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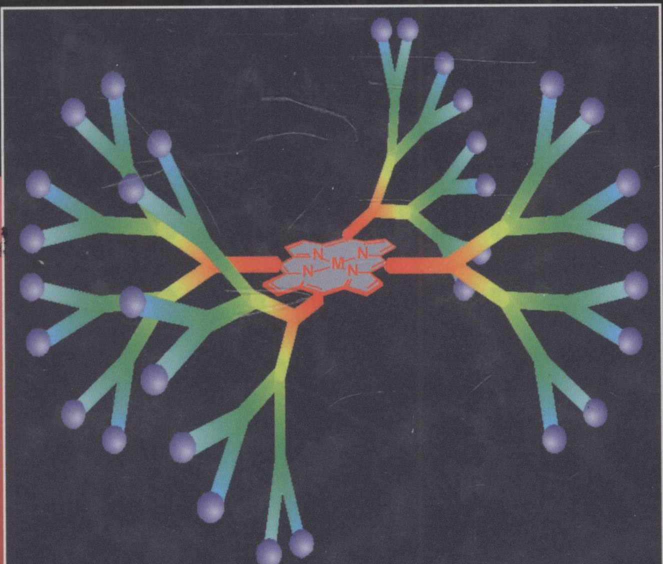
DENDRIMERS AND OTHER DENDRITIC POLYMERS



Edited by

Jean M. J. Fréchet and

Donald A. Tomalia

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Dendrimers have been referred to as "the polymers of the 21st Century." These macromolecules are characterized by "branch upon branch" architecture and are now rapidly expanding the general fields of polymer science and chemistry. Dendritic polymers are the most recently discovered, fourth major architectural class of macromolecules. They represent a fourth major class after traditional types which include (I) linear, (II) cross-linked and (III) branched architectures.

Dendrimers and Other Dendritic Polymers provides a detailed insight into dendritic polymers, and discusses all the known subclasses of dendritic polymers in addition to dendrons and dendrimers, including hyperbranched polymers, dendrigrafts and megamers.

Dendrimers possess unique structures and exhibit properties that differ dramatically from those of the more traditional polymer types. These features have contributed to multi-disciplinary applications and now many major chemical companies are investing extensively in dendritic polymer research as they are investigating their broad commercial applications. They are currently being developed for use in the pharmaceutical and chemical industries with identified applications in areas as diverse as: drug delivery, cancer therapy, nano-pharmaceuticals, nano-diagnostics, nanolithography, coatings and adhesives, separation technology and catalysis.

With contributions from many of the leading scientists in the field of dendritic polymers, this comprehensive volume provides:

- an overview of developments in the field of dendrimers, with a comparison of properties and synthesis to traditional polymers
- discussion of commercial and potential applications for dendritic polymers
- an identification of the key trends and analytical perspectives in dendrimer research
- practical procedures for the laboratory preparation of some of the more commonly used dendrimer families.

This will be essential reading for all chemists, polymer/material scientists, plastics engineers, nanotechnologists and postgraduate polymer scientists and engineers.

Cover Picture: 3D Dendrimer Porphyrin. Reproduced with permission of Dr Stefan Hecht, University of California, Berkeley, USA.

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Series Preface

The Wiley Series in Polymer Science aims to cover topics in polymer science where significant advances have been made over the past decade. Key features of the series will be developing areas and new frontiers in polymer science and technology. Emerging fields with strong growth potential for the twenty-first century such as nanotechnology, photopolymers, electro-optic polymers etc. will be covered. Additionally, those polymer classes in which important new members have appeared in recent years will be revisited to provide a comprehensive update.

Written by foremost experts in the field from industry and academia, these books place particular emphasis on structure–property relationships of polymers and manufacturing technologies as well as their practical and novel applications. The aim of each book in the series is to provide readers with an in-depth treatment of the state-of-the-art in that field of polymer technology. Collectively, the series will provide a definitive library of the latest advances in the major polymer families as well as significant new fields of development in polymer science.

This approach will lead to a better understanding and improve the cross fertilization of ideas between scientists and engineers of many disciplines. The series will be of interest to all polymer scientists and engineers, providing excellent up-to-date coverage of diverse topics in polymer science, and thus will serve as an invaluable ongoing reference collection for any technical library.

John Scheirs
June 1997

A Brief Historical Perspective

D. A. TOMALIA AND J. M. J. FRÉCHET

The dendritic architecture is perhaps one of the most pervasive topologies observed on our planet. Innumerable examples of these patterns [1] may be found in both abiotic systems (e.g. lightning patterns [1], snow crystals, tributary/erosion fractals), as well as in the biological world (e.g. tree branching/roots, plant/animal vasculatory systems, neurons) [2]. In biological systems, these dendritic patterns may be found at dimensional length scales measured in meters (trees), millimeters/centimeters (fungi) or microns (neurons) as illustrated in Figure 1. The reasons for such extensive mimicry of these dendritic topologies at virtually all dimensional length scales is not entirely clear. However, one might speculate that these are evolutionary architectures that have been optimized over the past several billion years to provide structures manifesting maximum interfaces for optimum energy extraction/distribution, nutrient extraction/distribution and information storage/retrieval.

The first inspiration for synthesizing molecular level tree-like structures evolved from a lifetime hobby enjoyed by one of the editors (D.A.T.) as a horticulturist/tree grower [3]. The first successful laboratory synthesis of such dendritic complexity did not occur until the late 1970s. It required a significant digression from traditional polymerization strategies with realignment to new perspectives. These perspectives utilized major new synthesis concepts that have led to nearly monodispersed synthetic macromolecules. The result was a new core–shell macromolecular architecture, now recognized as *dendrimers*.

The concept of repetitive growth with branching was first reported in 1978 by Vögtle [4] (University of Bonn, Germany) who applied it to the construction of low molecular weight amines. This was followed closely by the parallel and independent development of the divergent, macromolecular synthesis of true dendrimers in the Tomalia Group [5,6] (Dow Chemical Company). The first

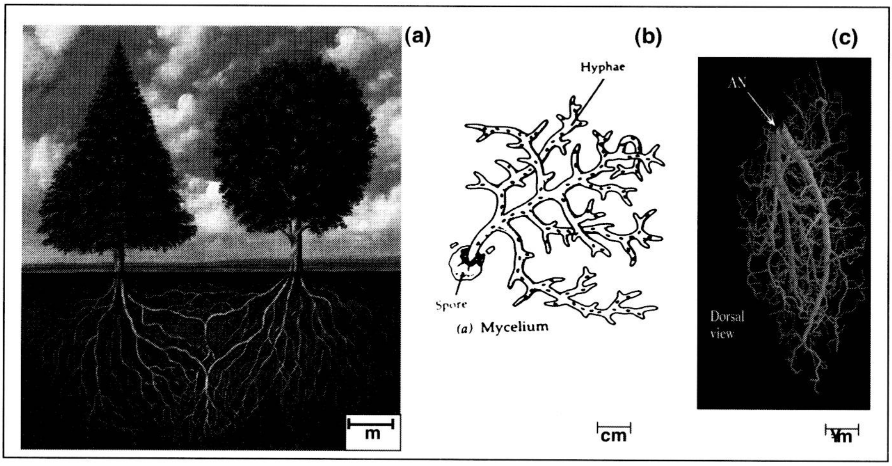

Figure 1 (a) Coniferous and deciduous trees with root systems, (b) fungal anatomy and (c) giant interneuron of a cockroach.

paper [6] describing in great detail the preparation of poly(amidoamine) dendrimers appeared in 1985, the same year a communication reported the synthesis of arborols [7] by Newkome et al. (Louisiana State University).

The divergent methodology based on acrylate monomers was discovered in 1979 and developed in the Dow laboratories during the period of 1979–85. It did not suffer from the problem of low yields, purity, or purification encountered by Vögtle in his 'cascade' synthesis, and afforded the first family of well characterized dendrimers. Poly(amidoamine) (PAMAM) dendrimers with molecular weights ranging from several hundred to over 1 million Daltons (i.e., Generations 1–13) were prepared in high yields. This original methodology was so successful that today it still constitutes the preferred commercial route to the trademarked Starburst® dendrimer family.

In contrast, the divergent iterative methodology involving acrylonitrile used by the Vögtle group [4] was plagued by low yields and product isolation difficulties and could not be used to produce molecules large enough to exhibit the unique properties that are now associated with the term 'dendrimer'. It was only a decade and a half later that two research groups Wörner/Mülhaupt [8] (Freiburg Univ.) and de Brabander-van den Berg/Meijer [9] (DSM), were able to develop a vastly enhanced modification of the Vögtle approach to prepare true poly(propyleneimine) (PPI) dendrimers. The route developed by the DSM group is particularly notable as it also constitutes a viable commercial route to this family of aliphatic amine dendrimers.

Since the 'dendrimers' discovery occurred in a Dow corporate laboratory, the period 1979–1983 was spent filing many of the original dendrimer 'composition of matter' patents [62–71]. The key Dow Starburst® dendrimer research team members associated with this initial research and development effort are shown in Figure 2. It was not until 1983, that corporate approval was given for the first public presentation of this work (by D.A.T.) at the Winter Polymer Gordon Conference in January (1983) (Santa Barbara, CA). It was after attending this Conference that de Gennes predicted the fundamental dendrimer surface congestion properties that are now referred to as the 'de Gennes [10] dense packing' phenomenon. Excitement and controversy generated at this Gordon Conference concerning this new class of monodispersed dendritic architecture led to an intense schedule of invited lectures during 1984–1985 which included: The Akron Polymer Lecture Series (April 1984), American Chemical Society Great Lakes/Central Regional Meeting (May 1984) and the 1st International Polymer Conference, Society of Polymer Science Japan, in Kyoto (August, 1984). The first use of the term 'dendrimer' to describe this new class of polymers, appeared in the form of several abstracts published during that year. The first SPSJ International Polymer Conference preprint [5] and the seminal full paper [6] that followed describe the preparation of dendrimers and their use as fundamental building blocks that may be covalently bridged to form poly(dendrimers) or so-called 'starburst polymers' as shown in Figure 3.

Figure 2 Original Dow dendrimer research team (l.-r back row: Pat Smith, Steve Martin, Mark Hall, John Ryder; front row: Jim Dewald, Don Tomalia, George Kallos, Jesse Roeck (photo taken (1982) in Dow's Functional Polymer Research Laboratory, 1710 Bldg, Midland, MI where first complete series of PAMAM dendrimers (G=1–7) were synthesized)

Polymer Journal, Vol. 17, No. 1, pp 117—132 (1985)

A New Class of Polymers: Starburst-Dendritic Macromolecules

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(Received August 20, 1984)

ABSTRACT: This paper describes the first synthesis of a new class of topological macromolecules which we refer to as "starburst polymers." The fundamental building blocks to this new polymer class are referred to as "dendrimers." These dendrimers differ from classical monomers/oligomers by their extraordinary symmetry, high branching and maximized (telechelic) terminal functionality density. The dendrimers possess "reactive end groups" which allow (a) controlled moelcular weight building (monodispersity), (b) controlled branching (topology), and (c) versatility in design and modification of the terminal end groups. Dendrimer synthesis is accomplished by a variety of strategies involving "time sequenced propagation" techniques. The resulting dendrimers grow in a geometrically progressive fashion as shown: Chemically bridging these dendrimers leads to the new class of macromolecules—"starburst polymers" (*e.g.*, $(A)_n$, $(B)_n$ or $(C)_n$).

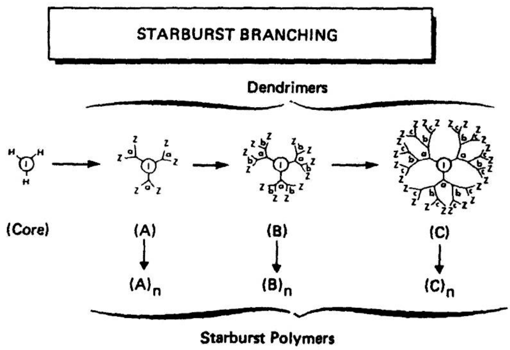

Figure 3 Abstract of first full paper (reference 6) describing dendrimers

After the appearance of the seminal 1985 paper from the Tomalia group, there was an enormous amount of intrinsic interest in dendritic polymer architecture. On the other hand, there was substantial resistance to accepting research results for publication by many of the major scientific journals, some of the reasons cited by the critics of that period included the following:

1. How can one be certain the higher molecular weight dendrimers (i.e., $> G = 2$) are as monodispersed as proposed?
2. Dendrimers are no different than 'microgels' –they are probably highly cross-linked particles akin to latexes,

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