DENDRIMER-BASED
DRUG DELIVERY
SYSTEMS
Wiley Series in Drug Discovery and Development

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DENDRIMER-BASED DRUG DELIVERY SYSTEMS

From Theory to Practice

Edited by

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FOREWORD

History has shown that seminal discoveries of the first three major traditional polymer architectures; namely: (I) linear, (II) cross-linked, and (III) branched architectures were in all cases followed by predictable patterns of intense international scientific and commercial activity. Unarguably, these activities were fueled by the emergence of unprecedented new architecturally derived properties and possibilities. Many of these architecturally driven properties have provided the basis for new scientific principles, applications, and commercial products which have served to enrich the human condition. Meanwhile, the past three decades since the discovery of the fourth major polymeric architecture; namely: “dendritic polymers/dendrimers” has proven to be no exception. Consistent with past patterns, a fivefold increase in literature publications (i.e., > 15,000) has been documented for the past decade (2000–2011) compared to the first two decades since the discovery of this new architectural class. Furthermore, a recent survey has predicted extraordinary demand for nanomedicine derived products to grow over 17% per year through 2014 to an estimated market size of $75.1 billion, with subsequent growth to exceed $149 billion by 2019.¹

Presently, dendrimers are viewed as one of the most preeminent and actively researched platforms in this rapidly emerging field of nanomedicine. More specifically, these precise nanostructures are presently receiving intense attention in the rapidly growing area of “dendrimer-based drug delivery.” This explosive activity is largely attributed to a growing list of unique architecturally driven properties manifested by dendrimers, which includes the following:

• Precise synthetic control over: size, shape, and surface chemistry to produce nanostructures that scale closely to proteins, yet do not exhibit immunogenic responses.

• Well defined, versatile surface/interior chemistry that may be engineered to deliver therapeutic levels of conjugated pro-drugs, nanocontainer, drug encapsulation features, targeting group/selected biodistribution properties in concert with designed surface moieties that exhibit acceptable toxicity properties and safety margins.

• Precise size calibrated nanostructures that may be suitably decorated with appropriate imaging or stimuli responsive moieties for \textit{in vivo} “theranostic” applications.

• Well-defined nanostructure sizes and features (i.e., self-immolative/biodegradable) suitable for engineering desirable excretion modes.

Professor Yiyun Cheng from East China Normal University has assembled an international team of esteemed dendrimer pioneers and researchers for the purpose of sharing their valued perspectives on all facets of \textit{Dendrimer-Based Drug Delivery—From Theory to Practice}. In this comprehensive survey, a number of critical issues are analyzed that bridge the critical path from fundamental concepts, design, synthesis, analytical methodologies, biological assessment to the practical use of dendrimers for drug delivery applications. More specifically, major points of emphasis may be categorized and summarized as follows:

• Introduction to dendrimer-based drug delivery systems, synthesis of dendrimers, physicochemical/biological properties of dendrimers and dendrimer complexes, synthesis and biological evaluations of dendrimer-based prodrugs, and the effect of dendrimers on the therapeutic properties of drugs: \textit{Chapters 1–5};

• The importance of biocompatibility to dendrimer-based drug delivery systems, and strategies used to improve the biocompatibility of dendrimers including stimuli-responsive, degradable, and self-immolative dendrimers: \textit{Chapters 6–8};

• Applications of dendrimers in the delivery of DNA and siRNA, including complex structures, \textit{in vitro} and \textit{in vivo} transfection efficiency, and potential administration routes, and the synthesis and pharmaceutical applications of glycodendrimers: \textit{Chapters 9–11};

• Nuclear magnetic resonance techniques in the analysis of dendrimer-based drug delivery systems, and the applications of dendrimers in magnetic resonance imaging and computed tomography: \textit{Chapters 12–14}.

In summary, based on the experience/quality of authorship and the range of critical issues reviewed, this book represents a unique collection of know-how for understanding and practicing unprecedented new drug delivery strategies in the context of nanomedicine. This book should serve as a valuable resource for both academic and commercial investigators who are seeking promising new strategies for the safe and effective delivery of \textit{in vivo} therapies, imaging and diagnostics.
PREFACE

Dendrimers are hot research points and have been widely used in supramolecular chemistry, host–guest chemistry, electrochemistry, photochemistry, as templates for nanoparticle synthesis, as scaffolds for catalysts, and in drug and gene delivery. Among these applications, biomedical applications of dendrimers have attracted increasing interest during the past decade. Because of the unique opportunities, issues, and challenges involved with exploiting dendrimers for drug delivery, there is a need for a book to help pharmacists and related scientists understand and work with this new class of promising biomaterials. This timely book covers topics including dendrimer history, synthesis, physicochemical properties, principles in drug delivery, and applications in miscellaneous biomedical fields, and provides practical suggestions for the design and optimization of dendrimer-based drug delivery systems.

This book includes 14 chapters. Chapter 1 presents a historical view on dendrimer chemistry and gives supramolecular perspectives on dendrimers. Chapter 2 focuses on the physicochemical properties of dendrimers and dendrimer complexes. Chapter 3 discusses the use of dendrimers to tailor the physicochemical and therapeutic properties of loaded drugs. In Chapter 4, Caminade and Majoral summarize the biological properties of phosphorus dendrimers that were developed in their laboratory. Chapter 5 reports the synthesis and biological applications of dendrimer-based prodrugs. Chapter 6 aims at the safety of dendrimers and proposes several strategies to improve the biocompatibility of dendrimers. Chapter 7 emphasizes the importance of dendrimer degradability for drug delivery. Chapter 8 focuses on the design of stimuli-responsive dendrimers for biomedical purpose. Chapter 9 presents dendrimer-based gene delivery systems. The administration routes and in vivo evaluations of dendrimer/DNAs complexes are also discussed. Chapter 10 also introduces dendrimer applications in gene delivery but emphasizes triazine dendrimers that were developed
in Simanek’s research group. In Chapter 11, Roy and coworkers introduce the use of carbohydrate-functionalized dendrimers as drug delivery Trojan horses. Chapter 12 relates the applications of NMR techniques in the analysis of dendrimer-based drug formulations. In Chapters 13 and 14, Shi et al. introduce the applications of dendrimers in magnetic resonance imaging and computed tomography imaging.

This book is directed primarily at the pharmaceutical sciences, and aims to be the definitive reference book for scientists in the field of biomaterials, nanomedicine, drug delivery systems, pharmacy, and dendrimer chemistry. It is my hope that it can stimulate the interest of researchers from these fields.

YIYUN CHENG
ACKNOWLEDGMENTS

Many people have helped with the book *Dendrimer-Based Drug Delivery Systems: From Theory to Practice*, and here is my chance to express my acknowledgments.

Firstly, I would like to thank the contributing authors (Prof. D. A. Tomalia from NanoSynthons, Prof. G.R. Newkome from University of Akron, Prof. A.M. Caminade from Laboratoire de Chimie de Coordination, Prof. T. Imae from National Taiwan University of Science and Technology, Prof. M.M. De Villiers from University of Wisconsin-Madison, Prof. A. D’Emanuele from University of Central Lancashire, Prof. M. Gingras from Aix-Marseille University, Prof. E. Simanek from Texas A&M University, Prof. R. Roy from Université du Québec à Montréal, Dr. A. Schatzlein from University of London, and Dr. C. Kojima from Osaka Prefecture University, and Prof. X.Y. Shi from Donghua University) for their cooperation to make this book a reality, and to Miss J.J. Hu and Miss L.B. Zhao in University of Science and Technology of China, and Mr X.Y. Feng in University of Akron for their efforts in editing this timely work. Special thanks are also given to Prof. T.W. Xu for his valuable comments and suggestions on the chapters.

Finally, I would like to dedicate this book to my wife, Jiepin Yang, for her assistance and encouragement during the preparation of this book.

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DENDRIMER CHEMISTRY: SUPRAMOLECULAR PERSPECTIVES AND APPLICATIONS

CHARLES N. MOOREFIELD, SUJITH PERERA, AND GEORGE R. NEWKOME

“There are many beautiful molecular architectures, it is just that some are easier to access than others.”

Roald Hoffman, Nobel Prize in Chemistry, 1981

1.1. INTRODUCTION

1.1.1. Historical Background

Dendritic chemistry, from its initial development to its application in the construction of utilitarian devices and materials, has provided a great amount of proverbial cement for interdisciplinary integration. Similar to polymer (or macromolecular) chemistry, conceptualized and postulated by luminaries such as Flory [1–3] (Nobel—1974) and Staudinger (Nobel—1953) who provided a new foundation for material sciences, dendrimer chemistry has generated another new level of scaffolding upon which a myriad of potential uses are being explored and exploited.

First introduced as “cascade” molecules due to their repeating motif by Vögtle and coworkers [4] in 1978, materials analogously termed arborols (derived from the Latin word arbor for tree) and dendrimers (derived from the Greek word dendro for tree) were reported by Newkome et al. [5] and Tomalia et al. [6] both in 1985, respectively. While these reports specifically addressed the potential to craft branching molecular architectures with multiple terminal functionality and repetitive branch junctures
(Tomaila, 1 → 2 branching based on linear building blocks; Newkome, 1 → 3 branching based on modular building blocks with preconstructed branching centers) another notable report appeared by Aharoni and coworkers [7] in 1982 describing the “Size and Solution Properties of Globular tert-Butoxycarbonyl-poly(α,ɛ-L-lysine).” Their study involved the characterization of 1 → 2, asymmetrically branched materials that were termed “nondraining globular biopolymers” that were iteratively prepared and reported in 1981 (U.S. patent 4289872, Denkewalter et al. [8]). Other notable and interesting reports prior to the explosive advent of dendritic chemistry, include the iterative synthesis of ultralong, linear paraffins reported by Bidd and Whiting [9], the early observation by Ingold and Nickolls [10] of the entrapment of gas molecules by methanetetaacetic acid, and Lehn’s elegant modular approach [11] to cryptate syntheses.

1.1.2. Architectural Concepts

Dendritic molecules can be envisioned by considering the repetitive layering of multifunctional building blocks based on a protection and deprotection scheme or the addition of increasing numbers of linear, complementary monomers. This generally results in a branched, tree- or fractal-like, molecular motif whereby each incorporated layer provides a foundation for the successive layer. Since the number of reactive sites and branching centers increases with each layer, a “mushrooming” framework is produced. The synthetic protocol can be visualized (Scheme 1.1) by considering the attachment of a generic 1 → 3 branched building block 1 that possesses three reactive sites differentiated from the 4th. Thus, treatment of monomer 1 with three equivalents of a like monomer produces a new monomer 2 with the same functional

![SCHEME 1.1](image-url)  
**SCHEME 1.1** Divergent and convergent routes to branched architecture.
group characteristics as the starting materials, except that the periphery has now grown and expanded to a $1 \rightarrow 9$ branched construct.

The iterative dendritic strategy has developed into two general modes of construction. The divergent route, initially introduced by Vögtle et al. [4], whereby molecular growth essentially proceeds from the “inside outward” and the convergent route, introduced in 1990 by Fréchet et al. [12], resulting in growth from the “outside inward.” Differences in the two methods arise from building block order of addition and can be affected by the control over functional group activation and deactivation. Thus, logical choices of protection–deprotection strategies derived from classical synthetic chemistry are a prime importance in dendritic chemistry. Addition of nine equivalents of a triprotected monomer $1$ to the surface of a growing specie $2$ will lead to the progressively greater branched construct $3$. The same material (i.e., $3$) can be derived convergently by inverting the process to add three equivalents of the $1 \rightarrow 9$ higher–order, branched monomer to the simple monomer. Both methods allow the construction of dendritic material and also have their individual strengths and weaknesses. For example, divergent syntheses requires an ever increasing number of monomer attachment reactions leading to a higher probability of incomplete reactions at the ever-expanding periphery leading to a greater number of imperfections; whereas, convergent methods instill a greater probability to generate perfect structures due to few required reactions for layer construction, albeit at lower molecular weights. The potential to locate and connect at a single site within a growing multifunctional monomer diminishes with size and the attendant steric hindrance. Predicated on these features and a comprehensive mass spectrometry analysis, divergent and convergent methods have been compared to polymer and organic syntheses, respectively, by Meijer et al. [13].

As with most other unique areas that attract much attention, descriptive terminology has been developed within the dendritic chemistry community. While much is intuitive, a brief discussion is warranted. The central point from which all branching emanates is described as a core; whereas, the outer surface, or peripheral region, is populated with terminal groups ($4$; Fig. 1.1). Branching centers define the branching multiplicity based on the number of functional groups or reactive sites that they possess (i.e., 2, 3, or greater) and layers are often referred to as generations to easily denote the number of iterations used in construction. Notably, dendritic void volume is a valuable and useful property and has been employed by many research groups for purposes such as micellar entrapment, host–guest interactions, and catalytic site construction, to mention but a few. This feature has given rise to a new area of study upon which this book is largely based—drug delivery and pharmacological agents using dendritic species.

Branched monomers, or building blocks, used in dendritic construction are now commonly referred to as dendrons, in analogy to synthons in classical organic chemistry. Many dendrimers have been reported [14] using nonbranched monomers; however, their monomers are usually not described as dendrons owing to their linear characteristic. Arising from the convergent protocol, the single reactive site on a multifunctional dendron is described as the focal site. The individual layers of building blocks that comprise dendritic structures are generally denoted as
generations, which in turn allow for easy descriptive terminology and a ready understanding of the potential number of surface moieties provided the multiplicity of the core and dendron(s) are known. The concept of dense packing arises from the consideration of increasing numbers of surface groups and a proportionately decreasing amount of available surface area; hence, at some level of construction there will not be enough surface area to accommodate a stoichiometric number of building blocks. This aspect may or may not be problematic and will depend on the desired end characteristics of the material(s) in question.

Ultimately, consideration of dendritic generation leads to the question – structurally, what constitutes a dendrimer? Numerous reports in the literature describe new dendritic species comprising only a single generation. In many cases, a zeroth-generation construct is reported. The importance, elegance, and usefulness of these materials notwithstanding, they are not dendrimers in an historical or idealized sense. They do not possess repeating architectural details at different generations. Therefore, we will herein only describe those materials possessing the attributes of greater than two generations as belonging to a dendrimer family and they must be structurally characterized.

1.1.3. Initial Reduction to Practice

In 1978, a branched covalent molecular architecture was initially reported (Scheme 1.2) by Vögtle et al. [4]. Their scheme represented the first report of a repetitively branched, polyfunctional molecule whereby all to the intermediates were isolated, purified, and substantially characterized in contrast to the traditional synthesis of a polymer whereby only the starting materials and products are isolated and verified. The synthetic protocol utilized Michael-type, nucleophilic amine
addition to an electron-poor cyanoalkene followed by reduction of the cyano groups to generate new amine moieties used for further reaction. Thus, for example, amine 5 was treated with acrylonitrile in the presence of glacial acetic acid to give bis-nitrile 6 that was then reduced with NaBH$_4$ and CoCl$_2$·6H$_2$O to afford diamine 7. Repetition of the sequence generated polynitrile 8 and subsequently polyamine 9 possessing 3 tertiary and 4 primary amino moieties. The procedure was also undertaken with diamines such as 2,6-diaminomethylpyridine and diaminoethane to give the corresponding 16 amine constructs.

The authors described these new materials as cascade- or nonskid-chain-like owing to the repeating pathway for bond formation and they devised the scheme for the construction of large molecular cavities capable of host–guest interactions. This general procedure was also applied to diaza-monocyclic rings for the construction of polycyclic medium- and large-ring materials.

Approximately 1 year later, in 1979, Denkewalter et al. [8] reported in a patent the construction of high molecular weight materials based on step-wise coupling (Scheme 1.3). This was the first example of dendritic materials construction using a protection–deprotection strategy and a preformed 1 → 2 C-branching center inherent in the building block. Their scheme employed the 4-nitrophenol-activated ester of N,N-bis(tert-butoxycarbonyl)-l-lysine (11), a chiral-protected amino acid, as the dendron. Treatment of an initial diamine 10 with the BOC-protected diamino-activated ester 11 followed by removal of the BOC groups (CF$_3$CO$_2$H) afforded the tetraamine trisamide 12. Repetition of the sequence generated the octaamine 13 and eventually led to dendrimers with theoretically 512 terminal lysine groups corresponding to nine generations. With no characterization reported in the patent, Aharoni et al. [7] subsequently aided in the characterization of these impressive materials by examining the viscosity, photo correlation spectroscopy (PCS), and size exclusion chromatography (SEC). It was concluded that each generation was monodisperse and that these materials behaved as nondraining spheres.
During 1985, Newkome and coworkers [5] published the first example of a $1 \rightarrow 3$ C-branched dendrimer, then termed an arborol for its likeness to tree architecture (specifically, the Leeuwenberg model [15] that branched $1 \rightarrow 3$ in a similar manner to that of tetrahedral, tetravalent carbon) and its terminal alcohol groups. In the same year, Tomalia and coworkers [6] reported their work with $1 \rightarrow 2$ $N$-branched materials, which they described as starburst dendrimers (derived from the Greek root dendro- for tree-like); these were the first series of polyamines to be prepared in high generation. These two dendritic examples are the first fractal families that were fully characterized.

Newkome’s synthesis [5] (Scheme 1.4) began with a polyalcohol (14) that was extended by reaction with chloroacetic acid, under basic conditions, and subsequently esterified to give triester 15. Reduction with LiAlH$_4$ and treatment with tosyl chloride afforded the activated triol 16 that was next reacted with the Na$^+$ salt of methane-tricarboxylic triethyl ester (17) to generate the nonaester 19 followed by amidation with tris(hydroxymethyl)aminomethane (18); the resulting 27-alcohol 20 was isolated as a white solid that was freely soluble in water. The requisite extension of the alcohol moieties was necessary due to substitution of the bulky triester nucleophile, which precluded repetition of the scheme, however, this was the first example of dendrons possessing preconstructed $1 \rightarrow 3$ branching centers.

Other arborols constructed using these building blocks included the bolaamphiphile, dumbbell-shaped [9]-(CH$_2$)$_n$-[9] and [6]-(CH$_2$)$_n$-[6] series [16,17], where [9] or [6] denotes the number of hydroxyl groups connected by alkyl chains with $n$. 

SCHEME 1.3  Synthetic method for Denkewalter et al. polylysine dendrimers.
equal 8 to 12 carbons. These materials formed thermally reversible gels upon cooling of aqueous and alcoholic solutions at low concentrations. Gel formation was characterized by electron microscopy and predicated on maximizing lipophilic–lipophilic and hydrophilic–hydrophilic interactions [28]. Arborols [18] constructed with an aromatic benzene core also formed spherical aggregates in solution with diameters of approximately 20 nm and have recently been shown to assemble into large, hollow, spherical motifs [18]. Notably, the globular shape was postulated to be reminiscent of a *unimolecular micelle* [5].

Tomalia’s protocol [6] was similar to that of Vögtle’s [4] in that it relied on the reaction of linear monomers and generated branching centers by the Michael-type reaction of electron-poor alkenes with a nucleophilic amine during the construction of successive layers. Thus, in an early example (Scheme 1.5), three equivalents of methyl acrylate (21) were reacted with ammonia to give the triester 22 followed by generation of a new triamine core (24) by treatment with diaminoethane (23). Based on the minimally sterically demanding building blocks, repetition of the sequence to afford hexamine 25 and higher generations was smoothly facilitated. This initial report described the second instance of an iterative synthesis accessing materials up to seven generations.

These manuscripts provided the foundation for the burgeoning field that dendritic chemistry is today, however, as it is with most scientific advances, chemistry before and after has played a major role. Thus, advances in the field of macromolecular science by pioneers such as Flory, who reported theoretical [1–3] and experimental [19] evidence for the existence of branched-chain, three-dimensional materials in 1941 and 1942, respectively, began to focus attention on the potential that macromolecules
might eventually play in the chemical and materials science arenas. Stockmayer [20] added to the interest by developing equations for branched-chain size distribution and the extent of reaction where a “gel,” or network, should be formed. Flory [21] later considered the formation of $1 \rightarrow 2$ branched polymers and their scaling properties, notably describing what has now become the well-known area of “hyperbranched” dendrimers. Along with growing interest in macromolecules during the formative years of polymer chemistry, scientists such as Staudinger [22] postulated that materials like rubber were really high molecular weight polymers and not aggregates of smaller species. Studies by Carothers [23] on condensation polymerizations supported this idea. Lehn [11] subsequently introduced step-wise strategies for the construction of macrocyclic rings in 1973 and later received the Nobel Prize in Chemistry (1987) for work on the host–guest chemistry of designed molecular cavities [24] (e.g., cryptands).

Following these initial reports of Vögtle [4], Newkome [5], Denkwalter [8], and Tomalia [6], research into dendrimer properties and chemistry began to accelerate. Balzani and coworkers [25] introduced metallodendrimers; Hawker and Fréchet [26] developed the convergent protocol; Masamune et al. [27] reported the first preparation of silicon-based dendrimers; de Gennes (Nobel 1991) and Hervet [28] described the first theoretical study of dendrimers; Seebach et al. [29] delineated their work in the preparation of chiral dendrimers; Hudson and Damha [30] described the construction of DNA-based dendrimers; Moore and

**SCHEME 1.5** Tomalia’s original dendrimer synthesis based on linear building blocks.
Xu [31] exploited phenylacetylene chemistry for dendrimer construction; Meijer and de Brabander-van den Berg [32,33] along with Wörner and Mülhaupt [34] reported, in back-to-back manuscripts, improved procedures for the large-scale preparation of Vögtle-type, polypropylenimine (PPI) dendrimers; Majoral and coworkers [35] reported the first phosphorous-based dendrimers; Zimmerman et al. [36] described the self-assembly of a complex dendrimer based on hydrogen-bonding at the core; and Schlüter et al. [37] reported their work on dendrimerization of a classic polymer framework.

This abbreviated historical account, while not all-inclusive, is intended to give the reader a flavor of the beginnings, or roots, of the current dendritic arena. There are many scientist and researchers, who have contributed to the milestones of dendritic chemistry, which not only strives for new synthetic methods for theoretical and utilitarian applications, but also include an element of artistic style. It is the relative simplicity of design and construction of these complex polyfunctional architectures along with their ease of integration and synergy with other areas of chemistry that affords dendritic chemistry its unique position among materials building blocks. Numerous accounts of the history [38], theory [39], syntheses [40], and applications [38,41] of dendrimers exist in the literature and it is assumed the reader will pursue their topic of choice; a selected survey is herein presented.

1.2. SUPRAMOLECULAR PERSPECTIVES

1.2.1. Unimolecular Micelles—The Advent of the Container

Early reports heralding the potential of dendritic architecture include Newkome and coworkers [42,43] construction of the first example of a unimolecular micelle (defined in the seminal 1985 report [18]) possessing an all saturated hydrocarbon infrastructure and charged carboxylate surface groups. The unimolecular micelle concept is illustrated in (Fig. 1.2) along with representations of a classical micelle comprising a collection of associated long chain hydrocarbons with polar head groups that are bound together by noncovalent van der Waals- and ionic-based forces and a surface-networked, micellar aggregate accessed from a classical micelle with polymerizable head groups. Surfactant-based, micellar aggregates have been known and used in numerous applications for many years, however, structural dependence on temperature, surfactant concentration, ionic strength, and hydrophilic–hydrophobic environment adds several “degrees-of-freedom” to their utilitarian considerations. Thus, dendrimer chemistry has provided a means to eliminate or control these aggregate phenomena.

Synthesis of the unimolecular micelle [42] was facilitated by the crafting of 1 → 3 C-branched dendrons (Scheme 1.6) possessing functional groups sufficiently removed (3 CH2 moieties) from the quaternary branching center to allow for smooth end group transformation [44]. Beginning with the Michael-type addition of acrylonitrile to nitromethane to generate a nitrotrinitrile, followed by hydrolysis of the nitrile groups to carboxylic acids and subsequent reduction to the corresponding
FIGURE 1.2 Idealized representations of a micelle, a polymerized aggregate, and a unimolecular micelle.

SCHEME 1.6 Synthesis of 1 → 3 C-branched, hydrocarbon-based dendrons.