# The Dotted Cap Notation: A concise notation for describing variegated dendrimers

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There is a need for simple, concise systems of notation to describe aspects of dendrimer chemistry. In this paper, such a system of notation, which describes the surface functionalisation of the dendrimer, is presented. This notation, which complements existing dendrimer nomenclatures, conveys to the reader the number and relative arrangement of a dendrimer's caps. To reduce complexity, caps are represented by symbols defined by the user. Dendrimer topology is indicated, as is chirality at branch points. The notation is not a complete nomenclature; the chemical nature of the underlying dendritic framework is not specified. Comparison and contrast between dendrimers on the basis of their surfaces is simplified by the use of this notation.

## 1 Introduction

Dendrimers are a class of synthetic polymers characterised by repeated chain branchings emanating from a central core, giving rise to a fractal-like molecular topology and a large number of chain endings. They occupy a region of chemical space intermediate in size between small molecules and conventional linear polymers, and have a variety of interesting properties, such as a molecular weight broadly similar to that of polypeptides, an inherent polyfunctionality, and a wide range of possible chemistries. Careful control of the synthetic process can yield monodisperse products of high purity. These novel molecular topologies and the potentially detailed control over composition have encouraged research in the use of dendrimers for medical and pharmaceutical applications[1] such as anticancer agents,[2,3] antiviral drugs,[4,5] DNA probes,[6] drug delivery devices,[7] gene transfection agents,[8] and *in vivo* imaging[9] and contrast agents,[10] as well as applications in light harvesting,[11] chemical sensing,[12] catalysis,[13] and polymer synthesis.[14]

Dendrimers can be described in terms of a core, one or more layers (or generations) of branched monomers, and a layer of end groups, or caps, which serve to terminate the various chains. To date, most reports concern dendrimers having only a single type of surface functionality. A more recent development is dendrimer variegation. A variegated dendrimer has more than one type of monomer or capping group incorporated into one generational layer. The compounds **1** and **2** (Fig. 1) are examples of variegated third-generation dendrimers, based on the PAMAM (Starburst) dendrimers of Tomalia *et al.*,[15] having homogeneous internal generations of monomers and containing two distinct types of capping group which are arranged in specific patterns. Shi *et al.* have reviewed multifunctional fifth-generation PAMAM dendrimers containing these and other capping groups, which are objects of research for therapeutic and biological applications.[16] Important types of variegated dendrimer include *heterogeneously functionalised dendrimers*,[17] in which the variegation takes place on the surface by introduction of different caps, and *asymmetric dendrimers*,[18] in which different dendrons are attached to the dendrimer core. Variegation of dendrimer caps has the potential to provide detailed control over the chemical composition of the surface and consequently to tune the bulk properties of the dendrimer and its interaction with the environment. In the pharmaceutical context, variegation is expected to be an important technique for control of dendrimer biostability, solubility and toxicity. In all applications, the ability to selectively modify monomers and capping moieties should allow for the design of intramolecular structural motifs, the controlled introduction of functional groups with synergistic activity, or the introduction of binding sites which can recognise other molecules in the environment. Because of these properties, variegated dendrimers have the potential to find use in a wide range of applications. Indeed, in certain applications such as dendrimer-assisted gene transfection[19] and the formation of covalently-bonded prodrugs,[3,20] they have already shown promise when compared to homogeneous dendrimers.

Many strategies for synthesising dendrimers are available.[4,21] These can be broadly classified as divergent,[15,22] where monomers are successively added to the growing dendrimer; or convergent,[23] in which preassembled subunits are combined into successively larger dendritic branches. Both divergent and convergent syntheses may, by careful choice of reagents and reaction conditions, produce a vast range of distinct variegated dendrimers. Under some conditions, variegation proceeds in a random fashion, generating a combinatorial library of closely related molecules; some synthetic techniques provide increased control over the dendrimer's connectivity and the arrangement of capping groups.

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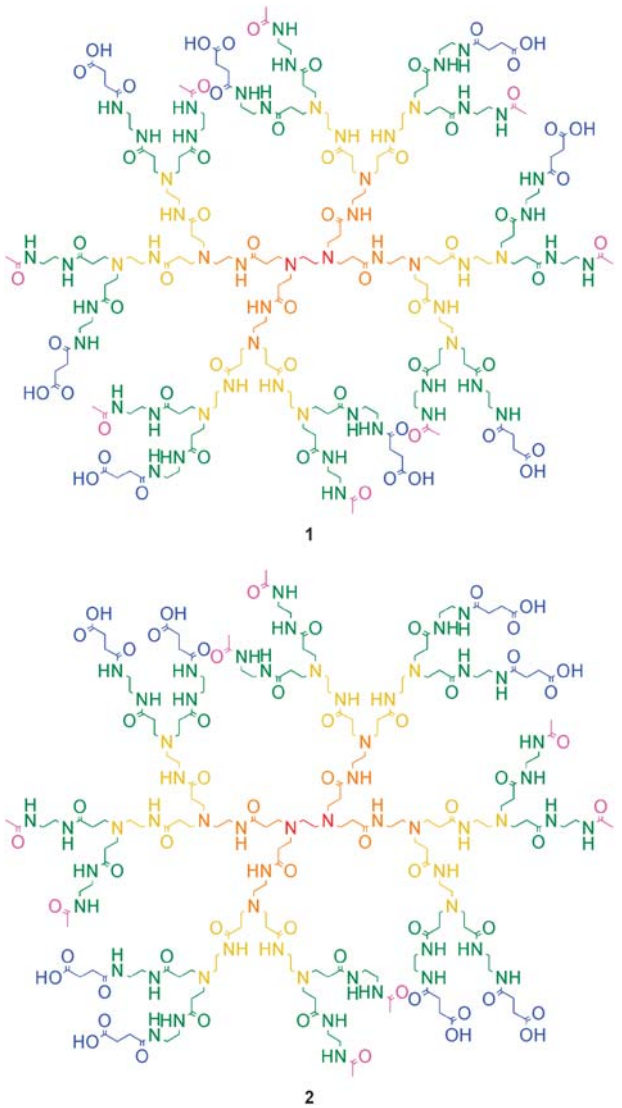

**Fig. 1** Two examples of surface-functionalised dendrimers, showing the successive generations in different colours. The core is shown in red. Generations of monomers are shown in orange (first), gold (second) and green (third). Caps are shown in magenta (acetyl) or blue (succinyl).

As dendrimers have become more widely researched, the need for a specific nomenclature to describe them (and other hyperbranched systems) has previously been identified. They are not usefully described by general naming systems such as the IUPAC nomenclature. In particular, the general naming systems do not easily convey the fractal-like nature of the structure. Graph-based nomenclatures such as the Nodal nomenclature of Lozac'h *et al.*[24] are applicable to dendrimers, but have not been widely adopted. To address these problems, systematic dendrimer nomenclatures have been devised. The first was published by Newkome *et al.* (the Newkome nomenclature),[25] and later refined by Friedhofen and Vögtle (the Cascadane nomenclature).[26] A simpler notation system (fractal notation) has been separately devised by Mendenhall,[27] but was intended for use with dendrimers containing homogeneous or nearly homogeneous layers.

While the Newkome and cascadane nomenclatures can describe the chemical structure of variegated dendrimers, as the complexity of a dendrimer increases, its name according to these nomenclatures quickly becomes lengthy and complicated. Furthermore, differences in patterns of variegation are not always immediately obvious to the reader. As examples, we show, in Table 1, the names of dendrimers **1** and **2** according to the Newkome and Cascadane nomenclatures and the Dotted-Cap notation.

To more easily describe dendrimers, particularly ones with complicated patterns of variegation, we sought a more concise representation than the nomenclatures given above. A further aim was to increase the comprehensibility of the notation by avoiding, as far as possible, abstract symbols and nested brackets. To achieve these aims, it was necessary to accept an incomplete description of the dendrimer molecule, focusing on some features of the molecule at the expense of others. Given our interest in dendrimers with complex arrangements of capping groups, we chose to focus particularly on a way to describe these arrangements. The topology of the dendrimer's framework is important for this purpose. It is not necessary in a dendrimer's descriptor to describe the precise nature of the core and the monomers. We prefer to establish the framework's topology by disconnecting at bonds formed during synthesis, thus dividing the dendrimer into monomers, rather than at branch points; but disconnections may certainly be performed at branch points if this is more desirable. Having established a topology, we can describe the relationship between two caps, as well as the number of generations any cap is away from the core.

**Table 1** Names of dendrimers **1** and **2** according to the Newkome and Cascadane nomenclatures and the Dotted-Cap notation

| Dendrimer | Name according to the Newkome nomenclature | Name according to the Cascadane nomenclature | Descriptor using the Dotted-Cap notation |
|---|---|---|---|
| **1** | 16-Cascade:1,2-diaminoethane[4-*N*,*N*,*N*′,*N*′]:(5-oxo-1,4-diazaheptylidene)$^2$:[2,7-dioxo-3,6-diazanonane]-[3,8-dioxo-4,7-diazaundecanoic acid] | 1,2-Diaminoethane[*N*,*N*,*N*′,*N*′]:{4,7-diaza-3-oxoheptyl(7,7)}$^{G1}_{4\times}$:{4,7-diaza-3-oxoheptyl($7^1$,$7^1$/$7^2$,$7^2$/$7^3$,$7^3$/$7^4$,$7^4$/$7^5$,$7^5$/$7^6$,$7^6$/$7^7$,$7^7$/$7^8$,$7^8$)}$^{G2}_{8\times}$:{$7^1$,$7^2$,$7^3$,$7^4$,$7^5$,$7^6$,$7^7$,$7^8$⟨3,8-dioxo-4,7-diazanonyl⟩$_8$$7^1$,$7^2$,$7^3$,$7^4$,$7^5$,$7^6$,$7^7$,$7^8$⟨3,8-dioxo-4,7-diaza-10-carboxydecyl⟩$_8$}$_{16}$-cascadane | A•B••A•B•••A•B••A•B•••<br>A•B••A•B•••A•B••A•B |
| **2** | 16-Cascade:1,2-diaminoethane[4-*N*,*N*,*N*′,*N*′]:(5-oxo-1,4-diazaheptylidene):[(5-oxo-1,4-diazaheptylidene):2,7-dioxo-3,6-diazanonane]-[(5-oxo-1,4-diazaheptylidene):3,8-dioxo-4,7-diazaundecanoic acid] | 1,2-Diaminoethane[*N*,*N*,*N*′,*N*′]:{4,7-diaza-3-oxoheptyl(7,7)}$^{G1}_{4\times}$:{4,7-diaza-3-oxoheptyl($7^1$,$7^1$/$7^2$,$7^2$/$7^3$,$7^3$/$7^4$,$7^4$/$7^5$,$7^5$/$7^6$,$7^6$/$7^7$,$7^7$/$7^8$,$7^8$)}$^{G2}_{8\times}$:{$7^1$,$7^1$,$7^3$,$7^3$,$7^5$,$7^5$,$7^7$,$7^7$⟨3,8-dioxo-4,7-diazanonyl⟩$_8$$7^2$,$7^2$,$7^4$,$7^4$,$7^6$,$7^6$,$7^8$,$7^8$⟨3,8-dioxo-4,7-diaza-10-carboxydecyl⟩$_8$}16-cascadane | A•A••B•B•••A•A••B•B•••<br>A•A••B•B•••A•A••B•B |

 

In this paper, we propose a notation system that concisely describes of the topology of the dendrimer and the relationships between the caps. This notation system, the Dotted Cap Notation, indicates the types, numbers and relative arrangement by connectivity of the capping groups on the dendrimer surface. The Dotted Cap Notation is designed for use in situations where a concise schematic representation of a dendrimer's capping groups is useful (*e.g.*, laboratory discussions), especially where the aim is to compare and contrast dendrimers which share a common or closely related underlying skeleton but differ in the nature and arrangement of the caps. The Dotted Cap Notation is not intended to replace any current or future complete nomenclatures, but rather to coexist with them.

Because of the topology of many dendrimers, it is easy to envisage connection sites in monomers that are equivalent when not derivatised, becoming distinguishable upon derivatisation. Most systems of nomenclature, whether specifically designed for dendrimers or not, address this problem by considering the final product, which takes into account the moieties attached during derivatisation. This allows determination of absolute configurations. However, in Dotted-Cap Notation, we wish to be able to change capping groups or dendritic motifs without being obliged to alter the order in which caps are ultimately listed. So we require, for the underlying dendritic framework, a means of determining the relative priorities of the capping sites, which is independent of the nature of any capping groups present in these sites. We present below a set of rules which allow the chemist to determine these relative priorities.

This paper is organised as follows. In section 2, we define various terms we use when describing dendrimer structures. In section 3, we set out the rules for dotted-cap notation, using generic representations of dendrimers as examples. Section 4 contains some specific examples of dendritic cores and dendrimers named according to the dotted-cap notation. A brief summary and conclusions are provided in section 5.

## 2 Definitions

The fundamental *building blocks* of a dendrimer are a *core*, *monomers* and *capping groups* (often abbreviated to *caps*). In a dendrimer, the core and monomers are bonded to one another in a fractal-like pattern, forming a dendritic *framework* to which the caps are attached. One aspect of a monomer's position in the dendrimer is the layer of monomers to which it belongs. This is usually termed the *generation number* of that monomer. For example, a monomer directly attached to the core is a 1st generation monomer; a monomer attached to a 1st generation monomer is a 2nd generation monomer, and so forth. Capping groups do not represent a further generation. The dendrimer may be incompletely functionalised; those reactive sites within monomers that are not functionalised by addition of either a cap or further generations of monomers are termed *vacant sites*.

A structural unit, consisting of a monomer together with all other monomers and capping groups connected to the core through that monomer, is a *dendritic motif*. Dendritic motifs vary in size. A dendritic motif may have as few as one monomer (of the outermost generation), along with any caps attached to this monomer. Such a motif is a *surface motif*. At the other extreme, a motif may be an entire branch that is attached directly to the dendrimer core. Complete branches of this kind are called *dendrons*; this term is also applied to isolated branches. A dendritic motif is described according to the total number of caps and vacant sites it contains, as *e.g.* a *doublet* or a *triplet*.

Another aspect of a residue's position in the dendrimer, then, is its relationship (by connectivity) to other residues in its motif. The terms *ancestor* and *descendant* are used for this purpose. For example, consider two residues in a dendrimer, **X** and **Y**. If **X** is attached to the core through **Y**, then **Y** is an ancestor of **X**, and conversely **X** is a descendant of **Y**. *Parent* and *daughter* are used for the special case in which **X** and **Y** are directly bonded to each other. A *common ancestor* of two or more residues is one through which all these residues are attached to the core.

When two variegated motifs are compared to each other, we describe them as *similar* or *dissimilar*. Motifs are similar if they contain the same capping groups in the same numbers, and these capping groups have, topologically speaking, the same relationships to each other, to the extent of being listed in the same canonical order. (The process of establishing a canonical order is described in section 3 below). Motifs are dissimilar if any of these criteria are not met. Differences between the monomers in the different motifs do not affect similarity.

Depending on how a dendritic motif has been synthesised, caps and vacant sites within the motif may be arranged in a precisely defined fashion, obey a random distribution, or some combination of the two. In the latter case, the motif is understood as consisting of two or more smaller motifs, each of which has caps in an entirely well-defined or entirely random arrangement, and which share a common ancestor.

## 3 Notation rules

Determining a Dotted-Cap string for a dendrimer is performed in three steps. The first step is a description of the caps and the underlying dendritic framework. In the second step, a canonical sequence for the various capping sites is determined (rule 2). Finally, the capping groups are listed in this sequence, along with a description of the topological and stereochemical relationships between them.

### 3.1 Cap representation

**Rule 1.** We represent each type of capping group by a single character, called a cap symbol. Any alphabetic character may be used as a cap symbol. Each vacant site is given the symbol $\varnothing$.

**Rule 2.** The dendrimer is described by a line notation (*e.g.*, **ABC**). To construct this notation, we list caps in order of priority, determined by traversing the dendrimer's framework and exploring the branches in order of precedence. The order in which the framework is traversed is determined by applying rules 2.1 to 2.5. Each branch, with its own subbranches, is fully explored before returning to the branch point and continuing exploration along the next branch. For the

purposes of this traversal, we ignore distinction between core and monomer residues.

**Rule 2.1.** We begin the traversal of the dendrimer by identifying its *primary atom*. This atom is located within the core of the dendrimer. It is found by treating the core as a molecule substituted with generic dendron radicals. Most often, this core residue will correspond closely to the chemical species used as a core, but in some cases it will be convenient to disconnect dendrons at another, nearby bond, to provide for a single, unambiguous connection point (*e.g.*, in the case of dendrimers formed by means of cycloaddition reactions). If the core residue is organic, the primary atom is atom 1 in the core's principal chain or ring according to the IUPAC nomenclature of organic chemistry.[28] If, on the other hand, the core residue is inorganic or organometallic in nature (such as a coordination compound), the primary atom is the central atom as defined by the IUPAC nomenclature of inorganic chemistry;[29] if there are several such central atoms, the primary atom is the central atom with the lowest locant.

**Rule 2.2.** Once the primary atom has been identified, the order of capping sites is determined by traversing the dendrimer from the primary atom. At each branch point the relative priorities of the branches are established according to the rules of Cahn, Ingold and Prelog[30] (the *CIP rules*), which have been incorporated into the IUPAC nomenclature of organic chemistry, supplemented here by rules **2.3** to **2.5** (see below). The branches are then traversed in priority order, exploring each branch in a recursive fashion and not traversing into any attached capping groups. A capping site, whether occupied or vacant, takes precedence over other ligands, and two capping sites attached to the same atom are of equivalent priority, regardless of what caps (if any) occupy them. The canonical order of capping sites, used to construct the dotted-cap notation, is the order in which they are reached as the framework is traversed. The traversal need only continue until all capping sites have been given relative priorities, and substituents on any atom which do not contain any capping sites may be safely ignored.

In simple cases, the above rules allow for unambiguous assignment of priorities to capping sites. Given a definition of the framework and a structure corresponding to each cap symbol, the chemist can deduce the structure of the corresponding dendrimer. However, some cores and monomers do not lend themselves to straightforward solutions. Problems arise if a branch point in a core or monomer has the potential to be a stereogenic centre, but this potential is only realised when different caps are introduced into the dendrimer. Since we wish the order of precedence of the caps to be independent of their composition, we cannot rely on absolute configurations to determine priorities. In some cases, a property of the branch itself can be used, thus:

**Rule 2.3.** Where a tetrahedral branch point has two identical but prochiral branches, the pro-*R* branch precedes its pro-*S* counterpart.

**Rule 2.4.** Where a planar branch point has two identical branches which are not interconvertible by rotation (*e.g.*, at the end of a double bond), the pro-*Z* branch precedes its pro-*E* counterpart.

More complicated cases exist, such as tetrahedral centres with three identical branches and co-ordination complexes (*e.g.*, Example 3, which is shown in Fig. 7). The common feature of these cases is that no intrinsic property of the branch can be used to determine a priority. We therefore adopt a manual definition of priority order, as follows.

**Rule 2.5.** Where a core or monomer has substituents which are identical apart from the nature of their attached caps, and their order of precedence cannot be determined by application of the above rules, the user must define an appropriate order of precedence for these substituents. We recommend that this be kept consistent as far as possible, especially among structurally similar monomeric units.

### 3.2 Topological relationships between caps

**Rule 3.** We now seek to describe the relationships between caps. For this purpose, we consider core, monomer and cap residues as discrete units. In Fig. 2, we show examples of the Dotted-Cap Notation for various motifs. Two or more caps directly attached to the same monomer, forming a surface motif, are represented as a string of cap symbols, with no punctuation separating them (*e.g.*, **3**). A more distant relationship between two caps is shown by inserting dots (•) between the corresponding cap symbols (*e.g.*, **4**). The number of dots in the longest single sequence of dots between any two cap symbols indicates the number of generations which must be traversed inwards from either of these caps (not including the monomers to which the caps are directly attached) until a common ancestor of both is reached (*e.g.*, **5**). If the caps are separated from the common ancestor by different numbers of generations, the greater number of generations is used to determine how many dots to write in the longest string. For example, in **6**, the absence of any single dots after the double dot indicates that caps **E** and **F** are connected to the common ancestor through a single monomer.

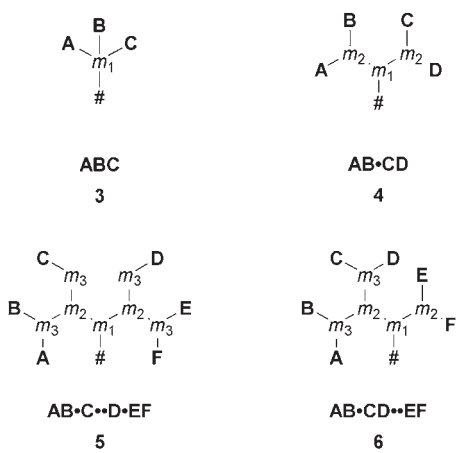


**Fig. 2** Examples of dendritic motifs with their corresponding Dotted-Cap Notation. In these structures, $m_1$, $m_2$, *etc.*, indicate monomers, and # indicates the remainder of the framework.

 

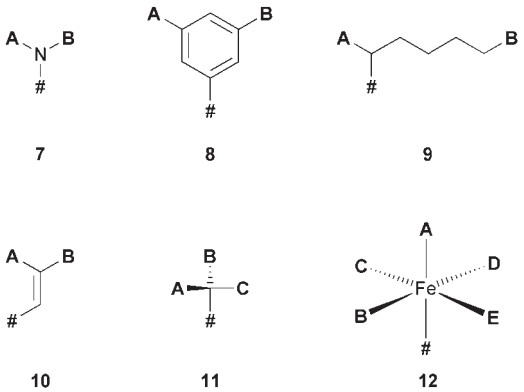


**Fig. 3** Examples of various surface motifs. Structures **7** and **8** bear interchangeable caps; structures **9** through **12** bear caps which are not interchangeable. # indicates the remainder of the framework.

**Rule 4.** Depending on the dendrimer framework, certain motifs may be *interchangeable*. The motifs attached to a common parent are interchangeable if *all* possible rearrangements of them produce a molecule which is superimposable on the original. Fig. 3 shows a number of surface motifs. Structures **7** and **8**, in which the caps **A** and **B** are interconvertible by rotation, are examples of interchangeable motifs. Rearranging motifs which are not interchangeable may result in either a molecule superimposable on the original or an isomer of the original. Structures **9** through **12** are examples of surface motifs which bear caps that are not interchangeable.

To show that caps in a surface motif are interchangeable, we underline their cap symbols, thus: **A**$\underline{\mathbf{B}}$. To show that motifs are interchangeable, we underline the dot or dots separating them, as shown in the examples in Fig. 4. Molecule **13** is represented by **A**$\underline{\mathbf{B}}$•$\underline{\mathbf{C}}$**D**. **A** is interchangeable with **B**, **C** with **D**, and **AB** with **CD**. There are therefore several equivalent notations for this dendrimer, such as $\underline{\mathbf{CD}}$•$\underline{\mathbf{AB}}$ and $\underline{\mathbf{BA}}$•$\underline{\mathbf{DC}}$. Molecule **14** is represented by **AB•CD**; **A** is not interchangeable with **B**, nor is **C** interchangeable with **D**. The motif **AB** is, however, interchangeable with **CD**, and therefore this dendrimer could alternatively be written as **CD**•$\underline{\mathbf{AB}}$. Molecule **15**, in which **A** is interchangeable with **B**, and **C** with **D**, but $\underline{\mathbf{AB}}$ is not interchangeable with $\underline{\mathbf{CD}}$, is denoted $\underline{\mathbf{AB}}$•$\underline{\mathbf{CD}}$. Alternatively, it could be denoted $\underline{\mathbf{AB}}$•$\underline{\mathbf{DC}}$, $\underline{\mathbf{BA}}$•$\underline{\mathbf{CD}}$ or $\underline{\mathbf{BA}}$•$\underline{\mathbf{DC}}$. Finally, molecule **16**, in which no caps or motifs are interchangeable, is denoted **AB•CD**. It is worth noting that caps on different parent monomers are never interchangeable in isolation. For example, in the molecules **13** to **16** above, pairs of caps such as **A** and **C**, or **B** and **D**, are not interchangeable.

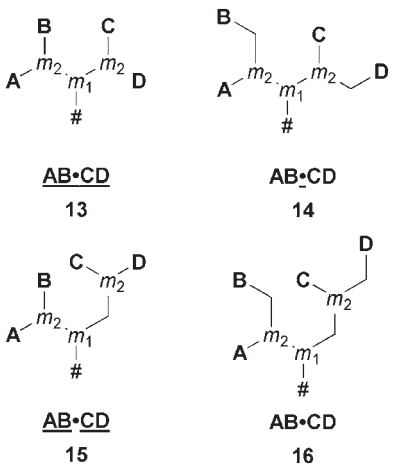


**Fig. 4** Examples of generic surface motifs, illustrating motifs which are interchangeable and those which are not. $m_1$ and $m_2$ denote monomers. On any monomer, equal chain length (*e.g.*, in **13**) is used to show interchangeable substituents, and unequal chain length (*e.g.*, in **16**) is used to show non-interchangeable substituents. # indicates the remainder of the framework. An underline in the notation indicates that substituents are interchangeable.

### 3.3 Condensed notation

**Rule 5.** Often, a dendrimer will have its outer layers comprised entirely of a certain repeated motif. It may be convenient to describe such a dendrimer in a condensed form. This notation is much simpler, but involves loss of generation information. We create a condensed notation by enclosing the motif in brackets, with a subscript indicating the total number of times the motif is repeated, thus: $\mathbf{(AB)_4}$. As described in rule 4, the motif in the brackets may be underlined at appropriate points (that is, cap symbols and dots) to indicate that the corresponding parts of the motif are interchangeable. Likewise, if the subscript number is underlined, the motifs as a whole are interchangeable with each other.

### 3.4 Randomly distributed capping groups

**Rule 6.** Some methods for synthesising dendritic motifs introduce mixtures of capping groups. For example, the capping reaction may use a mixture of capping reagents with the product mixture determined by the reactivities of the capping reagents and their relative stoichiometries. A mixture of dendrimers is formed by this process, and any one capping site may be occupied by one of several different moieties. The mixed capping sites which exist in such dendrimers are described by listing the capping moieties together in curly braces, forming a *random distribution descriptor*, thus: "**{AB}**". Within curly braces, optional subscript numbers indicate the relative proportions of the capping groups in that site, such as "$\mathbf{\{A_{0.4}B_{0.6}\}}$" (a capping site which in 40% of cases contains **A** and in 60% of cases contains **B**). A random distribution descriptor for a site functions as a cap symbol, and can be used in conjunction with dots, underlines and brackets. An attempt to describe a dendrimer containing large numbers of mixed capping sites using the corresponding random distribution descriptors may produce a dotted cap descriptor which is long and complex. To address this, we may define a single cap symbol to represent the corresponding random distribution descriptor, *e.g.*, $\mathbf{X} = \mathbf{\{A_{0.4}B_{0.6}\}}$.

## 4 Examples

In this section, we illustrate the use of the Dotted Cap Notation. Using examples, we show how the primary atom in a dendritic core is determined, along with the priorities of attached motifs. We then show several examples of dendrimers

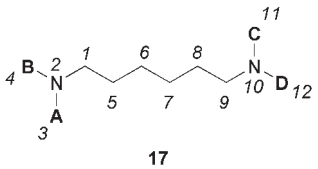


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**Fig. 5** Hexamethylene used as a dendrimer core with four substituents.

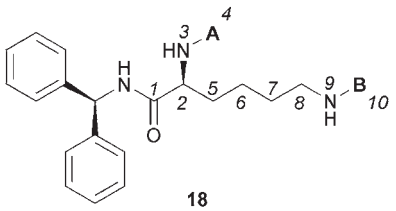


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**Fig. 6** Benzhydrylamide of lysine used as a dendritic core with two substituents.

from recent literature, in which we establish the order of precedence of the capping sites, and construct the appropriate notation.

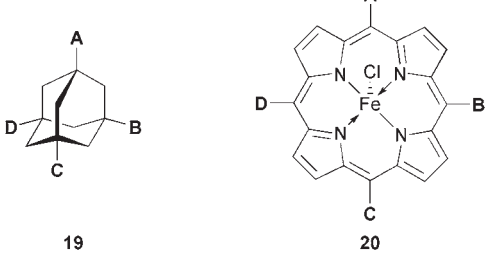
### 4.1 Primary atoms and dendron priorities in dendritic cores

Here, we present five examples of molecules that are used as dendritic cores. For each of these, we indicate the primary atom and the order of priority of the attached dendritic motifs. By way of example, we use "$0^{th}$ generation" dendrimers (*i.e.*, the core and directly attached caps). A corresponding dotted-cap notation is shown for each dendrimer.

**Example 1: Hexamethylenediamine.** Hexamethylenediamine (Fig. 5) can be used as a dendrimer core with four substituents, two on each of the terminal nitrogen atoms (**17**). We first identify the primary atom, by replacing the attached dendrons with radicals and identifying the principal chain and the locants of the atoms in this chain. The primary atom is one of the two carbon atoms adjacent to the nitrogen atoms, *i.e.*, *1* or *9*; in this case, we select *1* as the primary atom. We begin a traversal of the molecule from this atom, which also acts as a branch point. Applying rule 2, we reach the atoms and substituents in the order shown in Fig. 5. The caps are not all interchangeable: for example, if the caps **A** and **C** are swapped, a structural isomer is obtained. We therefore denote this dendrimer **ABCD**.

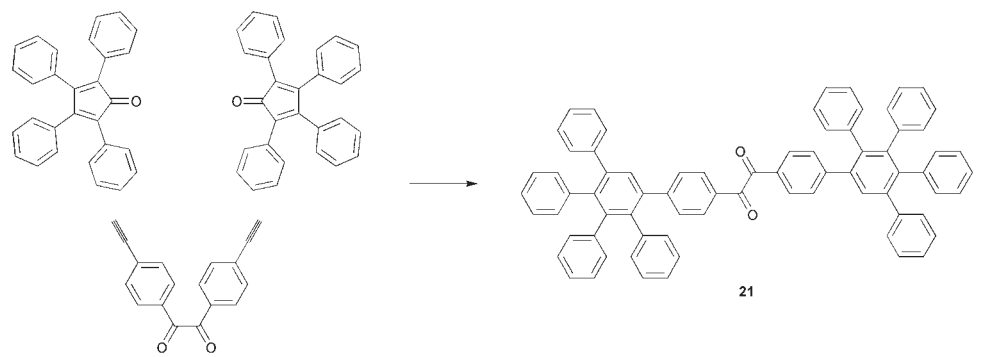
**Example 2: Benzhydrylamide of lysine.** The benzhydrylamide derivative of lysine (**18**) has been used in the preparation of a number of asymmetric dendrimers, such as SPL7013, the active ingredient of the microbicide product VivaGel™.[5,31] In this case, two dendrons are attached, one on each of the lysine amino groups. The substituted core has as its primary atom (*1*) the carbonyl carbon atom. Traversing the molecule from this atom and ignoring branches without dendrons attached, the other atoms are reached in the order shown in Fig. 6. Cap **A**, attached to the α nitrogen atom with a locant of *4*, has priority over cap **B**, on the ζ nitrogen atom with a locant of *10*. The two dendrons are not interchangeable; swapping them would produce a structural isomer. The dendrimer is thus denoted **AB**.

**Example 3: Highly symmetric dendritic cores.** This example presents two cores for which, because of their high symmetry, assignment of capping group priorities cannot be performed procedurally (Fig. 7). The adamantane core (**19**), used by Reichert and Mathias,[32] has four attachment points for dendritic motifs. The attached capping sites are equivalent, but the caps are not interchangeable, as swapping any two of them produces a stereoisomer. Similarly, porphyrin complex cores, as described by Kimura *et al.*[33] (**20**), have four equivalent dendritic substituents. These also are not interchangeable, as swapping any two *trans* substituents produces a stereoisomer, while swapping any two *cis* substituents produces a structural isomer. For both these dendrimers, then, we choose a suitable order of precedence of the substituents, as described in rule 2.5: **A** > **B** > **C** > **D**. Both these dendrimers are therefore denoted **ABCD**.




19 20

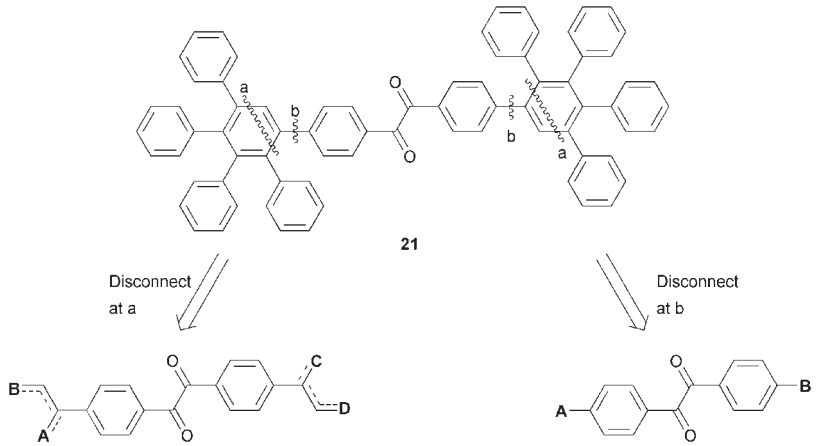
**Fig. 7** Examples of highly symmetric dendritic cores. Distinction between the branches in these cores cannot be made except by considering the natures of the attached caps.




21

**Scheme 1** The initial condensation step in the synthesis of Wiesler and Müllen's polyphenylene dendrimer.




**Scheme 2** Two possible disconnections of Wiesler and Müllen's polyphenylene dendrimer for notation purposes.



**Example 4: A polyphenylene core.** Finally, we consider a core formed by irregular disconnections. This is best illustrated by a dendrimer formed through cycloaddition reactions, such as the polyphenylene dendrimers of Wiesler and Müllen, who utilised the Diels–Alder reaction.[34] The reaction in their first condensation step is shown in Scheme 1. Two possible disconnections of the product **21** to identify the core are shown in Scheme 2.

As previously mentioned, we prefer to perform disconnections which yield the actual synthetic precursors to a dendrimer. However, when **21** is disconnected in such a way (disconnection "a"), we find that the core fragment ends up bearing four attachment points, two for each dendron. In the general case, this could introduce ambiguity into the determination of the primary atom and the subsequent assignment of branch priorities. We avoid this problem by disconnecting instead on nearby

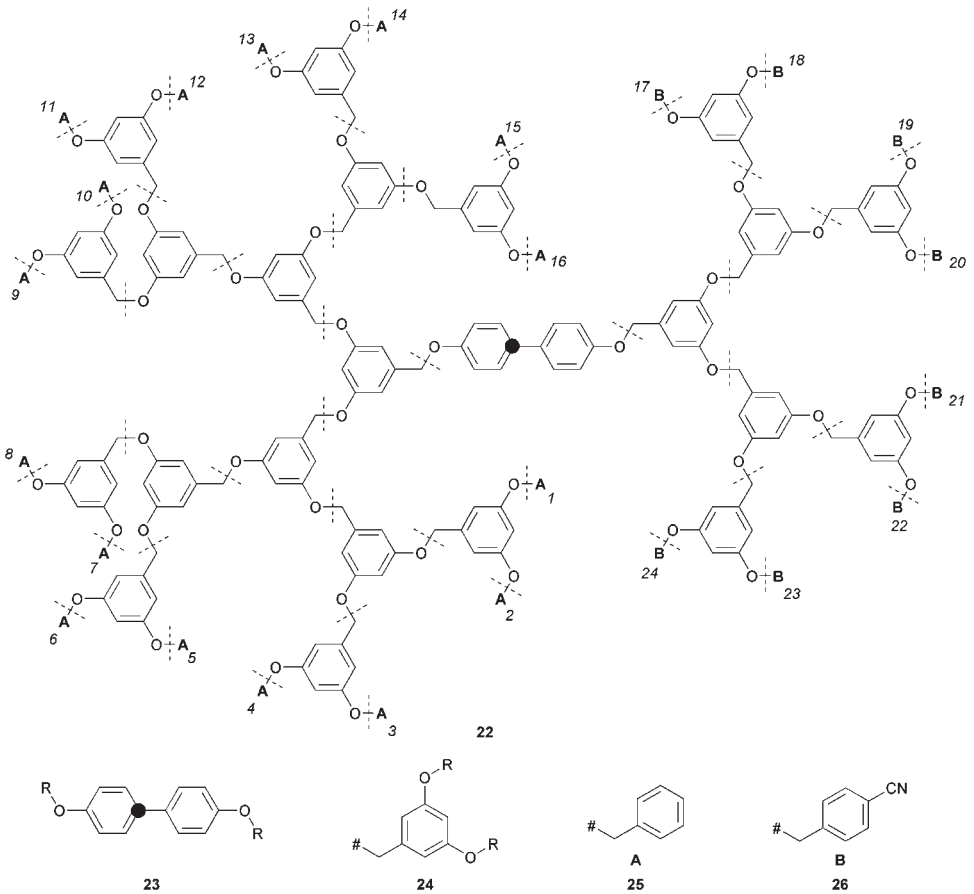



**Fig. 8** A Wooley dipolar dendrimer (**22**) and its constituent core (**23**), monomer (**24**) and caps (**25** and **26**). The primary atom is indicated by • in **22** and **23**. Dashed lines in **22** indicate residue boundaries.

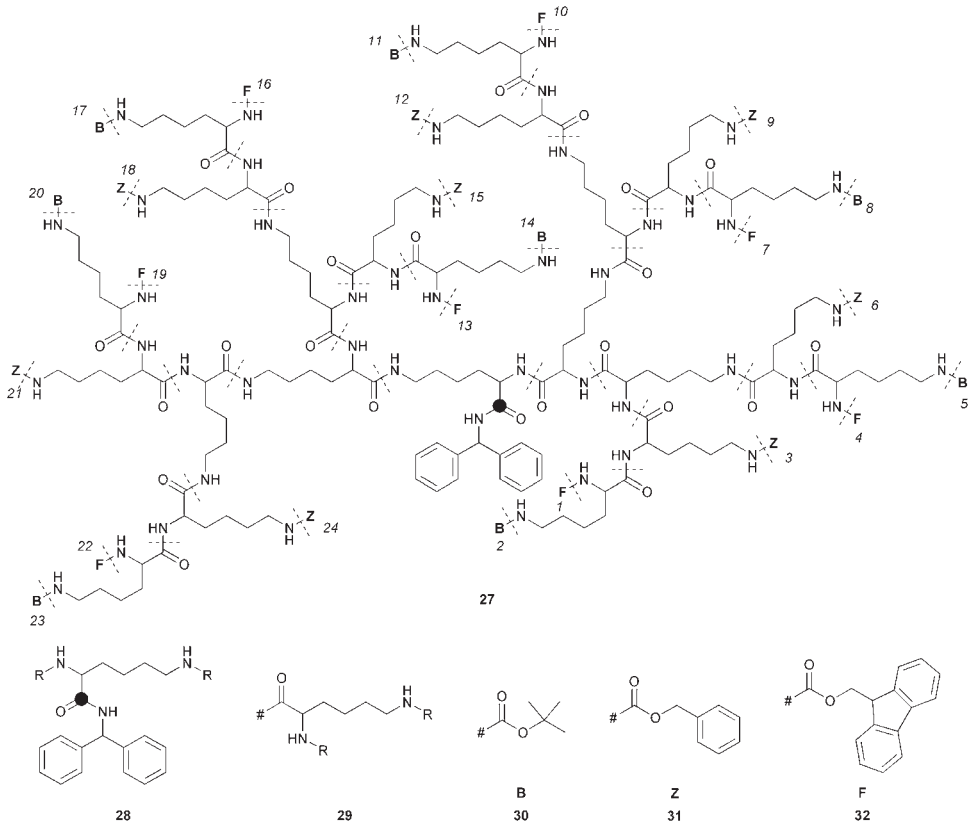



**Fig. 9** A polylysine dendrimer (**27**) with three different caps and partially complete generations of monomers. Its constituent core (**28**), monomer (**29**) and caps (**30–32**) are also shown. The primary atom is indicated by • in **27** and **28**. Monomer boundaries in **27** are indicated by dashed lines.

bonds which create for each dendron a single attachment point to the core, which resolves this ambiguity (disconnection "b"). In this case, we see that, because of the symmetry present in the core, the caps **A** and **B** are interchangeable with each other. We accordingly describe **21** as **AB**.

### 4.2 Examples of dendrimers described using Dotted-Cap notation

**Example 5: A Wooley dipolar dendrimer.** In 1993, Wooley *et al*. synthesised a number of strongly dipolar dendrimers.[18] In these cases, the core bears two dendritic motifs, and all caps on each motif are identical, but the motifs differ from each other. We present as an example one of their dendrimers, referred to in their paper as "11" (Fig. 8).

The dendrimer **22** can be disconnected to provide a symmetric core (**23**), several generations of benzyl monomers (**24**), and two types of caps, benzyl (**25**) (cap symbol **A**) and *p*-cyanobenzyl (**26**) (cap symbol **B**). After determining the primary atom, we envisage a dendritic framework corresponding to **22**, but with all caps removed and replaced with capping sites which are equivalent to each other. Traversing this framework from the primary atom, we determine the canonical order of caps, as indicated in **22** by the numbers *1* to *24*. The symmetries of the core and the monomers allow us to interchange any motifs attached to the same parent. We therefore denote this dendrimer as

**AA•AA••AA•AA•••AA•AA••AA•AA••••BB•BB••BB•BB**, or, in condensed notation, as **$(AA)_8$•$(BB)_4$**.

**Example 6: A polylysine dendrimer.** Dendrimer **27**[35] (Fig. 9) is constructed from a benzhydrylamide–lysine core (**28**) and generations of lysine monomers (**29**). As capping moieties, it has three orthogonal protecting groups: *tert*-butoxycarbonyl (Boc, **30**), benzyloxycarbonyl (CBz, **31**) and 9-fluorenylmethoxycarbonyl (Fmoc, **32**). The primary atom is shown as • in **27** and **28**. Traversing from this point, we reach the caps (*1* to *24*) in the order indicated in **27**. Since no caps are interchangeable, we describe the dendrimer as **FB•Z•FB•Z•••FB•Z••FB•Z••••FB•Z••FB•Z•••FB•Z••FB•Z**, or, in condensed notation, as **$(FB•Z)_8$**.

**Example 7: A dendrimer containing several varieties of dendrons.** A more complicated example is shown in Fig. 10. In this dendrimer, described by Galliot *et al*.,[36] two varieties of dendritic motif are attached to each of the first generation monomers.

In core **34**, the three phosphorus atoms are equivalent, as are the three nitrogen atoms, so there is no obvious primary atom. For our purposes, the primary atom can therefore be any of the atoms in the central ring. No substituents on any one phosphorus atom (whether in the core or any of the monomers) are interchangeable, as the phosphorus atoms are tetrahedral and therefore chiral centres. Traversal follows the CIP rules. The motifs attached to any phosphorus atom are equivalent (apart from the caps), so the pro-*R* motif takes precedence (rule 2.3); but, because the caps attached are the same, the question of which motifs are pro-*R* need not be answered in this particular case. We note that, of the

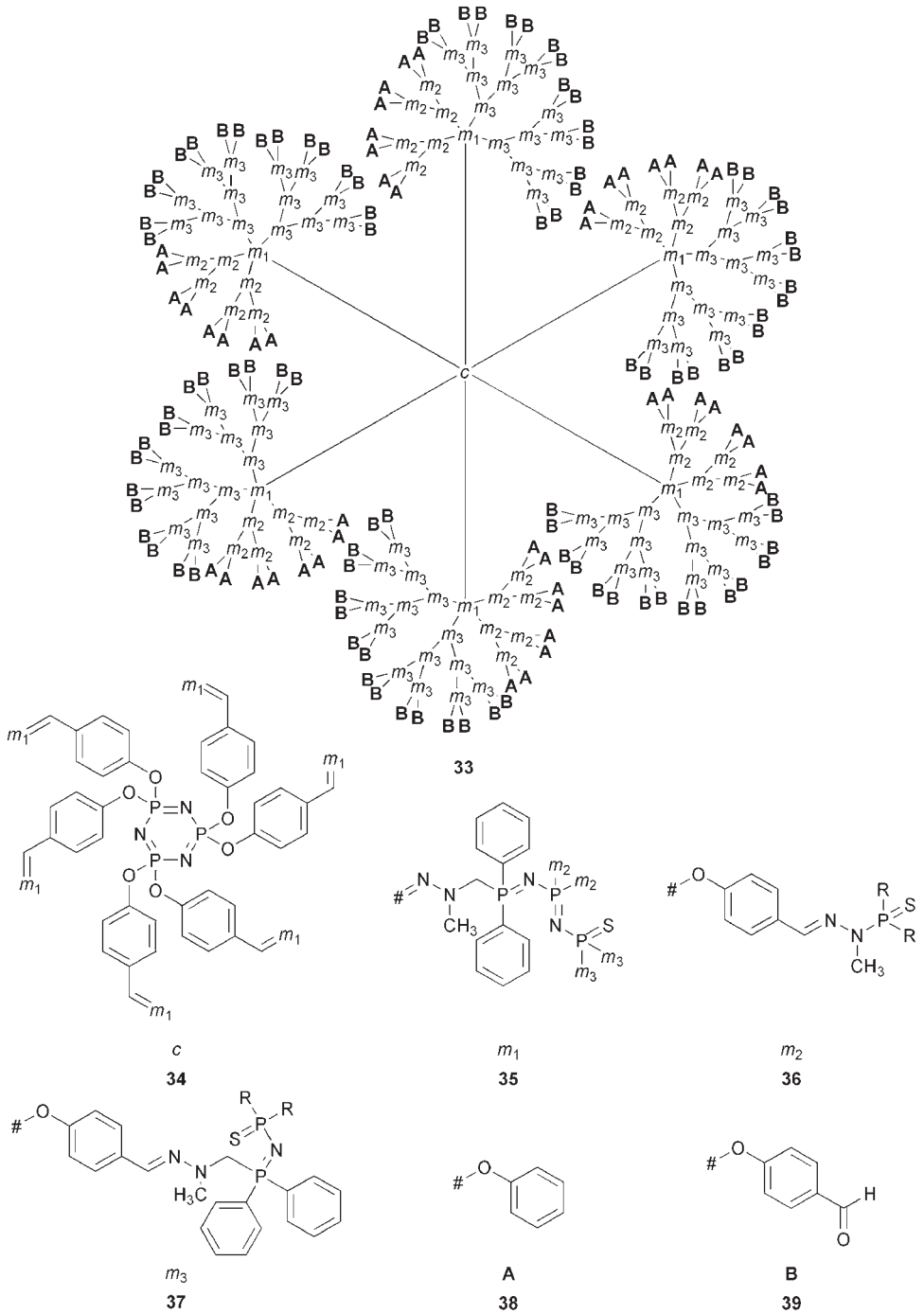



**Fig. 10** A dendrimer (**33**) containing mixtures of dendritic motifs. Only monomer boundaries are shown in **33**. The core (**34**), monomers (**35–37**) and caps (**38** and **39**) are shown separately.

monomers attached to the first-generation monomer **35**, **36** takes precedence over **37**, as it is attached to **35** through oxygen atoms. Therefore, a suitable descriptor for this dendrimer is: **AA•AA•••AA•AA•••BB•BB••BB•BB-•••BB•BB••BB•BB••••AA•AA•••AA•AA•••BB•BB••BB-**BB••••AA•AA•••AA•AA•••BB•BB••BB•BB•••BB•BB•-••AA•AA•••BB•BB••BB•BB•••BB•BB••BB•BB••••AA-•BB••BB•BB•••BB•BB••BB•BB••••AA•AA•••AA•AA•-•BB•BB••BB•BB••••AA•AA•••AA•AA•••BB•BB••BB•-•••AA•AA•••AA•AA•••BB•BB••BB•BB•••BB•BB••BB-•BB••••AA•AA•••AA•AA•••BB•BB••BB•BB•••BB•BB-••BB•BB••••AA•AA•••AA•AA•••BB•BB••BB•BB•••B-B•BB••BB•BB••••AA•AA•••AA•AA•••BB•BB•BB•BB-•••BB•BB••BB•BB In the condensed dotted-cap notation, this reduces to $((AA)_4•••(BB)_8)_6$.

**Example 8: A combinatorial dendrimer.** Finally, we illustrate the application of Dotted Cap Notation to combinatorial dendrimers, in which caps are present in various arrangements but their stoichiometry is known. Newkome *et al*. reported the

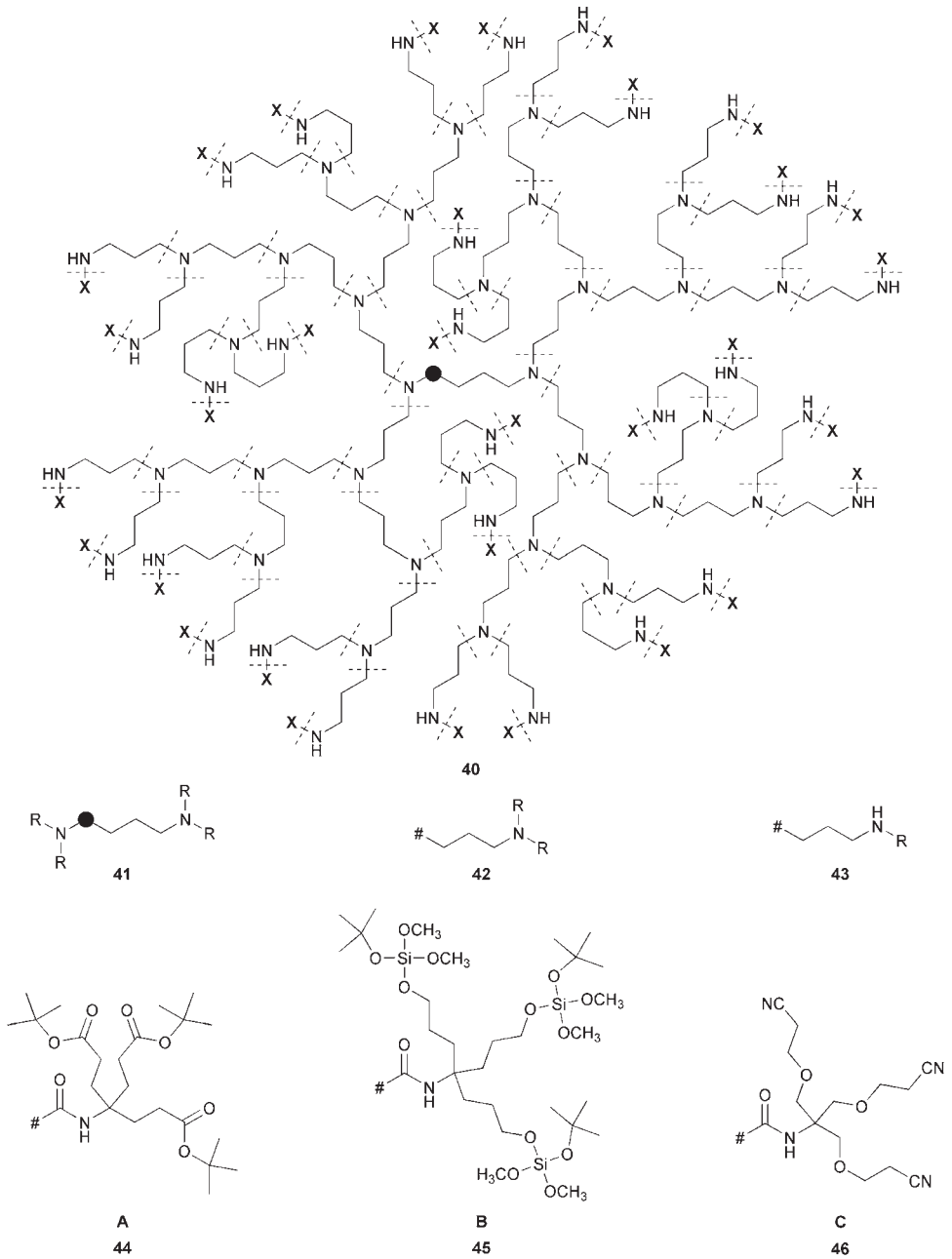



**Fig. 11** A variegated dendrimer with a combinatorial mixture of capping groups. **40** shows the entire dendrimer, with the framework presented explicitly, caps indicated by **X** and monomer boundaries shown as dashed lines. The dendrimer's core (**41**), monomers (**42** and **43**) and caps (**44–46**) are also shown. The primary atom is indicated by • in **40** and **41**.

synthesis of a number of these in a 1999 paper;[37] here, we construct a Dotted-Cap descriptor for a dendrimer which is referred to in that paper as "Combinatorial Dendrimer 18", and which is shown below (Fig. 11).

The dendrimer **40** is constructed from a poly(propylene imine) framework with terminal amine functionalities, capped with a mixture of capping groups: 50% tris-ester (**44**), 40% tris-silyloxy (**45**) and 10% tris(nitrile) (**46**). Assuming that the synthetic precursors to these caps are equally reactive with the dendrimer framework, and that the caps are found equally in all sites, we can construct a corresponding random distribution descriptor, $\{\mathbf{A_{0.5}B_{0.4}C_{0.1}}\}$. To simplify the full representation, we represent this descriptor with another cap symbol, **X**, which we define as $\mathbf{X} = \{\mathbf{A_{0.5}B_{0.4}C_{0.1}}\}$. We further note that the core's substituents are not all interchangeable, but that substituents on other monomers in the dendrimer are interchangeable; and treating the spacer **43** as a monomer in its own right which bears only one capping site (as it is used in the reported synthesis of this dendrimer),[37] we denote **40** as

**X•X••X•X••X•X••X•X••••X•X••X•X••X•X••X•X••••-**
**X•X••X•X••X•X••X•X••••X•X••X•X••X•X••X•X,**

or, in condensed notation, $(\{\mathbf{A_{0.5}B_{0.4}C_{0.1}}\})_{32}$.

## 5 Conclusions

The approach taken in development of previous systems of dendrimer nomenclature has been a full description of the chemical nature of the dendrimer. There is a need for a complement to these systems which concisely describes dendrimers with complex topologies or functionalisation. To achieve this, we propose a notation system which uses a symbolic representation of dendrimer caps. Dendrimers represented using this notation are easily written; even those with complex topologies can be described within a single line of text. Asymmetric dendrimers with complex topologies are described in a very simple manner, while still conveying information about generations of monomers, framework topology and chirality at branch points.

A condensed version of the dotted-cap notation takes advantage of any symmetry present in a dendrimer to further simplify the description of that dendrimer. Thus, if an explicit description of the dendrimer's topology is omitted, the notation can in many cases be reduced to a few characters in length.

This notation is of particular use when comparing caps on a dendrimer. In particular, it can be easily used to compare and contrast similar caps arranged in a different topology, or different caps arranged in a similar topology. Dotted-cap notation is expected to be particularly useful in laboratory discussions, where it provides a quick and straightforward way to describe variegated dendrimers, but should, with appropriate definitions, also be able to be used in more formal contexts.

Dendrimer variegation is still a novel area of research. As the science becomes more established, we expect that ever more complicated variegated systems will be studied. We believe the Dotted-Cap Notation will be useful for these complicated systems, as it is for the cases presented in this work.

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