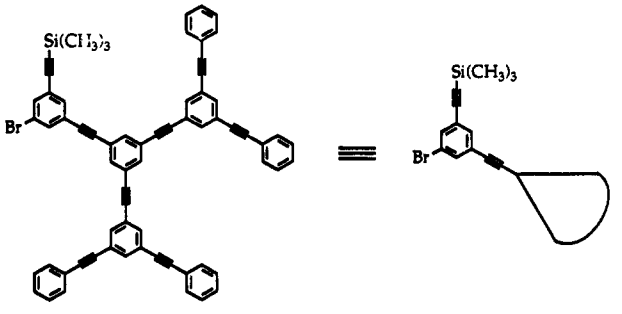
Synthesis of Rigid Dendritic Macromolecules: Enlarging the Repeat Unit Size as a Function of Generation Permits Growth To Continue

We have initiated a program of research on the synthesis of rigid dendritic macromolecules. Dendrimers prepared from rigid units are attractive since they may possess a more precisely defined three-dimensional structure compared to their flexible counterparts. This follows from the geometrical restrictions and lack of conformational freedom imposed by rigid repeat units. To date, most synthetic methods developed for preparing dendritic molecules have employed repeat units that possess considerable flexibility.[1] It is presently unclear as to whether these methodologies can be applied directly to systems constructed from more rigid units.[2] This paper addresses some of the difficulties we have encountered in our initial studies on rigid dendritic macromolecules. In addition, we report a modified convergent strategy which avoids the very serious problem of steric inhibition in these systems. Finally, we have investigated the use of peripheral functionality to enhance the solubility of rigid dendritic wedges.

Our initial synthetic approach followed the convergent strategy[1c] outlined in Scheme I. The repeat unit was based on a 1-ethynyl-3,5-disubstituted benzene derived from dibromide monomer 1. The repetitive chemistry for wedge preparation began with palladium-catalyzed cross coupling using 2 equiv of a terminal acetylene with 1. The trimethylsilyl-masked acetylene serves to prevent self-condensation during cross coupling and could easily be removed under mild conditions to regenerate a new terminal acetylene completing the synthetic cycle. Each of these transformations is well-known and can be performed in high yield with minimal side reactions, thus satisfying the necessary requirements for dendrimer growth. The wedge synthesis shown in Scheme I proceeded smoothly only through generation two. Repeated attempt to prepare the third generation wedge of the parent system (S=Ph) gave none of the desired product. Instead, the major product isolated was the half-wedge W2.5-TMS. We suspected two factors contribute to this surprising result, namely, poor solubility and steric inhibition.



W2.5-TMS

The first problem is that the solubility of W2.5-TMS in the reaction medium is quite low and precipitation of this intermediate would obviously terminate the reaction. To overcome the poor solubility of these wedges, we have incorporated various functionalities on the wedge periphery. Examples of the functional groups we have used are shown in Table I along with the corresponding yield data. Note that although we were unable to prepare the third generation wedge having no peripheral substitution, when solubility was improved through the addition of peripheral methoxy or *tert*-butyl groups, it proved possible to obtain

Scheme I
Synthesis of Arylacetylenic Wedges

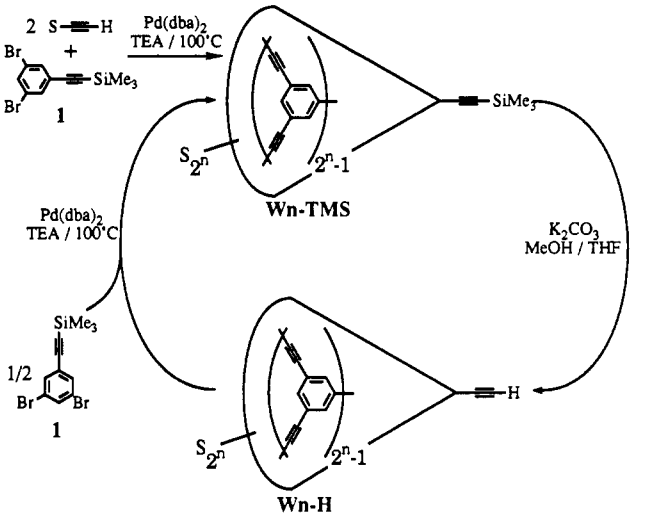


Table I
Yield Data of Early-Generation Dendritic Wedges

	peripheral group				
generation	Ph	*p*-MeOPh	$C(CH_3)_2OMEM$	n-C_5H_{11}	*t*-BuPh
W1-TMS	74	58	90	83	81
W2-TMS	67	34	81	67	73
W3-TMS	0	22	67[a]	70[a]	27 61[a]

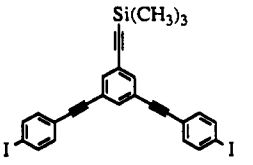
[a] Represent yields in which the enlarged monomer 2 was used.

third generation wedges, albeit in low yield. These materials displayed reasonable solubility in the reaction medium but still appeared to suffer from diminished reactivity.[3] Thus, it was clear that solubility alone was not the only factor that accounted for poor yields.

The second problem we suspected is that of steric inhibition. Steric inhibition is the term used[1c] to describe the diminished reactivity experienced by functional groups at the focal point of dendritic wedges. Molecular modeling studies[4] suggest that our dendritic wedges may experience this problem even as early as the third generation. The rapid onset of this phenomenon for rigid dendrimers apparently arises from the geometrical restrictions imposed by rigidity that confines the growing dendritic branches to narrow regions of space.

To reduce the steric inhibition problem, we considered a scheme of dendrimer growth in which the monomer size was enlarged as a function of generation. As illustrated in Figure 1, it is easy to see that by increasing the monomer size it is possible to reduce or even eliminate the interaction of neighboring wedge segments. In fact, if monomer size increases at a sufficient rate, *it is in principle possible for dendrimer growth to continue indefinitely even in two dimensions* (see Figure 1).

To test this idea, we prepared[5] enlarged monomer 2, which was then used in the third generation step instead of monomer 1. Monomer 2 contains a linear arylacety-



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lenic extension which should help reduce steric interaction between neighboring wedge segments. The chemical

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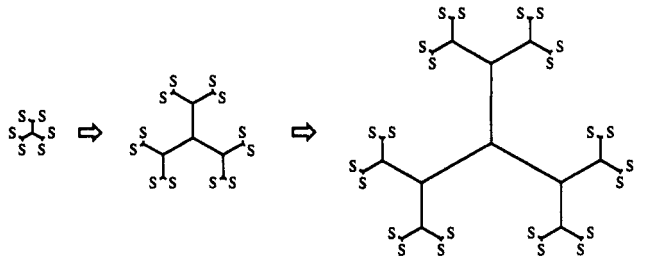
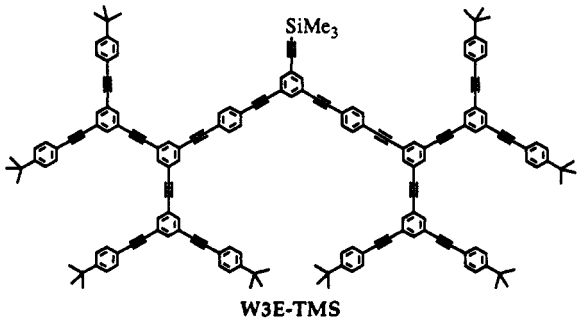


Figure 1. Changing the monomer size as a function of generation could allow rigid dendrimers to be grown indefinitely even in a plane.



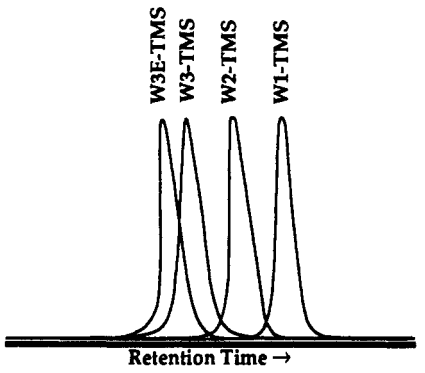


Figure 2. Chemical structure of a third generation dendritic wedge prepared with the enlarged monomer **2**. The size-exclusion chromatographs compare retention times of this wedge with other *tert*-butylphenyl-substituted dendritic wedges prepared according to Scheme I for which monomer **1** was used throughout the synthesis. SEC data were obtained in THF at room temperature.

structure of a third generation dendritic wedge prepared by using the enlarged monomer **2** is shown in Figure 2. Also shown in Figure 2 is a comparison of size-exclusion chromatographs for the conventional dendritic wedges (generations one through three) and the wedge obtained by using monomer **2** in the third generation. The slightly enlarged size of this third generation wedge is readily apparent from its shorter retention time relative to W3-TMS.

It is interesting to note that, in all cases studied to date, yields for generation three wedges prepared with monomer **2** have been significantly higher than when monomer **1** was used throughout the synthesis. This trend is readily apparent from the data shown in Table I (yields of generation three wedges prepared with enlarged monomer **2** are indicated by footnote *a*). The most direct comparison can be made for the *tert*-butyl-substituted wedges for which the use of enlarged monomer **2** gave more than twice the yield compared to when **1** was used. While we cannot rule out the possibility that some of the improved yield is due to the use of an aryl diiodide (monomer **2**) relative to aryl dibromide (monomer **1**), we suspect this to be of only minor significance. What is clear is that the combination of solubilizing groups (n-C_5H_{11}, 4-*tert*-butylphenyl, or the -OMEM derivative) and the use of enlarged monomer **2** have allowed us to obtain W3-TMS wedges in good yield.

The biggest drawback to this modified convergent approach is a more tedious synthesis. It is necessary to prepare monomers that systematically increase in size using chemistry compatible with that used for conventional dendritic wedge growth. In recognition of this difficulty, we have recently developed[6] an efficient strategy for synthesizing linear segments of controlled length which can readily be incorporated with the chemistry employed in Scheme I.

In conclusion, early generation rigid dendritic wedges based on 1,3,5-trisubstituted phenylacetylenic linkages have been synthesized by using a modified convergent approach. Findings from this work suggest that the problem of steric inhibition is quite dramatic in rigid dendritic systems.

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Supplementary Material Available: Experimental details for monomers **1** and **2**, general procedures for the synthesis of dendritic wedges, and spectroscopic data for all the new compounds (7 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For leading references, see: (a) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138. (b) Newkome, G. R.; Yao, Z.-Q.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003. (c) Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

(2) While this work was in progress, the synthesis of a rigid dendrimer based on 1,3,5-trisubstituted benzenes was reported. However, only third generation dendrimers were achieved, and no mention was made of any potential difficulties of extending the synthesis to higher generations. Miller, T. M.; Neenan, T. X. *Chem. Mater.* **1990**, *2*, 346.

(3) Reaction times required for generation three wedges were several times longer than those for generation one.

(4) Martin, D. C.; Xu, Z.; Moore, J. S., unpublished results from our laboratories.

(5) Experimental details are available in the supplementary material.

(6) Moore, J. S.; Zhang, J.; Xu, Z., unpublished results from our laboratory. See also: Moore, J. S.; Weinstein, E. J.; Wu, Z. *Tetrahedron Lett.* **1991**, 2465.

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Registry No. (1)(2) (copolymer), 135853-30-4; W2.5-TMS, 135853-26-8; W3-TMS (*t*-Bu), 135989-32-1; W3E-TMS, 135853-27-9.