonds (e.g. epoxidation). Since click chemistry in itself does not represent a new type of synthesis, but merely facilitates the course of synthesis and workup of the products through favorable choice of reaction parameters mentioned above:

Wooley and Hawker et al. prepared second and third-generation dendrimers with a "divergent click strategy". For this purpose, a first-generation azido-dendrimer was transformed in a Cu(I)-catalyzed reaction with an alkynylated monomer into a triazole dendrimer with terminal hydroxyl groups, which in turn were transformed in a second step into azido functions, in order to again undergo repetitive reaction with fresh alkynylated monomers. Unprotected glycol-dendrimers, peptido- and redox-dendrimers and dendronized polymer organogels can also be prepared by click chemistry.

## Solid phase synthesis

Solid-phase methodology was established in 1963 in pioneering work conducted by Merrifield in the area of peptide synthesis. Interest in this synthetic strategy continues unabated to this day, particularly in connection with the production of new active components for drugs, since the repetitive amide bond formation performed in automated synthesizers lends itself ideally to the construction of extensive substance libraries by combinatorial chemistry.

The synthesis proceeds in the first step as a covalent coupling of substrate (B) via a linker to the functional group A (e.g.  $-NH_2$ ) attached in a prior step to a commercially available solid phase. This solid phase usually consists of an insoluble polymeric material, (polystyrene most frequently serving as the polymeric support) generally in the form of beads.

Of critical importance for optimum reaction are good swelling properties of the support material: the greater the swelling, the greater the surface area available for chemical reactions.

Reaction of the new substrate C with the previously coupled substrate (solid phase–A–B) is followed either by (generally hydrolytic) cleavage of the product B–C formed on the solid phase from the support, or by further reaction with substrates D, E, F, to give a linear sequence B–C–D–E–F or isomers thereof with the letters in a different order – should the substrate solutions be added in a different order.



**Fig. 2.8** Divergent synthesis of dendritic molecules on a solid phase (C=coupling group, F=functional group; P=protective group)

In contrast to reactions in solution, solid-phase synthesis has the advantage that excess amounts of reactants can be used and the yields thus increased.

Work-up and purification processes – which often prove difficult in homogeneous solution – are rationalized as straightforward washing or filtration. Recycling of the support material after cleavage of the product from the solid phase also has cost benefits.

Notwithstanding all its advantages, the principle of solid-phase synthesis cannot be applied to all kinds of chemical reactions. Although reactants are used in excess, reaction is not always quantitative. The resulting impurities cannot be separated on the solid phase, giving rise to separation problems particularly in multistep systems.

In the present context, solid-phase synthesis has been used primarily for the preparation of peptide and glycopeptide dendrimers. For example, a second-generation dendrimer could be prepared by successive addition of branched polyproline building blocks to a solid phase. The divergent synthesis of polyamide dendrimers on polystyrenes was accomplished by Fréchet et al. 1991. PAMAM dendrons could be grown up to the fourth-generation. Solid-phase synthesis was also employed for polylysine dendrimers, whose basic structures are used as "multiple antigen peptides" (MAP).

#### **Coordination-chemical synthesis**

Dendritic building blocks having the nature of complex ligands can coordinate with a central metal unit. Such "self-assembly" opens up direct access to metallodendrimers.

The strong Ru<sup>2+</sup> bond to the bipyridine nitrogen – although non-covalent – is not regarded as "supramolecular" by some chemists because of its lack of reversibility. That is why we consider it from a coordination-chemical viewpoint.

#### Metal complex as core unit

There are basically two routes available for the preparation of dendrimers with a metal complex as core unit. One of these approaches starts from a preconstructed metal complex, whose ligand framework is covalently substituted with dendritic groups.

In a second variant, growth of metallodendrimers can proceed via complexation of a metal cation with dendritic ligands. In this way, photoactive ruthenium complexes obtained by spontaneous self-assembly of the components starting from various dendritically substituted bipyridines.



Fig. 2.9 Ru<sup>2+</sup>-tris-bipy complex with dendritic periphery

#### Metal complexes as branching unit

Balzani et al. prepared dendrimers with metal complexes serving both as core and as branching unit. The metallodendrimer is constructed solely from polypyridine ligands and transition metal ions. Such dendritic transition metal complexes can be synthesized both convergently and divergently and different transition metal ions (ruthenium/osmium) can be incorporated.

This provides a means of influencing the luminescence properties of the dendrimer. Thus the energy transfer process proceeds from the inside outwards in a dendrimer with a ruthenium ion as central metal and peripheral osmium. If the central atom is osmium, then energy transfer proceeds in the opposite direction, from the outside inwards.

Newkome et al. prepared metallodendrimers with a ligand/metal/ligand architecture allowing separate construction of the dendrons. Two polyamide dendrons were preconstructed and linked to a ruthenium complex.



Fig. 2.10 Metallodendrimers (according to Balzani et al.)

#### Supramolecular synthesis

In contrast to the methods already presented, the supramolecular synthesis of dendrimers does not involve covalent bond formation, but instead exploits non-covalent interactions.

Fréchet et al. were able to coordinate polyether dendrons having carboxylate functional groups at the focal point with lanthanide ions up to the fourth generation. Preparation by straightforward ligand exchange starting from lanthanide triacetates with dendron carboxylates was made possible by the predominantly ionic – and reversible – interactions between the lanthanide ion bearing a triple positive charge and carboxylate groups.

A dendritic "two-component gelator" was synthesized by Smith et al. on the basis of self-assembling acid-base/hydrogen bond interactions. Dendritic lysine building blocks serve as dendrons, and an aliphatic diamine as core.

Depending upon the choice of building blocks, the supramolecular complex forms fibrous gel phases by hierarchic self-organization. The dendritic peptides used with d- and l-lysine building blocks each contain three stereocentres. The chirality of d- and l-lysine exerts a controlling effect on structure during self-assembly in the gel fibres and hence on the morphology and macroscopic properties of the product. Ill- or ddd enantiomeric units lead to fibres, whereas the corresponding racemic gels are more prone to form planar structures. The chirality accordingly affects the pattern of hydrogen bonding during the formation of molecular aggregates.



Fig. 2.11 Lanthanide ion as core unit of a dendritic metal complex

Lüning et al. reported on attempts at supramolecular linkage of branching units and core units to form dendrimers. To this end, the building blocks are provided with recognition units, which can undergo spontaneous selective self-assembly with other non-identical components via hydrogen bonds.

In order to assure the desired strength of bonding and stability, the recognition units must have several positions suitable for hydrogen bonding in the molecule. Moreover, certain sequences of acceptor (carbonyl oxygen) and donor properties (HN groups) generate a "supramolecular regioselectivity", in that only those molecular building blocks which have adequate complementary bonding sites dock onto one another.



H-donor- and acceptor units (according to Lüning et al.)

stereocentres are marked red

This concept could be used for self-organized generation-wise growth of dendrimers by controlled shell-by-shell construction around the core utilizing various recognition units. However, the poor solubility of the multiple amide and urea structural elements has so far made isolation of pure oligomeric products difficult.

Complete self-construction of dendrimers according to a modular principle was accomplished by Hirsch et al. Starting from a core unit with three recognition domains and two recognition units (identical with those of the core unit), a branching unit is bound to a complementary recognition domain via hydrogen bonding and built up to the desired generation, whereupon appropriate end groups are attached.

![](_page_42_Figure_2.jpeg)

Fig. 2.14 Supramolecular self-construction of dendrimers (schematic; according to Hirsch *et al.*)

#### Hyperbranched polymers

Preparation of dendrimers requires a high degree of purity of the starting materials and high yields of the individual synthetic steps, all of which generally increases the effort involved.

Polydisperse, hyperbranched compounds, which admittedly show defects often display properties similar to their ideally perfect dendritic relations, can readily be synthesized.

Synthesis of hyperbranched polymers proceeds in a single-stage process via polyaddition, polycondensation, radical polymerization, and so forth, of an FCn monomer.

Reaction of the functional F groups with the functional C (coupling) groups of a second monomer molecule gives rise to randomly branched molecules.

Since the C groups are present in excess (n2), crosslinking reactions are avoided from the outset. Reaction can be brought to a standstill by addition of stopper components.

Since the synthesis of hyperbranched polymers does not involve coupling to a core molecule, but only FCn monomers react with one another, both branched molecules and linear sequences may be formed.

If reactive groups are present during the synthesis of hyperbranched polymers, then a protective group technique is required because the desired molecular architecture would otherwise not be formed (appropriate protective groups enhance the selectivity of selected groups for bond formation).

Owing to their molecular structures and their properties, hyperbranched polymers represent a transition between linear polymers and highly branched dendrimers.

![](_page_44_Figure_2.jpeg)

Fig. 2.15 Synthesis of a hyperbranched dendritic polymer (from a  $FC_n$  monomer; schematic). F = functional group, C = coupling site

![](_page_44_Picture_4.jpeg)

## **Dendronized linear polymers**

Dendronized linear polymers are polymers which bear dendrons at more or less regular intervals along their polymeric backbone. They can be assigned to the comb polymers, since the arrangement of dendrons resembles that of the teeth of a comb. Apart from polymer-analogous "graft-to-" and "graft-from-" approaches, the commonest synthetic route to dendronized linear polymers is the macromonomer method.

## Polymer-analogous method a) "Graft-to" method

The "graft-to" method of attaching dendrons numbers among the polymer-analogous synthetic strategies which start from a functionalized polymer backbone to which convergently preconstructed dendritic units of the desired generation can be fixed in a dense sequence. This variant can be used for the preparation of dendronized poly(*p*-phenylene) polymers.

![](_page_45_Figure_4.jpeg)

## b) "Graft-from" method

The "graft-from" strategy is a variant of the "graft-to" method since the starting material is again a functionalized polymer, on which the dendritic unit is assembled generation by generation. Specifically, a first-generation dendron is linked to a functionalized polymer and then undergoes divergent growth. Amidoamine dendrimers could be prepared in this way starting from a polyethylenimine (PEI) backbone.

![](_page_46_Picture_2.jpeg)

Polymer-analogous variants reach their limits in the face of insufficient rigidity of the functionalized linear polymers which can lead to undesired coiled structures. These have to re-assume a linear structure, with an attendant loss of entropy, in order to assure reaction of all the dendrons with the functional groups attached to the backbone. The dendrons are mostly added in excess in order to facilitate complete reaction, which in turn necessitates tedious purification of the products.

The additional steric hindrance occurring on attachment of larger dendrons if higher generation dendrons are already located in the close vicinity of the polymer backbone can slow down the reaction even to the point of non-reaction. A low reaction rate can lead to side reactions which do not take place when the reaction is fast.

Table 2.1 lists a number of reactive coupling sites – for attachment of dendrons – on various polymer structures.

| Polymer                               | Reactive group<br>as linkage sites |  |
|---------------------------------------|------------------------------------|--|
| Cellulose                             | –OH                                |  |
| Poly(vinyl alcohol)                   | -OH                                |  |
| Poly(vinyl chloride)                  | -Cl                                |  |
| Poly(acrylic acid)                    | -COOH                              |  |
| Polyamide                             | -COOH                              |  |
| Partly hydrolysed poly(vinyl acetate) | -OH                                |  |
| Styrene-divinylbenzene copolymer      | vinyl group                        |  |

Table 2.1 Possible coupling sites on a polymer backbone

#### Macromonomer method

An alternative approach uses macromonomers, that is monomeric building blocks already bearing dendrons, which subsequently undergo polymerization. Percec et al. described the synthesis of dendronized methacrylate monomers and their radical polymerization. They introduced the term tapered side chains for polymers bearing one dendron per repeating unit. It is essential for the success of the concluding polymerization step that the dendronized monomers bear polymerizable functionalities such as vinyl, acryl, or oxiran end groups. Apart from radical polymerization, ring-opening metathetic polymerization, Suzuki polycondensation, as well as Heck coupling were also employed.

![](_page_48_Picture_2.jpeg)

The macromonomer route assures uniform distribution of dendrons along the polymer backbone. Acrylates and styrenes with pendant dendrons proved to be well suited for polymerization. However, steric hindrance between monomers bearing higher-generation dendrons and the spatial requirements of the end of the chain cause problems: The monomer reacts with the chain end only in the case of slight, if any, steric hindrance.

To summaries, a common feature of all methods for the preparation of dendronized linear polymers is the change of shape of a formerly flexible filamentary molecule by attachment of dendrons to the backbone of the polymer. As the extent of demonization increases, the coil structure extends and acquires greater rigidity, until the polymer assumes a linear extended form with a stiffened backbone.

Stiffening of the polymer molecules to this extent has hitherto only been accomplished by such attachment of dendrons. Convincing proof was provided by Schlüter, Rabe et al. on the basis of STM/AFM images of individual polymer molecules. These molecules could also be moved and manipulated on the surface with the tip of the STM/AFM probe.

Extreme loading of the polymer with dendrons results in a cylindrical shape of the "denpol" polymer with polydisperse properties. It is thus possible to influence or even control the size of the coupled dendron and the density of its coverage on the polymer backbone through choice of the type of polymer (e.g. polyacrylate or polystyrene).

The dimensions of the dendritic cylinder depend on the degree of polymerization (determines the length) and the generation of the dendron (determines the diameter; about twice the size of the attached dendron). Conventional polymers have diameters in the Ångström range, whereas the dendronized linear polymers described here have nanometre diameters.

Such well-defined architectures could be useful for nanoscale applications in, for example, catalysis or as carrier materials for chemical transport. The parallel arrangement of dendrons on the polymer backbone is also attractive for surface orientation in liquid crystal displays.

![](_page_50_Figure_2.jpeg)

Fig. 2.19 Cylindrical shape of a *den*dronised linear *polymer* molecule (*denpol*; schematic)