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THE CONVERGENT ROUTE TO GLOBULAR DENDRITIC MACROMOLECULES: A VERSATILE APPROACH TO PRECISELY FUNCTIONALIZED THREE-DIMENSIONAL POLYMERS AND NOVEL BLOCK COPOLYMERS

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Dedicated to the memory of our friend and colleague Tatsuya Kato (1962–1992)

ABSTRACT

The convergent growth approach to dendritic macromolecules is a versatile method for the preparation of globular molecules with highly controlled three-dimensional architectures. The method, inspired from a classical organic disconnection approach, starts growth of the globular dendrimer at what will become its chain-ends and proceeds toward what will become its center. The convergent growth has been applied to the preparation of a number of unconventional dendritic block copolymers as well as hybrid globular–linear copolymers that are not readily accessed by other routes. Control of the chemistry and the precise location of the chain-ends in convergent dendrimers is essential for the preparation of micellar, amphiphilic, dipolar, or other structures that may be useful in applications as varied as drug delivery and molecular devices.

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INTRODUCTION

The importance of molecular architecture and its control is being recognized to a greater extent as synthetic molecules are increasingly targeted to perform the functions of natural polymers, such as enzymes, or to be used as building blocks for molecular devices or other nanotechnologies. The field of supramolecular chemistry has seen an explosion of activity in recent years, and advances are expected to be made at a rapid pace as the field is approached from several directions including, but not limited to, biology, organic chemistry, polymer science, and material science.

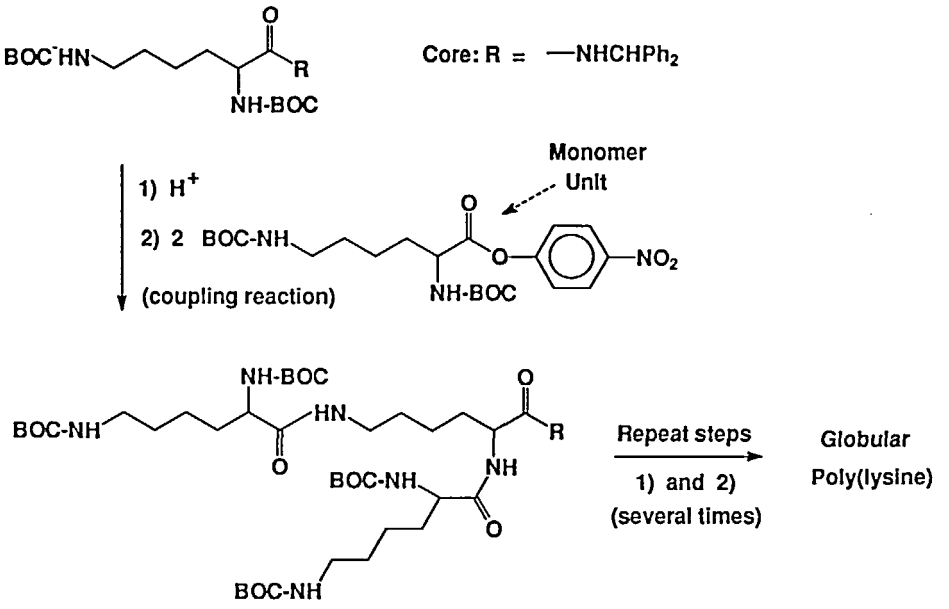
Due to their highly branched nature and three-dimensional architecture, dendritic macromolecules adopt a globular shape that is very different from the random coil structure of classical one-dimensional linear polymers. While the latter have properties that reflect their extensive entangled state, globular dendrimers are believed to be essentially free of chain entanglement. It is the nature of their surface that is expected to have the most influence on their ultimate properties. The well-defined molecular topology of dendrimers has stimulated much research as exciting new applications are being anticipated in areas that range today from medical imaging to rheology control.

Following a brief historical introduction to dendritic macromolecules, this article will focus on our own laboratory's approach to dendritic macromolecules involving a highly versatile *convergent growth approach*. Although emphasis will be directed toward the controlled synthesis of novel globular and hybrid globular–linear architectures, a glimpse into their unusual properties will also be included.

THE DIVERGENT OR STARBURST APPROACH TO DENDRIMERS: A BRIEF HISTORICAL ACCOUNT

The early days of dendritic macromolecules saw the development of several related synthetic strategies for the preparation of highly branched structures. All of these approaches feature target molecules containing a layered arrangement of bonds emanating from a central core, with a branch point at each monomer repeating unit. The poly(lysine) "compounds" reported by Denkewalter [1] in 1981 were the first globular polymers prepared by a repetitive stepwise process originating from a polyfunctional core, a process we now refer to as *divergent growth*. In this process shown in Scheme 1, a protected lysine with two reactive amino groups is used for the attachment of two molecules of bis(*t*-BOC)-L-lysine nitrophenyl ester using standard peptide coupling procedures. After removal of the *t*-BOC protecting groups, four reactive amino groups are available for yet another coupling step, and the process of coupling/deprotection is used over and over again until a highly branched poly(lysine) of the desired size is obtained.

Although the *concept* of the divergent synthesis of dendritic structures was outlined in Denkewalter's patents [1, 2] as well as in an earlier publication by Vögtle [3], the products that were obtained in all cases have remained poorly characterized and it is likely that they were highly contaminated by unwanted structures. For example, the divergent "cascade" growth of an oligomeric polyfunctional nitrile by a series of Michael addition and reduction reactions could not be carried out to a



SCHEME 1.

molecular size sufficient for the resulting molecule to behave as a dendritic polymer. This early drop-off in reactivity, coupled with the limited characterization data made available [3], suggests that significant side-reactions may indeed have interfered with true and regular dendritic growth.

It was not until 1984–5 that the potential of the divergent approach to this type of globular molecules became fully apparent. Both Tomalia [4, 5] and Newkome [6] reported their successes in the preparation of highly regular Starburst and Arborol dendritic structures by very different divergent growth chemistries. It was Tomalia who coined the term "dendrimer" in the first conference report of his work in 1984 [4]. Unlike Denkewalter's poly(lysine)s that were obtained from the unsymmetrical building block, both Tomalia's and Newkome's globular macromolecules were obtained using building blocks and synthetic steps that preserved a high degree of symmetry about the junction points. This choice of building blocks and synthetic steps has proven critical as globular poly(lysine)s that have unequal branch segments appear to have rather unremarkable physical properties [7] when compared to those of the symmetrical and more regular Starburst and Arborol structures [8].

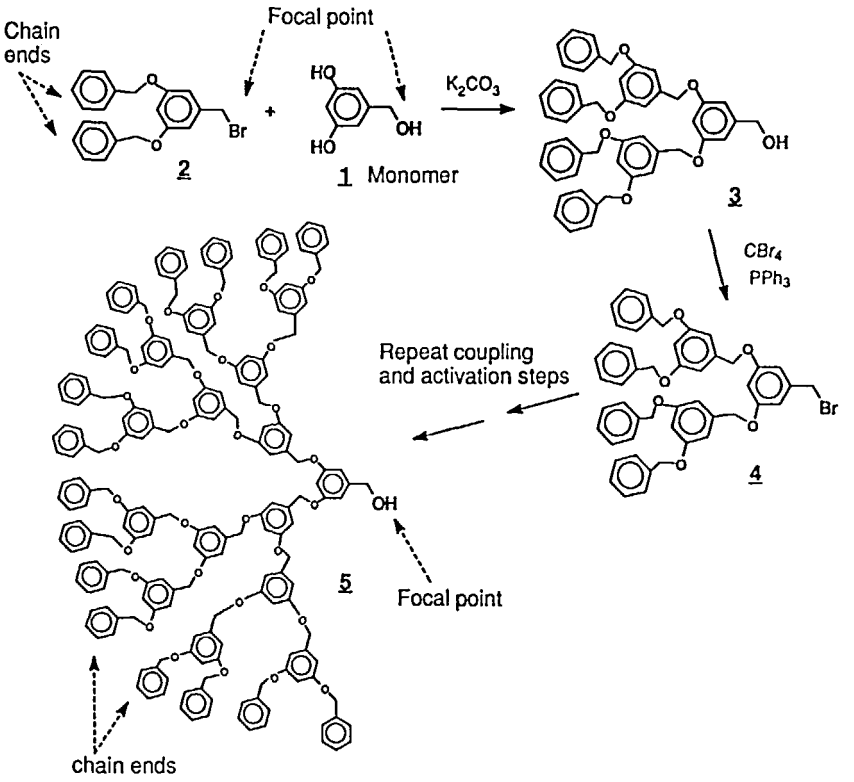
As emphasized earlier, a characteristic feature of these divergent dendrimer syntheses [5, 6, 8–10] is that growth begins at a central polyfunctional core, proceeding radially outwards in a series of two-step (coupling and activation) processes. The repeat unit contains a single coupling site and at least two protected branching sites. For example, Tomalia's well-known Starburst polyamidoamide dendrimers [5] grow from a trifunctional ammonia core through coupling of methyl acrylate to each of the three reactive sites in a Michael addition. Following purification, the growing molecule is activated by exhaustive amidation using excess 1,2-diaminoethane, a process that leads to a doubling of the number of active N—H

groups in the growing molecule. The coupling-activation procedure, as well as the critical intermediate purification steps, are repeated for each generation growth until the desired molecule with multiple ester or amine chain-ends is obtained. Through clever engineering, Tomalia and coworkers have been able to carry out the routine production of PAMAM dendrimers on a scale of several hundred grams [11]. A somewhat similar concept is used in Newkome's Arborol synthesis [10] that also proceeds via divergent growth with several reactions required for each generation growth. The ingenious use of a variety of branched building blocks and spacer groups has led to an array of different Arborol structures with significant variations in inner and end-groups chemistries [10, 12, 13]. However, because the number of chain ends increases rapidly at each stage of the divergent growth process, care must be taken to ensure that all of these reactive sites react in the same way in order to preserve the ultimate regularity of the dendrimers.

DEVELOPMENT OF THE CONVERGENT GROWTH APPROACH

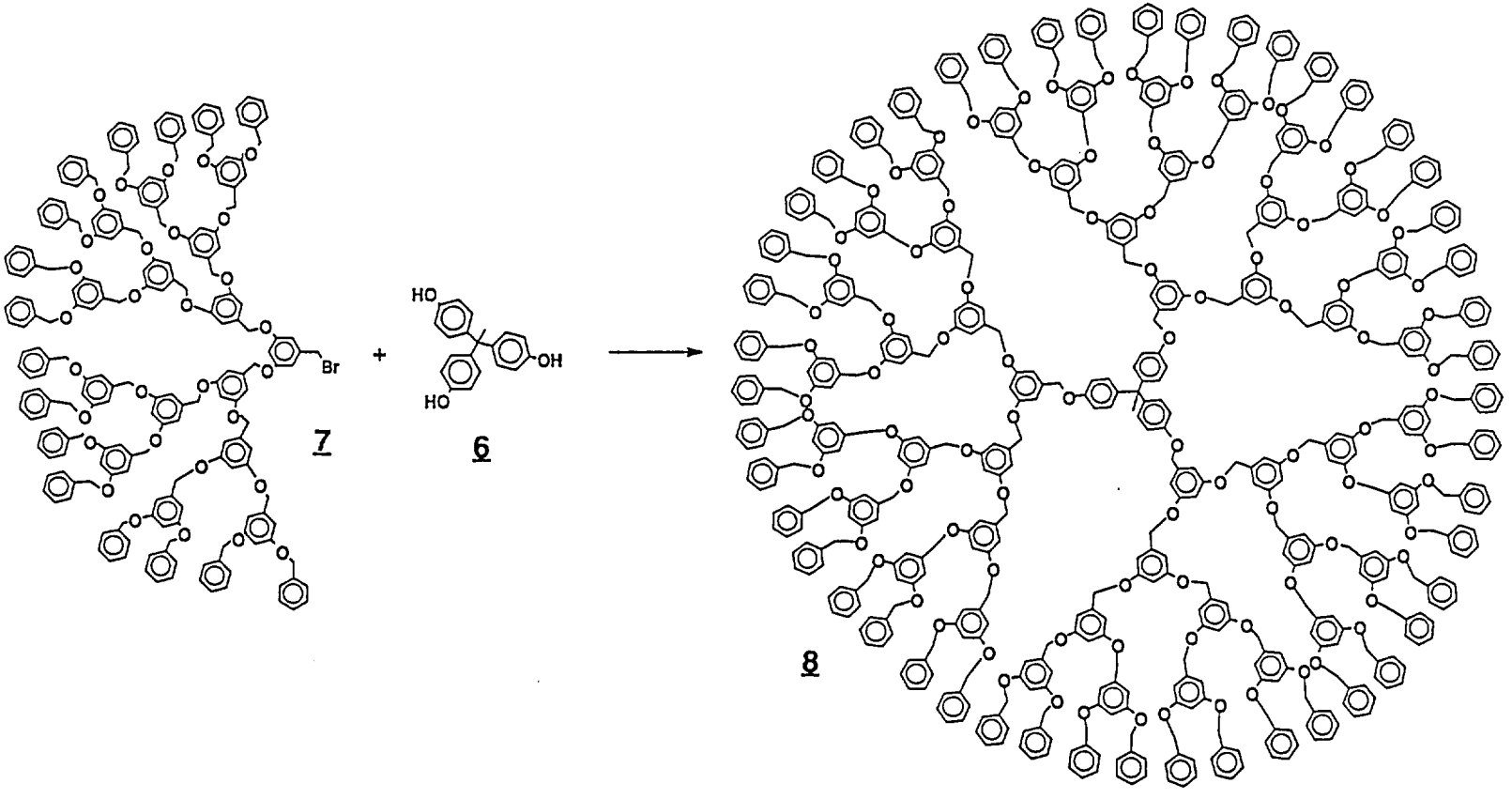
From a synthetic chemist's viewpoint the divergent approach, although very successful, is relatively uncontrolled. A conscious decision was made to apply the disconnection approach used in classical organic synthesis to the preparation of dendritic macromolecules. Due to the highly symmetrical nature of dendrimers, disconnection eventually leads to the chain ends as the logical starting point for the synthesis. Therefore, growth is begun at the chain ends, and repetition of a two-step growth process involving coupling to the branching sites of the monomer, followed by activation of the single remaining reactive site, leads to larger and larger dendritic fragments. If desired, a final reaction may consist of the attachment of several of these large fragments (also known as dendritic "wedges" or "dendrons") to a polyfunctional core. In essence, this new approach is the opposite of the divergent growth approach, and we termed it the *convergent growth approach to dendritic macromolecules* [14–16]. Unlike the divergent approach, generation growth involves only coupling reactions at a finite and constant number of reactive sites of a *monomer* rather than at an ever-increasing number of sites of a growing *dendrimer*. This leads to a greater degree of control over the purity and structural integrity of the products. A very convenient feature of dendrimers prepared by convergent growth is the continuous presence of a unique functional group at the "focal point" of the molecule. While the primary role of this unique functional group is to provide a site for reaction with the monomer in the coupling step, it can also be used to attach pre-formed dendrimers to other molecules through highly controlled and simple processes.

To demonstrate this new "convergent" approach, the synthesis of a series of dendritic polyether macromolecules based on 3,5-dihydroxybenzyl alcohol **1**, as the monomer unit, was carried out as shown in Scheme 2 [15]. The first step of the two-step process involves a reaction of the benzylic bromide [G-1]-Br, **2**, which is our first generation dendrimer, with the monomer unit, **1**, in the presence of potassium carbonate and 18-crown-6 to give the next generation alcohol [G-2]-OH, **3**. It is worth noting that monomer **1** is selected both for its symmetry and its regiochemistry with two phenolic sites to be used in generation growth and branching, and a unique benzylic alcohol functionality that will constitute the focal point of all



SCHEME 2.

successive generations of dendrimer. Activation of the benzylic alcohol focal point group by a simple bromination reaction is the second step of the synthetic strategy that allows for further growth through coupling with the monomer. Compound **2** itself is derived from monomer **1** by attachment of the chain-ends (in this case a simple unsubstituted benzyl group) to the phenolic sites and bromination of the focal point. Conversation of **3** to the corresponding second generation bromide, [G-2]-Br **4**, is followed by attachment of two molecules of **4** to monomer **1**. Repetition of this two-step process leads to successive generations such as the fourth generation alcohol **5** with a single reactive focal point and 16 chain-ends (Scheme 2). We have continued to the sixth generation bromide [G-6]-Br, having the molecular formula $C_{889}H_{763}BrO_{126}$ (molecular weight 13,542), with a single reactive bromide group at its focal point and 64 chain-ends [15]. Yet larger dendrimers may be obtained by coupling several of the individual dendrons to a polyfunctional core. For example, a series of highly regular polyether dendrimers was prepared by alkylation of 1,1,1,-tris(4′-hydroxyphenyl)ethane, **6**, used as a core molecule with a very slight excess (typically 5%) of the individual dendrons. The choice of a phenolic core allows this final reaction to be carried out using the same high yielding *O*-alkylation chemistry previously optimized for generation growth. Scheme 3 shows the reaction of three molecules of the fourth generation bromide, **7** or [G-4]-Br (a *mono*dendron), with one molecule of the core **6** to afford the *tri*dendron dendrimer, $[G\text{-}4]_3$-



SCHEME 3.

[C], **8** ($C_{671}H_{576}O_{93}$, MW = 10,127). The largest dendritic macromolecule in this series was prepared by threefold attachment of the sixth generation bromide, [G-6]-Br, to the same triphenolic core to afford a macromolecule of molecular formula $C_{2687}H_{2304}O_{381}$ (MW = 40,689) with no remaining reactive focal point groups but with 192 chain-ends. At every step of the synthesis the products were readily purified by either recrystallation or flash chromatography, allowing the isolation of essentially monodispersed dendrimers. Purification is greatly facilitated by the fact the "impurities" resulting from a partial reaction, such as the coupling of only two dendrons to a trifunctional core, are very different in both molecular weight and polarity from the product obtained by normal coupling at all three sites. In the example given above, the possible "impurities" (e.g., mono or bidendron) obtained in the last step would have a molecular weight lower by more than 13,000 a.m.u. than that of the desired tridendron product. The presence of an unreacted phenolic site on any "impurity" would also suffice to ensure its removal by chromatography. The same applies to incomplete reactions at the two sites of a monomer unit during generation growth. We have recently shown that high performance liquid chromatography is a powerful tool that can easily distinguish between closely related dendritic structures [17]. Numerous other characterization tools were also applied to the various dendrimers to confirm their purity after the appropriate purification step [15].

An apparent limitation of the convergent approach is the requirement that increasingly larger dendrons must be used for generation growth, leading to potential steric problems. Though real at high generations, this limitation is of little practical concern as very large and essentially monodisperse dendrimers can be prepared, as demonstrated above, even with a very "compact" monomer unit such as **1**. As will become apparent later, even dendrimers of relatively modest sizes such as the fourth generation **5** adopts the globular shape for which properties associated with this shape are seen.

A broad spectrum of core molecules and monomers is available for use in the convergent growth. Less compact, "looser" building blocks can be used to prepare even larger dendrimers less susceptible to steric inhibition at high generation. For example, large dendritic polyphenols, termed hypercores, containing up to 24 phenolic groups have been used successfully in the preparation of high molecular weight dendritic polyethers [18]. Alternatively, the core or focal point group may be selected to provide access to dendrimers with different topological characteristics. We have tested the use of fullerene derivatives containing a precisely controlled number of phenolic groups to afford unconventional globular macromolecules with a C_{60} spherical core [19]. Similarly, the attachment of a polymerizable molecule such as *p*-chloromethylstyrene or acryloyl chloride at the focal point of a dendritic alcohol such as **5** can be employed [20] to prepare dendritic macromonomers.

Subsequently, we have extended the convergent growth approach to the synthesis of polyesters [21], polyamides [22], and sterically less demanding polyethers [18]. In all cases the products were fully characterized and defects could be readily distinguished. Other workers in the field have also employed the convergent growth approach, notably Miller and Neenan who have independently reported the convergent synthesis of dendritic polyphenylenes [23], polyesters [24], and polyamides [25]. Several other groups have also used the convergent growth approach to prepare a variety of materials such as polyamides [26], polyetherketones [27, 28],

polyphenylacetylenes [29], polysiloxanes [30], dendritic nucleic acids [31], dendritic polyradicals [32], organometallics [33], polyethers with a porphyrin core [34], etc.

SOME UNIQUE FEATURES OF DENDRITIC MACROMOLECULES

Having confirmed the viability and versatility of the convergent growth approach as well as demonstrated that the method can lead to essentially monodispersed dendrimers, we initiated a study of the properties of dendrimers. The aim of this study was to explore any unique characteristic that may be derived from the dendritic architecture.

Polyether dendrimers based on 3,5-dihydroxybenzyl alcohol were used in the first stage of the study. The test group included both dendritic wedges (or monodendrons) and tridendrons dendrimers resulting from the attachment of three monodendrons to trifunctional core 6 from generation 0 to generation 6 (molecular weights ranging from 576 to 40,689). In collaboration with researchers at the Eastman Kodak Company, a comprehensive study of the variation of intrinsic viscosity with molecular weight was undertaken [35].

It is well known that for classical linear polymers such as poly(styrene), the viscosity increases sharply with molecular weight according to the Mark–Houwink–Sakurada equation, $[\eta] = KM^a$, in which $[\eta]$ is the intrinsic viscosity of the polymer

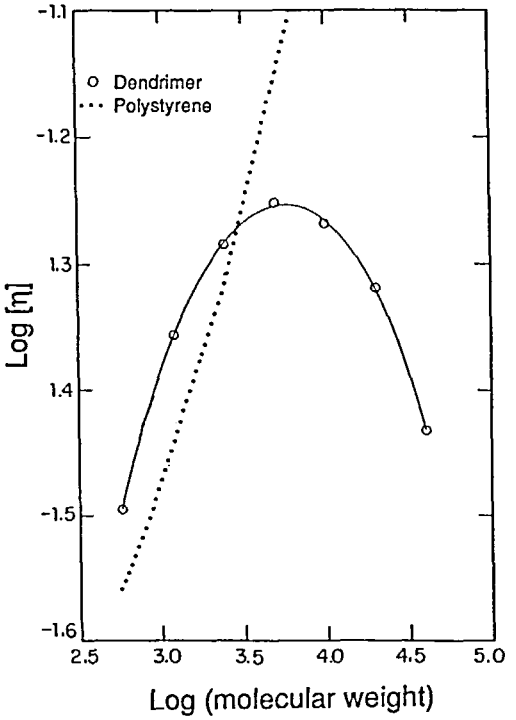


FIG. 1. Intrinsic viscosity behavior as a function of molecular weight for polyether dendrimers such as **8**.

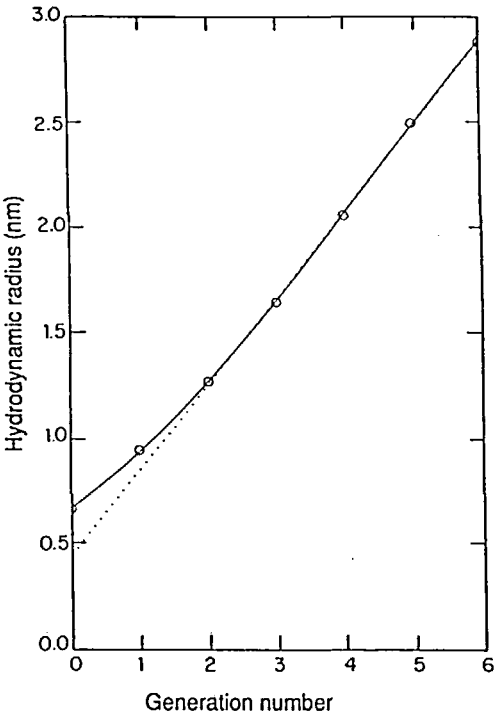


FIG. 2. Variation of hydrodynamic radius for polyether dendrimers (such as 8) as a function of their generation number.

while M is its molecular weight and K and a are constants for a given polymer. Unlike almost all other macromolecules, even including branched and star polymers, dendrimers do not obey this relationship once a threshold molecular weight is reached. In the case of the polyether dendrimers this threshold is reached near 5000 a.m.u. and further increases in molecular weight result in a lowering of the intrinsic viscosity as shown for polyether tridendrons in Fig. 1. For regular dendrimers, generation growth can be regarded as the simple addition of another layer of monomer units, and it can be shown experimentally that, within a homologous series, the radius of the dendrimer increases linearly with generation number (Fig. 2). Therefore, the interesting and most unusual phenomenon observed for intrinsic viscosity is easily understood if one considers that during generation growth the volume of dendrimers increases cubically ($V = 4/3\pi r^3$) while their mass increases exponentially (mass is proportional to $2^{(G\#-1)}$), a relationship that does not hold true for other polymers.

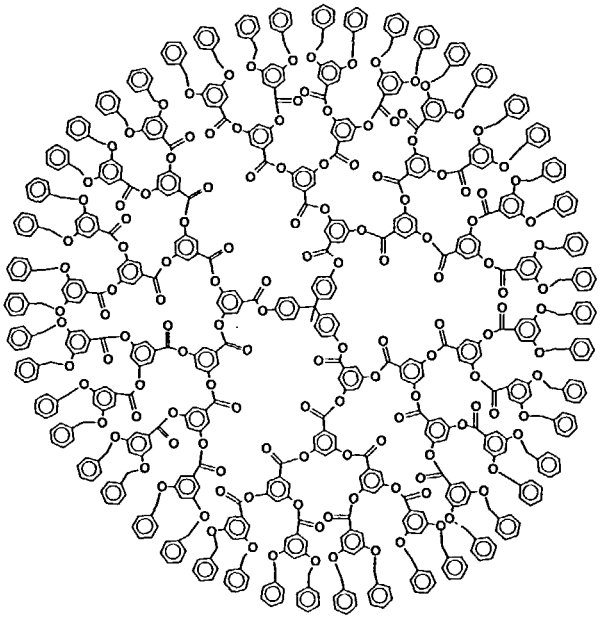
The uncommon relationship between intrinsic viscosity and molecular weight for dendrimers can be correlated with their shape which changes progressively from an extended to a globular structure. Evidence for this shape transition can also be gleaned from a study of the variation in λ_{max} as a function of molecular weight for a series of dendritic polyether wedges containing a solvatochromic molecule covalently attached to their focal point [36]. In a variety of low polarity solvents the absorption maximum of the solvatochromic probe increases with generation num-

ber (i.e., molecular weight). This increase correlates with the greater influence of the dendrimer building blocks on the solvatochromic probe and the concomitant lowering of solvent penetration to the interior of the dendritic macromolecule. However, this increase is not linear and a marked discontinuity is observed between generation 3 and generation 4. This discontinuity corresponds to the onset of the transition from an extended to a globular structure as the steric requirements of the dendritic branches increase. It should be noted that the discontinuity occurs at approximately the same molecular weight as the shape transition implied from the intrinsic viscosity results. These results, taken together with the findings of Turro et al. [38] and the molecular modeling experiments of Goddard [39], suggest that a characteristic feature of regular dendritic macromolecules is a transition from an extended to a more compact globular structure as the molecular weight increases. The behavior of the solvatochromic probe also suggests that the interior of dendritic macromolecules represents an unique microenvironment. Exploitation of this microenvironment can be envisaged in applications such as molecular catalysts, drug-delivery systems, artificial enzymes, etc.

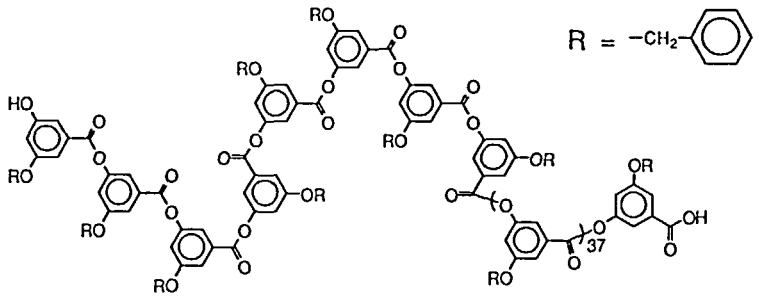
For example, Inoue and coworkers [34] reported the preparation of a porphyrin covalently encapsulated into a dendritic cage consisting of four "convergent" polyether dendritic wedges attached to the porphyrin nucleus. Fluorescence quenching experiments showed that when relatively bulky fourth generation dendrimers analogous to **7** were used to form the cage, the porphyrin core was effectively shielded from other relatively large molecules in solution while still remaining accessible to small molecules. This type of steric isolation of the metalloporphyrin, which is important to achieve certain biological functions, is uniquely realized through the use of the functional dendrimers prepared by convergent growth [15]. In addition, the work of Inoue confirms our observation [36] of an interesting size- and shape-related microenvironment effect within dendrimers. In this instance the reactivity of the porphyrin caged by large dendritic macromolecules toward small molecule quenchers is actually enhanced when compared to the reactivity of analogous porphyrins caged by smaller molecules.

In contrast to the untypical behavior described above, the thermal properties of dendrimers correlate well with those of linear polymers. For example, the variation of their glass transition temperature with molecular weight and chain-end composition obeys a modified version of the chain-end free volume theory [40]. Similarly, the thermogravimetric behavior of dendritic polyesters is the same, within experimental errors, as that of linear polyesters composed of the same building blocks [37].

Any experimental polymer chemist working with dendrimers will not fail to notice their unusually high solubility when compared to analogous linear polymers. This solubility difference has been measured for two types of polyesters prepared from the same monomer, 3,5-dihydroxybenzoic acid: dendritic polyester **9** with benzyl ether end-groups [21], and linear polyester **10** obtained by polycondensation of the monobenzyl ether derivative of the monomer [37] (Fig. 3). In order to facilitate a direct comparison, both polymer samples had molecular weights near 11,000; therefore, both polymers contained approximately the same number of monomer units and the same number of benzyl ether functional groups. Using THF as the solvent, the solubility of dendrimer **9** was found to be extremely high given its aromatic polyester structure: 1.15 g/mL vs 0.025 g/mL for the analogous linear



Polyester dendrimer 9 with benzyl ether chain-ends



Linear polyester 10 with benzyl ether pendant groups

FIG. 3. Structures of dendritic and linear polyesters.

polyester **10**. Compound **9** was also highly soluble in less polar solvents such as chloroform or dichloromethane; however, upon cleavage of the benzyl ether chain-ends, the phenolic-terminated product was only soluble in very polar solvents. Further comparisons with a linear polyester derived from 3-hydroxybenzoic acid, therefore devoid of any benzyl pendant groups, reveals that the latter is totally insoluble in THF. Miller and Neenan [23] reported solubility enhancements of more than a factor of 10^5 for dendritic poly(phenylenes) when compared to linear poly(paraphenylene). This figure may be somewhat excessive since the more soluble meta-linked poly(phenylene) should have been used for comparison purposes, but it does

illustrate the great solubility of dendrimers. These comparative studies strongly suggest that both the shape and the functionality (chain-ends) of the dendritic molecules have a great effect on their solubility.

Dendritic Block Copolymers

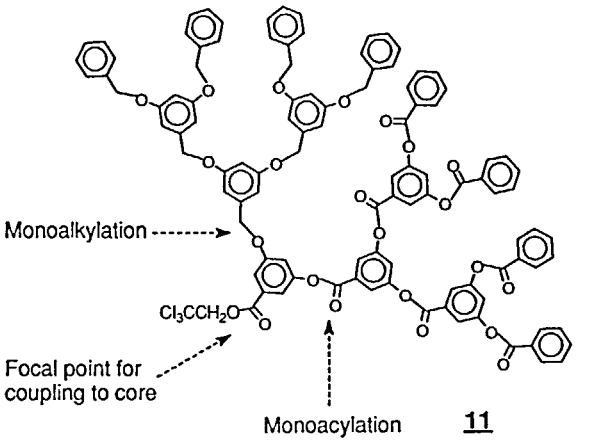
Having confirmed the usefulness of the convergent growth approach with the preparation of several families of regular dendrimers, its versatility was used to advantage in the preparation of innovative globular block copolymers. The convergent growth approach is the most suitable for this purpose since it gives a high degree of control over the internal placement of building blocks. In considering block copolymers, a fundamental difference between dendritic and linear macromolecules is again encountered. Linear polymers can simplistically be thought of as one-dimensional structures for which only a single broad type of block copolymer exists with variations possible in the make-up of the blocks, their lengths, and their sequence of placement within the linear chain. On the other hand, the three-dimensional nature of dendritic macromolecules allows the design of numerous different types of block copolymers. Only a few of the many possibilities that exist have been explored to date but they already provide fascinating insight into the degree of synthetic and architectural control that is available in the design of novel three-dimensional globular macromolecules.

Two structures that differ only in the three-dimensional arrangement of their buiding blocks, but can be regarded as different block copolymers, are dendritic *segment-block* and dendritic *layer-block* copolymers. These unusual globular block copolymers were first prepared by the controlled placement of different ether and ester chemistries in radical or concentric fashion around a central polyfunctional core. For the dendritic *segment-block* copolymer, a monomer unit derived from 3,5-dihydroxybenzoic acid is alkylated on one of its phenolic sites with a polyether dendron, then acylated on the second phenolic hydroxyl with a polyester dendron. The resulting dendritic molecule **11**, itself a block copolymer, can then be attached through its focal point to a core such as **6** to give dendrimer **12** [41]. Figure 4 shows a planar representation of one of the several possible conformations for **12**. It should be noted that other conformations are possible due to free rotation about the single bonds. However, constraints arising from the branching sequence do not allow a structural isomer where all three polyester fragments are adjacent [41].

Similarly, a dendritic *layer-block* copolymer is obtained by the concentric alternation of ether and ester-linked layers. Therefore, convergent growth is initially begun with ether chemistry, and dendritic wedges are prepared with a change in coupling chemistry—from ether to ester—implemented at some point in the growth. If successive changes are made at each generation, the final product is a dendrimer containing both ester and ether chemistry in discrete layers. Figure 5 shows the dendritic layer-block copolymer **13** that has two inner concentric layers of ester functional groups surrounded by three outer concentric layers of ether groups [41].

It is interesting to note that these block copolymers having intimately linked layers of ether and ester functionalities show only a single glass transition temperature near the value predicted by standard theories for linear copolymers.

The globular architecture of dendritic macromolecules can also be combined with a linear architecture to give a novel family of *hybrid linear-globular* block



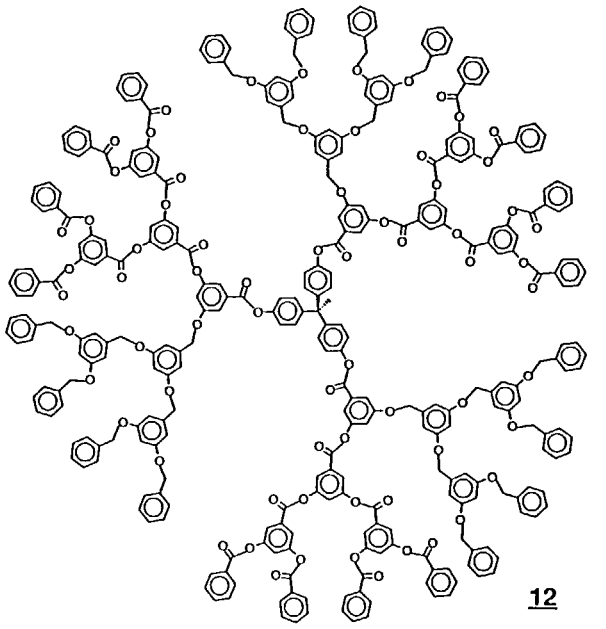


FIG. 4. Structures of segment-block copolymers.

copolymers. Due to the high degree of structural control associated with the convergent growth approach, a number of different sites of attachment are possible. Initially, the single unique functionality at the focal point was examined as the coupling site between the linear and dendritic blocks [42, 43]. For example, reaction of telechelic poly(ethylene glycol) with two equivalents of a dendritic bromide gives a "barbell-like" dendritic–linear–dendritic triblock copolymer, **14** (Fig. 5). Alternately, monofunctional linear polymers can be employed to give a different archi-

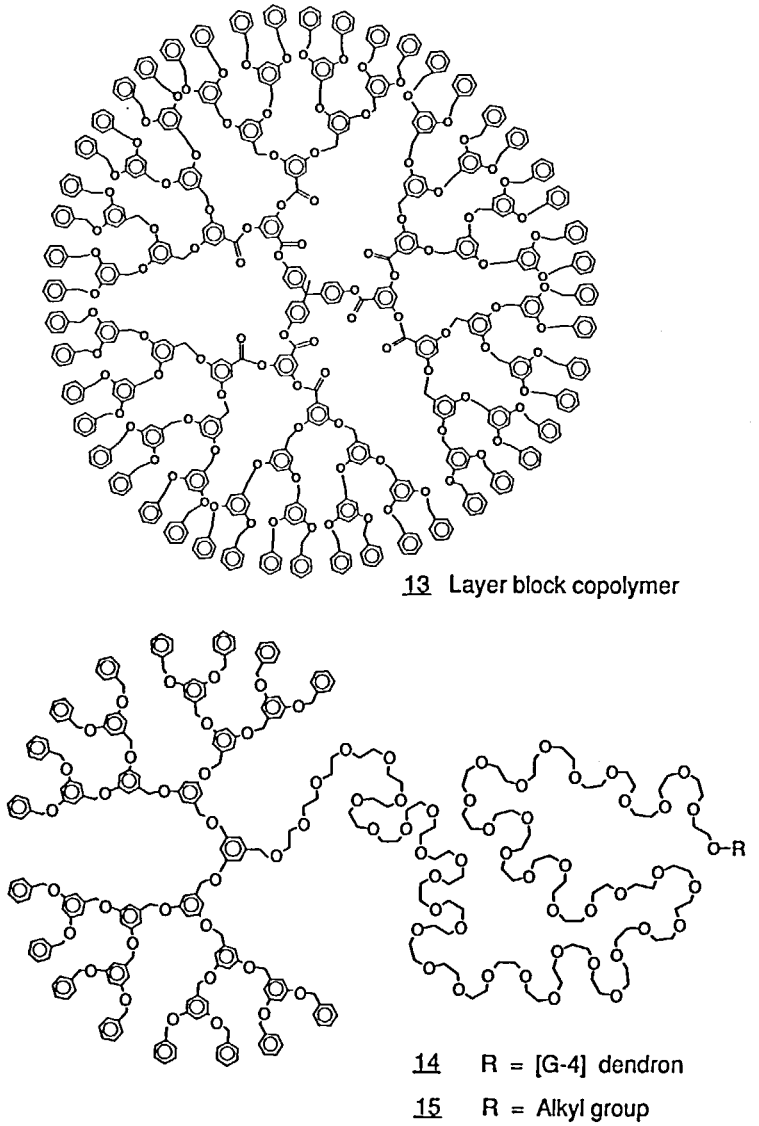


FIG. 5. Structures of layer-block and hybrid linear–globular block copolymers.

tecture such as **15** where a single linear chain of poly(ethylene oxide) is attached to the focal point of the globular dendritic block, effectively a "sperm-shaped" linear–dendritic block copolymer (Fig. 5) [43]. The versatile nature of the convergent growth approach allows other linear polymers, coupling sites, and coupling chemistries to be used in the reaction [44, 45]. Preliminary investigation of the physical properties of these novel hybrid block copolymers has shown that they exhibit unusual solubility behavior and are able to form micelles in solvents selective for

one of the blocks. In the solid state, phase separation has been shown to occur, but only after the linear block has reached a critical molecular weight [43, 46].

Control of Terminal Functional Groups

The high degree of control offered by the convergent growth approach allows unprecedented control over the number, nature, and, to a certain extent, the placement of functional groups at the chain ends of dendritic macromolecules. The fundamental reason for this control is the stepwise nature of the generation growth process that only involves a very limited number of coupling reactions (typically two), allowing for purposeful variations in the order of attachment of the dendritic wedges to either the monomer unit or the polyfunctional core. This stepwise methodology has been demonstrated in the synthesis of a dendrimer that contained a single nitrile chain-end different from all other chain-ends [47], or in the preparation of dendrimers obtained by sequential coupling of dendrons made from the same monomer but each containing different chain-ends [48, 49]. Once again, the efficient *O*-alkylation chemistry selected for this family of unsymmetrical dendrimers allows their facile preparation and purification; the different chain-ends are introduced in the very first step of convergent growth using substituted or unsubstituted benzylic bromides [47, 48]. The structure of these dendritic macromolecules and the extent of chain-end functionalization could be fully determined by a combination of spectroscopic techniques. By using a combination of the synthetic blueprints for these two extreme examples, both the number and placement of the functional groups at the chain ends can be accurately controlled to afford a large variety of specifically functionalized dendritic macromolecules. Exploitation of this potential has already led to the synthesis of some very promising and exciting materials that may be used in nanotechnology or molecular devices. For example, the placement of electron-withdrawing cyano groups as chain ends on one-half of the dendrimer and electron-donating benzyl ethers as chain ends on the other half leads to fascinating molecular dipoles that can be oriented in an electrical field [48].

These dendrimers with an unsymmetrical distribution of chain-end functionalities also represent a new family of block copolymers termed dendritic *surface-block* copolymers [47]. Given the influence of the large number of chain ends on the properties of these macromolecules, dendritic *surface-block* copolymers such as **16** behave as amphiphiles. Because half of the chain ends of **16** are made up of hydrophilic carboxylate groups whereas the other half are hydrophobic phenyl groups, this molecule is expected to orient itself at a variety of interfaces and surfaces (Fig. 6) [49]. Initial experiments have shown that dendritic macromolecules are capable of forming monolayers [50], and that **16** stabilizes emulsions very efficiently [49]. The protonated form of **16** is also the first example of a purely dendritic block copolymer that exhibits two glass transition temperatures. However, the respective glass transition temperatures for each block are not what would be expected from studies of linear block copolymers, suggesting that microdomains are being formed with a degree of higher, or long range, order.

A derivative of the hydrophilic/hydrophobic dendrimer **16** is the water-soluble hydrophilic dendrimer **17** that can be considered to be the monomolecular equivalent of a micelle since it is built of an outermost layer with hydrophilic carboxylate

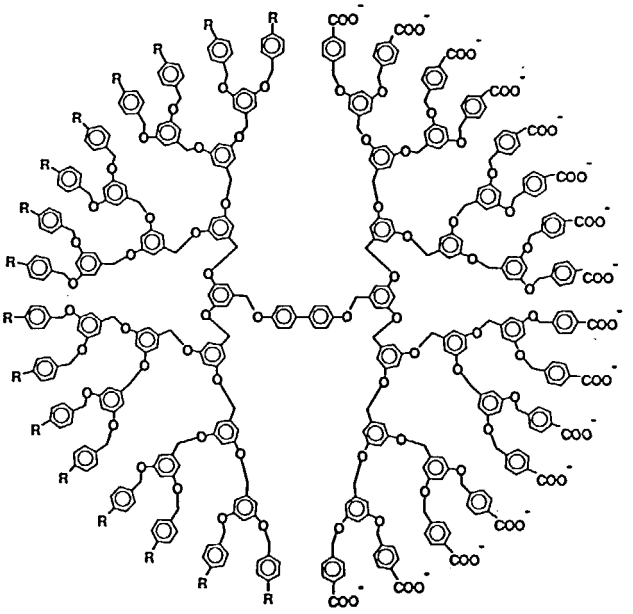


FIG. 6. Structures of the dendritic amphiphile **16** and unimolecular micelle **17**.

chain-ends which is covalently bound to a highly branched hydrophobic inner core. As expected, **17** demonstrates properties fully consistent with a micelle-like structure [49]. For example, an aqueous solution of **17** is able to solubilize a variety of hydrophobic polycyclic aromatic compounds such as pyrene. Interestingly, and despite its very modest size, the efficiency of dendrimer **17** in this process is essentially the same as that of traditional sodium dodecyl sulfate micelles. However, there is a substantial difference between the dendritic and traditional micelles since aqueous solutions of **17** do not display a critical micelle concentration and a plot of concentration of pyrene solubilized vs concentration of dendritic micelle **17** is linear, with **17** displaying solubilizing ability at concentrations as low as 10^{-7} M. The stability of the covalently-bound dendritic micelle has allowed the development of a novel recyclable solubilization and extraction system for hydrophobic compounds such as pyrene [49] as tested in a model study of the extraction of pollutants such as PCBs from contaminated aqueous solutions.

In related work we have recently been able to carry out the internal functionalization of polyether dendrimers using the acidity of both their various benzylic hydrogens and of some of their aromatic hydrogens for the metalation of various sites within the dendrimers. When this metalation is followed by reaction with appropriate electrophiles, internally functionalized dendrimers are obtained [51]. For example, if carbon dioxide is used as the electrophile, carboxylate groups are incorporated in the inner layers of the dendrimer, rendering them hydrophilic. This process may be applicable to the preparation of reversed micelles.

Recent studies [43] have also confirmed that both the focal point and the

chain-end functional groups are readily available for chemical modification reactions. High yields are obtained even in instances where large dendrimers contain a single reactive group. In fact, the groups located at the chain ends of globular polyester dendrimers have been shown [37] to be more reactive than analogous groups on hyperbranched or linear polymers. How this correlates with the theoretical work of Muthukumar [52], which suggests that all the chain ends are folded back into the interior of the dendritic macromolecule, is not fully understood at the present time. However, neutron diffraction studies using specifically deuterated dendritic macromolecules may help settle the controversy [39, 52] over the position of the chain ends of dendritic macromolecules.

OUTLOOK

While significant progress has been made in the study of dendritic macromolecules in recent years, a large amount of work remains to be done to fully understand these unique and potentially useful globular macromolecules. The versatility of the convergent growth approach allows the design of tailor-made dendrimers and block copolymers with a variety of shapes, functionalities, and functions. In particular, control over the chain ends provides much latitude in the tuning of physical and other properties such as solubility, thermal characteristics, aggregation, polarity, interfacial behavior, etc. In addition, modification of the internal building blocks also allows for the introduction of catalytic sites, probe moieties, sensor components, etc. Therefore, judicious control of these parameters enables the preparation of extremely sophisticated three-dimensional materials for either technological (molecular machines) or biological (artificial enzymes, drug delivery systems) applications.

Obviously, the large number of steps used in the preparation of highly regular and monodisperse dendrimers makes their cost relatively high, thereby restricting their use to high added-value applications. However, it may be possible to devise alternate procedures [53–55] for the accelerated synthesis of these materials, perhaps at the cost of a slightly lower purity. For less sophisticated applications such as rheology control or reactive injection molding, the more readily accessible hyperbranched macromolecules [56–58] prepared in one step from AB_2 monomers may be quite attractive, although it must be emphasized that their properties are not identical to those of dendrimers.

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