

Characterizing Pseudodendrimers. I. Graph Representations of Pseudodendrimers Formed by Enhancements to Propagation of Linear Units

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Abstract

Graph theory was used to analyze a series of small pseudodendrimeric structures. Descriptive indices were developed to characterize the pseudodendrimer graphs. The relative proportion of these dendrimers in typical samples was estimated based on three growth models. Weighted average values for the descriptive indices over typical aggregate samples were found to differ only slightly from values for perfect dendrimers.

Introduction

Dendritic polymers based upon AB_2 subunits are ostensibly divided into the categories of dendrimers and hyperbranched polymers. Dendrimers^[1-6] are polymers that are perfectly symmetrical and perfectly branched, but typically require iterative syntheses based on protecting group chemistry or orthogonal functional group reactivities. Hyperbranched polymers^[7-13] contrast dendrimers with a highly random structure, imperfect branching, but a single-reaction synthesis. The differences between hyperbranched polymers and dendrimers are usually described using the degree of branching formulae developed by Fréchet^[14] and revised by Frey.^[15] In these formulae, the relative proportion of

terminal (repeat units bonded to one other monomer), linear (a repeat unit bonded to two other monomers) and dendritic (a repeat unit bonded to three other monomer) units is used to generate an index which is 0 for linear polymers, 1 for perfect dendrimers, and normally 0.5 for random hyperbranched polymers.

A third class of materials, pseudodendrimers, has been proposed as an intermediate class between hyperbranched polymers and dendrimers. These materials were defined by Haag et al. as hyperbranched polymers without linear units;^[16] thus these polymers are comprised of only dendritic and terminal units. Similar to dendrimers, pseudodendrimers have degrees of branching of 1. Unlike dendrimers, they are not perfectly symmetric, making pseudodendrimers isomers of dendrimers. It should be noted that, despite the name, hyperbranched polymers are not as highly branched as dendrimers or pseudodendrimers.

The first examples of pseudodendrimer synthesis were post-synthetic modification of hyperbranched polymers by Lach and Frey,^[17] and later extended by Haag et al.^[18] The sizes and shapes of these pseudodendrimers are strongly influenced by those of the starting hyperbranched polymers. Frey^[19] suggested a second method to synthesize pseudodendrimers by increasing the reactivity at branching points relative to other propagation. Hobson and Feast^[20] have demonstrated the only current example of this process; they report the melt polymerization of ethanediamine mono-acrylamide hydrochloride leads to highly branched polymers. A different approach to synthesizing highly branched polymers, reported by Maier et al.^[21] uses a reversible single addition to an AB₂ monomer followed by an irreversible second addition.

The present work details a simple model for characterizing such pseudodendrimers based on graph theory, and determining the degree with which their structure will deviate from the structure of dendrimers by analysis of the graph representations of pseudodendrimers. Specifically, since pseudodendrimers formed by enhancement of reactivity at branching points (graphically analogous to Frey's suggestion^[19]) will always possess an A functional, the resulting pseudodendrimers will be compared to dendrons (subunits of dendrimers with a single A functional group at core and B functional groups on the periphery). This characterization is important, as it is the basis for justifying the substitution of dendrimers with pseudodendrimers^[22] in applications.

Results and Discussion

Description of Graph Representations of Pseudodendrimers. In this context, a graph is a collection of vertices connected by edges. The graphs presented herein are used to represent pseudodendrimers. Specifically, repeat units are represented as vertices and connections between them as edges. In this preliminary communication, we will exclude the possibility of cycles. This simplification reduces the graphs to a simpler subset of diagrams known as trees. An example of a graph and nomenclature of an imperfect G2-Dendron is shown in Figure 1.

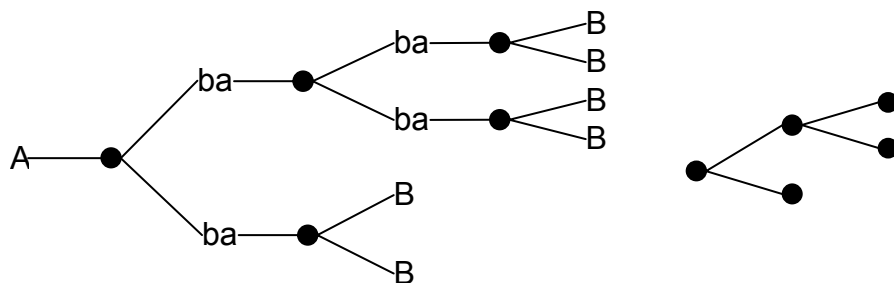


Figure 1. Graph representations of a pseudodendrimer

The first representation corresponds to a chemically intuitive version of the graph, where unreacted functional groups are shown as capital letters, reacted functional groups are shown in lower case letter, similar to Voit's convention,^[23] and the vertices (represented as heavy dots) represent the repeat unit cores.

In the second (simpler) representation, the repeat unit cores are specified and the functional group connections are implied. Throughout this work, the functional groups will be connected A to B as the reader looks left to right. Additionally, the leftmost vertex (also called the root) will **always** possess an unreacted A functional group, and the rightmost vertices will possess two unreacted B functional groups (and are referred to as leaves or terminal units).

The trees will be named by listing the number of vertices traversed between the leftmost vertex and each terminal (rightmost) vertex in order downwards. Permitting rotation about A-B bonds creates the potential for several nomenclatures to describe the same tree, analogous to chemical conformers. We treat all potential graphical conformers as equivalent and; choose the graph identification which is greatest under the lexicographic ordering. Thus the graph in Figure 1 is named 221.

Growth of Pseudodendrimer Graphs. The method for pseudodendrimer growth based on enhancement of reactivity at branch points has been modeled kinetically by assigning relative rate constants for propagation at linear (k_l) and terminal (k_t) units. It has been shown that monomers polymerized with high ratios of k_l/k_t will lead to polymers with high degrees of branching.^[20] For the

purposes of this modeling, we assume a very high (effectively infinite) k_i , along with a small (effectively finite) k_t . The net result is that whenever a propagation occurs, **two** monomers *must* add to a terminal unit, analogous to divergent growth. Alternatively, analogous to convergent growth, one monomer may add to the A functional group of the growing polymer, and a second monomer **must** add to the other B-functional group of what will be the new root. One consequence of this simple model is that the root will always be a linear unit. However, knowing the identity of this repeat unit as the root, allows the critical distinction of the root's reactivity from other linear units formed by monomer addition. By extension to the terminology for dendrimers, these fragments are pseudodendrons.

The first nontrivial addition occurs when the 5-mer (221) adds two repeat units. There are four possibilities for propagation: addition to either of the longest branches from the B side, addition to the shortest branch from the B side, or addition to the A side. Addition to the shortest branch B function leads to 2222, while other propagations lead to 3321. These possibilities are shown in Figure 2.

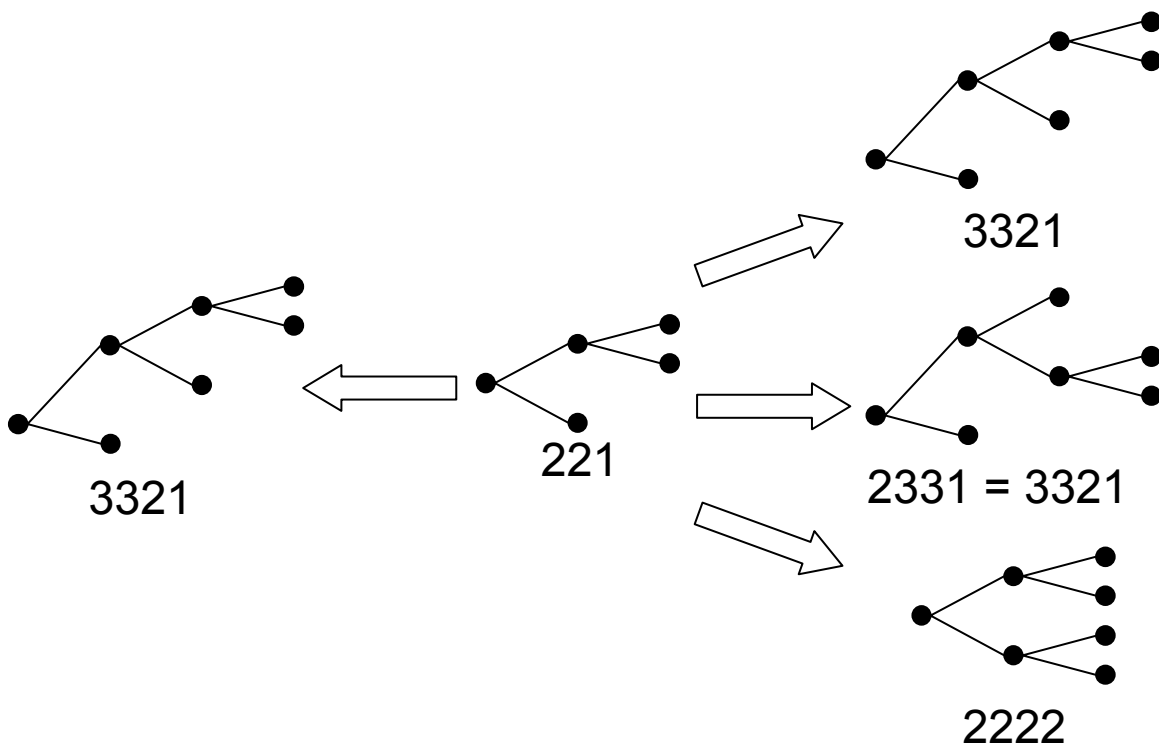


Figure 2. Possibilities for Growth of 221

Using this growth paradigm, we find two pseudodendritic structures for the 7-mer, three structures for the 9-mer, five structures for the 11-mer, eleven structures for the 13-mer, and twenty-three structures for the 15-mer. Careful analysis all of the possible structures suggests that the ultimate distribution of the various 15-mers can be predicted.

We can construct several probability distributions for these structures. The simplest is the equimolar distribution which assumes all sites are equally reactive (and is subsequently referred to as the equal reactivity paradigm). Two other, more complex, distributions are based on pseudo-geometric considerations described in later sections.

Characterization of Pseudodendrimer Graphs. Since the root of the tree is readily identified as the repeat unit with an unreacted A functional group, the distance of any leaf to the root (as traversed by the unique shortest walk) may be determined. Average leaf-to-root distances were then used to characterize the trees. Relative standard deviations (RSD) on these distances were also determined. The root-mean-squared difference (RMSD) of these averages from the perfectly dendritic structure was also calculated.

An additional method based on graph theory will also be employed: distance of a leaf from the center of the graph. The center of the graph is defined as the subgraph of vertices with minimum eccentricity (where the eccentricity of a vertex is defined as the distance to the farthest other vertex). The center of a tree is readily determined by Jordan's method^[24] which says that for any given tree, deletion of the leaves results in a tree with the same center as the original tree. This leads to two possible cases, a center which is a vertex or a center which is an edge. The average distance of the leaf to the center of the graph was then determined in the usual way. In cases where an edge was the center, fractional measurements were employed, such that half of an edge-length was added to the distance. The average leaf-to-center distance was then computed. Relative standard deviations on these distances were also determined. The root-mean-squared difference of these averages from the perfectly dendritic structure was also calculated. The summary data (Supplementary Table 1) allows determinations of the differences between pseudodendrimers and perfect dendrons.

Another growth paradigm may be employed which biases the reactivity of sites based on their distance from the center. This is approximately analogous to accounting for steric hindrance. Each individual leaf-to center distance is added to one to produce a modified leaf-to-center distance. The individual probabilities are assigned by dividing the modified leaf-to-center distances by the sum of all modified leaf-to-center distances ($p_i = \frac{d_i + k}{\sum (d_j + k)}$; referred to as the linear reactivity paradigm). The addition of the constant one is necessary to accommodate the potential for reaction at the center of the graph. The addition of this linear weighting of reactivity produces modest changes in the observed distribution of 15-mers (Figure 3).

A modification of this steric hindrance paradigm involves weighting the propagation probabilities by squaring the modified leaf-center distance and dividing by the sum of the squares of modified leaf-to-center distances

($p_i = \frac{(d_i + k)^2}{\sum (d_j + k)^2}$; referred to as the squared reactivity paradigm). This

modification to the steric hindrance paradigm may model a three-dimensional pseudodendrimer better than the linear model. This treatment further refines the distribution (Figure 3).

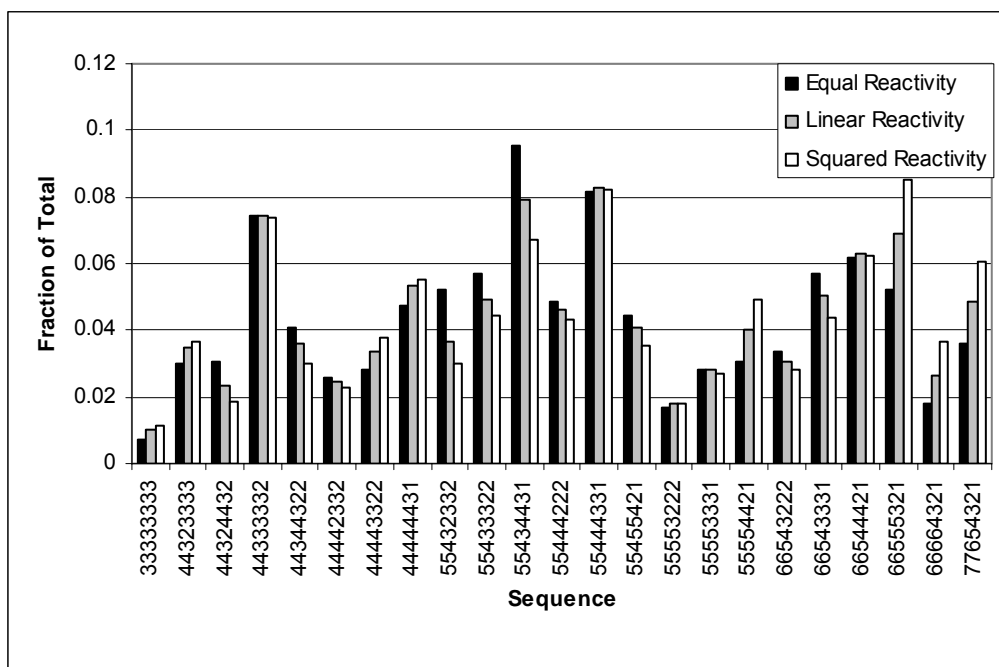


Figure 3. Sequence versus Fraction of 15-mer Pseudodendrimers.

Analysis of Pseudodendrimer Graphs. The resulting data suggest that pseudodendrimers, created in the fashion modeled above, do not grow with perfect symmetry but instead form a distribution of several pseudodendrimers (Figure 3). Summary statistics for the populations of dendrimers determined by the various growth paradigms were determined by weighting versus the fraction of population for each monomer. In an effort to discern deviation of the pseudodendrimer aggregate from a sample of perfect dendrimers, these values were then compared to the “most dendritic” structure for the same number of monomers by dividing the root mean squared values for the pseudodendrimers with the value for the dendrimer (Table 1). Unsurprisingly, the summary statistics suggest that the larger structures show a relatively larger variation in leaf-to-root distances for agglomerations of pseudodendrimers generated. The deviations

for leaf-to-center appear to be independent of the number of monomers for the samples studied, regardless of the propagation model used.

Table 1. Deviations of populations of pseudodendrimers from dendrimers

	Relative RMS deviation from Dendritic Leaf-to-Center Average Distance			Relative RMS deviation from Dendritic Leaf-to-Root Average Distance		
	15-mer ^a	13-mer ^b	11-mer ^c	15-mer ^a	13-mer ^b	11-mer ^c
Equimolar	0.067	0.077	0.063	0.199	0.159	0.104
Equal Reactivity ^d	0.071	0.082	0.079	0.203	0.161	0.122
Linear Reactivity ^e	0.072	0.084	0.080	0.212	0.168	0.126
Squared Reactivity ^f	0.072	0.086	0.080	0.221	0.174	0.130

^a relative to 33333333

^b relative to 3333332

^c relative to 332332

^d equal reactivity paradigm

^e linear reactivity paradigm

^f squared reactivity paradigm

While the root-mean-squared method converts the numbers to absolute values, it should be noted that unlike the leaf-to-root index, the leaf-to-center index contains a significant proportion of structures with smaller leaf-to-center distance averages. The overall averages for the leaf-to-center distances were smaller than the perfect dendron in all cases studied, contrasting the corresponding averages for the leaf-to-root index.

Another very interesting result occurs when the maximum expected relative standard deviations for leaf-to-root and leaf-to-center distances are determined. The highest leaf-to-root RSD will always be achieved by the polymer of named by the sequence [k, k, (k-1), (k-2), ... , 2, 1]. This has sum $k + \frac{k(k+1)}{2}$ and mean

$$\mu = \frac{k(k+3)}{2(k+1)}. \text{ We first calculate:}$$

$$\sum_{i=1}^k (i - \mu)^2 = \sum i^2 - 2\mu \sum i + \sum \mu^2 = \frac{k(k+1)(2k+1)}{6} - 2\mu \frac{k(k+1)}{2} + k\mu^2. \quad (1)$$

The square of the standard deviation is

$$\sigma^2 = \frac{(k - \mu)^2 + \sum_{i=1}^k (i - \mu)^2}{k + 1}. \quad (2)$$

when combined with above yields

$$\sigma^2 = \frac{(k - \mu)^2 + \frac{k(k+1)(2k+1)}{6} - 2\mu \frac{k(k+1)}{2} + k\mu^2}{k + 1} = \frac{k(k^3 + 4k^2 - 6k + 2)}{12(k + 1)^2}. \quad (3)$$

This allows the calculation of σ/μ :

$$\frac{\sigma}{\mu} = \frac{2(k+1)}{k(k+3)} \sqrt{\frac{k(k^3 + 4k^2 - 6k + 2)}{12(k+1)^2}} = \frac{1}{\sqrt{3}} \sqrt{\frac{1 + \frac{4}{k} - \frac{7}{k^2} - \frac{2}{k^3}}{1 + \frac{6}{k} + \frac{9}{k^2}}}. \quad (4)$$

As $k \rightarrow \infty$, (4) approaches $\frac{1}{\sqrt{3}} \approx 0.577$ as an upper bound. This places a maximum limit on the relative standard deviation for the leaf-to-root distance. Additionally, the same result occurs upon analysis of the leaf-to-center distances, with $\frac{1}{\sqrt{3}}$ as an upper bound for the RSD. Corresponding values for random hyperbranched polymers are $\sqrt{2} \approx 1.414$. One would expect similar values for pseudodendrimers synthesized by post-synthetic modification, since this synthetic method does not significantly change the overall length of the leaf-to-center or leaf-to-root distances in the limit of $k \rightarrow \infty$.

Conclusions

For the present initial study, the tree diagrams were produced for all potential pseudodendrimers that are likely formed during the continuous reaction of an AB_2 monomer with an enhancement of reactivity at linear branch points during polymerization. The relative proportions of various pseudodendrimers based on three models of reactivity were determined. Indices describing the pseudodendrimers were applied, and averages based on the relative proportions were estimated. This work provides five significant outcomes:

1. A method for predicting the precise difference between likely pseudodendrimer structure and perfect dendronic structure based on the number of monomers is proposed.
2. This method can be easily applied to expected distributions of various structures to yield average differences in structure.
3. The determined differences for the set of compounds studied were relatively small, suggesting larger pseudodendrimeric structures may exhibit the same similarities to larger dendrimeric structures.
4. The development of the leaf-to-center index suggests a simple method to bias growth models for generation of pseudodendrimeric trees.
5. The number of potential structures is growing quickly, mandating that analyses of larger structures be performed computer simulation. This will be the subject of our upcoming publication.

Acknowledgement

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Supplementary Table 1. Descriptive indices for 15-mer pseudodendrimers^a

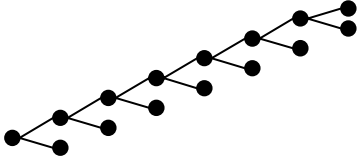
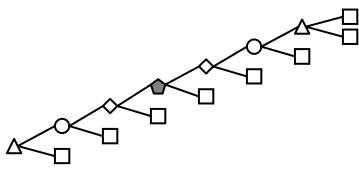
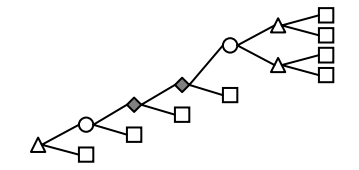
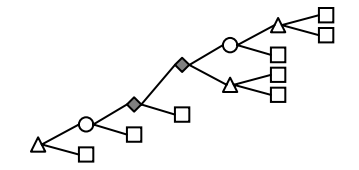
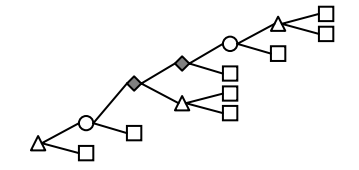
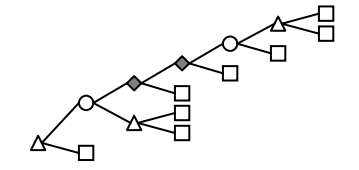
Sequence	Root Mean	Root RSD	Root RMSD ^b	Center Mean	Center RSD	Center RMSD ^b
33333333	3.00	0.00	0.00	3.00	0.00	0.00
44323333	3.13	0.19	0.04	3.13	0.22	0.04
44324432	3.25	0.26	0.08	3.25	0.26	0.08
44333332	3.13	0.19	0.04	3.00	0.17	0.00
44344322	3.25	0.26	0.08	2.63	0.18	0.13
44442332	3.25	0.26	0.08	3.13	0.22	0.04
44443322	3.25	0.26	0.08	2.75	0.16	0.08
44444431	3.50	0.29	0.17	2.75	0.16	0.08
55432332	3.38	0.33	0.13	3.13	0.34	0.04
55433322	3.38	0.33	0.13	2.88	0.24	0.04
55434431	3.63	0.34	0.21	2.88	0.24	0.04
55444222	3.50	0.35	0.17	2.38	0.29	0.21
55444331	3.63	0.34	0.21	2.63	0.18	0.13
5545421	3.88	0.37	0.29	2.63	0.18	0.13
55553222	3.63	0.39	0.21	3.00	0.29	0.00
55553331	3.75	0.37	0.25	2.75	0.24	0.08
55554421	3.88	0.37	0.29	2.63	0.18	0.13
66543222	3.75	0.44	0.25	3.00	0.37	0.00
66543331	3.88	0.42	0.29	2.88	0.30	0.04
66544421	4.00	0.41	0.33	2.75	0.24	0.08
66555321	4.13	0.43	0.38	2.75	0.24	0.08
66664321	4.25	0.45	0.42	2.88	0.30	0.04
77654321	4.38	0.48	0.46	2.88	0.37	0.04

^a graphs of trees presented in Appendix

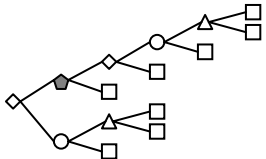
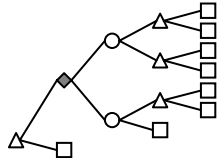
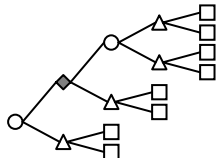
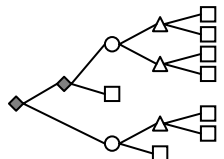
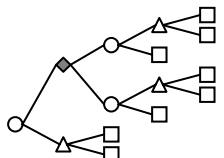
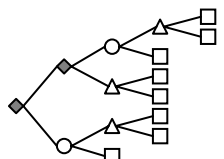
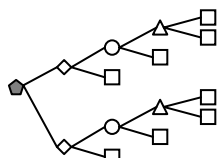
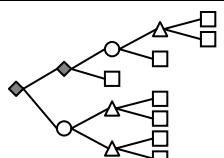
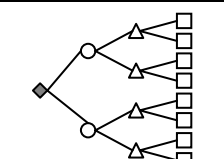
^b relative to 33333333

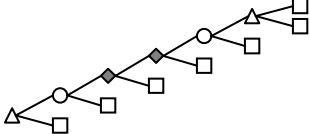
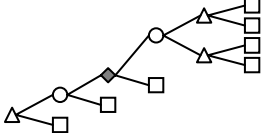
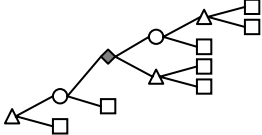
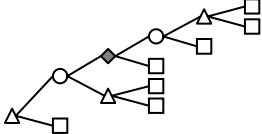
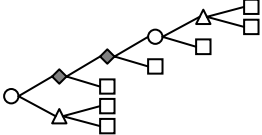
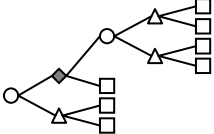
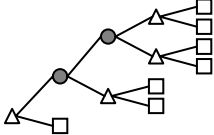
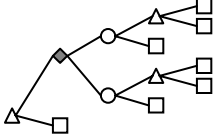
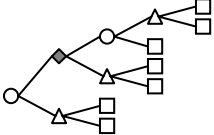
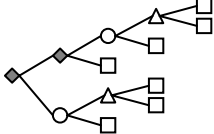
Supplementary Table 2.

A table of all structures studied follows. The center-finding algorithm is also shown by changing the shapes of the vertices which are deleted according to Jordan's method. To follow the deletion, squares are deleted first, then triangles, then circles, then diamonds, and finally pentagons. The resulting center is colored gray to ease identification. An analogous graph in the style described in the text is indicated for the first structure to aid the reader.

# Repeat Units	Structure	Identifier
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15		55434431
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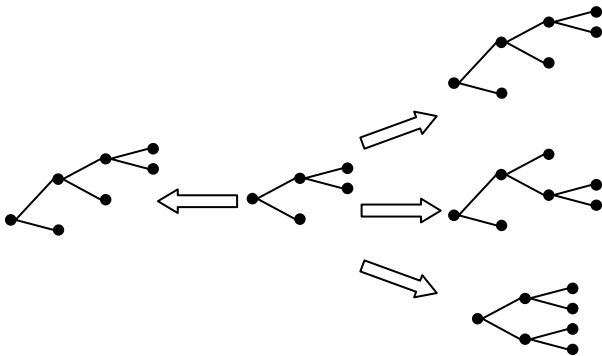
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15		33333333

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13		4444331
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13		4432332

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9		44321
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7		3321
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5		221
3		11

Table of Contents

Graphic



Text

The use of graph theory allows simulation of the generation of pseudodendrimers as well as the comparison of the structures of pseudodendrimers to dendrimers. The resulting analysis indicates that likely aggregates of pseudodendrimers structures will have properties that deviate only slightly from dendrimers.