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ScienceDirect

Polymer 49 (2008) 1−173

polymer

www.elsevier.com/locate/polymer

Feature Article

Poly(amidoamine), polypropylenimine, and related dendrimers and dendrons possessing different 1 → 2 branching motifs: An overview of the divergent procedures

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Received 9 July 2007; received in revised form 8 October 2007; accepted 17 October 2007
Available online 24 October 2007

Abstract

This review presents an overview of 1 → 2 branched dendrimers and dendrons, created by a divergent procedure, from their synthesis to modern day applications. The first members of this branched class of fractal macromolecules were prepared through a cascade synthesis, which was later replaced by the iterative divergent synthetic approach. Most classes of this 1 → 2 *N*-, *Aryl*-, *C*-, *Si*-, and *P*-branched families are included and catalogued by their mode of connectivity. Dendritic macromolecules have had significant impact in the field of material sciences and are one of the major starting points for nanotechnology as a result of the numerous modifications that can be conducted, either on the surface or within their molecular infrastructure, thus taking advantage of their unimolecular micelle properties. These host cavities, maintained by the dendritic branches, allow for the incorporation of nanoparticles as well as metal particles, which make these attractive in catalysis and imaging studies. The solubility of these fractal constructs can be tailored depending on their surface modifications. Highly water-soluble, neutral dendrimers appended with, grown from, or acting as hosts to specific molecules give rise to a wide variety of biomedical applications such as drug delivery systems and MRI imaging agents. The inherent supramolecular or supramacromolecular chemistry has been exploited but the design and construction of uniquely tailored macrostructures have just begun. Laser dyes, as well as electron and energy donor and acceptor functionality, have also been paired with these fractal constructs in order to probe their uses in the field of molecular electronics. With their synthetic control, seemingly limitless modifications and wide variety of potential applications, as well as their now commercial availability, these 1 → 2 branched dendrimers have become an important nanostructured tools for diverse utilitarian applications. This review mainly covers 1 → 2 branched non-chiral dendrimers prepared by a divergent process but selected chiral surfaces are considered as well as metal encapsulation and a few hyperbranched routes to related imperfect dendrimers.

Keywords: Dendrons; Dendrimers; Polyamidoamine (PAMAM) dendrimers; poly(propylene imine) dendrimers; divergent synthesis; P-dendrimers; Si-dendrimers; Aryl-dendrimers; review; 1 → 2 branching

1. General concepts

The divergent route to dendrimer synthesis is based on the construction of a molecular superstructure starting with a focal point or core and progressing outward to the periphery, as illustrated in Scheme 1. Dendrimers are built in layers, or generations, upon a defined core that possesses a specific number of active sites, to which the successive tiers are, for the most part, covalently attached. The number of active sites on the core determines their *n*-directionality and limits the number of building blocks that can be added to form the next generation. This trend is repeated (iterative synthesis) as the reactive sites on the periphery of the previous generation are revealed for the assembly of the next generational growth layer. Assuming that the monomer's functional group(s), steric

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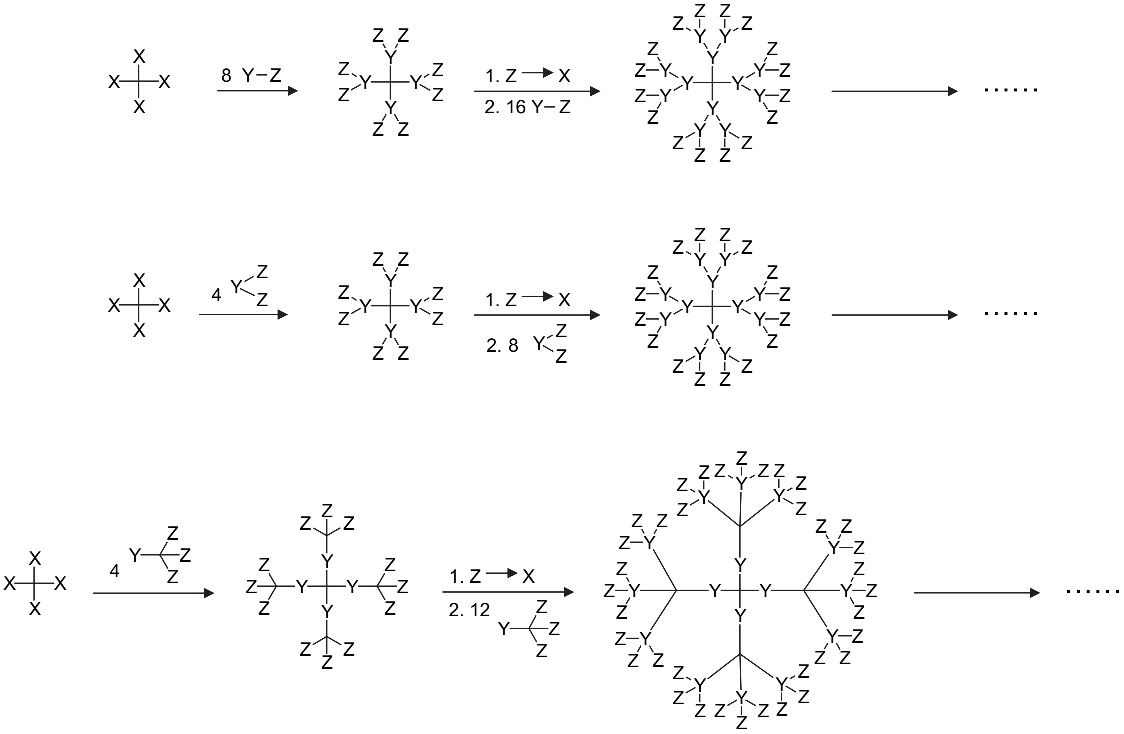
doi:10.1016/j.polymer.2007.10.021



Scheme 1. Divergent procedures for macromolecular construction.

hindrance, and active site accessibility do not interfere with the construction of ideal dendrimers, the divergent process permits the exponential growth of free active sites per generation.

Perfect growth is only achieved when each active site is occupied by a building block (monomer) denoting the next tier; otherwise, imperfect structural assembly results leading to internal termini and variable internal void regions, which starts to resemble a hyperbranched motif normally derived by a random one-step procedure. If these imperfections or "branching defects" occur early in the generational growth, they can have serious repercussions on the overall micellar properties of the resulting dendrimer.

The number of branches in a dendritic structure is dependent on the branching valency of the monomeric building blocks, including the core. If the core is a primary amine, the amine nitrogen would then be divalent, leading to a 1 → 2 branching motif. If three building blocks were added to the primary amine generating an ammonium salt, a 1 → 3 branching motif would result. With a neutral divalent amine core, proceeding with a 1 → 2 fractal branching pattern with a simple commercial (1 → 1) monomer leads to a 1 → 2 → 4 → 8 → 16 → 32 → ⋯ motif. If a tetravalent core is used [Scheme 1 (top)], the procession would follow a 4 → 8 → 16 → 32 → ⋯ branching pattern. Using the same tetravalent core with a 1 → 2 branched monomer [Scheme 1 (middle)] would lead to the same 4 → 8 → 16 → 32 → 64 → 128 → ⋯ branching series; whereas using the 1 → 3 branched monomer [Scheme 1 (bottom)] would lead to a 4 → 12 → 36 → 108 → 324 → 972 → ⋯ branched series with a notable increase in the number of peripheral groups, this latter branching motif will be addressed in a forthcoming review.

2. Early procedures

The preparation and characterization of straightforward fractal-like structures constructed by an iterative approach were first reported in 1978 by Vögtle et al. [1], in the quest for multiarmed, supramolecular materials [2]. This "cascade synthesis" was defined as "reaction sequences which can be conducted repeatingly." The prominent features of polyamine **2d** included the trigonal *N*-branched centers and the minimal distance imposed by the propyl linkage between branching centers and terminus in order to prevent diminished yields resulting from steric hindrance caused by the branching center. A Michael-type addition between amine **2a** and an activated olefin afforded the dinitrile **2b**, which was subsequently reduced to give the terminal diamine **2c**. This simple process was repeated to give the desired heptaamine **2d**. However, due to synthetic difficulties necessary to achieve high yield conversions, the iterative process was curtailed but the most important aspect of this original synthetic methodology [Scheme 1 (top)] was that it introduced the iterative "cascade" method to the chemist's repertoire. Interestingly, Tomalia and Dewald [3] defined a "dendrimer" as a branched macromolecule, which had three or more tiers, and thus heptaamine **2d** is technically not a dendrimer; it is, however, an example of a multi-armed [2], meso- [4] or medio-molecule (Scheme 2).

In a series of patents from 1979–1983, Denkewalter et al. [5–7] reported the first divergent preparation of fractal-like polypeptides possessing an 1 → 2 *C*-branching pattern