Synthesis and Characterization of Water-Soluble Dendritic Macromolecules with a Stiff, Hydrocarbon Interior

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Received April 3, 1997; Revised Manuscript Received August 5, 1997[⊗]

ABSTRACT: Phenylacetylene dendrimers terminated with *tert*-butyl esters on their periphery up to the fifth generation were synthesized by a modified convergent growth protocol. A solid-state thermolytic process involving no solvents, reagents, or catalysts accomplished transformation of the *tert*-butyl esters to carboxylic acids. The carboxylic acid terminated dendrimers possessed solubility characteristics orthogonal to those of the *tert*-butyl esters. Capillary electrophoresis and electrospray mass spectrometry were used to characterize the carboxylate terminated dendrimers. These techniques suggested that some form of cross-linking between or within higher generation dendrimer molecules was occurring during the thermolysis reaction. To overcome this problem, a second series of dendrimers terminated with (2-[2-(2-methoxyethoxy)ethoxy]ethyl) esters on their periphery were prepared, enabling aqueous solution hydrolysis to produce the carboxylic acids. The dendrimers that resulted by this approach were found to be more homogeneous products.

Introduction

The rapid growth of research in the area of dendritic macromolecules since the pioneering work of Newkome[1] and Tomalia[2] has led to a variety of structurally intriguing polymers with the potential for use in a number of applications.[3] Dendrimers are constructed by a stepwise process to give macromolecules with precisely controlled structures (ideally a single composition and constitution) and of globular shape.[4] By exploiting these architectural features, dendrimers have been used as size standards,[5] "molecular boxes" capable of selective guest liberation,[6] homogeneous catalysts,[7] and light-gathering antennae.[8] If functionalized with hydrophilic groups on their periphery, dendrimers adopt a structure similar in both size and shape to that of the Hartley micelle model (i.e., spherical, with hydrophilic exterior and hydrophobic interior, Figure 1).[9] Indeed, several groups have demonstrated this analogy with a variety of systems.[10] Much like micelles, dendrimers possess the ability to solubilize otherwise insoluble organic substrates in aqueous media. An important difference between these two hosts is that the dendrimer is a single molecule incapable of disintegration (except by covalent bond rupture) while the micelle is dynamic on some time scale. While the stability of micelles depends on a variety of factors (pH, concentration, ionic strength, temperature),[11] dendrimers (or unimolecular micelles)[12] retain their structure (and utility) regardless of the physical environment (i.e., the critical micelle concentration is zero in all conditions). Such structures may have application in catalysis[7b] and as controlled release agents for drugs.[10f,13]

Our group has reported a convergent[14] synthesis of a series of all-hydrocarbon dendrimers based on a 1,3,5-trisubstituted phenylacetylene repeat unit.[15] This particular backbone, like those of Miller and Neenan,[14e−g] Webster and Kim,[12] and Müllen,[16] imparts a certain stiffness or "shape-persistence" to the structure. Flexible systems have been shown to change size in different physical environments. For example, Newkome's polyamide dendrimers functionalized with carboxylic acids on the periphery were found to shrink with decreasing pH.[17] In contrast, the stiff, phenylacetylene dendrimers should be less susceptible to collapse.

Another unique characteristic of phenylacetylene dendrimers is their all-hydrocarbon skeleton. The absence of heteroatoms within the backbone makes the interior more hydrophobic than other systems such as Tomalia's PAMAM series,[2] Newkome's polyamides,[17] or Fréchet's poly(benzyl ether) dendrimers.[10f] The combination of stiffness and hydrophobic interior could provide some unusual properties to a phenylacetylene dendrimer functionalized with hydrophilic groups on the periphery. It is possible that they could show size, shape, or chemical selectivity for guest molecules. The stiff nature of the structure might also cause it to retain guests more tightly.

While the study of dendritic macromolecules provides a wealth of opportunity in materials research, the reliability of these observations ultimately depends on the quality of the sample studied. Accurate measurements may best be done on pure samples rather than mixtures. The nature of dendrimer syntheses, particularly by divergent protocols, often results in imperfect or impure structures, the extent to which increases with higher generations.[18] For example, to obtain the sixth generation dendrimer which is 99% pure from a fifth generation (96 reactive sites) by a divergent route, the coupling reaction must proceed to 99.99% conversion.[19] Separation of these impurities also becomes much more difficult at higher generations. The convergent approach[14] circumvents some of these shortcomings but can still give imperfect structures depending on mono-

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[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1997.

S0024-9297(97)00454-3 CCC: $14.00

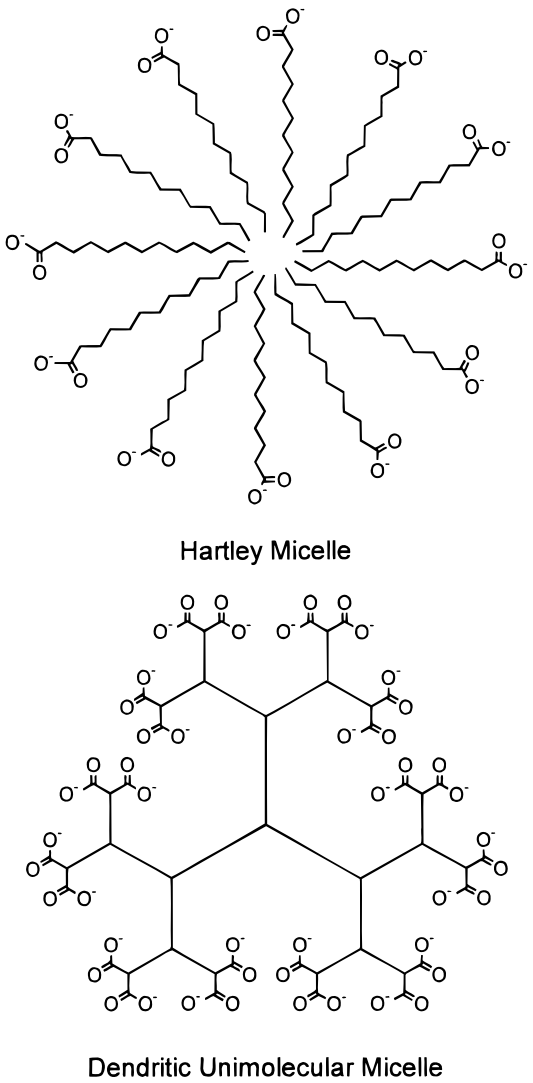


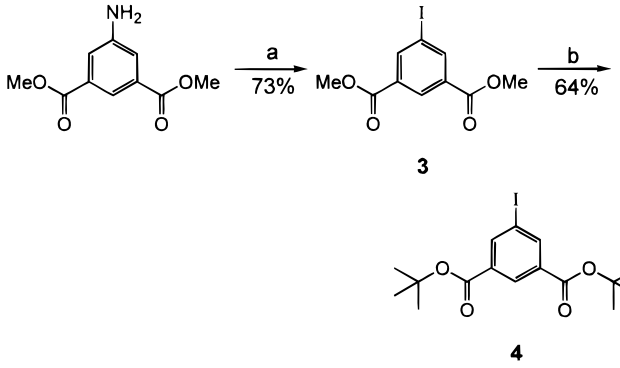
Figure 1. Schematic representation showing the structural similarity between the traditional Hartley micelle model and a dendrimer.

mer purity and reaction efficiency. It is thus important to have analytical tools capable of reliably and accurately assessing the purity of dendrimers and also identifying the structural features of impurities and defect containing dendrimers. This poses special problems and unique opportunities when the dendrimer bears ionic charges and they are soluble in water. This paper describes our initial efforts toward the synthesis and characterization of a series of water-soluble phenylacetylene dendrimers terminated with hydrophilic groups on their periphery.

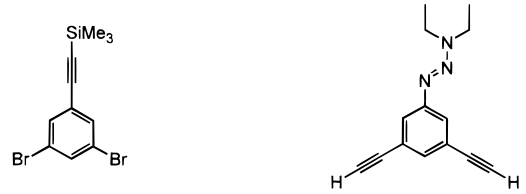
Results and Discussion

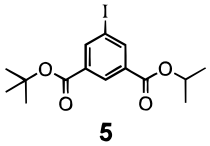
Focal point monomer **2** was selected on the basis of its proven coupling efficiency at all generations.[15c] It was previously found that coupling yield decreased substantially at higher generations utilizing focal point monomer **1**, while yield remained essentially constant employing monomer **2**. The convergent approach requires attachment of the peripheral groups at the first step. We selected the isophthalic acid moiety[14d,20] as a suitable peripheral monomer based on its stability, hydrophilicity, and relative ease of preparation from readily available starting materials. The carboxylic acid group, however, is unsuitable since it would certainly reduce solubility during monodendron construction. The carboxylic acids were thus protected such that the monodendrons would retain solubility yet could undergo facile and quantitative removal. The *tert*-butyl ester appeared to fulfill both of these requirements. Its steric bulk provided good solubility in a variety of solvents, on the one hand, while its removal is affected either by acid catalysis[21] or by simple heating.[22] We have previously employed the solid-state thermolytic conversion of *tert*-butyl esters to carboxylic acids with good success on a number of structures.[23] This process has also found use in photolithography.[24] Peripheral monomer **4** was thus synthesized in modest yield in two steps from commercially available dimethyl 5-aminoisophthalate (Scheme 1).[25] GC analysis of the product showed that it contained approximately 1.6% of an impurity. GCMS suggested a composition consistent with isopropyl-*tert*-butyl 5-iodoisophthalate (**5**). It is believed that the *tert*-butyl alcohol is contaminated with a small amount (<0.5%) of isopropyl alcohol. The consequences of this impurity will be discussed later.

Scheme 1. Synthetic Route to the Peripheral Monomer 4[a]



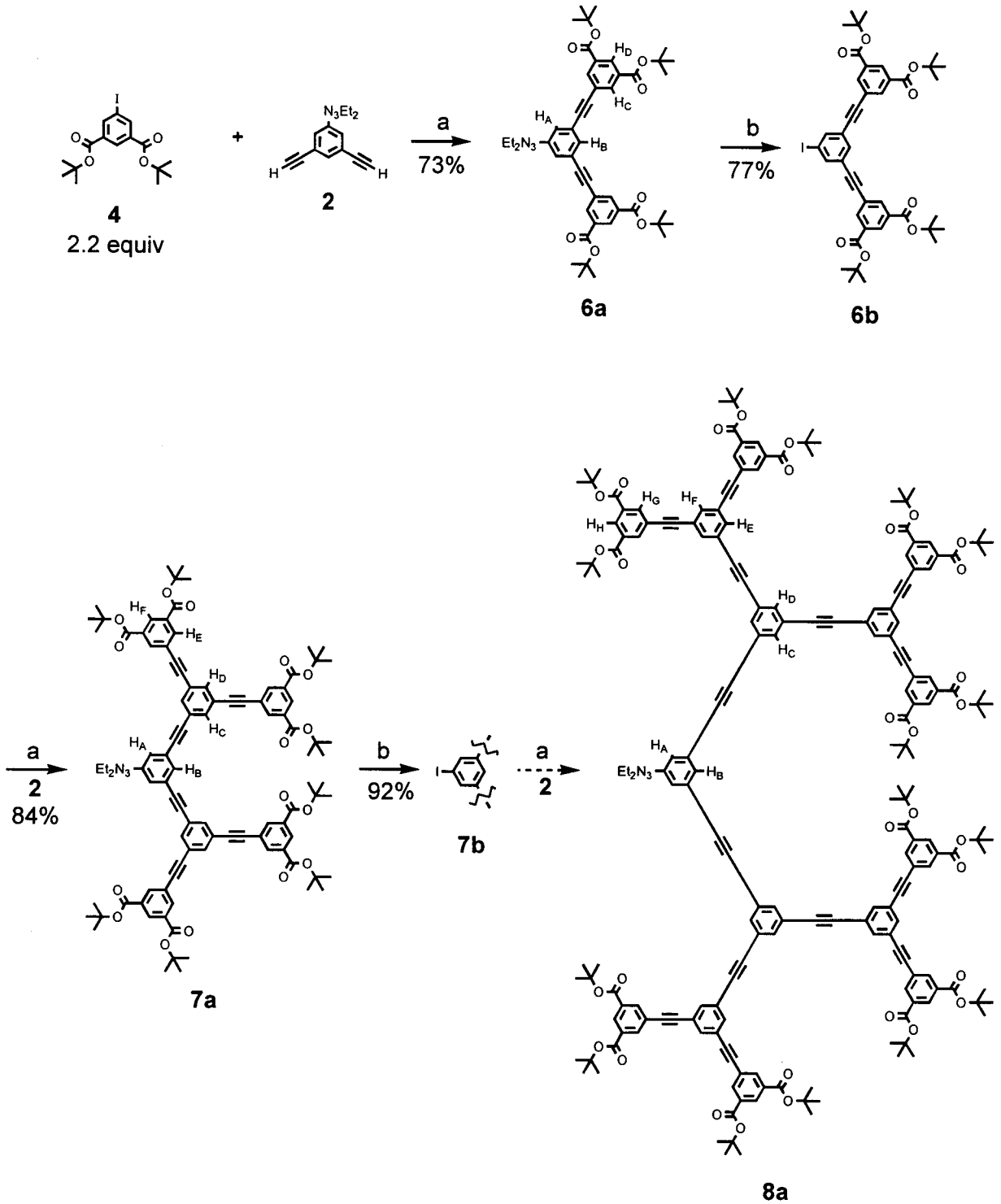
[a] Reagents: (a) (i) HCl, H_2O, CH_3CN; (ii) $NaNO_2$, H_2O, 0−5 °C; (iii) KI, I_2, H_2O. (b) *t*BuOH, *n*BuLi, THF.





Monodendron construction began by palladium-catalyzed cross coupling between monomer **2** and 2.2 equiv of monomer **4** (Scheme 2).[26] Purification of the resulting 3-mer (**6a**) was accomplished by filtration through a short plug of silica gel followed by recrystallization. The triazene at the focal point was then converted to the corresponding aryl iodide (**6b**) by treatment with methyl iodide in a sealed tube at 110 °C.[27] Care had to be taken when running this reaction on these particular substrates. Lower yields and the appearance of significant baseline material by TLC were observed if the reaction were run for extended periods of time. This could be explained by partial hydrolysis

Scheme 2. Synthetic Route to Lower Generation Monodendrons[a]

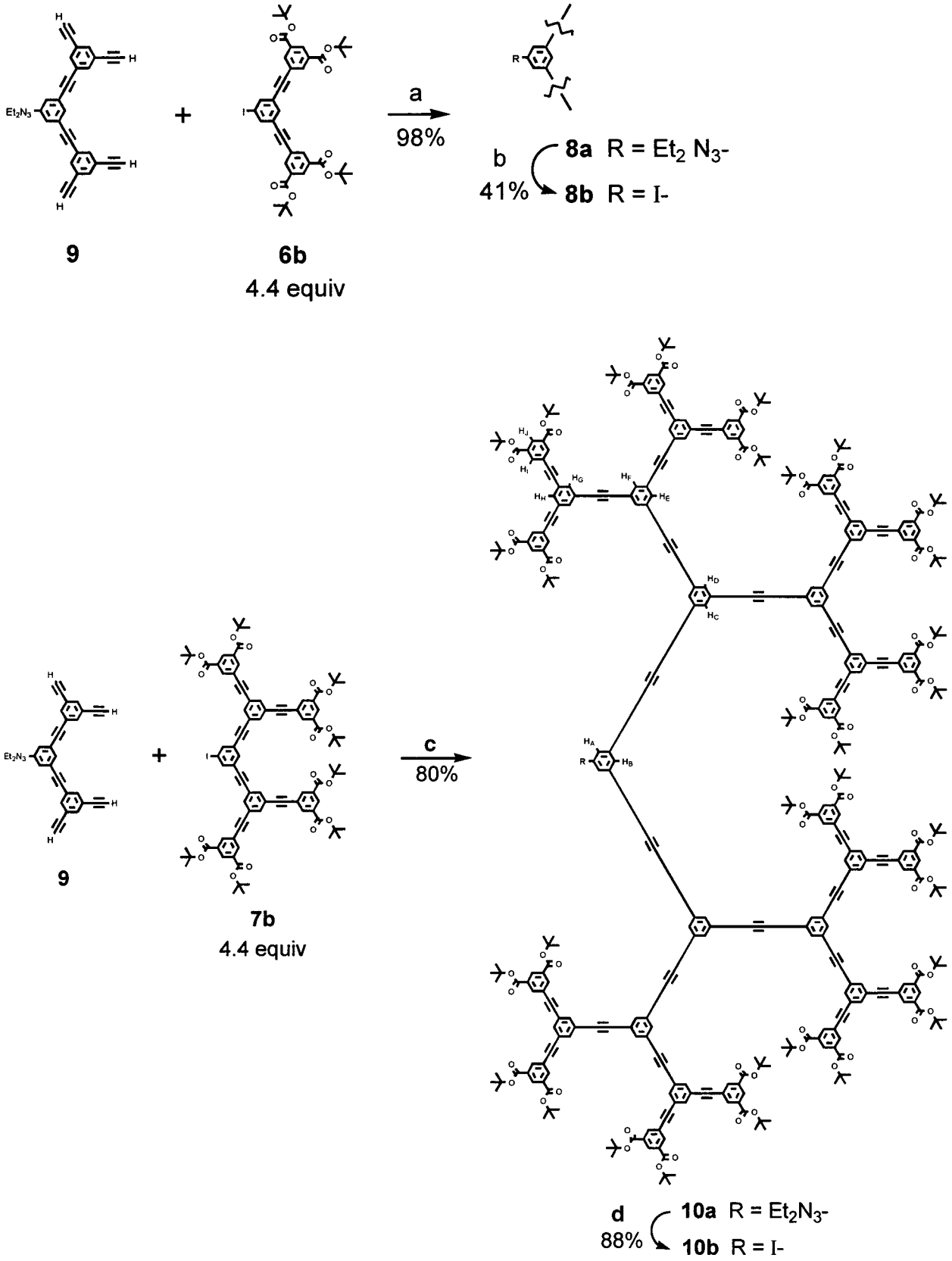


[a] Reagents: (a) $Pd_2(dba)_3$, CuI, PPh_3, Et_3N, 60−75 °C. (b) CH_3I, 110 °C, 12 h. Note: letters next to various positions on the structures refer to assignments on NMR spectra (Figure 3).

of some of the *tert*-butyl esters to carboxylic acids, a consequence of the generation of small amounts of HI in the reaction. Addition of potassium carbonate to the reaction had no appreciable effect on the outcome; however, addition of propylene oxide to the methyl iodide completely suppresses conversion of the triazene to the iodide.[28] This suggests that HI is present and necessary for the conversion.

Two equivalents of this first generation monodendron (3-mer, **6b**) was then coupled to the focal point monomer **2** to give the second generation 7-mer (**7a**). Treatment with hot methyl iodide gives the 7-mer functionalized with iodide at the core (**7b**). Interestingly, the solubilities of both the 3-mer and 7-mer were quite low in hexane despite the presence of multiple *tert*-butyl esters (4 and 8, respectively). Both generations were, however, soluble in many other solvents such as chloroform, THF, and benzene. The next logical step in the repetitive cycle would be coupling 2 equiv of the 7-mer (**7b**) with the core monomer **2** to give the third generation 15-mer (**8a**). While this reaction does produce the 15-mer, separation from excess 7-mer becomes difficult. Chromatographically, the R_f difference between the 7-mer and the 15-mer is rather small. Another undesirable

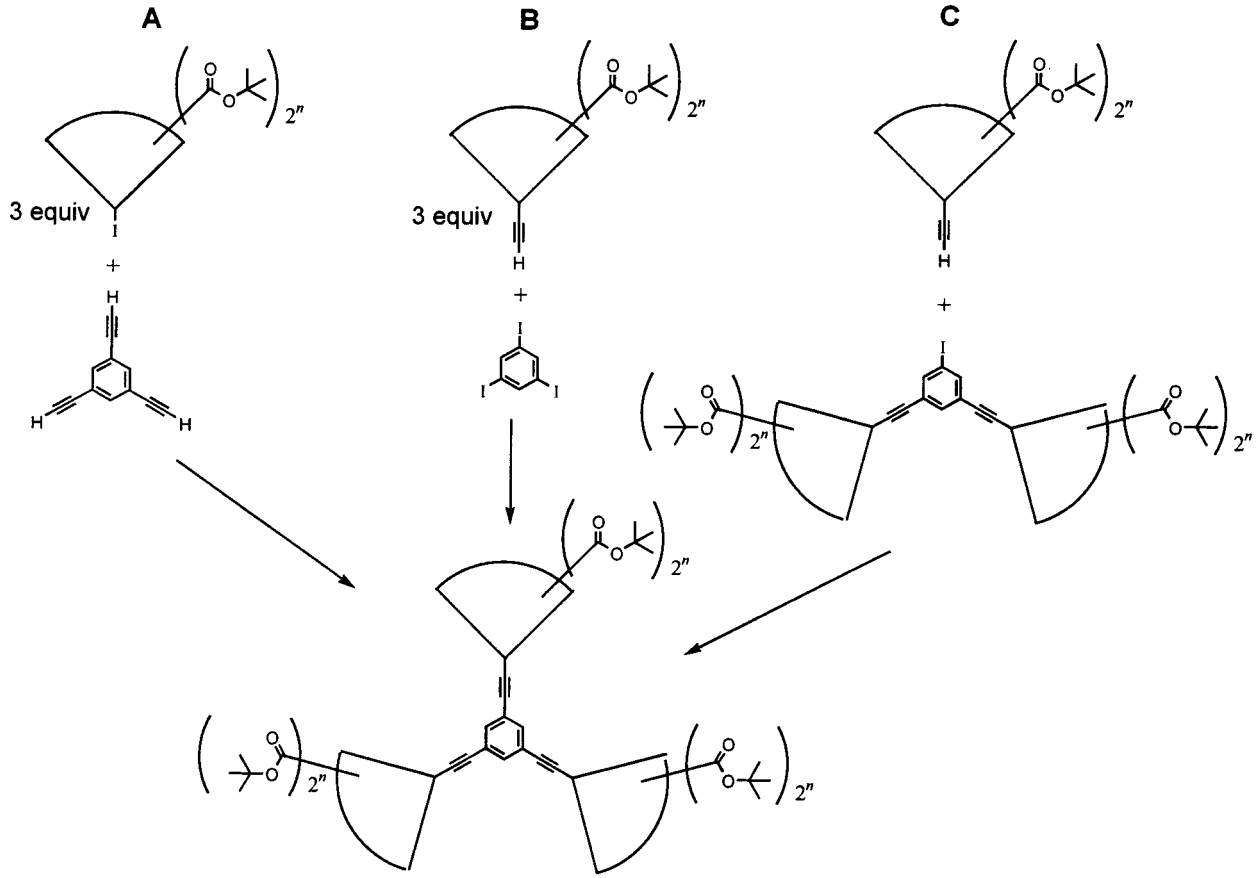
Scheme 3. Synthetic Route to Higher Generation Monodendrons Employing the Hypercore 9[a]



[a] Reagents: (a) $Pd_2(dba)_3$, CuI, PPh_3, Et_3N, 60−75 °C. (b) CH_3I, 110 °C, 12 h. (c) $Pd_2(dba)_3$, CuI, PPh_3, Et_3N, 60−75 °C. (d) CH_3I, I_2, 98 °C, 12 h. Note: letters next to various positions on the structures refer to assignments on NMR spectra (Figure 3).

property is the chromatographic broadening (streaking) exhibited by the 15-mer and higher generations. To circumvent this shortcoming, an intermediate was used which results in the "skipping" of a generation, in analogy to the double stage construction method described by Fréchet.[29] Hypercore **9** is a first generation monodendron (3-mer) functionalized with a triazene group at its focal point and four terminal acetylenes on its periphery.[15b] Coupling 4.4 equiv of the 3-mer (**6b**) to hypercore **9** gives the desired 15-mer (**8a**) (Scheme

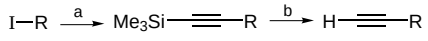
Scheme 4. Potential Routes to Phenylacetylene Tridendrons



3). This coupling scheme is simplified since chromatographic separation of the 15-mer (**8a**) from the starting material (**6b**) is much easier than separation of **8a** from **7b**. This same protocol was utilized to obtain the fourth generation (31-mer) monodendron **10a** (Scheme 3). An attempt was made to synthesize the fifth generation; however, the product showed severe chromatographic broadening, making purification very difficult.

To make 3-fold symmetric tridendrons, 3 equiv of the monodendrons functionalized with iodide groups at the focal point could be coupled to 1,3,5-triethynylbenzene (route A, Scheme 4).[30] This process, however, was low yielding (10−30%) even for the smallest tridendron (4-mer, **11a**), presumably because of the relative instability of triethynylbenzene. Given this shortcoming, the focal point of each monodendron was converted to an ethynyl group by first reacting with (trimethylsilyl)acetylene under palladium catalyzed cross-coupling conditions followed by removal of the trimethylsilyl group with tetrabutylammonium fluoride (Table 1). Three equivalents of these acetylene-terminated monodendrons was then coupled to a triiodobenzene core (route B, Scheme 4) to give tridendrons much more efficiently. Alternatively, a monodendron with a terminal acetylene at its focal point was coupled to an iodo-terminated monodendron of the next or previous generation to give tridendrons (route C, Scheme 4). This protocol was useful for preparing lower generation tridendrons; however, separation considerations made the former process (route B) more appropriate for the higher generations. A fourth procedure was developed using the 3-fold symmetric hypercore (**14**). Attempts to make the 94-mer by this double stage method utilized **14** and 12 equiv of the 15-mer with iodine at its focal point (**8b**) (Table 2).

Table 1. Yields of Monodendron Coupling Reactions and Focal Point Deprotections[a]



I—R	yield % Me$_3$Si—R	yield % H—R
4 (monomer)	96 (**12**)	93 (**13**)
6b (3-mer)	73 (**6c**)	77 (**6d**)
7b (7-mer)	91 (**7c**)	68 (**7d**)
8b (15-mer)	92 (**8c**)	68 (**8d**)
10b (31-mer)	96 (**10c**)	92 (**10d**)

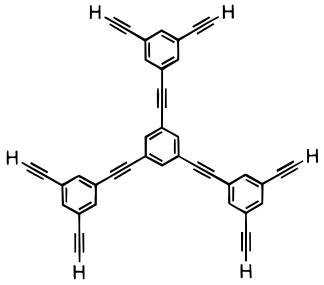
[a] Reagents: (a) (trimethylsilyl)acetylene, $Pd_2(dba)_3$, CuI, PPh_3, Et_3N, 60−75 °C; (b) TBAF, THF.

Table 2. Yields of Tridendron Preparations

tridendron	synthetic route (Scheme 4)	yield (%)
4-mer (**11a**)	C	55
10-mer (**15a**)	C	80
22-mer (**16a**)	B	93
46-mer (**17a**)	B	62
94-mer (**18a**)	double stage	50[a]

[a] HPLC of the 94-mer showed three very broad, overlapping peaks. Presumably, one of these components does correspond to the 94-mer. It is also likely that, contained within the eluting components, there are defect-containing dendrimers resulting from incomplete reaction of all acetylene groups on hypercore **14**.

These mono- and tridendrons with *tert*-butyl esters on the periphery were amenable to many common characterization techniques. Solubility in a variety of solvents was maintained throughout the series. The lower generations (3-mer, 4-mer, 7-mer, and 10-mer) had limited solubility in hexane, while larger dendrimers (15-mer and larger) all exhibited high solubility in hexane. Most of the mono- and tridendrons gave satisfactory elemental analyses. Electron impact (EI)



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and fast atom bombardment (FAB) mass spectrometry provided molecular ions of mono- and tridendrons of up to 15 monomer units (MW ca. 3000). Matrix-assisted laser desorption ionization (MALDI) mass spectrometry did not give molecular ions for the higher generation dendritic structures (MW > 3000) with a variety of matrices. Only broad signals of lower molecular weight were observed. The phenylacetylene structures do absorb light at the operational wavelength (337 nm) of the laser, thus opening the possibility of photoinduced reactions. Thermolytic removal of the *tert*-butyl groups during laser ablation may also be a problem. Gel permeation chromatography (GPC) provided information on relative sizes of the dendrimers (Figure 2). All compounds showed traces with low polydispersities (<1.04), and increasing generations followed the expected trends in molecular weight. The higher generations did show minor fronting, the origin of which is unknown.

The aromatic region in the ^{1}H-NMR spectra is of key importance in the characterization of all mono- and tridendrons. Shown in Figure 3 is the aromatic region of the first four generations of monodendrons. The solvent had to be adjusted to provide both high resolution and adequate chemical shift dispersion. Chloroform-*d* was useful for only the smallest mono- and tridendrons. Benzene-d_6 was useful up to the 31-mer; however, higher temperature was necessary to resolve splitting patterns. For even larger species (46-mer tridendron, **17a**), a mixture of chloroform-*d* and benzene-d_6 was needed to provide both the dispersion and resolution necessary for assignment (Figure 4). In most cases, the signals were dispersed well enough that each could be assigned to a single resonance.

Normal-phase HPLC provided information on the homogeneity of the lower generation mono- and tridendrons. Interestingly, compounds which gave satisfactory elemental analyses had elution profiles showing multiple peaks. For example, an "analytically pure" 7-mer (**7d**) showed two distinct peaks at slightly longer retention times relative to the main product peak (Figure 5). Preparative HPLC was employed to isolate the major impurity. NMR and FAB mass spectrometry suggest it is a 7-mer with seven *tert*-butyl esters and one isopropyl ester on the periphery. The utility of HPLC was limited only to compounds with molecular weights less than ca. 3000. HPLC showed behavior similar to that observed in thin layer chromatography, i.e., compounds which "streaked" on TLC plates (higher generations) exhibited broad elution profiles by HPLC.

Conversion of the *tert*-butyl ester groups to hydrophilic carboxylic acids was accomplished by a solid-state thermolytic process.[22−24] Solid dendrimer samples were heated under an inert atmosphere to ca. 230 °C for 15 min. Isobutylene gas was liberated, leaving a carboxylic acid on the substrate. For some of the generations, foamed materials resulted. The reaction can be monitored quantitatively by simulating the reaction conditions with thermal gravimetric analysis as shown in Figure 6. Table 3 shows the theoretical and observed weight loss for the five generations of tridendrons.

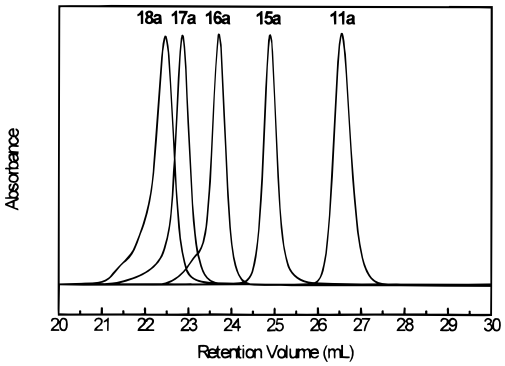


Figure 2. Size-exclusion chromatograms of five generations of *tert*-butyl ester terminated phenylacetylene tridendrons.

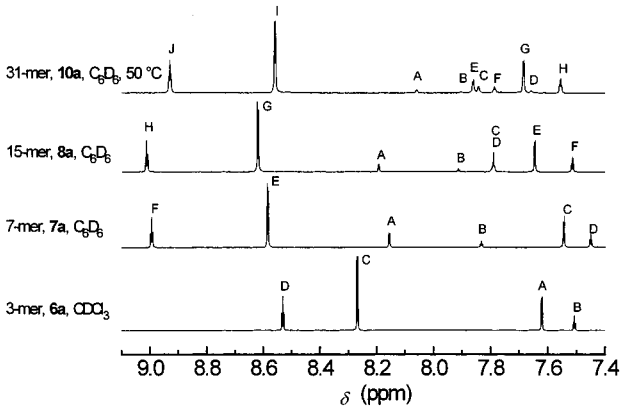


Figure 3. Aromatic region of the 400-MHz ^{1}H NMR spectra of four generations of *tert*-butyl ester terminated phenylacetylene monodendrons **6a**, **7a**, **8a**, and **10a**.

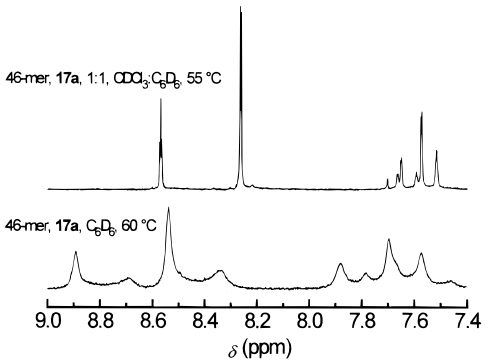
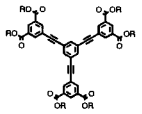
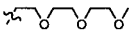


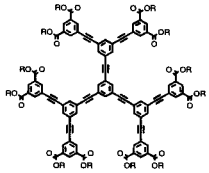
Figure 4. Aromatic region of the 400-MHz ^{1}H NMR spectrum of *tert*-butyl ester capped 46-mer tridendron in benzene-d_6 at 60 °C (bottom) and 1/1 (v/v) chloroform-*d*/benzene-d_6 at 55 °C (top).

Characterization of the carboxylic acid terminated dendrimers (**11b**, **15b**−**18b**) presented a much greater challenge as their solubility was limited. They were soluble in aqueous media (pH > 6) and polar aprotic solvents such as DMSO, DMF, and NMP. ^{1}H NMR was useful only up to the second generation (10-mer, **15b**), beyond which only broad, ill-defined signals were observed even at elevated temperatures.

Among the most useful techniques for analyzing the homogeneity of ionic, water-soluble molecules (small and large) is free zone capillary electrophoresis.[31] Separa-



11a R = *t*-Bu
11b R = H
11c R = 



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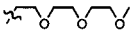
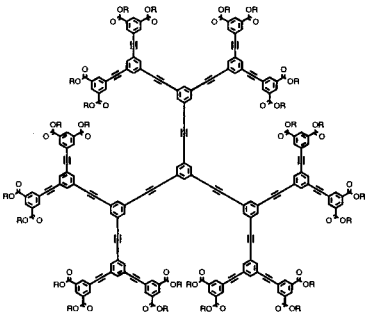
15c R = 



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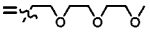
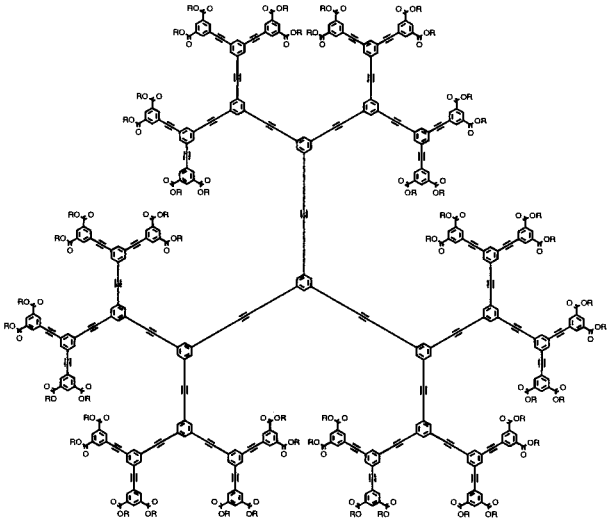
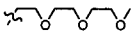
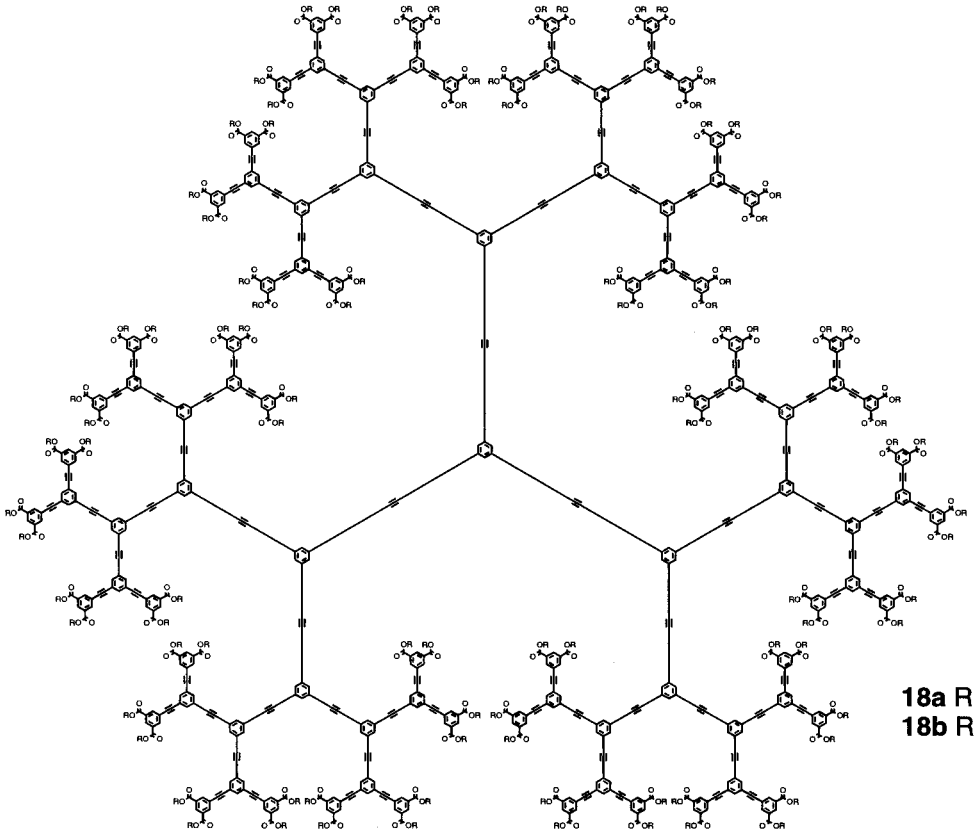
16b R = H
16c R = 



17a R = *t*-Bu
17b R = H
17c R = 



18a R = *t*-Bu
18b R = H

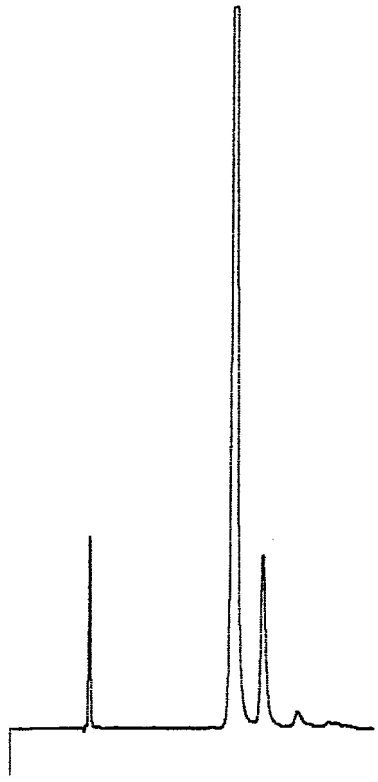


Figure 5. HPLC trace of an "analytically pure" sample of 7-mer **7d** run in 1/9 (v/v) ethyl acetate/*n*-hexane at a flow rate of 1.0 mL·min^{-1}.

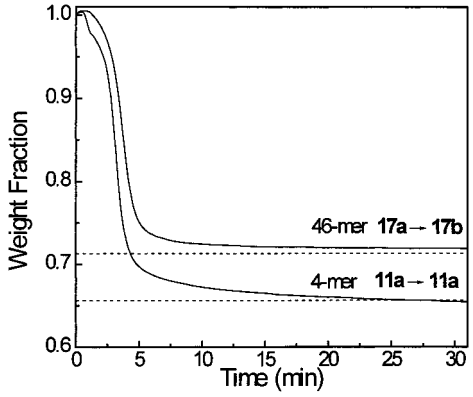


Figure 6. TGA curves recorded on samples of small (4-mer) and large (46-mer) tridendrons. The temperature program simulates reaction conditions: r.t. → 230 °C at 200 °C·min^{-1} and then held isothermal at 230 °C for 30 min under N_2(g). Theoretical mass loss for each is indicated by the dashed line.

Table 3. Calculated and Observed Weight Losses for the Thermolytic Conversion of *tert*-Butyl Esters to Carboxylic Acids

tridendron	% weight loss (theory)	% weight loss (obs)[a]
4-mer (**11a**)	34.4	34.1
10-mer (**15a**)	30.9	29.8
22-mer (**16a**)	29.4	28.3
46-mer (**17a**)	28.7	28.0
94-mer (**18a**)	28.3	30.5

[a] Value corresponds to weight loss recorded from TGA curves 20 min into the temperature program (200 °C·min^{-1} ramp to 230 °C and then held isothermal at 230 °C for 30 min).

tion is based on the mobility of the charged solute in an applied electric field. Figure 7 shows the electropherograms of the five generations of carboxylate terminated dendrimers. The first two generations exhibited single narrow peaks. The larger dendrimers,

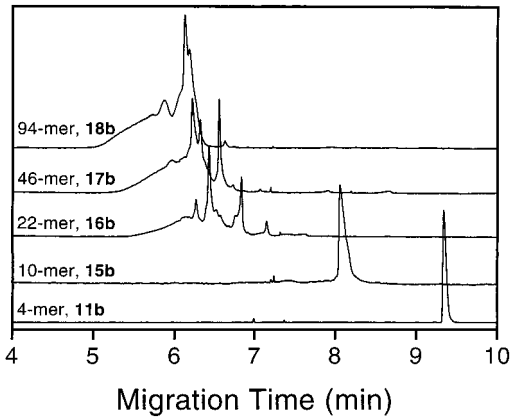


Figure 7. Free zone capillary electropherograms for five generations of carboxylate-terminated tridendrons (buffer: 10 mM $Na_2B_4O_7$, 1 mM EDTA, pH 9.3).

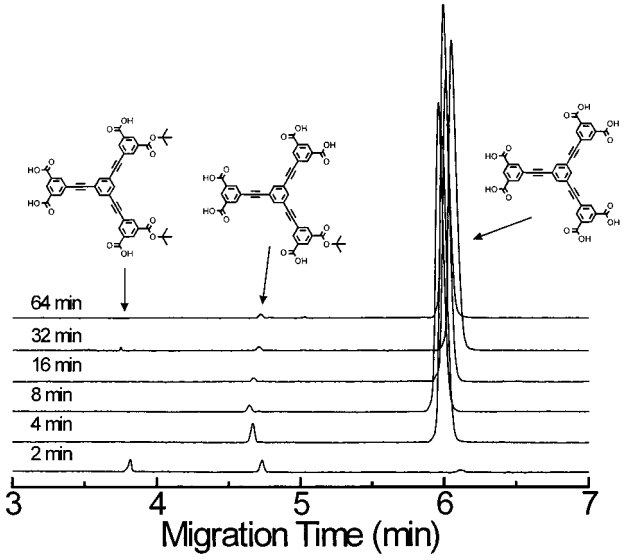


Figure 8. Free zone capillary electropherograms of carboxylate-terminated 4-mers derived from solid-state thermolysis of *tert*-butyl esters. The thermolysis time is indicated (buffer: 10 mM NaOH, 1 mM EDTA).

however, showed multiple peaks as well as broad fronting. Such behavior could be explained by the presence of dendrimers still containing *tert*-butyl or isopropyl groups and/or aggregation or light cross-linking.

In order to assess the efficiency of the thermolysis reaction to convert *tert*-butyl esters to carboxylic acids, a sample of the 4-mer (**11a**) was carefully purified by preparative HPLC so as to remove the trace levels of dendrimers containing one or more isopropyl esters. We verified that isopropyl esters, which, in principle, are capable of being converted to acids by the same mechanism as *tert*-butyl esters, are not removed under the conditions used here. This highly purified 4-mer was subjected to thermolysis for varying lengths of time. CE traces of the resulting products are shown in Figure 8. For short thermolysis times, three components are observed. Based on order of elution (early to late), these components correspond to a 4-mer with two *tert*-butyl esters and four carboxylic acids, a 4-mer with one *tert*-butyl ester and five carboxylic acids, and a 4-mer with six carboxylic acids. With increasing thermolysis time,

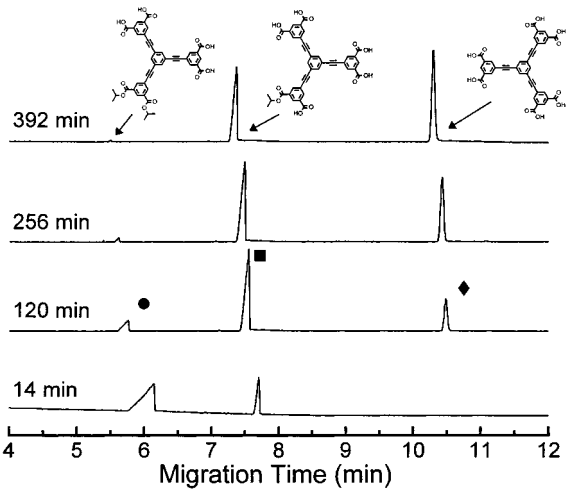
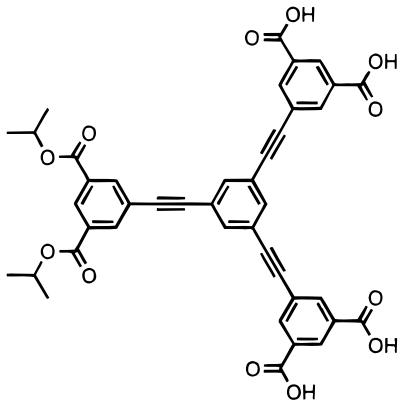


Figure 9. Free zone capillary electropherograms of **19** taken at the indicated times after dissolution in 0.01 M NaOH. In order of increasing migration time, the three components are assigned to the diiopropyl ester tetraacid (●), the monoisopropyl ester pentaacid (■), and the hexaacid (♦) (buffer: 10 mM $(NH_4)_2CO_3$, 1 mM EDTA, adjusted to pH 10.5 with concentrated NH_4OH(aq)).

the earlier components diminish in comparison to the fully converted material (ca. 6.0 min migration time) as expected; however, even at long reaction times, the peak corresponding to a 4-mer with one *tert*-butyl ester still present (ca. 4.7 min) is not eliminated. This peak does fade away if the sample is left in aqueous base for several days. On the basis of integration of the observed peaks at longer reaction times, we determined that 99.93% of the *tert*-butyl groups is removed by the thermolytic process.

Peak assignments in the CE traces of Figure 8 were verified by preparation of authentic diisopropyl ester 4-mer **19**. This molecule was prepared from the corresponding tetra-*tert*-butyl diisopropyl ester by selective thermolysis of *tert*-butyl groups. TGA simulating the reaction conditions shows that after 20 min at 230 °C the sample has lost 24.5% of its weight. Theoretical weight loss of just the *tert*-butyl groups is 23.6%. When **19** was dissolved in 0.01 M NaOH and analyzed by CE, three peaks were observed (Figure 9). The peak at 6 min diminished in intensity with time. The peak at 7.7 min increased at first and then gradually decreased while the peak at 10.5 min slowly grew with time. This can be explained by sequential hydrolysis of the isopropyl esters to ultimately produce the hexaacid **11b**. We feel these observations corroborate our assignment of



19

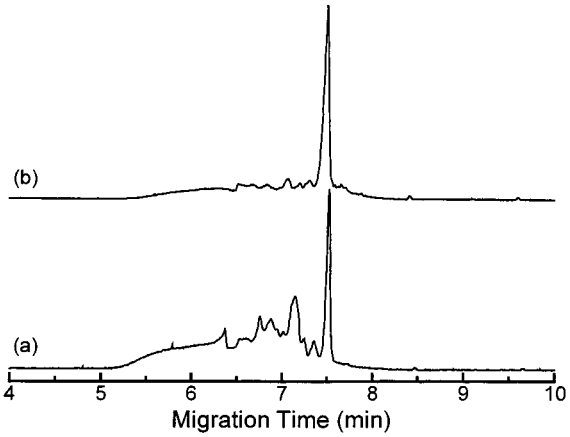


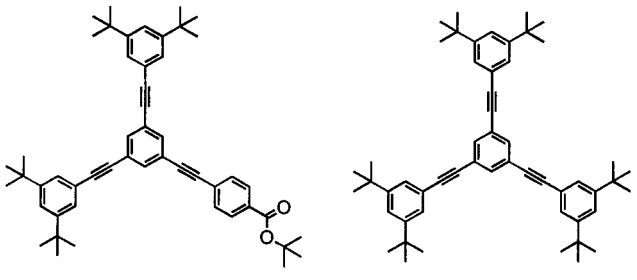
Figure 10. Free zone capillary electropherograms of carboxylated-terminated 22-mer (**16b**) derived from solid-state thermolysis of *tert*-butyl esters. The bottom trace (a) is representative of untreated samples (immediately following thermolysis). The top trace (b) shows the effect of treatment with hot aqueous base (buffer: 10 mM $(NH_4)_2CO_3$, 1 mM EDTA, adjusted to pH 10.5 with concentrated NH_4OH(aq)).

the di- and mono-*tert*-butyl ester molecules in Figure 8 (the difference in the observed migration times is a consequence of different buffer compositions). Thus, the presence of trace levels of isopropyl ester groups could explain the appearance of multiple peaks in the CE traces of the higher generation dendrimers (Figure 7). However, given the high efficiency of the thermolysis of *tert*-butyl esters and low levels of isopropyl esters, the expected distribution of peaks in the CE traces would look quite different from that observed in Figure 7 (see below). Residual ester groups also would not explain the broad fronting seen in the higher generation CE traces (Figure 7).

To further investigate the possibility of cross-linking or aggregation, a sample of the 22-mer (**16a**) was prepared which was purified very carefully (i.e., so as to be free of isopropyl ester groups) and subsequently thermolyzed to remove *tert*-butyl groups. The CE trace of this material was very similar to that of material prepared from 22-mer containing isopropyl ester contaminants. Dynamic light scattering measurements on this sample suggested that particles on the order of 12−14 nm were present, indicating either cross-linking and/or aggregation was occurring, since individual 22-mers are only about 3.5 nm in diameter.[32] Treatment of the carboxylic acid terminated 22-mer with hot aqueous base, in an effort to break up any cross-linking which may be occurring, resulted in a significant change in the appearance of the CE trace (Figure 10). The latest eluting peak greatly increased in intensity relative to the earlier eluting components; however, dynamic light scattering indicated an average particle size similar to that before treatment with base. Further treatment with hot base did not have any appreciable effect on the appearance of the electropherogram. These observations suggest that some form of cross-linking, capable of being degraded by a hydrolytic process, is occurring during the thermolytic process. One possible mode of cross-linking could involve inter- or intramolecular anhydride formation.

Studies to probe this idea were undertaken. The thermolysis reaction was run in liquid 2-naphthoic acid. Such a medium, if used in great excess, would favor intermolecular anhydride formation between the acid terminated 4-mer and the 2-naphthoic acid rather than between two 4-mer molecules. Subsequent analysis of

any organic soluble components by GPC and mass spectrometry, however, revealed no incorporation of the 2-naphthoate group. These observations do not necessarily rule out the possibility of anhydride formation, for to detect the compound(s) of interest one would require the incorporation of at least four (perhaps more) naphthoate groups onto the periphery of the 4-mer to impart organic solubility. Given the heterogeneous character to this reaction, such an expectation seems unlikely. To circumvent these shortcomings, a 4-mer was prepared with only a single *tert*-butyl ester group which should also have better solubility characteristics (**20**). This molecule, however, also did not show incor-



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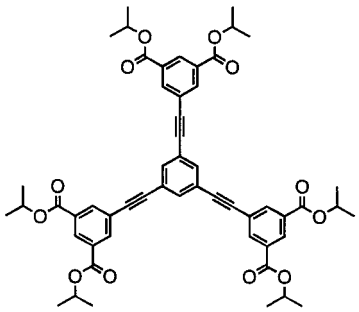


22

poration of the naphthoate group when thermolyzed in 2-naphthioc acid.

Another mode of cross-linking might involve addition of a carboxylic acid across a triple bond to form vinyl esters.[33] When the all-hydrocarbon 4-mer (**21**) was subjected to the thermolysis conditions in liquid 2-napthoic acid, it showed no incorporation of the naphthoate group. A substrate electronically similar to the *tert*-butyl ester terminated 4-mer, but incapable of undergoing the thermolytic conversion to carboxylic acids (i.e., hexaisopropyl ester **22**), was also subjected to thermolysis conditions in liquid 2-naphthoic acid. It too showed no incorporation of the naphthoate group.

Still another mode of cross-linking might involve reaction of adjacent triple bonds.[34] Both an all hydrocarbon 4-mer (**21**) and the isopropyl ester terminated 4-mer (**22**), when subjected to thermolysis conditions in the solid-state, did not show the presence of higher molecular weight components by GPC as would be expected if light cross-linking through the triple bonds were taking place. Thus, it would appear that if any of the above possible cross-linking reactions are taking place in the dendrimers, they are occurring to a very small degree. This is not unreasonable since extensive cross-linking would lead to networks which would be insoluble.

Negative ion electrospray ionization (ESI) mass spectrometry provided indirect evidence of structure. The 4-mer (**11b**) showed a series of signals corresponding

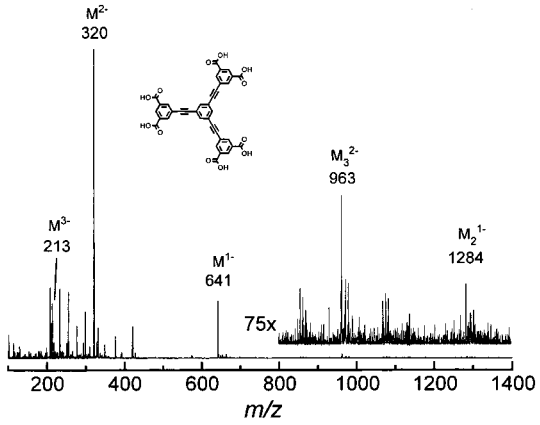


Figure 11. Negative ion electrospray mass spectrum of carboxylate-terminated 4-mer (**11b**). Sample was dissolved in 1% NH_4OH in 1:1 (v/v) methanol/water at a concentration of ca. 300 μM.

to singly ($m/z = 641$) and doubly ($m/z = 320$) charged molecules (Figure 11). Also observed are higher m/z signals at 962 and 1284. These are believed to be gas phase aggregates. The 962 signal corresponds to a three-molecule aggregate containing two negative charges. The 1284 signal corresponds to a two-molecule aggregate containing one negative charge (or a four-molecule aggregate with two charges). In addition to the product signals, a small peak corresponding a 4-mer molecule with a single *tert*-butyl ($m/z = 697$) group still attached is also observed. Several other signals are observed in the m/z 200−420 range. At present, none are readily assigned, although it is likely that they are related to **11b**. Aggregation in combination with coordination to adventitious counterions could result in any number of discrete species in solution. The mass spectrum cannot be interpreted as a quantitative assessment of purity, however, since both CE and NMR seem to indicate low levels of these impurities.

ESI was successfully employed up to the 46-mer. The spectra, however, do not show molecular ions but rather a series of multiply charged species. Assignment of the signals to various charge states of each molecule and subsequent deconvolution give simulated spectra for a singly charged molecule. The experimental and deconvoluted spectra of the 22-mer (**16b**) are shown in Figure 12. Signals corresponding to dendrimers with three to nine negative charges are observed. Deconvolution yields a spectrum with the desired molecular weight of m/z 3237 along with some higher molecular weight species (Figure 12, inset). As with the 4-mer, gas phase aggregation explains the observed higher molecular weight peaks of the 22-mer. For example, the signal at m/z 3251 can be assigned to a quadruply charged tetraaggregate of 22-mers, one of which still contains a single *tert*-butyl ester. The peak at m/z 3259 can be assigned to a quintuply charged pentaaggregate of 22-mers, which contains two *tert*-butyl esters. Such an explanation is not unreasonable given the direct observation of aggregates in the case of the 4-mer and the known efficiency of the thermolysis reaction. The possibility of condensed alkali-metal ions could also explain some of the higher molecular weight peaks. For example, a mass of m/z 3259 is also consistent with a single 22-mer which has a sodium ion condensed onto a carboxylic acid.

Treatment of 22-mer (**16b**) with hot aqueous NaOH results in the reduction of components of lower migration time (Figure 10). A sample of **16b** treated with hot

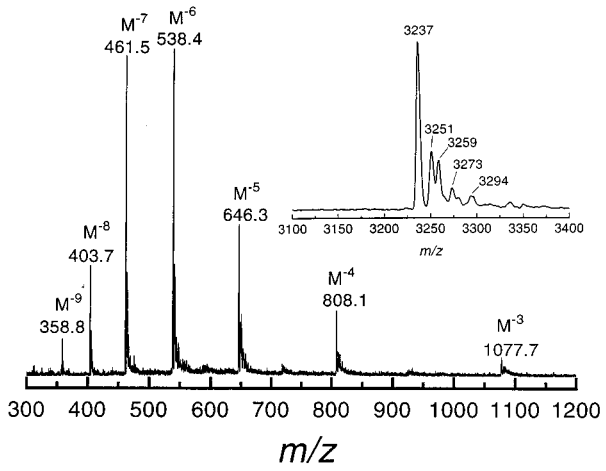


Figure 12. Negative ion electrospray mass spectrum of carboxylated-terminated 22-mer (**16b**). Indicated above the *m/z* is the charge state assigned to that particular signal. The inset shows the deconvolution of the observed spectrum.

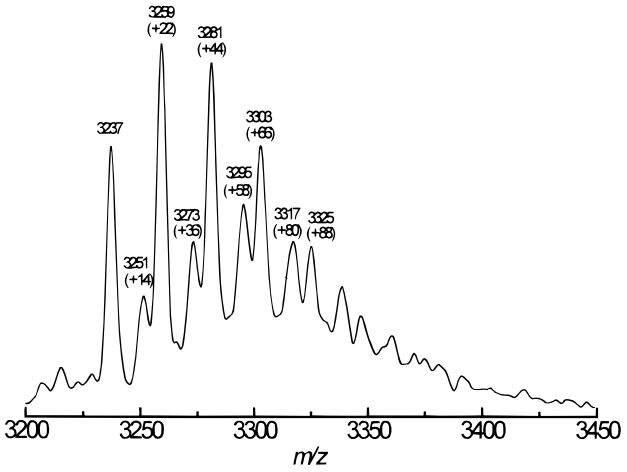


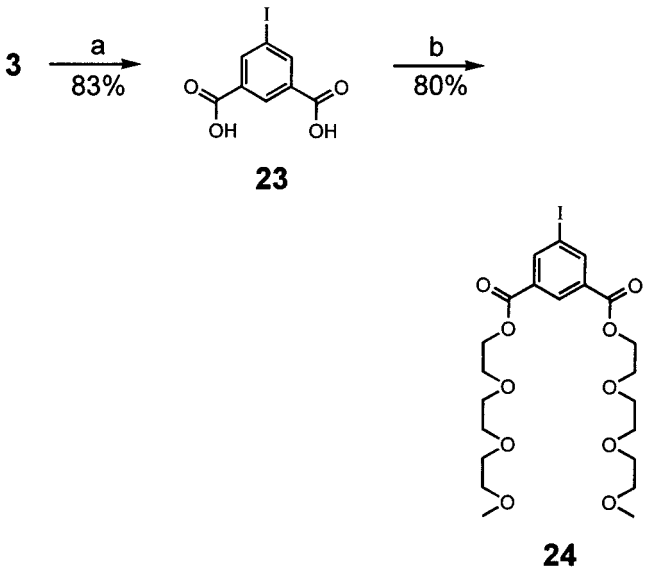
Figure 13. Deconvoluted negative ion electrospray mass spectrum of carboxylated-terminated 22-mer (**16b**) after treatment with hot aqueous 1% NH_4OH for 12 h.

1% NH_4OH(aq) was analyzed by ESI mass spectrometry. The resulting deconvoluted spectrum (Figure 13) showed several signals starting with the expected mass of *m/z* 3237. A series of higher mass signals were also seen at multiples of 22 Da, suggesting displacement of carboxylic acid protons with sodium ions. The origin of the sodium atoms may be the glassware in which the reaction is run as base is known to etch glass.

Alternative Synthesis of Carboxylate-Terminated Dendrimers. The above observations suggested that the thermolysis reaction to remove *tert*-butyl esters resulted in some sort of cross-linking between dendrimers of higher generation. A solution-based hydrolysis could potentially avoid these problems. Unfortunately, all attempts to completely hydrolyze the *tert*-butyl esters in solution failed owing to the orthogonal solubility characteristics of the *tert*-butyl ester terminated dendrimers and the carboxylic acid terminated dendrimers. Test reactions with the 4-mer showed the onset of insolubility to occur after the removal of three to four of the *tert*-butyl groups under standard trifluoroacetic acid/dichloromethane hydrolysis conditions.[21] Attempts to affect the conversion in a two-step process whereby solvent composition was adjusted to insure homogeneity throughout the reaction also proved to be unsuccessful.

This lack of success forced us to reevaluate our original synthetic approach. Though the *tert*-butyl ester

Scheme 5. Synthetic Route to Pheripheral Monomer 24[a]



[a] Reagents: (a) NaOH, H_2O, 100 °C, 12 h; (b) triethylene glycol monomethyl ether, DCC, DMAP, *p*-toluenesulfonic acid, CH_2Cl_2.

met the initial design criteria, its removal led to inhomogeneous products. It was thought that a similar process run at lower temperature could reduce the observed cross-linking. This could be realized by using a β-hydrogen containing ester substituent with more steric bulk than the *tert*-butyl group.[35] An even more appealing alternative would involve a process which would eliminate altogether the extreme conditions apparently responsible for cross-linking and avoid the consequences associated with the orthogonal solubility of products and starting materials. Knowing that the products were soluble in aqueous base, a basic hydrolysis seemed to be the obvious choice. The *tert*-butyl ester is, of course, unsuitable for this type of transformation since the starting material is insoluble in aqueous media and the basic hydrolysis of tertiary esters is exceedingly slow. The ideal peripheral group would be one which is readily hydrolyzed (primary ester) and imparts partial water solubility to affect the hydrolysis in an aqueous environment. In addition, the peripheral group must keep the monodendrons soluble in organic solvents during the construction phase. The (2-[2-(2-methoxyethoxy)ethoxy]ethyl) ester appeared to fulfill all of these requirements.

The desired peripheral monomer **24** was prepared in two steps from **3**. Hydrolysis of the methyl ester followed by DCC mediated esterification with triethylene glycol monomethyl ether gave the new peripheral monomer in good yield (Scheme 5). Mono- and tridendron synthesis proceeded in the same manner as that for the *tert*-butyl ester terminated dendrimers including the employment of hypercore **9** to obtain the 15-mer, **29a**. Coupling reactions as well as triazene unmasking required the use of acetonitrile as a cosolvent to achieve homogeneous reaction media (Tables 4 and 5). An unusual side reaction occurred during the conversion of the triazene to the aryl iodide. Mass spectrometry and NMR spectra suggest the displacement of one of the methoxy groups by an iodine atom. This side reaction seems to occur at a rate much slower than that of triazene unmasking since the impurity is present in only ca. 10% and none of the products contained more than one iodo group.

Table 4. Yields of Monodendrons Terminated with (2-[2-(2-Methoxyethoxy)ethoxy]ethyl) Esters on Their Periphery

monodendron	yield % Et_2N_3-R	yield % I–R	yield % $Me_3Si-\equiv-R$	yield % $H-\equiv-R$
monomer		80 (**24**)	94 (**25**)	80 (**26**)
3-mer	84 (**27a**)	84 (**27b**)	96 (**27c**)	99 (**27d**)
7-mer	98 (**28b**)	64 (**28b**)	89 (**28c**)	87 (**28d**)
15-mer	75 (**29b**)	51 (**29b**)	89 (**29c**)	65 (**29d**)

Table 5. Synthetic Routes and Yields of (2-[2-(2-Methoxyethoxy)ethoxy]ethyl) Ester Terminated Tridendrons

tridendron	synthetic route (Scheme 4)	yield (%)
4-mer (**11c**)	B	85
10-mer (**15c**)	B	97
22-mer (**16c**)	B	86
46-mer (**17c**)	B, double stage	*a*

[a] All attempts to make the 46-mer were carried out on a small scale (<50 mg). Because of severe chromatographic broadening and instability to silica gel, isolation of product was difficult. MALDI mass spectrometry was the only means by which definitive evidence of structure could be obtained. In all cases, either no 46-mer was detected or 46-mer was present with multiple impurities, i.e., defective dendrimers.

Dendritic molecules from **24** are much more polar and therefore required significantly higher polarity solvent systems for chromatography. For the lower generations, mixtures of acetone and chloroform proved effective, while for the higher generations, mixtures of isopropyl alcohol and dichloromethane were used. Chromatographic broadening was also observed and was more pronounced than that with the *tert*-butyl ester terminated dendrimers. Two-dimensional TLC also suggested that the higher generation dendrimers were unstable to silica gel, which made isolation even more difficult. Slow hydrolysis on silica gel could explain the chromatographic observations and low yields. Given this obstacle, attempts to prepare a 46-mer tridendron (**17c**) by this route were only partly successful. Two methods to prepare the 46-mer were attempted. The first was method B (Scheme 4) using 15-mer, **29d**, and a triiodobenzene core, and the second was the double-stage method employing 7-mer **28b**, with hexaethynyl hypercore **14**. In both cases, yields were low and products contained dendrimers with defects as indicated by MALDI mass spectra.

Characterization of the (2-[2-(2-methoxyethoxy)ethoxy]-ethyl) ester terminated dendrimers followed standard organic techniques. In most cases, the aromatic regions of the ^{1}H NMR spectra displayed well-resolved and highly dispersed signals with the expected integration and splitting patterns for the various generations. FAB and MALDI mass spectrometry provided signals corresponding to singly charged sodium and/or potassium adducts for all dendrimers.

Good solubility for all dendrimers in a variety of solvents was observed for this series as well as partial solubility in water. Interestingly, these compounds exhibited an inverse solubility relationship with temperature. Lower temperatures favored dissolution, while phase separation was observed at higher temperatures. This lower critical solution temperature (LCST) behavior is similar to that displayed by other nonionic surfactants.[11] The room-temperature consistency of these dendrimers was quite different from those having *tert*-butyl[15a] and *tert*-butyl esters on their periphery. While the latter are both solids up to their decomposition temperatures, the (2-[2-(2-methoxyethoxy)ethoxy]-ethyl) ester terminated dendrimers are pastelike at room temperature and exhibit phase transitions to isotropic liquids at temperatures less than 250 °C. Complete details on the liquid crystalline phases exhibited by these dendritic molecules are reported elsewhere.[36]

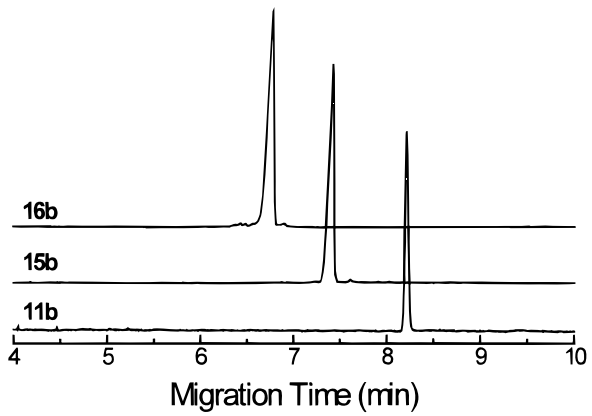


Figure 14. Free zone capillary electropherograms of carboxylate-terminated tridendrons derived from a basic aqueous solution hydrolysis of the (2-[2-(2-methoxyethoxy)ethoxy]ethyl) esters. Notice that the 22-mer (**16b**) lacks the broad fronting and multiple peaks observed when this compound is derived from the *tert*-butyl ester terminated dendrimer by solid-state thermolysis (Figure 7) buffer: 10 mM EDTA, adjusted to pH 10.5 with concentrated NH_4OH(aq)).

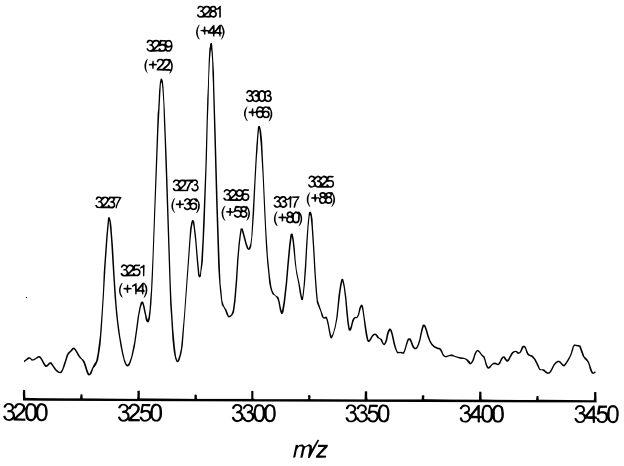


Figure 15. Deconvoluted negative ion electrospray mass spectrum of carboxylate-terminated 22-mer (**16b**) derived from hydrolysis of **16c** with hot aqueous 1% NH_4OH for 3 days.

Hydrolysis of **11c**, **15c**, and **16c** to the corresponding carboxylate terminated tridendrons (**11b**, **15b**, and **16b**) was affected by 0.1 M NaOH/1 mM EDTA at elevated temperatures. All three generations of tridendrons gave CE traces showing a single major component (Figure 14). Note also that the 22-mer (**16b**) does not show the broad fronting observed from samples obtained from *tert*-butyl esters by the thermolytic process. The negative ion ESI mass spectrum of **16b** derived from the solution hydrolysis (Figure 15) showed a pattern nearly identical with that obtained from **16b** prepared by thermolysis of **16a** which was subsequently treated with hot aqueous ammonium hydroxide (Figure 13). Light scattering data of the 22-mer, **16b**, prepared by basic solution phase hydrolysis of **16c** did not provide reproducible results on different samples. Particle sizes from 6 to 110 nm were observed and varied with the time of data acquisition. CE traces of these solutions showed two sharp peaks but no broad fronting. While cross-linking seems unlikely, aggregation resulting from the

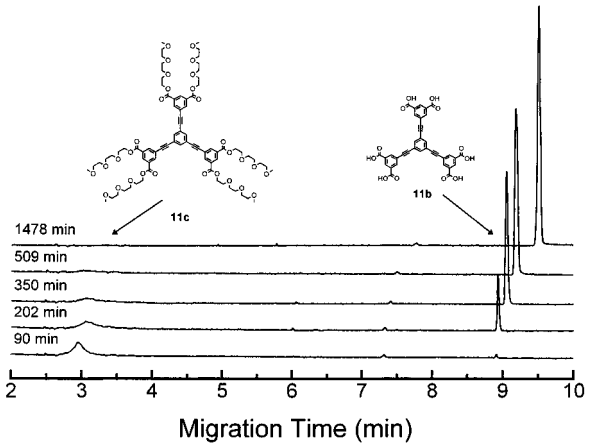


Figure 16. Free zone capillary electropherograms of (2-[2-(2-methoxyethoxy)ethoxy]ethyl) ester terminated tridendron 4-mer (**11c**) taken at various times after dissolution in 0.06 M NaOH (buffer: 10 mM $(NH_4)_2CO_3$, 1 mM EDTA, adjusted to pH 10.5 with concentrated NH_4OH(aq)).

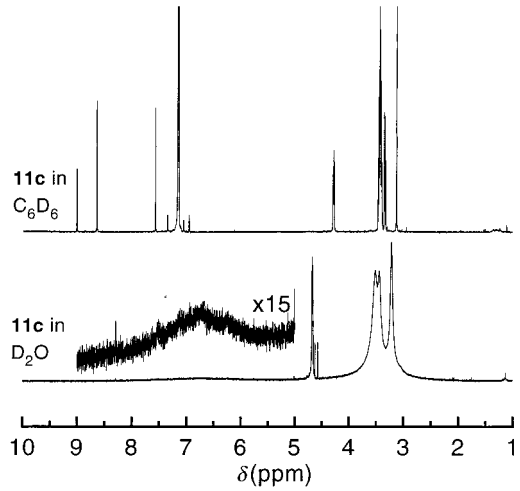


Figure 17. 400-MHz ^{1}H NMR spectra of (2-[2-(2-methoxyethoxy)ethoxy]ethyl) ester terminated tridendron 4-mer (**11c**) taken in benzene-d_6 (top) and D_2O (bottom).

presence of triethylene glycol monomethyl ether in solution may explain this behavior.

An interesting observation was made during the hydrolysis of the 4-mer, **11c**. CE traces taken at various times after dissolution in 0.06 M NaOH show only two peaks (Figure 16). A broad peak is observed with a migration time of about 3 min which diminishes in intensity and a peak at about 9 min grows in intensity (this peak actually slowly drifts to longer migration times due to slowly changing buffer composition). Previous studies indicate that the 9-min peak corresponds to the fully hydrolyzed 4-mer (**11b**), while peaks with migration time around 3 min are eluting with the electroosmotic flow (neutral species). Thus, in contrast to the hydrolysis behavior observed with the diisopropyl ester tetraacid **19**, only completely unhydrolyzed 4-mer (**11c**) and completely hydrolyzed 4-mer (**11b**) (no intermediates) are observed. This suggests that the molecule remains in some form, incapable of hydrolysis with a certain lifetime. Once hydrolysis begins, it takes place at a rapid rate. Such behavior may be the result of solution aggregation. Evidence of aggregation was seen by NMR (Figure 17). In benzene-d_6, **11c** gives a well-resolved spectrum with the expected splitting patterns. In D_2O, however, extreme broadening is observed in the aromatic region along with poorly resolved glycol methylene signals. Such behavior is indicative of large particles in solution. These observations ultimately led to the discovery of liquid-crystalline mesophases exhibited by **11c**, **15c**, and **16c**.[36]

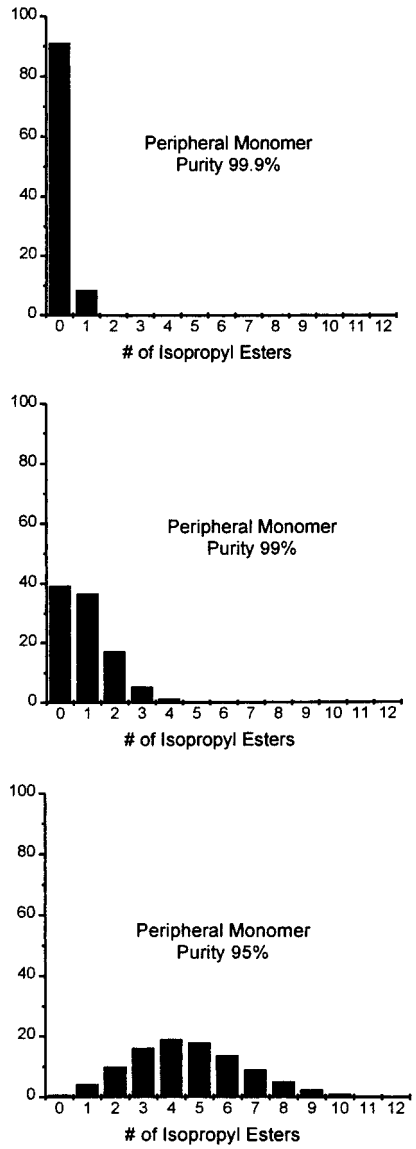


Figure 18. Simulated distributions of fifth-generation tridendrons (94-mer) derived from a peripheral monomer containing 0.1%, 1%, and 5%, respectively, of an impurity. The *x*-axis represents the number of peripheral groups bearing the undesired functional group, and the *y*-axis is the percent of each of these components in the mixture.

Comment on Monomer Purity in Dendrimer Synthesis. The identification of lower generation dendritic species containing isopropyl esters raises some interesting questions with regard to purity levels of larger generation dendrimers and the pitfalls of doing functional group conversions on dendritic molecules. Our initial lot of the peripheral monomer **4** contained approximately 1.6% of the monoisopropyl ester impurity **5**, which was not readily removed by recrystallization. Given the seemingly small quantity of this impurity, monodendron construction was commenced with this lot. Throughout the synthesis, NMR spectra, mass spectra, and elemental analyses were consistent with perfect (all *tert*-butyl esters) dendrimers. Our observations in the ESI mass spectra and CE of the carboxylate-terminated dendrimers, however, prompted us to investigate more systematically the effect of monomer purity on homo-

geneity of higher generation dendrimers. Simulated dendrimer product distributions prepared from hypothetical lots of monomer of varying purity were calculated. Assuming monomer lots consisting of only two components, the desired functional monomer (**4**), and an impurity of equal and analogous reactivity (**5**), the distribution of resultant dendritic structures at any given generation can be modeled from a binomial expansion

$$(a + b)^{x-3} \quad (1)$$

where a and b represent the mole fractions of monomer and monomer impurity and x is the number of peripheral groups in the dendrimer. Shown in Figure 18 are hypothetical product distributions of fifth generation tridendrons (94-mer) starting with monomers of 99.9%, 99%, and 95% purity. One can see that, even with 0.1% impurity, ca. 10% of a dendrimer containing an impurity monomer is present. With an impurity at the 1% level, the desired perfect structure makes up less than half of the distribution of products, while at the 5% level almost none of the perfect dendrimer is present in the product mixture. This type of analysis, though specific to a convergent growth scheme in which only the peripheral monomer is impure, illuminates an issue always relevant but seldom addressed in dendrimer syntheses.[37] In a divergent growth scheme, one must not only consider monomer purity when synthesizing dendrimers but also the efficiency of coupling reactions. For a reaction which goes to 99% completion, 1 out of every 100 functional groups will be left unreacted. Separation of this species from the perfect dendrimer is by no means trivial. It is also possible that this defect could remain dormant through subsequent synthetic transformations, leading to not only peripheral imperfections but internal imperfections as well. This type of analysis brings into question the purity level and structural make up of some recently reported tenth-generation dendrimers.[38] Additionally, one should be aware of this issue when obtaining dendrimers from commercial suppliers, all of which are prepared by a divergent growth scheme.[18]

Conclusions

The synthesis of stiff phenylacetylene dendrimers terminated with *tert*-butyl esters has been described. A modified convergent approach was necessary to overcome difficulties in purification brought about by chromatographic broadening at higher generations. Transformation of the *tert*-butyl esters to carboxylic acids was affected by a convenient solid-state thermolytic process. While this reaction is nearly quantitative and very efficient for the lower generation carboxylic acid terminated tridendrons, undesirable cross-linking reactions occurred in higher generations possibly involving intermolecular anhydride formation. Carboxylate-terminated dendrimers containing fewer impurities were obtained by a basic aqueous solution-phase hydrolysis of (2-[2-(2-methoxyethoxy)ethoxy]ethyl) ester terminated tridendrons. The carboxylic acid terminated dendrimers proved to be difficult to characterize and required ESI mass spectrometry and capillary electrophoresis as methods to probe structure and dendrimer purity. Modeling the effect of an impurity on the homogeneity of higher generation dendrimers reveals that even small fractions of impurities can lead to relatively impure dendrimer samples.

Experimental Section

General Procedures. Unless otherwise indicated, all starting materials were obtained from commercial suppliers (Aldrich, Lancaster, Fischer, Mallincrodt, J. T. Baker, EM Science) and were used without purification. Hexane, dichloromethane, and ethyl acetate were distilled before use. (Trimethylsilyl)acetylene was obtained from Farchan Labs, Gainsville, FL, and vacuum transferred from magnesium sulfate. All atmosphere-sensitive reactions were done under nitrogen with a Schlenk vacuum line or in a drybox. Bulb to bulb distillation was done with a Aldrich standard Kugelrohr distillation apparatus. Analytical TLC was performed on Kieselgel F-254 precoated silica gel plates. Visualization was accomplished with UV light, iodine vapor, or phosphomolybdic acid stain. Flash chromatography was carried out with silica gel 60 (230−400 mesh) from EM Science. Dry triethylamine was obtained by vacuum transfer from calcium hydride. Dry THF was obtained by vacuum transfer from sodium benzophenone. Dry methyl iodide was obtained by vacuum transfer from phosphorus pentoxide and sodium sulfate.

^{1}H and ^{13}C NMR spectra were recorded on a Varian XL 200, Varian Unity 400, or Unity 500 spectrometer. Chemical shifts were recorded in parts per million (δ), and splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; spt, septet, m, multiplet; br, broad. Coupling constants, J, are reported in Hertz (Hz). Chloroform (δ 7.26 for ^{1}H, δ 77.0 for ^{13}C) was used as an internal standard for chloroform-*d*, benzene (δ 7.15 for ^{1}H, δ 128 for ^{13}C) as an internal standard for benzene-d_6, DMSO (δ 2.49 for ^{1}H, δ 39.5 for ^{13}C) as an internal standard for DMSO-d_6, and THF (δ 2.58 for ^{1}H, δ 67.4 for ^{13}C) as an internal standard of THF-d_8. Gas chromatography (GC) was performed on a HP-5890 Series II gas chromatograph equipped with a 12.5 m × 0.2 mm × 0.5 μm HP-1 methylsilicone column and fitted with a flame ionization detector helium carrier gas (30 mL/min). HPLC was performed on a Rainin binary gradient system equipped with two SD-200 pumps, an Si 80−125-C5 analytical column (4.6 × 250 mm) or Si 80−120-C5 preparative column (21.4 × 250 mm), and a UV-1 detector operating at 275 nm. Gel permeation chromatography was performed using a Waters 510 HPLC pump, Waters 996 photodiode array detector, and a series of three Waters Styragel HR 4E 7.8 × 300 mm columns which were calibrated with narrow molecular weight polystyrene standards. GPC data were obtained in THF at 35 °C. Capillary electrophoresis was performed on an ATI Crystal CE system Model 300 equipped with a Unicam 4225 variable-wavelength UV detector operating at 275 nm. Fused-silica capillaries, 75 and 50 μm i.d., were obtained from Supelco and cut to lengths of 72 cm (58 cm to the detection window). All runs were carried out using an applied potential of 30 kV in normal polarity mode. Dynamic light scattering was performed using a BI-200 SM light scattering system equipped with a BI-9000 AT digital correlator (Brookhaven Instruments Corp.) and a Lexel Model 95 argon ion laser operating between 50 and 100 mW at 514.5 nm. Low resolution mass spectra were obtained on either a Hewlett-Packard GC-MS equipped with a 30 m HP-1 capillary column operating at 70 eV or a Finnigan-MAT CH5 spectrometer operating at 70 eV. High-resolution electron impact mass spectra were obtained on a Finnigan-MAT 731 spectrometer operating at 70 eV. Low- and high-resolution fast atom bombardment (FAB) mass spectra were obtained on VG ZAB-SE and VG 70-SE-4F spectrometers. Electrospray mass spectra were obtained on a VG Quattro spectrometer running in negative ion mode. The sample was prepared as a 200−400 μM solution in 1% NH_4OH diluted with 30−50% (v/v) methanol or 2-propanol. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory using a Leeman Labs CE440 elemental analyzer or using classical wet methods. Melting points were reported as the onset temperature from differential scanning calorimetry traces run at a heating rate of 20 °C·min^{-1} on a Perkin-Elmer 7 Series thermal analysis system. Thermal gravimetric analyses were also performed on this system. Infrared spectra were recorded on an IBM IR/32 FTIR spectrometer; absorptions are reported in reciprocal centimeters.

Cascade nomenclature follows the procedure reported by Newkome et al.[39]

Starting Materials. The following compounds were prepared according to literature methods: 1,3,5-triiodobenzene,[15a] 1-(3,5-dibromophenyl)-3,3-diethyltriazene,[15c] 1-(3,5-diethynylphenyl)-3,3-diethyltriazene (**2**),[15c] 3-cascade:benzene[3−1,3,5]:5-ethynyl-1,3-di-*tert*-butylbenzene (**21**),[15a] 2-cascade:1-(phenyl)-3,3-diethyltriazene[2−3,5]:5-ethynyl-1,3-diethynylbenzene (**9**).[15b]

General Procedure for the Pd(0)-Catalyzed Coupling of Aryl Halides with Terminal Acetylenes. A Schlenk flask was charged with aryl halide (1.1 equiv/terminal acetylene), terminal acetylene (1 equiv), tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$) (0.01 equiv), copper(I) iodide (0.02 equiv), triphenylphosphine (0.10 equiv), and dry triethylamine. The concentration of reactants varied from 0.3 to 0.02 M depending on the solubility, molecular weight of the reactants, and scale of the reaction. The flask was then capped, evacuated, backfilled with nitrogen three times, and stirred at 60−75 °C for 12 h or longer. When the reaction was complete as indicated by GC or TLC, the solvent was removed under reduced pressure and the remaining residue dissolved in dichloromethane and filtered through a short pad of silica gel, eluting with either 100% dichloromethane or 5−10% ethyl acetate in dichloromethane. Following concentration of the filtrate, the crude product was purified as outlined below.

General Procedure for the Deprotection of 1-Aryl-3,3-dialkyltriazenes to Aryl Iodides. A heavy-walled, teflon-sealed, screw-capped sealed tube was charged with aryltriazene and dry methyl iodide. Concentrations ranged from 0.3 to 0.005 M depending on the molecular weight of the triazene. The flask was evacuated and backfilled with nitrogen three times and then evacuated, sealed, and stirred for 12 h at 110 °C. The unreacted methyl iodide was vacuum transferred for recycling and the resulting residue dissolved in dichloromethane and filtered through a short pad of silica gel, eluting with either 100% dichloromethane or 5−10% ethyl acetate in dichloromethane. Following concentration of the filtrate, the crude product was purified as outlined below.

General Procedure for Trimethylsilyl Deprotection. Tetrabutylammonium fluoride in THF (1.1 equiv) was added to a stirred solution of the terminal acetylene in THF. Concentrations ranged from 0.3 to 0.02 M depending on the molecular weight of the substrate. After 15 min the solvent was removed and the resulting residue vacuum dried and purified as outlined below.

General Procedure for Thermolytic Conversion of *tert*-butyl Esters to Carboxylic Acids. The solid sample of *tert*-butyl ester is heated to 230 °C (by immersion into a bath of tetraglyme at that temperature) for 15−20 min under a nitrogen atmosphere. The resulting solid required no purification.

Dimethyl 5-Iodoisophthalate (3). A solution of dimethyl 5-aminoisophthalate (10.023 g, 0.479 mol) in 6 M HCl (20 mL), water (20 mL), and acetonitrile (ca. 50 mL) was heated to ca. 70 °C for a few minutes (ca. 5 min) and then cooled to 5−10 °C in an ice bath. To this stirred suspension was added dropwise to a solution of $NaNO_2$ (4.268 g, 61.8 mmol) in water (ca. 20 mL). The mixture was allowed to stir for 15 min after completion of the addition. This diazonium solution was then slowly added to a solution of KI (79.53 g, 0.479 mol) in water (100 mL). A total of 15 min after completion of the addition, the dark brown mixture was extraced with ether (3 × 75 mL). The combined extracts were washed with saturated $Na_2S_2O_3$ and saturated NaCl and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **3** as an orange solid (11.209 g, 73%): mp 105 °C; R_f 0.34 (1:6 ethyl acetate/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (t, J = 1.5 Hz, 1H), 8.54 (d, J = 1.5 Hz, 2H), 3.95 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 142.4, 132.1, 129.8, 93.4, 52.7; MS (GCMS/EI) (calcd for $C_{10}H_9O_4I^+$, 319.9546; found, 319.9543) *m/e* 320 (100), 289 (100), 262 (21), 246 (14), 102 (2), 75 (15). Anal. Calcd for $C_{10}H_9O_4I$: C, 37.52; H, 2.83. Found: C, 37.62; H, 2.82.

Di-*tert*-butyl 5-Iodoisophthalate (4). A solution of lithium *tert*-butoxide was prepared by slowly adding *n*-BuLi (0.375 mol) to *tert*-butyl alcohol (260 mL, 2.75 mol) under nitrogen. This solution was then slowly added to a solution of **3** (28.9 g, 90.3 mmol) in dry THF (300 mL). After the solution was stirred at room temperature for ca. 2 h, the solvent was removed under reduced pressure. The resulting residue was mixed with saturated NH_4Cl (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to afford a brown solid. Recrystallization of the solid from 5:95 ethyl acetate/*n*-hexane resulted in an orange solid (23.29 g, 64%): R_f 0.27 (1:1 dichloromethane/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (t, J = 1.5 Hz, 1H), 8.43 (d, J = 1.5 Hz, 2H), 1.59 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 141.8, 133.8, 129.6, 93.2, 82.2, 28.1; IR (KBr) 3079, 2979, 1715, 1565, 1433, 1370, 1312, 1256, 1156, 752 cm^{-1}; MS (GCMS/EI) (calcd for $C_{16}H_{21}O_4I^+$, 404.0485; found, 404.0489) *m/e* 404 (29), 348 (19), 331 (49), 293 (34), 292 (99), 275 (66), 248 (14), 229 (8), 202 (4), 120 (5), 75 (17), 57 (100). Anal. Calcd for $C_{16}H_{21}O_4I$: C, 47.54; H, 5.24. Found: C, 47.92; H, 5.37.

5-Iodoisophthalic Acid (23). A suspension of **3** (21.052 g, 65.77 mmol) in 15% aqueous NaOH (600 mL) was heated under reflux for 14 h. The solution was then carefully acidified, causing precipitation of the product. The suspension was then centrifuged and the supernatant liquid poured off. The remaining residue was resuspended in deionized water and centrifuged again. This cycle was repeated three times. Finally, the residue was dissolved in methanol, gravity-filtered, and concentrated to afford **23** as an off white powder (16.0 g, 83%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.5 (v br, 2H), 8.72 (t, J = 1.5 Hz, 1H), 8.60 (d, J = 1.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3, 141.5, 133.1, 129.2, 95.0; MS (EI) (calcd for $C_8H_5O_4I$, 291.9233; found, 291.9236) *m/e* 292 (100), 275 (17), 247 (7), 165 (16), 119 (8), 92 (11), 75 (23), 65 (13).

5-Iodoisophthalic Acid Bis(2-[2-(2-methoxyethoxy)-ethoxy]ethyl) Ester (24). A 500 mL Schlenk flask was charged with **23** (14.9998 g, 51.4 mmol), triethylene glycol monomethyl ether (25 mL, 156 mmol), DMAP (1.2570 g, 10.3 mmol), *p*-toluenesulfonic acid (1.5540 g, 8.2 mmol), and dichloromethane (300 mL). The solution was degassed and cooled in an ice bath. Next, DCC (25.532 g, 124 mmol), was added all at once to the stirred solution. After 1.4 h the ice bath was removed and the mixture allowed to warm to room temperature. After stirring overnight, the mixture was gravity filtered to remove DCU and concentrated. The resulting yellow oil was then purified by column chromatography eluting first with 2:1 ethyl acetate/*n*-hexane followed by 100% ethyl acetate. The product containing fractions were combined and concentrated to afford a yellow oil with a little solid (presumably DCU). Oil was redissolved in 1:2 ethyl acetate/*n*-hexane, gravity filtered, and concentrated once again to afford a yellow oil now essentailly free from DCU (24.189 g, 80%): R_f 0.23 (1:6 acetone/chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (t, J = 1.5 Hz, 1H), 8.55 (d, J = 1.5 Hz, 2H), 4.50 (m, 4H), 3.84 (m, 4H), 3.73−3.64 (m, 12H), 3.54 (m, 4H), 3.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 142.5, 132.1, 130.1, 93.3, 71.8, 70.58, 70.56, 70.54, 68.9, 64.7, 59.0; MS (FAB) (calcd for $C_{22}H_{34}O_{10}I$, 585.1197; found, 585.1192) *m/e* 585, 465, 333, 303. Anal. Calcd for $C_{22}H_{33}O_{10}I$: C, 45.22; H, 5.69; I, 21.72. Found: C, 45.15; H, 5.51; I, 21.70.

Acknowledgment. We thank Professor Charles Zukowski and Michael Farnum of the University of Illinois for their assistance in running the dynamic light scattering experiments. This research was supported by the National Science Foundation (Grant DMR 95−20402), 3M Co., and DuPont Co.

Supporting Information Available: Experimental details of the preparations of and characterization data for monomers **12**, **13**, **25**, and **26**, and mono- and tridendrons **6**−**8**, **10**, **11**, **15**−**18**, **27**, **28**, and **29** and synthetic schemes, experimental details, and characterization data for triethynylbenzene, compounds **14**, **19**, **20**, and **22**, and all intermediates (30 pages). This material is contained in libraries on microfiche, immediately follows this paper in the microfilm version of the

journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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MA970454P