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New Bifunctional Polyglycerol Dendrons for Biomedical Applications

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Monika Wyszogrodzka

from Rymań (Poland)

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„Das Wichstigste ist es,
nicht mit den Fragen aufzuhören.”

“The important thing is
not to stop questioning.”

Albert Einstein (1879 – 1955)

Dla Jacka

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6. F. Koc, M. Wyszogrodzka, P. Eilbracht, R. Haag, **Highly Regioselective Synthesis of Amino-Functionalized Dendritic Polyglycerols by a one-pot Hydroformylation /Reductive Amination Sequence** *J. Org. Chem.* **2005**, *70*, 2021-2025.
   DOI: 10.1021/jo0481304
7. M. Wyszogrodzka, R. Haag, **Protein Resistant Properties of Bifunctional Glycerol Dendrons**, *Poly. Mat. Sci. Eng.*, **2007**, *48*, 760-761.

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1 Introduction

The dendritic architecture is a widespread motif in nature such as trees (Figure 1), dendritic cells, neurons in the brain etc. and therefore, this type of architecture is undoubtedly one of the most fascinating polymeric topologies. Their unique properties,[1] which differ significantly from their linear counterparts resulting in an enormous number of applications. These spawn a whole range of new research areas, beginning from biomedical applications through catalysis to material science and nanoengineering.[2-8]

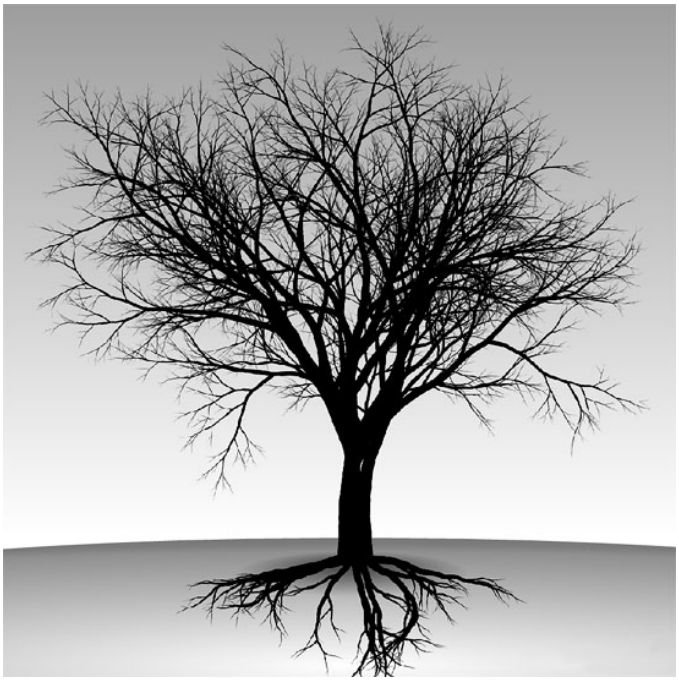


Figure 1. Dendritic structures in nature – a tree with roots.[9]

1.1 Classification of polymers

Staudinger is generally recognized as the father of modern polymer chemistry. In 1920 in his paper "Über Polymerisation" he proposed the "macromolecular hypothesis".[10] He contradicted the theory that polymeric substances are held together by partial valences and instead correctly proposed structures of polymers like polystyrene or polyoxymethylene (paraformaldehyde) as long molecular chains. In this moment the evolution of the different synthetic polymer architectures began, namely: (I) linear, random coil thermoplastics such as nylon or plexiglas; (II) cross-linked thermosets such as epoxides and rubbers; (III)

branched systems based on long chain branching in polyolefins such as low density poly(ethylene); and (IV) dendritic architectures (**Figure 2**).[4]

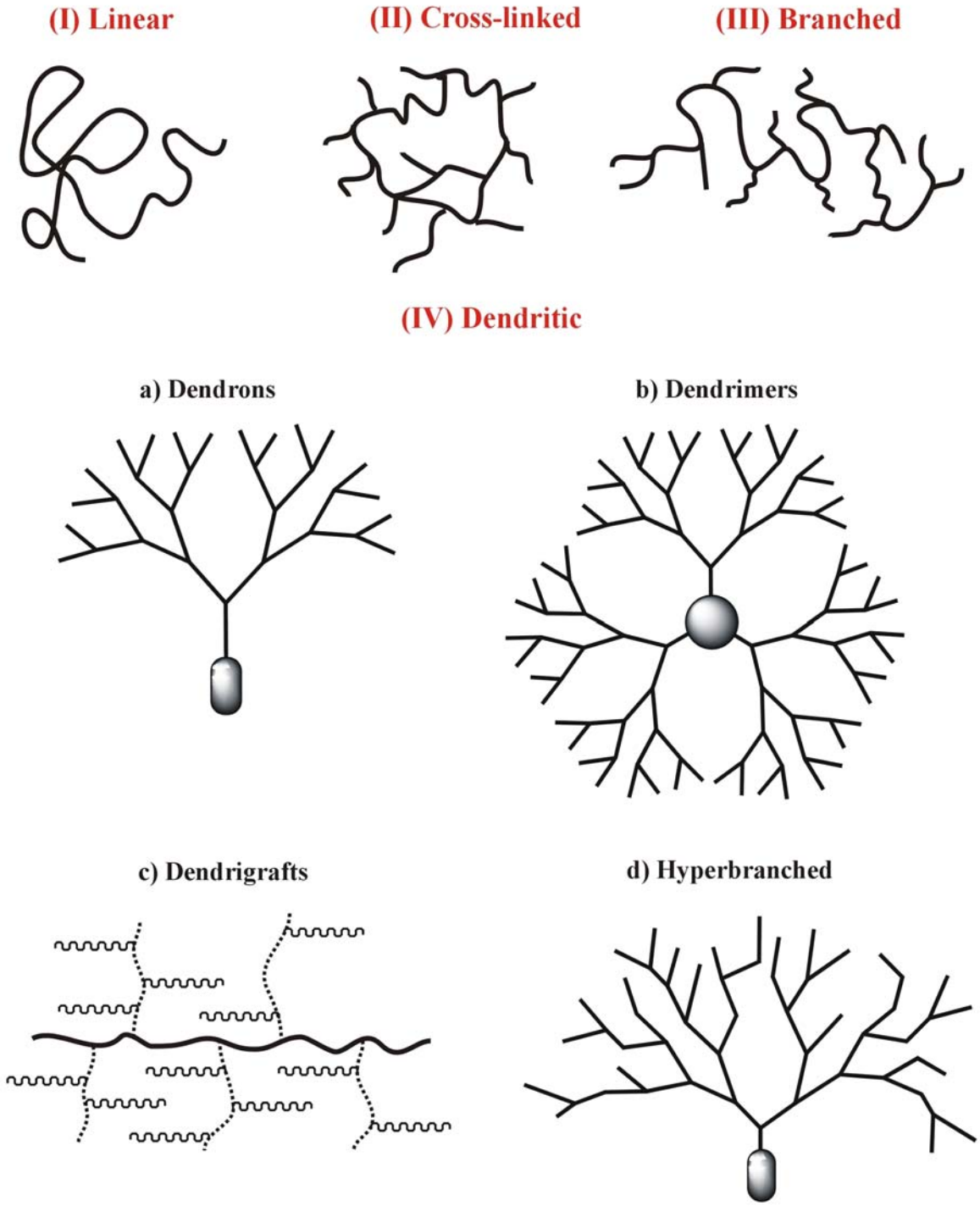


Figure 2. Evolution of synthetic polymers classified into four types of topology: (I) linear, (II) cross-linked, (III) branched and (IV) dendritic.

The first three classes nowadays are recognized as traditional synthetic polymers[10,11] and usually they are characterized by high polydispersity (i.e. **P**oly**D**ispersity **I**ndex PDI = Mw/Mn > 2-10). However, recent developments involving better understanding and therefore control of the polymerization reactions have led to more defined molecular weights.[11-14] Nevertheless, they often show problematic characteristics, such as poor water solubility, chemical stability or accessibility for functionalization.[15-18] Some of the disadvantages of linear polymers may be overcome by using dendritic polymer architectures.

Dendritic macromolecules are a relatively young member of the big family called "synthetic polymers". This new group can be divided into four sub-classes, where the development of different synthetic approaches is mainly emphasized on the controlled structural manipulation of three-dimensional structures (from well-controlled synthesis of dendrons/dendrimers, through semi-controlled process dendrigrafts to uncontrolled synthesis of hyperbranched polymers) (**Figure 2, structures IV**).[3,4,19] *Dendrimers* and *dendrons* are highly uniform, three dimensional, monodisperse polymers with a tree-like, globular structure and a large number of functional groups. The synthesis of dendrimers has been initiated in the late 1970s by Vögtle *et al.*,[20] followed by the pioneering work of Tomalia *et al.*,[21,22] Newkome *et al.*[23] and Fréchet *et al.*[24,25] Since strict control is attained over molecular architectures in this approach, dendrimers/dendrons can have extremely narrow polydispersity (PDI < 1.01) and exactly predictable molecular weights. However, many reaction cycles are necessary to synthesize molecules with high molecular weight. This step-by-step approach can be avoided by the synthesis of *hyperbranched polymers*, the second family member of dendritic polymers. Self-condensation of AB_n monomers leads in one step to high molecular weight macromolecules, albeit with limited structural control. The random polymerization process results in polymers with many structural flaws and high PDIs = 2-10.[26-29]

The last class of dendritic polymers are *dendrigraft systems*, which were independently introduced at the same time by Tomalia *et al.*[30] (as Comb-burst® polymers) and Gauthier and Möller[31] (as arborescent polymers). Dendrigrafts are typically obtained by ionic polymerization and grafting. They combine the features of hyperbranched polymers and dendrimers; namely, their synthesis follows a generation-based growth scheme as in the case of dendrimers, but polymeric chains are used as building blocks. Such approach leads to a very rapid increase in molecular weight per generation, and additionally high molecular weight branched polymers can be produced in a few steps. Therefore, relatively narrow

PDIs (PDI < 1.1) can be obtained, even though the architecture is not as exact as in dendrimers.[2,32,33]

These macromolecules typically exhibit globular structures in combination with a high number of functional groups, good solubility and at the same time low viscosity.[1,34] Therefore, dendritic polymers have been exploited in a remarkable variety of applications. The number of patents and publications concerning dendritic polymers, which have been published over the last three decades, speaks for itself (**Figure 3**).

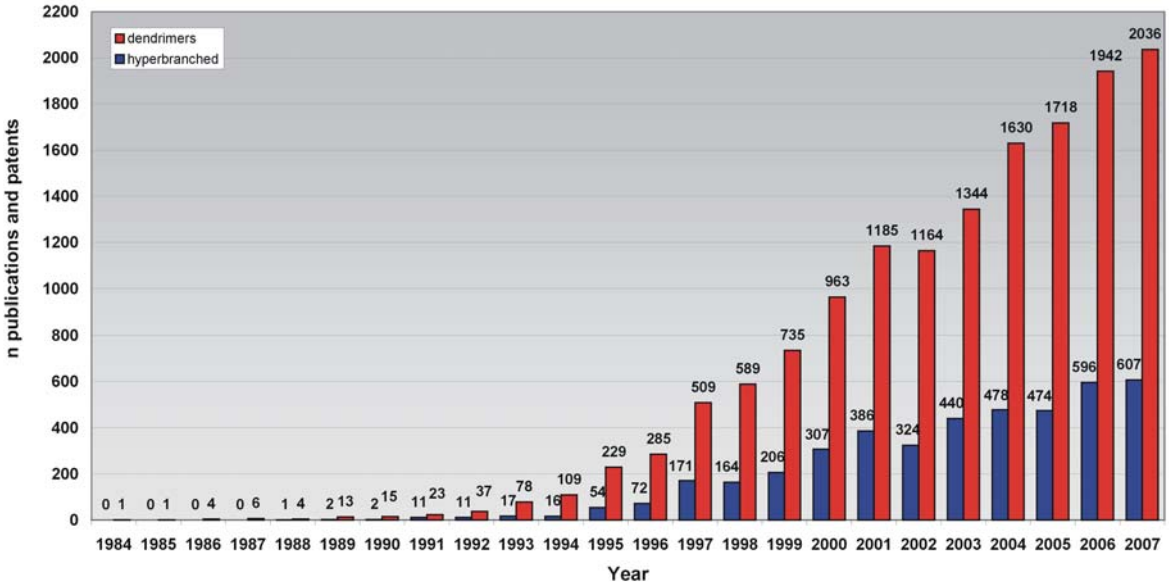
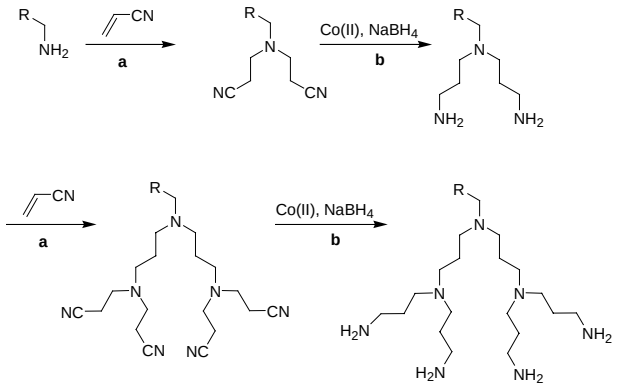


Figure 3. Number of publications and patents with the concept "dendrimer" (red) and "hyperbranched" (blue) in the years 1985 to 2007 (source: SciFinder Scholar 2006).

1.2 Dendrimers and dendrons

1.2.1 Historical aspects

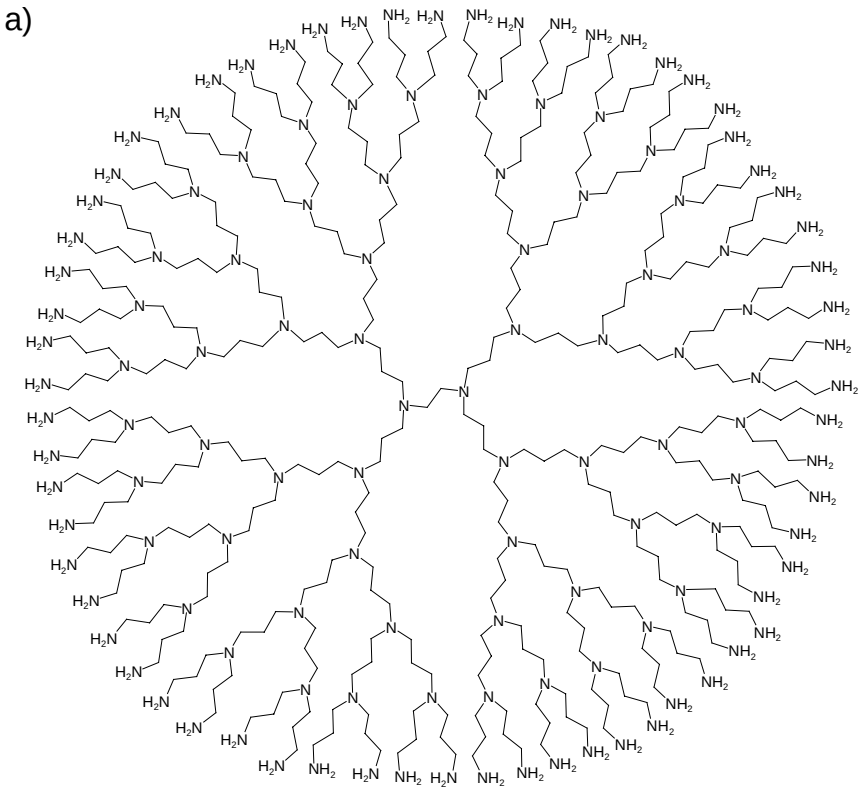
Long before the first dendrimer "was born", Flory proposed in the early 1950s (in his theoretical studies) that the polymerization reaction of the AB_2 monomer might form unusual architectures.[35] In 1978 Vögtle *et al.* reported the first synthetic approach to 'cascade molecules', applying an exhaustive Michael-type addition of acrylonitrile to an amine followed by the reduction of the nitrile groups to primary amines (**Scheme 1**).[20]



Scheme 1. First synthesis of 'cascade molecules' according to the Vögtle's initial publication.[20]

Because of the problems with the work-up after each reduction step the reaction sequence was only repeated twice. Fifteen years later, the above-mentioned problem was successfully solved by two independent research groups, Mülhaupt *et al.*[36,37] and Meijer *et al.*,[36] allowing the synthesis of commercially available poly(propyleneimine) (PPI) dendrimer (**Figure 4a**).

In the early 1980s, Denkewalter filed a patent on the divergent growth approach to obtain dendrimers based on L-lysine up to high generations. However, aside from size exclusion chromatography, no other analytical data were presented.[38-40] Around the same time, two new types of architectures were published by Newkome *et al.*[23] ('arborols')[41] and Tomalia *et al.*[21,22] ('dendrimers'),[42] in which the interactive protocol towards 'tree-like' molecules was applied. However, Tomalia *et al.* reported for the first time the preparation of the whole series (up to 7th generation) of polyamidoamine (PAMAM) 'starburst' polymers (**Figure 4b**). The synthesis was initiated by the Michael addition of three molecules of methyl acrylate to an ammonia core, followed by exhaustive amidation of the resulting ester with large excess of ethylenediamine.



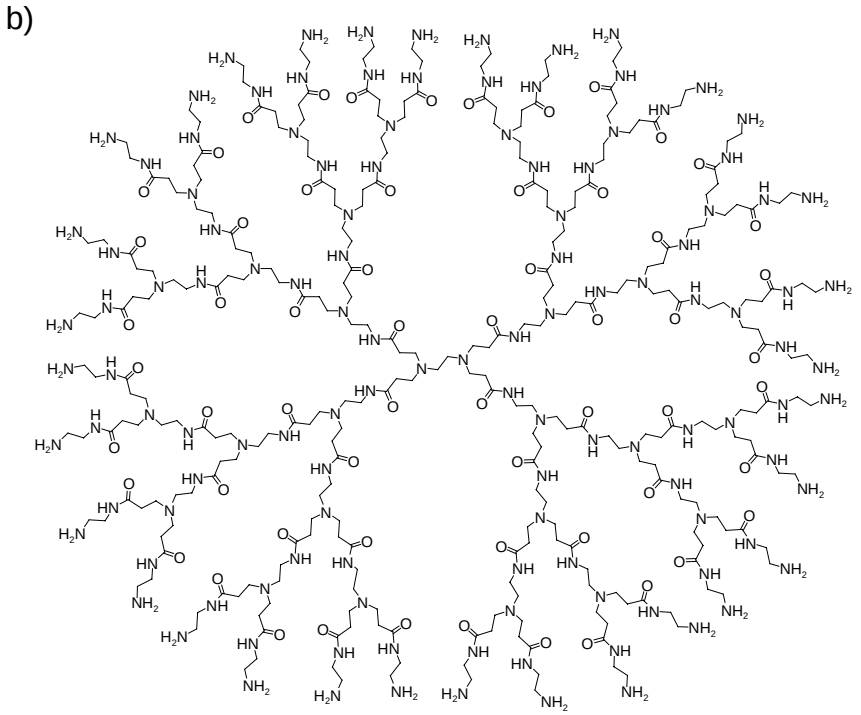


Figure 4. Chemical structure of: a) [G5]-PPI dendrimer[20,36,37] and b) [G4]-PAMAM dendrimer[21,22].

In 1989-1990 Hawker and Fréchet introduced the convergent growth approach, a second general route to synthesize dendrimers (**Figure 5 a**).[24,25] Moore applied this same

approach to produce his phenylacetylene dendrimers (**Figure 5 b**).[43-47] Because of their early synthesis and/or commercial availability all these series'/classes of dendrimers are nowadays the most thoroughly investigated and began to promote the field of dendrimer chemistry (**Figure 2**).

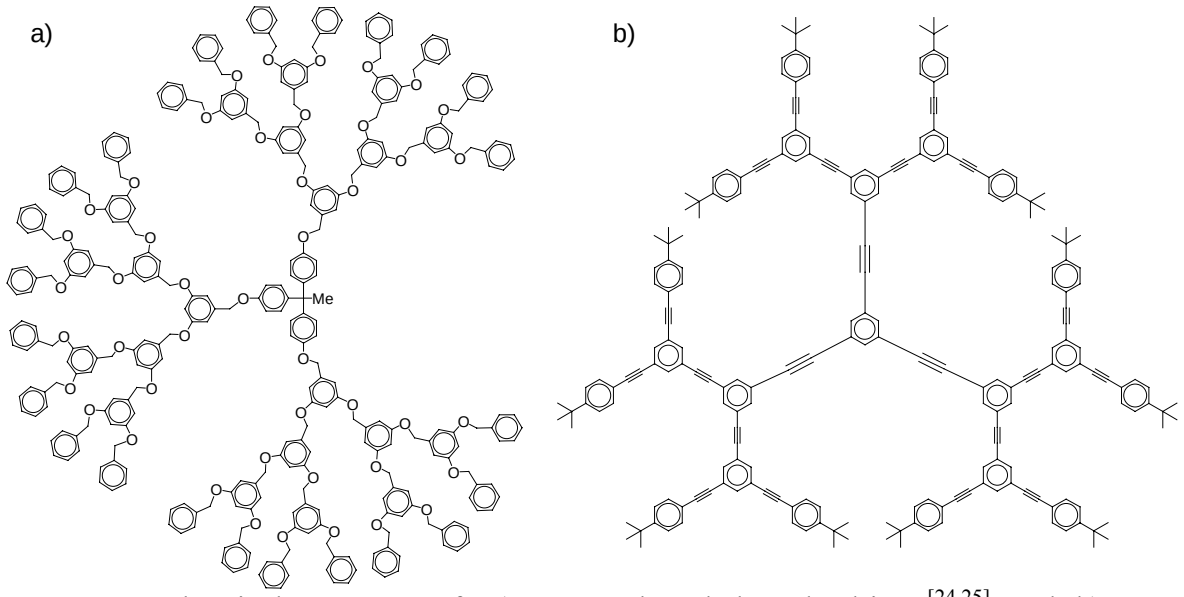


Figure 4. Chemical structure of: a) [G4]-polyarylether dendrimer[24,25] and b) [G3]-polyacetylene dendrimer [43,47,48].

Although the first publication on dendrimers appeared in the late 1970s[20] it is only in 1990 that the first report on phosphorus-containing dendrimers was published.[49-52] The insertion of phosphorus groups into dendrimers, giving new properties, allows the simple synthesis of the highest generation known up to date: generation 12 with a molecular weight above 3.000.000 Da).[53,54] Practically at the same time the description of a silicon containing dendrimer was published.[51,55,56] In addition to generally used building blocks, biologically relevant molecules like carbohydrates[57] or amino acids[58-60] have been applied as monomers.

1.2.2 Synthesis

Two complementary general methods, the divergent approach initiated by Tomalia *et al.*[21] and Newkome *et al.*[23] and the convergent approach by Hawker and Fréchet,[24,25] have been developed for the synthesis of dendrimers, with both leading to the same structure (Figure 6). Choosing the appropriate synthetic method for the preparation of dendrimers enables the control of their molecular weight, size and shape, as well as their functionalization, which might be introduced at the core, at the periphery, or both, depending on the nature of the synthesis. Despite the fact that both approaches lead to the

same dendritic structures, there are some fundamental advantages and disadvantages associated with each synthetic method.

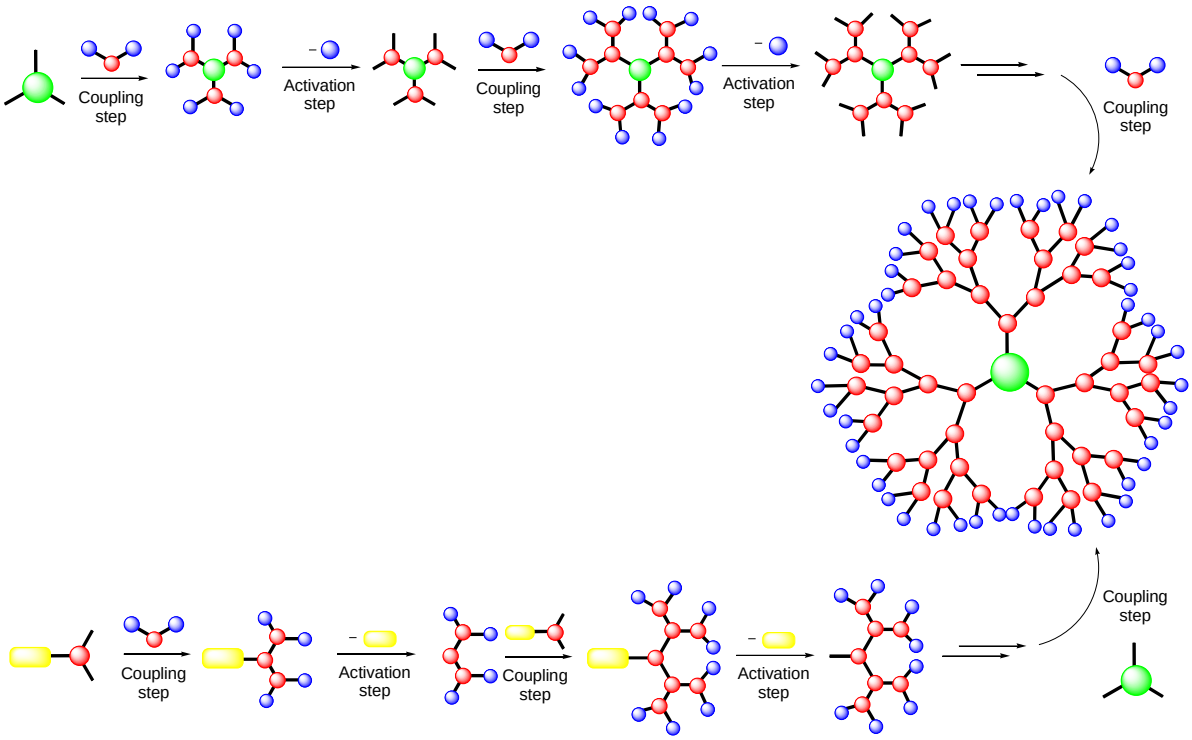


Figure 6. Divergent (upper) and convergent (lower) growth approach to dendrimers. Both approaches are based on the repetition of coupling and activation (or deprotection) steps.

In the divergent approach, the dendrimer grows from a polyfunctional core and expands outwards with the stepwise addition of layers of building blocks to the periphery. As a consequence, numerous reactions have to be performed on a single molecule. Even, when the selectivity of the single reaction is above 99.5 %, the generation [G5.0] of a PPI dendrimer, will be obtained with only 23 % defect-free molecules.[61,62] Although a significant amount of defect molecules is produced, from which purification even by HPLC is impossible, this method is still ideal for the preparation of high dendrimer generations in large quantities. In addition, high generations of dendrimers produced by the divergent approach are still highly monodisperse compared to the narrowest polydispersity linear polymers, even though they contain a number of structural flaws.

The problem of the structural purity of single molecules in the divergent approach has been overcome by the convergent growth approach.[63] Here the synthesis of dendrimers starts from the periphery to a polyfunctional core and therefore the number of reactions performed on a single molecule is reduced. Since the reactions performed on each molecule are not quantitative and purification causes additional losses, the product yield decreases with increasing generation number. Consequently, in the convergent method each molecule

has a precise molecular weight and structure, and can be easily separated from the small amount of by-products. Additionally, the reactions can be performed with a slight excess of the reagents, in contrast to the divergent approach, where a huge excess of the reagent is required to obtain full conversion on high generations. Also, the dendron[64] can be modified at both ends – the focal point and the shell, and further used in coupling with many other dendritic cores. However, a decrease of the yields for dendrimers above the sixth generation caused by steric hindrance is observed.[24,25] In both cases the structural purity of the designed macromolecules can be proved by mass spectroscopy techniques (e.g. MALDI-TOF, ESI-MS etc.).[61]

Besides the above-described two general methods used for the preparation of perfect polymers, a few other approaches have been described in order to accelerate the long and tedious synthetic methodologies. These include the double-stage convergent method (known as well as 'hypercore' method),[45,65-67] hypermonomer method,[68,69] double exponential method[44] and others.[63,70] Nevertheless, the current method dominant in bio-organic chemistry is the copper(I) catalyzed 1,3-dipolar cycloaddition between azide functionality and acetylene unit ("click" reaction),[71] which has attracted significant attention in the material science community. Three years after the seminal work of Sharpless *et al.*,[71] the first synthesis of dendrimers *via* click-type reaction[72] was published by Hawker, Fokin and co-workers.[72] Soon thereafter, Wooley and Hawker described a complementary divergent click approach method to 1,3,5-triazole dendrimers.[73] Albeit, with the introduction of the new highly efficient reactions (e.g. copper-catalyzed azide-alkyne cycloaddition – CuAAC), the synthetic approaches still involve traditional multistep procedures. Recently, the development of an accelerated growth approach to dendrimers based on the chemoselectivity and efficiency of "click" chemistry in combination with traditional etherification/esterification has been described (Scheme 2).[70]