in room light for 3.5 h and then worked up to give 0.238 g (98% recovery) of pure (VPC, NMR) dinitro compound II: $\alpha$ −0.35 ± 0.02° (1 dm); $[\alpha]^{26.2}_D$ −2.5° (*c* 14.3, benzene).

**Acknowledgment.** We are indebted to The National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

**Registry No.** (−)-II, 110637-93-9; (±)-II, 110637-94-0; (±)-III, 110637-95-1; (±)-IV, 110637-96-2; (±)-V, 110637-97-3; (±)-VI, 110637-98-4; (±)-VII, 110637-99-5.

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# Starburst Polyether Dendrimers

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*Received December 23, 1986*

The synthesis of two starburst polyether dendrimers, by a protection–deprotection scheme, is described. A bicyclic ortho ester or a dioxane is used to temporarily mask three or two hydroxyl groups, respectively. Dendrimer type I was synthesized with a pentaerythritol core and a hydroxymethyl bicyclic orthoformate as the dendrimer synthon, while in dendrimer type II, 1,1,1-tris(hydroxymethyl)ethane and a (hydroxymethyl)dioxane were used. Dendrimer type I is the most compact starburst molecule synthesized to date. No spacer groups or excess reagent are needed in the synthesis, even though all reactions occur at neopentyl positions. In just three generations, 108 functionalities are present in the exterior layer. The size of these molecules calculated from CPK models is in excellent agreement with the data obtained from size-exclusion chromatography.

The successful synthesis and characterization of starburst dendrimers have allowed precision control of space at the molecular level as a function of size, shape, and disposition of desired organic moieties.

Preliminary accounts of the synthesis and concept of the starburst topology are described in earlier papers.[1-3] More recently, considerable theoretical[4,5] and synthetic interest has evolved, wherein Newkome and co-workers have synthesized similar molecules, which they refer to as "cascade molecules".[6,7]

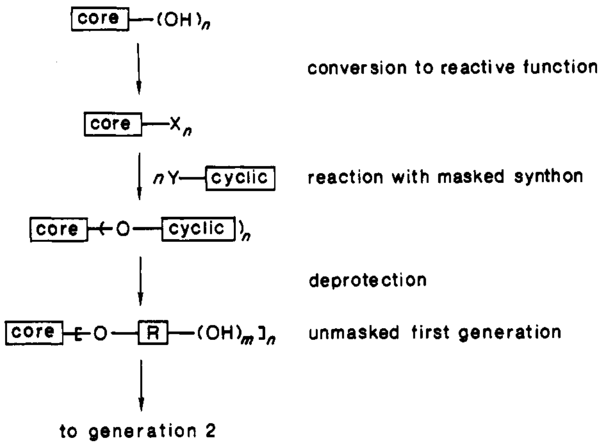
Starburst dendrimers are constructed from various initiator cores, upon which concentric, branched layers (generations) are built up that follow geometric progressions. The final exterior layer allows introduction of a variety of terminal moieties that reside on the surface of the dendrimer. The shape of the core, as well as its multiplicity ($N_c$) and that of the repeating unit ($N_r$), determines the general shape and ultimately the size of the dendrimer. The number of functionalities in each generation can be calculated by using the following formula:

$$\text{number of terminal units} = N_c(N_r)^G$$

in which $G$ = number of generations.

Previously, the synthesis of starburst polyamidoamine dendrimers with a core multiplicity $N_c = 3$ and repeating unit multiplicity $N_r = 2$ has been reported.[1] In this study, we describe the synthesis of highly branched starburst polyether dendrimers, whose core is pentaerythritol (PE, $N_c = 4$) and the repeating unit is a pentaerythritol ether ($N_r = 3$). A two-dimensional representation of the two first generations of these two cases is shown in Figure 1, parts A and B, respectively. In addition, an account is given of efforts to synthesize starburst polyethers derived from a tris(hydroxymethyl)ethane core (THE, $N_c = 3$) with a repeating unit with a multiplicity $N_r = 2$.

**Scheme I**[a,b]



[a] Route A: X = electrophile; Y = nucleophile. Route B: X = nucleophile; Y = electrophile. [b] $n = N_c$, $m = N_r$.

**Dendrimer Synthon Strategy.** The synthesis of polyamidoamine dendrimers was based upon two consecutive reactions to build each generation in which the second reaction reintroduced the functional group on which the first reaction could take place. Exhaustive Michael addition of an amine with excess methyl acrylate was followed by exhaustive amidation of the resulting ester with an excess of diamine. The branching junctures were built-in so that the number of functionalities increased in each generation. This scheme led to rather loosely spaced dendrimers in that about five-carbon chains were present

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[1] Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, C.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* (*Tokyo*) **1985**, *17*, 117.

[2] Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, C.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466.

[3] Tomalia, D. A.; Dewald, J. R. U.S. Patent 4 507 466, Mar 26, 1985; U.S. Patent 4 558 120, Dec 10, 1985; U.S. Patent 4 568 737, Feb 4, 1986; and U.S. Patent 4 587 329, May 6, 1986.

[4] DeGennes, P. G.; Hervet, H. *J. Phys. Lett.* **1983**, *44*, 351.

[5] Burchard, W.; Kajiwara, K.; Nerger, D. *J. Polym. Sci., Polym. Chem. Ed.* **1982**, *20*, 157.

[6] Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003.

[7] Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K.; Russo, P. S.; Saunders, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 849.

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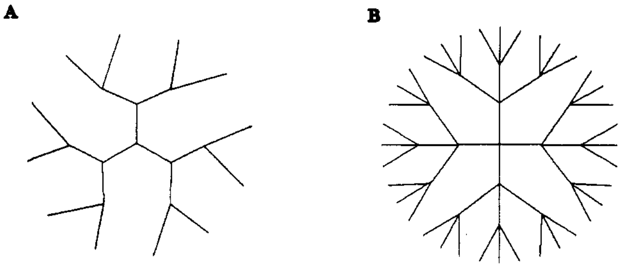
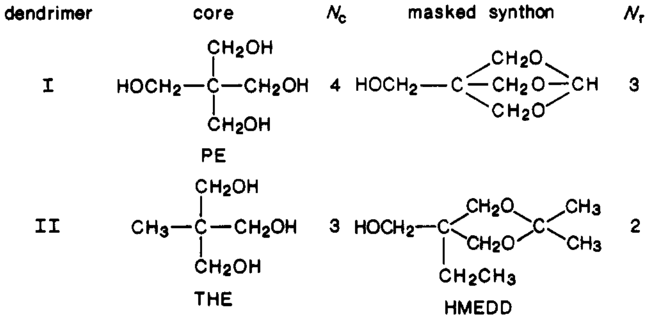


**Figure 1.**

Scheme II



between the branching junctures.

In another synthetic approach to form dendrimers, spacer groups have been deliberately introduced to relieve the steric hindrance in order to be able to build the next generation. This also led to a rather spacious topology.[6]

In order to build more compact starburst dendrimers, and also to avoid the need for excess reagent, the use of a protecting group has been introduced in this study. The general concept has been outlined in Scheme I. In this approach, the building block for the next generation contains, in addition to the reactive functionality, multiple functionalities that are masked in a cyclic structure. For example, a bicyclic ortho ester structure can be used to mask three hydroxyl functions or a cyclic acetal can mask two hydroxyls.

Specifically in this study, two combinations of initiator cores and partially masked hydroxyl reactants were used. In the first case, pentaerythritol (PE) is the initiator core and 4-(hydroxymethyl)-2,6,7-trioxabicyclo[2.2.2]octane (HTBO)[8] is the building block for the consecutive generations (dendrimer type I). In the second case, 1,1,1-tris(hydroxymethyl)ethane (THE) is the core with 5-(hydroxymethyl)-5-ethyl-2,2-dimethyl-1,3-dioxane (HMEDD) as the building block (dendrimer type II). After reaction with the initiator core, hydrolysis of the cyclic structure yields the deprotected generation. The branching structure has been introduced, and the new generation contains respectively 3 or 2 times more hydroxyl groups than the core. The next generation can now be built-up in a similar manner (Scheme II).

A very important requirement for this synthesis is the efficient formation of ether linkages. More specifically, the ether bond in dendrimer type I has to be formed in the presence of "neopentyl type" centers occurring on the core as well as on the masked hydroxyl intermediate.

## Results

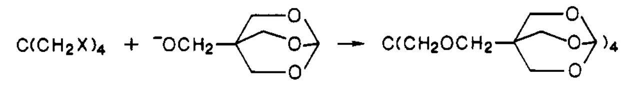
**Model Reactions.** Ether-forming model reactions were examined under classical Williamson conditions, as well as under more recently reported phase-transfer conditions.[9]

A few cases of tetraether formation involving PE have been described in the literature: the reaction of pentaerythritol tetraiodide with sodium 2-methoxyethanol at 130 °C proceeds in 80% yield;[10] the reaction of pentaerythritol tetratosylate with sodium alkoxides on the other hand proceeds in only 15% yield.[11]

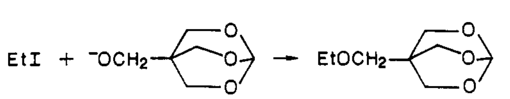
Two possible strategies for forming the required ether linkages are the core contains electrophilic substituents that are allowed to react with a nucleophilic-masked reagent (route A) or the core has nucleophilic functionalities that are allowed to react with an electrophilic-masked reagent (route B).

For the dendrimer type I synthesis, route A would involve reaction of the PE core, possessing terminal electrophilic leaving groups with the nucleophilic alkoxide of HTBO.

route A

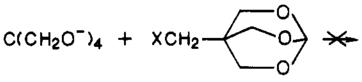


The alkoxide of HTBO could be formed by potassium hydride at room temperature in tetrahydrofuran, as shown by the model reaction with ethyl iodide, which proceeded in quantitative yield.



Route B would require reaction of the tetraalkoxide of the PE core with a bicyclic ortho ester possessing an electrophilic leaving group substituent. Despite several attempts, PE did not form the tetraalkoxide with strong bases.

route B



In a parallel investigation into the synthesis of dendrimer type II, a model reaction supporting route B was examined under phase transfer catalysis (PTC) conditions. By use of a literature procedure developed by Freedman et al.,[9] THE was allowed to react with 2-chloroethyl methyl ether to give the desired tris product in 81% yield under mild conditions. Here the reaction conditions may involve

$$\mathrm{CH_3C(CH_2OH)_3 + ClCH_2CH_2OCH_3 \xrightarrow{PTC} CH_3C(CH_2OCH_2CH_2OCH_3)_3}$$

repetitive formation of monoalkoxides and thus the requirement for forming a multialkoxide is avoided.

**Dendrimer Type I Synthesis (Route A).** On the basis of the model reaction, starburst polyethers ($N_c = 4$, $N_r = 3$) were synthesized according to Scheme III.

**First Generation.** The potassium salt of HTBO, formed with potassium hydride, was reacted with PE-Br(4). Refluxing in diglyme overnight was necessary to obtain the desired product PE-BO(4). Two different leaving groups were studied. The potassium salt of HTBO did not react with PE-Tos(4), but reacted with PE-Br(4) in good yield, thus identifying bromide as the leaving group of choice. The purity of PE-BO(4) was checked by IR, $^1$H NMR, and $^{13}$C NMR. No residual peaks of PE-Br(4) were

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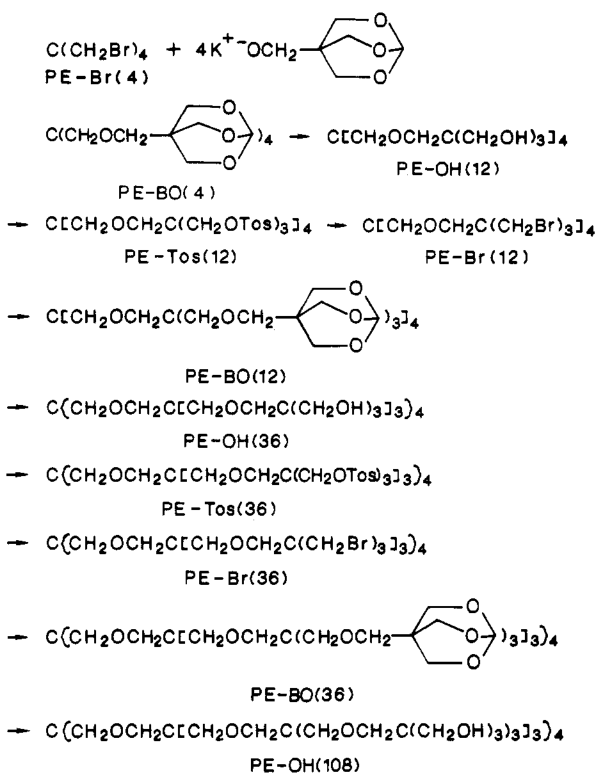
(8) Padias, A. B.; Hall, H. K., Jr. *Macromolecules* **1982**, *15*, 217.

(9) Freedman, H. H.; Dubois, R. A. *Tetrahedron Lett.* **1975**, 3251.

(10) Chisso Corp., Japan Kokai Tokyo Koho JP 59/82328, 1984; *Chem. Abstr.* **1984**, *101*, 130232s.

(11) Haines, A. H.; Karntiang, P. *Carbohydr. Res.* **1980**, *78*, 205.

**Scheme III**



observed. The elemental analysis was within 0.2% of the theoretical value.

Hydrolysis of the bicyclic orthoformate groups to three alcohol functions per core terminal group was initially performed in refluxing water and without catalysis. The spectra of PE-OH(12) were consistent: the formate proton disappeared in the $^1$H NMR spectrum, and the IR spectrum exhibited no carbonyl peak, although all the peaks were very broad. The results of the elemental analysis were acceptable if the high hydrophilicity of this compound was taken into account. IR spectra of the subsequent products in the reaction sequence, namely PE-Tos(12) and PE-Br(12), exhibited a persistent absorption for a carbonyl function, despite extensive purification attempts. Also, in the $^{13}$C NMR spectrum of PE-OH(12), a peak was observed at 162 ppm, indicating the presence of a small amount of ester functions in the product. Therefore, the hydrolysis had been incomplete and some residual formate functions remained in the molecule. In methanolic hydrochloric acid, the hydrolysis of PE-BO(4) proceeded quickly and efficiently. IR and $^{13}$C NMR spectra and elemental analysis confirmed the purity of this product.

Dodecaalcohol PE-OH(12) was converted to the dodecatosylate PE-Tos(12) with 28 equiv of *p*-toluenesulfonyl chloride in pyridine. When poured into ice water, PE-Tos(12) is obtained as a very sticky substance, which can be recrystallized. Spectra were in excellent agreement with the structure: IR, $^1$H NMR, and $^{13}$C NMR spectra showed no absorptions for remaining carbonyl or hydroxyl functions, supporting the exhaustively tosylated product.

It was necessary to convert PE-Tos(12) to the dodecabromide derivative PE-Br(12), since the tosylate group could not be displaced by the HTBO alkoxide as was proven by a comparison of the reactivity of PE-Br(4) and PE-Tos(4) (see above). Replacement of tosylate by bromide using sodium bromide was studied in detail (see the Experimental Section). In dimethylacetamide (DMAc) at 150 °C after 1 h, a yield of about 70% was obtained. The product was very insoluble. The IR, $^1$H NMR, and $^{13}$C NMR spectra were in agreement with the proposed structure; elemental analysis was slightly off.

**Second Generation.** The reaction of the dodecabromide PE-Br(12) with 12 equiv of HTBO (potassium salt) in diglyme yields PE-BO(12). A 60% yield is obtained after recrystallization. The product softens at 105–110 °C and does not give a distinct melting point, but it may polymerize. All the spectra and elemental analysis are in agreement with the proposed structure.

Hydrolysis of PE-BO(12) to form the alcohol PE-OH(36) was performed as described above in MeOH/HCl. No carbonyl absorptions were present in either IR or $^{13}$C NMR spectra of the compounds. PE-Tos(36) was obtained by tosylation of PE-OH(36) in the presence of 75 equiv of *p*-toluenesulfonyl chloride in pyridine for 7 days. The reaction proceeded in 88% yield, and all spectra were in agreement with the proposed structure. Conversion to PE-Br(36) proceeded in 52% yield by using sodium bromide in DMAc for 1 h at 150 °C. PE-Br(36) is extremely insoluble. The elemental analysis of PE-Br(36) was again slightly off. The reactions in this second generation still proceeded as efficiently as in the previous generation.

**Third Generation.** As for the reaction of PE-Br(36) with 36 equiv of HTBO (potassium salt) in diglyme, facile conversion to the third generation was noted. A 70% yield of PE-BO(36) is obtained after purification, giving spectra and analysis that are in agreement with the proposed structure. PE-BO(36) is much less soluble than PE-BO-(12), and this causes some difficulties in the purification. Hydrolysis in MeOH/HCl proceeds very efficiently, and a 40% yield of PE-OH(108) is obtained after purification. The elemental analysis is consistent with the proposed structure. The $^1$H NMR spectrum shows considerable broadening of the peaks, and some broadening is also observed in the $^{13}$C NMR spectrum, possibly indicating increased steric hindrance of the groups in the exterior layer of this dendrimer, analogous to broadening noted by Voegtle et al. for highly congested "octopus molecules".[12]

**Dendrimer Type I Characterization.** One of the major problems with the synthesis described for dendrimer I is that it is extremely difficult to verify the purity of the isolated products. Infrared spectroscopy is only sensitive to the functions that are dominant in the molecule. For example, the IR spectrum of the PE-Tos(4) and PE-Tos-(12) are identical, because of the presence of so many *p*-toluenesulfonate groups relative to other functions. If every PE-Tos(12) molecule was defective and contained only 11 tosylate groups, we would not be able to detect it by IR spectroscopy. $^1$H NMR spectroscopy is even worse, because so many very similar methylene functions are present, and only broad peaks can be obtained, which are difficult to accurately integrate. Elemental analysis is not accurate enough to reliably represent the purity of a product.

**$^{13}$C NMR Spectroscopy.** $^{13}$C NMR spectra of all the compounds were recorded and analyzed, and here we have a method that is appropriate to pinpoint the impurities. (See paragraph at the end of paper about supplementary material.)

In contrast with the $^1$H NMR spectra, the methylene functions in the $^{13}$C NMR spectra are easily distinguishable. Even though $^{13}$C NMR is usually considered to be rather insensitive, in this case it is very useful and accurate in pinpointing the incomplete reactions. Widely different chemical shifts are observed for $CH_2$ functions with OH

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[12] Voegtle, F.; Weber, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 814.

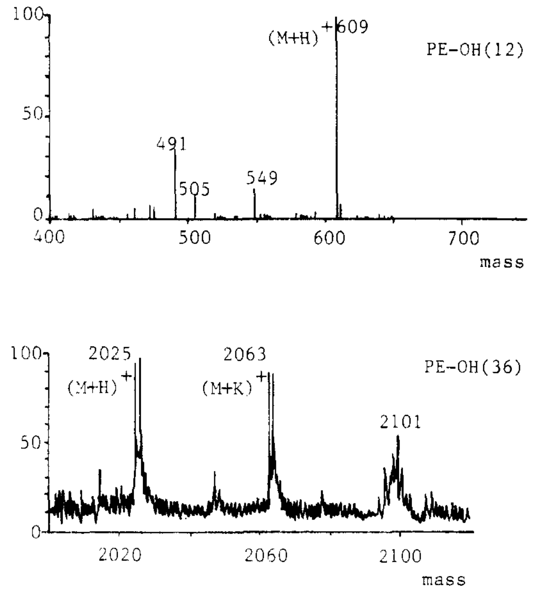

**Figure 2.**

**Table I. Size of Dendrimer I Generations Determined from CPK Models and by SEC**

| | CPK models | | |
|---|---|---|---|
| generation | 3-dimensional contracted | 3-dimensional extended | SEC[b] |
| 1.0 PE-OH(12) | 10.4 Å | 12.0 Å | 9.8 Å |
| 2.0 PE-OH(36) | 16.2 Å | 18.4 Å | 18.6 Å |
| 3.0 PE-OH(108) | 22.4 Å | 24.0 Å | 25.0 Å |
| 4.0[a] PE-OH(324) | 28.0 Å | 32.0 Å | |

[a] Uncertain; model too congested to be completed. [b] Size-exclusion chromatography.

(61 ppm), OTos (66 ppm), or Br (35 ppm) substituents. (For second generation spectra, see paragraph at the end of paper about supplementary material.) Due to its low solubility, the purity of PE-Br(12) is confirmed by infrared. Incomplete reactions in any of these transformations can be detected. Moreover, these $^{13}C$ NMR spectra are very sensitive for detection of any residual carbonyl groups in the hydrolysis step. The formate carbonyl in these dendrimers absorbs in a region (162 ppm) where no other signals are observed in these compounds. Residual carbonyl groups can also be observed in the IR spectra, but the presence of so many hydroxyl groups in the hydrolyzed product results in an overtone band in the same region, which makes identification more difficult.

**Mass Spectroscopy.** The hydroxyl intermediates of the first and second generation were analyzed by fast atom bombardment mass spectrometry (FAB/MS). Figure 2 shows the positive-ion spectrum for both PE-OH(12) and PE-OH(36).

The proposed molecular weight for PE-OH(12) of 608 is confirmed by the presence of the expected molecular ion $(M + H)^+$ and also by the complementary deprotonated $(M - H)^-$ molecular ion in the negative-ion mass spectrum. Species of lower molecular weight are also present in the spectrum and are believed to be due to irregularities in the HTBO building block step of the synthesis. Specifically, the peak at 490 is due to a compound in which one bicyclic unit is missing or is cleaved by a subsequent reaction step. Due to the complex relationship between molecular structure and FAB/MS signal intensity, it is difficult to advance data on the relative concentration of these secondary species.

PE-OH(36) has a calculated molecular weight of 2024 amu based on its most abundant isotope formula. Isotope pattern analysis provides important supporting data in large molecules and is included here. Due to the high number of carbon mass atoms in the emperical formula ($C_{85}H_{172}O_{52}$), the M + 1 single $^{13}C$ isotope peak size is quite high (94%). Natural deuterium inclusion raises the M + 1 peak to 96%, and $^{17}O$ raises it further to 98% of the parent peak. As shown in Figure 2, the spectrum shows the expected $(M + H)^+$ protonated molecular ion at $m/z$ 2025. The isotope pattern is present within the statistical limits of the collected signal. Evident too is an ion 38 amu higher than the parent ion. Potassium cationization yielding $(M + K)^+$ is common when such species are present in the sample. The source of the contamination can be traced to the potassium salt of HTBO used in the reaction sequence. Such potassium attachment to the molecular species is usually viewed as further evidence for positive molecular weight determination. A third cluster of ions is approximately one potassium higher. This cluster appears due to several species, and no structure is proposed. No other impurities are seen in this sample, but due to the low signal and chemical noise present from the matrix, they may be present at lower levels.

Isotope-pattern analysis for bromine-containing compounds was performed visually across the mass spectra of both samples. $^{79}Br$ and $^{81}Br$ are naturally present at about equal abundance, providing an easy means by which they can be identified. No evidence of bromine-containing compounds was seen for either species.

**CPK Models and Size-Exclusion Chromatography.** CPK models of the consecutive generations of dendrimer type I were constructed. The size of the different generations was determined from the models in two ways: three-dimensional contracted and three-dimensional extended.[13] The three-dimensional contracted size is the diameter of a CPK model suspended on a stand, while the extended size corresponds to the diameter of the model spread out on a flat surface. The obtained values are summarized in Table I and range from 10.4 Å for the first generation to about 24 Å for the third generation. The spherical shape of dendrimer I can already be observed in the CPK model of the second generation and is even more obvious in the third generation.

The model for the fourth generation could not be totally completed, because the model became too congested. This points to our assertion that "starburst surface dense-packing"[4] in this dendrimer system would be expected to take effect in the fourth generation. Dense-packing describes the predicted phenomenon in which the outer layer of the dendrimer becomes too congested to allow all the terminal sites to react. As one approaches the "starburst surface dense-packed" generation, (a) digressions from surface stoichiometry, (b) changes in reaction kinetics, and (c) broadening of $^1H$ NMR and $^{13}C$ NMR spectral features for the dendrimer surface groups should be expected. The broadening of the NMR peaks can be observed in the third generation spectra. The other aspects will be reported later.

Size-exclusion chromatography (SEC) is a method mostly used by polymer chemists in which molecules are separated according to size (the largest molecules are eluted first).[14] SEC was performed on the three generations of dendrimer type I at the hydroxyl stage. The SEC

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(13) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466.

(14) *Steric Exclusion Liquid Chromatography of Polymers*, Chromatography Science Series; Janca, J., Ed.; Marcel Dekker: New York, 1984; Vol. 25.

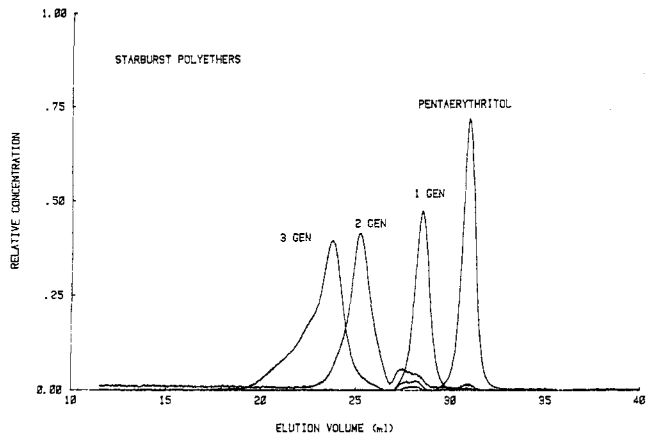


**Figure 3.**

traces are represented in Figure 3.

In previous work, the size of polyamidoamine starburst dendrimers was determined by electron microscopy at different generations.[2] Single spheroidal dendrimer molecules were observed and found to be highly monodisperse. The actual size of these dendrimers was found to be in good agreement with the values from three-dimensional collapsed/extended CPK models. These dendrimers can be used as standards for these SEC measurements. The sizes in angstroms for the different generations of dendrimer I are listed in Table I, and excellent agreement with the values obtained from the CPK models is evident. To our knowledge this is the first report in which actual sizes of molecules are determined by SEC. This is possible for these starburst molecules because they all have basically the same spherical shape. The results are in very good agreement with values determined from space filling CPK models (see Table I).

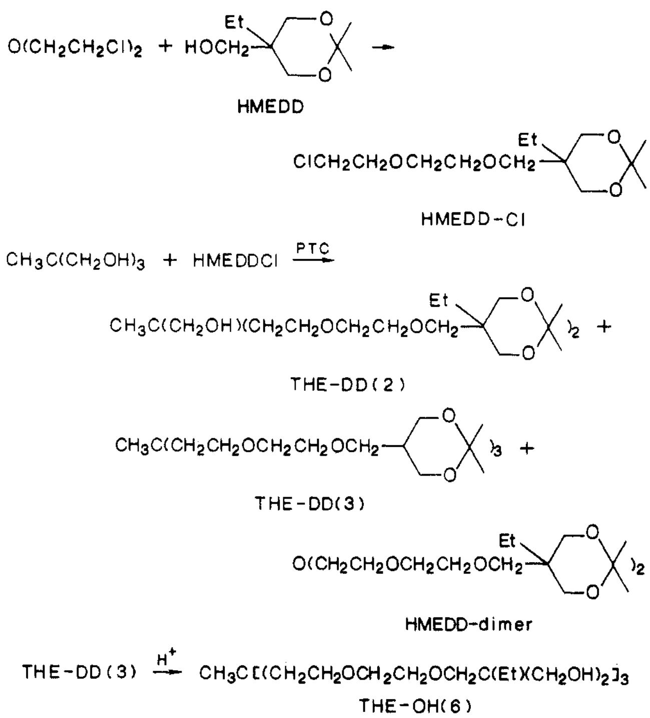
In the SEC trace, a shoulder is visible on the peak for the third generation. The size of this molecule is 38 Å, which would correspond to the size of a dimer of the third generation; this value can be obtained by statistical averaging of its length and width. The origin of this dimer is unknown at this time.

**Dendrimer Type II Synthesis (Route B).** An exploratory study of the synthesis of dendrimer type II is based on the reaction of a core with nucleophilic functionalities with a HMEDD derivative under phase transfer catalysis (PTC) conditions (Scheme IV).

In order to convert HMEDD to an electrophile, the same type reaction to be used for the generation build-up was employed. In a first attempt, HMEDD was reacted with 1,2-dichloroethane under PTC conditions, but due to side reactions of the dichloroethane, the approach failed. A satisfactory result was obtained by the reaction of the masked triol HMEDD with bis(2-chloroethyl) ether (80% yield of HMEDD-Cl); this introduced a spacer group in this system.

The reaction of HMEDD-Cl with THE can potentially yield three compounds, the monoalkylated product, the bisalkylated THE-DD(2), and the trisalkylated THE-DD(3). The reaction was run under varying conditions with a phase-transfer catalyst as in the model reaction. In all cases, the starting triol was consumed, and two new components of slightly higher $R_f$ value were formed. Despite extended reaction times (i.e., greater than 170 h), higher temperatures (75–80 °C), and addition of fresh base or phase-transfer catalyst, it was not possible to obtain a single new component. Workup of the reaction mixture afforded a yellow oil consisting of the two new $R_f$ components. These compounds were subsequently separated by preparative column chromatography on silica gel. Structural characterization was done by $^1$H NMR, $^{13}$C NMR, IR, mass spectral analysis, and identification of the hydrolysis products.

**Scheme IV**



The lower $R_f$ component was proven to be pure bisalkylated THE-DD(2). The $^1$H NMR spectrum of the higher $R_f$ component varied depending upon the reaction time. In a sample from a 100-h reaction, the methyl group of the core was clearly visible, but the spectrum of a sample from a 170-h run showed no discernible singlet in the same region. An examination of the total ion chromatogram in the mass spectral analysis suggested that the material was a mixture. Hydrolysis of this sample in dilute aqueous acid led to an oil whose $^1$H NMR spectrum showed no discernible singlet for the methyl substituent of the core. The spectra indicated that the oil was a mixture of HMEDD dimer (Scheme IV) and THE-DD(3), which is high in the dimer.

The formation of the HMEDD dimer can be rationalized in the following way: hydrolysis of HMEDD-Cl in the alkaline reaction medium leads to the alcohol derivative, which then in turn can couple with the HMEDD-Cl to form the dimer. The longer reaction times favor this side reaction.

## Discussion and Conclusions

The primary aim of this work was to explore novel methods for the synthesis of polyether starburst dendrimers. The concept of using a bicyclic or cyclic structure to temporarily mask multiple hydroxyl functions had two potential advantages: first, the cyclic structure introduces the branching functionality needed for the starburst geometry, and second, it allows us to build more compact dendrimers. These were realized in practice. This protection–deprotection synthetic scheme results in highly functionalized molecules in very few generations. The repeating-unit multiplicity of 3, combined with the core multiplicity of 4 in the pentaerythritol case, results in a molecule with 108 terminal functionalities in just three generations. These are the starburst dendrimers with the highest density synthesized to date. The highly compact nature of the dendrimers of type I is illustrated by the CPK models. These dendrimers are spherical molecules, and from the models we can conclude that dense-packing[4] would already occur in the fourth generation.

The ether bond forming reaction used in the building of the consecutive generations of dendrimer type I proved to be highly effective. Reaction of the multibromide substrates with the potassium salt of HTBO in diglyme was virtually quantitative. Although the substituents on the PE core, or on the PE ether derivatives in the consecutive generations, are in formally neopentyl positions, they do not behave as such and display only a diminished reactivity compared to other alkyl halides. No rearrangements can occur in these compounds, and thus vigorous reaction conditions can be used without side reactions interfering. Due to the compact nature of the dendrimers in the different generations, the bromide substituents are also very exposed on the surface of the molecule. What is rather remarkable is that the bicyclic ortho ester function does not decompose or polymerize. It is a very stable protecting group for three hydroxyl functions in alkaline conditions, which can easily and quantitatively be deprotected in mildly acidic conditions.

In the dendrimer type I synthesis, no spacer groups are necessary as the reactions all proceed in good yield. Also, no excess reagent is needed, which greatly simplifies the purification of these compounds. Furthermore, these dendrimers are all crystalline solids, in contrast to the polyamidoamine dendrimers, and this again makes the purification easier. Even the first generation dendrimers are solids, and the intermediates in all three generations are comparable in melting point, crystallinity, and solubility.

The characterization of the consecutive generations in the dendrimer type I series is reliable and sensitive. $^{13}$C NMR is without a doubt the best suited method to identify the intermediates and to check the purity of the consecutive reaction products. In the mass spectra, the molecular ion peaks for PE-OH(12) and PE-OH(36) can be observed, proving that these species are indeed formed. Size-exclusion chromatography proved to be very powerful and accurate in determining the size of the consecutive generations. This is a novel method for determining the size of molecules.

The synthesis of dendrimer type II relies on phase transfer catalysis conditions. Two hydroxyl groups on the THE core are easily displaced, but the third substitution is much slower and difficult and is also plagued by a side reaction. This is probably due to the fact that the first and second alkoxide are stabilized by hydrogen bonding with the residual hydroxyl groups. The third alkoxide, meaning the alkoxide salt of THE-DD(2), does not have this stabilization, and this would reduce its solubility in the organic layer, explaining the reduced reactivity.

The protection–deprotection reaction scheme is firmly established as a viable method for synthesizing multigram quantities of polyether dendrimers. These dendrimers have polyether repeating units inside the dendrimer that are hydrophobic, while the terminal hydroxyl functions on the exterior layer are hydrophilic. These microdomains may be the closest mimics to so called "covalently fixed micelles".[15] Also, the hydroxyl groups can be easily converted to other functionalities and are thus very appropriate for further synthetic and analytical studies. The dendrimers of type I were synthesized up to the third generation in this study. According to CPK models, it should be possible to establish dense-packing in the fourth generation due to the predicted congestion. The examination of this phenomenon will be part of future studies.

## Experimental Section

**General Methods.** Melting points were measured in a Thomas-Hoover Meltemp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 spectrometer. NMR spectra were recorded on 60-MHz Varian EM-360 and 90-MHz Varian EM-390 instruments, and the $^{13}$C NMR spectra were recorded on a 250-MHz Brucker AM-250 instrument. Chemical analyses were performed by Desert Analytics, Tucson, AZ. All reagents were used without additional purification, unless specified in the procedure. The mass spectra were obtained on a V.G. ZAB mass spectrometer operating at medium (3000) resolution. A few tens of micrograms of each sample was dissolved in a few microliters of suitable matrix. The sample was placed on the target of the FAB probe and inserted into the ionization source of the mass spectrometer where it was bombarded by 8–10 keV xenon atoms. Sample PE-OH(12) was analyzed in a glycerol matrix. Positive and negative ion mass spectra were recorded to provide complimentary molecular weight information. PE-OH(36) was analyzed under similar conditions, with a 1:4 mixture of dithiothreitol/dithioerythritol, commonly known as Magic Bullet, as the matrix. Due to the weak signal produced, complimentary negative ion data were not obtained. The data were collected in a continuum mode through which added sensitivity is gained.

The size-exclusion chromatography was performed with the following columns: Toyosoda TSK 5000PW, 3000PW, and 2000PW (30 cm each); the eluent was 0.05 M $Na_2HPO_4$ (pH adjusted to 11 with 50% NaOH), the flow rate was 1 mL/min, the temperature was 35 °C, the detector was a Waters R401 differential refractive index detector, and the injection volume was 100 $\mu$L (0.10 % wt).

**4-(Hydroxymethyl)-2,6,7-trioxabicyclo[2.2.2]octane (HTBO).** This is a slightly modified procedure from the literature procedure.[8] In a 250-mL round-bottom flask are mixed 13.6 g (0.1 mol) of pentaerythritol, 16 mL of triethyl orthoformate (0.1 mol), a trace of *p*-toluenesulfonic acid, and 100 mL of dioctyl phthalate. The mixture is heated to 120 °C, and 1–1.5 equiv of ethanol are distilled off. The flask is then placed in a big Kugelrohr apparatus (Aldrich) and heated to ~180 °C at 0.1 mmHg. Two receiving bulbs are used, the first of which is cooled in a MeOH/ice mixture. After no more solid distills over, the distilled material is dissolved in $CH_2Cl_2$; the insoluble part is polymeric. After filtration and evaporation of the solvent, petroleum ether, which will dissolve any distilled dioctyl phthalate, is added to the material. Filtration yields a white crystalline material, which is the desired product in about 50% yield. HTBO is recrystallized from toluene, but can be used without purification. Mp: 87–88 °C. NMR ($CDCl_3$): $\delta$ 5.5 (s, 1 H), 4.0 (s, 6 H), 3.45 (d, 2 H), 2.2 (t, 1 H). IR (KBr): 3200, 2960, 2900, 1580, 1380, 1155, 1060, 1040, 1000, 920, 755 cm$^{-1}$.

**Pentaerythritol Tetrabromide PE-Br(4).** Pentaerythritol is treated with *p*-toluenesulfonyl chloride in pyridine and subsequently with sodium bromide in diethylene glycol according to the procedure in the literature.[16]

**PE-BO(4).** Diglyme is dried over sodium and distilled just before use. In a three-neck flask under argon atmosphere equipped with a magnetic stirrer, a reflux condenser, and an addition funnel, potassium hydride (0.1 mol, 16 g of 25% suspension) is washed twice with petroleum ether, and 100 mL of diglyme is added. A solution of 12 g (0.08 mol) of HTBO in 200 mL of diglyme is added dropwise at 0 °C, and the mixture is stirred for 3 h. A solution of 8 g (0.02 mol) of PE-Br(4) in 200 mL of diglyme is then added dropwise, and the reaction mixture is refluxed overnight. The mixture is then poured in ice water, and the precipitate is filtered, washed with water, and dried. Yield: 70% (9 g). The Beilstein test for bromide is negative. The product can be recrystallized from acetonitrile. Mp: >250 °C. NMR (acetone-$d_6$): $\delta$ 5.3 (s, 1 H), 4.9 (s, 6 H), 3.3 (2 s, 4 H). IR (KBr):

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2880, 1595, 1580, 1370, 1158, 1110, 1040, 990, 920 cm$^{-1}$. Anal. Calcd for $C_{29}H_{44}O_{16}$: C, 53.70; H, 6.79. Found: C, 53.73; H, 7.00.

**Hydrolysis to PE-OH(12).** Recrystallized PE-BO(4) (9 g, 13.8 mmol) is mixed with 100 mL of methanol, containing 1 mL of concentrated HCl. MeOH is distilled off very slowly during 3 h. Upon cooling, a white solid precipitates from the remaining MeOH. Yield: 6.2 g (75%). Mp: 190 °C softening, 210 °C dec. IR (KBr): 3350 (br), 2940, 2887, 2500 (br), 1500, 1460, 1380, 1127, 1044, 1002 cm$^{-1}$. NMR ($D_2O$): 2 br s at $\delta$ 3.6 and 3.4, roughly in a 3:2 ratio. Anal. Calcd for $C_{25}H_{52}O_{16}$: C, 49.34; H, 8.55. Found: C, 49.19; H, 8.54.

**PE-Tos(12).** PE-OH(12) (4.25 g, 7 mmol) is dissolved in 85 mL of pyridine. At 0 °C, a solution of 37.2 g of *p*-toluenesulfonyl chloride (0.2 mol, 28 equiv) in 150 mL of pyridine is added dropwise. The mixture is stirred for an additional hour at 0 °C and then left at room temperature for 4 days. The reaction mixture is then poured into ice water, and the water is decanted. Yield: 16 g (93%). This product is recrystallized from 80:20 ethanol/chloroform mixture. Mp: 134 °C. NMR ($CDCl_3$): $\delta$ 7.5 (q, 12 H), 3.9 (s, 6 H), 3.2 (2 br peaks, 4 H), 2.3 (s, 9 H). IR (KBr): 2960, 2920, 2880, 1600, 1495, 1460, 1365, 1195, 1190, 1100, 980, 820, 670 cm$^{-1}$. Anal. Calcd for $C_{109}H_{124}O_{40}S_{12}$: C, 53.26; H, 5.05; S, 15.63. Found: C, 53.19; H, 5.10; S, 15.47.

**PE-Br(12).** The substitution reaction of tosylate to bromide was studied in detail with the conversion of PE-Tos(4) to PE-Br(4) as a model reaction. The reaction of PE-Tos(4) with sodium bromide was run in several solvents, namely acetonitrile (with or without crown ether), diethylene glycol, *N*-methylpyrrolidinone, diglyme, and sulfolane. A 70% yield of PE-Br(4) was obtained with PE-Tos(4) and NaBr in sulfolane at 170 °C for 16 h. One drawback to this method was that some decomposition of the products was observed when these conditions were used on PE-Tos(12); the reaction mixture would turn black by the end of the reaction. In DMAc at 150 °C after 3 h or overnight, the desired PE-Br(12) is obtained, but in rather low yield. If the reaction is terminated after 1 h, a yield of about 70% is obtained.

The dodecatosylate PE-Tos(12) (16 g, 6.5 mmol) is dissolved in 85 mL of DMAc. NaBr (16 g, 28 equiv) is added, and the mixture is heated for 1 h at 150 °C and then poured into water. The precipitate is filtered after salting out. The solid is recrystallized from acetonitrile. Yield: 5.5 g (60%). Mp: 240 °C shrinks, 290 °C dec. NMR (DMSO-$d_6$): two broad peaks at $\delta$ 3.6 and 3.4 in roughly 3:2 ratio. IR (KBr): 2872, 1486, 1454, 1423, 1275, 1240, 1171, 1104, 848, 671, 607 cm$^{-1}$. Anal. Calcd for $C_{25}H_{40}O_4Br_{12}$: C, 21.99; H, 2.93. Found: C, 21.06; H, 2.37.

**Second Generation: Dodecabicyclo[2.2.2]octane PE-BO(12).** The procedure is identical with the one used for the first generation. Potassium hydride (30 mmol, 6 g, 25% suspension) is washed twice with petroleum ether in an argon atmosphere, and 80 mL of diglyme is added. At 0 °C, a solution of 4.4 g (30 mmol) of HTBO in 120 mL of diglyme is added, and the mixture is stirred for 3 h at room temperature. The dodecabromide is insoluble in diglyme and thus should be added as a solid. The mixture is heated to reflux for 20 h. The solution is poured into 500 mL of ice water, and the precipitate is filtered off immediately. Crude yield: 100%. Recrystallize from toluene/acetonitrile mixture. The Beilstein test is negative. Mp: 105–110 °C turns gummy. NMR (DMSO-$d_6$): $\delta$ 5.5 (s, 1 H), 3.95 (s, 6 H), 3.2 (m, 5 H). IR (KBr): 2884, 1475, 1369, 1157, 1104, 1046, 994, 858, 753 cm$^{-1}$. Anal. Calcd for $C_{97}H_{148}O_{52}$: C, 54.29; H, 6.90. Found: C, 54.43; H, 7.22.

**Hydrolysis to PE-OH(36).** The dodeca(bicyclic ortho ester) (2 g, 1 mmol) is mixed with MeOH (100 mL) and 0.5 mL of concentrated HCl. MeOH and methyl formate are distilled off very slowly during 3 h. After evaporation, a solid is obtained that is very hygroscopic. IR (KBr): 3400 (br), 2890, 1495, 1475, 1110, 1040 cm$^{-1}$. NMR ($D_2O$): 2 broad peaks at $\delta$ 3.6 and 3.4, roughly in 6:5 ratio.

**PE-Tos(36).** PE-OH(36) (800 mg, 0.4 mmol) is dissolved in 40 mL of pyridine, and at 0 °C, a solution of 6 g (30 mmol) of *p*-toluenesulfonyl chloride in 40 mL of pyridine is added dropwise. The mixture is stirred for an additional hour at 0 °C and then left at room temperature for 7 days. The reaction mixture is poured into ice water, and the precipitate is filtered off. Only an oil can be obtained from an EtOH/$CHCl_3$ mixture, which forms a foam under vacuum. Yield: 88%. Mp: 230–250 °C. NMR (DMSO-$d_6$): $\delta$ 7.4 (q), 3.8 (br), 3.1 (br), 2.3 (br s). IR (KBr): 2876, 1597, 1456, 1363, 1191, 1177, 974, 813, 790, 668 cm$^{-1}$. Anal. Calcd for $C_{337}H_{388}O_{124}S_{36}$: C, 53.43; H, 5.12; S, 15.22. Found: C, 53.40; H, 5.18; S, 15.28.

**PE-Br(36).** PE-Tos(36) (2 g, 0.25 mmol) is dissolved in 35 mL of DMAc, and 2 g of NaBr (20 mmol) is added. The mixture is heated to 150 °C for 1 h and then poured into ice water. The precipitate is filtered after salting out and dried. The bromide is very insoluble. Yield: 52%. Mp: 43 °C shrinks, 55–60 °C. IR (KBr): 2868, 1484, 1426, 1274, 1239, 1106, 668 cm$^{-1}$. Anal. Calcd for $C_{85}H_{136}O_{16}Br_{36}$: C, 23.76; H, 3.17. Found: C, 24.79; H, 3.32.

**Third Generation: PE-BO(36).** Potassium hydride (7 mmol, 1.2 g, 25% suspension) in 25 mL of diglyme is cooled to 0 °C, and a solution of 660 mg of HTBO (4.5 mmol) in 20 mL of diglyme is added. After 3 h at 0 °C, PE-Br(36) (430 mg, 0.1 mmol) is added as a solid, and the mixture is refluxed for 20 h. The reaction mixture is then poured into ice water, and salt is added. The precipitate is filtered and washed with water and methanol. The product is recrystallized from an acetone/$CH_3CN$ mixture. Yield: 65%. Mp: 125–140 °C softening. NMR (DMSO-$d_6$): $\delta$ 5.45 (s, 1 H), 4.0 (s, 6 H), 3.4, 3.3 (2 br s, 6 H). IR (KBr): 2883, 1475, 1370, 1157, 1104, 1046, 995, 922, 858 cm$^{-1}$. Anal. Calcd for $C_{301}H_{460}O_{160}$: C, 53.18; H, 6.77. Found: C, 53.48; H, 7.46.

**Hydrolysis to PE-OH(108).** PE-BO(36) (400 mg, 0.06 mmol) is dissolved in 100 mL of MeOH in the presence of 0.5 mL of concentrated HCl. MeOH and methyl formate are distilled off during 3 h, and the remaining methanol is evaporated. A precipitate can be obtained in a petroleum ether/MeOH mixture, which is then dried. Yield: 40%. NMR (DMSO-$d_6$): $\delta$ 4.2, 3.3 (2 broad peaks). IR (KBr): 3394 (br), 2884, 1100, 1042 cm$^{-1}$. Anal. Calcd for $C_{265}H_{532}O_{160}$: C, 50.70; H, 8.48. Found: C, 50.73; H, 8.80.

**HMEDD-Cl.** To a 1-L three-necked flask, equipped with an overhead mechanical stirrer, internal thermometer, and pressure equalizing addition funnel, were added 50% aqueous NaOH (w/w, 400 mL), tetrabutylammonium hydrogen sulfate (10.0 g, 0.029 mol), and bis(2-chloroethyl) ether (150 mL). The rapidly stirred mixture was warmed to 45 °C, and HMEDD (100 g, 0.51 mol) in bis(2-chloroethyl) ether (100 mL) was added over 15 min via the addition funnel. The reaction mixture was heated to 75 ± 5 °C and stirred for 4 h. An exotherm was noted at this temperature, and the heating mantle may have to be removed and the flask cooled in an ice bath to keep the temperature below 80 °C. After 4 h, the reaction was cooled to room temperature and divided into three equal portions. Cold water was added to each portion, and the aqueous layer was extracted with $CHCl_3$ (3 × 200 mL), and the $CHCl_3$ layer was dried through a cone of sodium sulfate and concentrated in vacuo. The excess bis(2-chloroethyl) ether was removed from the resulting reddish-orange oil under vacuum (0.1 mmHg) with mild heating. This procedure afforded 182 g of reddish-orange oil, which was fractionally distilled through a 10-cm Vigreux column to yield 80.5 g of HMEDD-Cl, bp 114–116 °C (0.1 mm), and 34.8 g of impure HMEDD-Cl at a lower boiling point. This lower boiling fraction was redistilled as above to yield 23.2 g of HMEDD-Cl. The combined yield is 103.8 g (64%) of HMEDD-Cl as a colorless liquid. $^1H$ NMR ($CDCl_3$, 90 MHz): $\delta$ 0.82 (t, $J$ = 7 Hz, 3 H), 1.16–1.48 (s overlapping m, 8 H), 3.33–3.82 (m, 14 H). IR (KBr): 2860, 1450, 1370, 1300, 1250, 1200, 1120, 834 cm$^{-1}$. Anal. Calcd for $C_{13}H_{25}O_4Cl$: C, 55.61; H, 8.97. Found: C, 56.20; H, 9.03.

**THE-DD(2) and THE-DD(3).** Tetrabutylammonium hydrogen sulfate (0.56 g, 10 mol %), 50% w/w aqueous NaOH (20 mL), THE (2.0 g, 16.65 mmol), and HMEDD-Cl (40 g, 156 mmol) were combined in a 125-mL flask equipped with an overhead mechanical stirrer and a thermometer. The reaction mixture was warmed to 65 ± 5 °C and stirred for 48 h, at which time fresh 50% NaOH (10 mL), 0.56 g of ammonium salt, and sodium iodide (0.55 g) were added. The reaction mixture was stirred for an additional 66 h. The reaction was still progressing slowly, as judged by TLC. Tetraethylammonium hydroxide (10% w/w in water, 10 mL) was added, and the mixture was stirred at 75 °C for 28 h, cooled to room temperature, and extracted with $Et_2O$ (6 × 50 mL). The combined ethereal phase was dried through a cone of sodium sulfate and concentrated in vacuo at 50 °C to afford 44.5 g of yellow oil. This material was subjected to vacuum distillation through a short-path distillation head to remove the more volatile components. A fraction boiling at 40–140 °C at 0.1 mm contained primarily recovered HMEDD-Cl. The pot residue, a yellow oil (13 g), was predominantly a mixture of two compounds as determined by TLC. This material was slurried with 10 g of silica gel and flash chromatographed on silica gel (4/1 petroleum ether/ethyl acetate, 4 × 16 cm). Elution proceeded as follows: first 100 mL nil, second 200 mL, 3.8 g of THE-DD(3) and HMEDD dimer (see below), third 860 mL, 2.4 g of a mixture of the same, fourth 1100 mL, 1.31 g of a mixture of the three reaction products, fifth 500 mL of 1/1 petroleum ether/EtOAc, 1.7 g of slightly impure THE-DD(2), sixth 500 mL of EtOAc brought off 2.0 g of pure THE-DD(2).

**Low-$R_f$ Component THE-DD(2).** $^1$H NMR (CDCl$_3$, 90 MHz): $\delta$ 0.80 and 0.86 (t, $J$ = 6.0 Hz, and s, overlapping, 9 H), 1.38 (s overlapping m, 16 H), 3.38–3.72 (m, ~34 H). IR (KBr): 2860, 1450, 1370, 1250, 1200, 1150, 1020, 830 cm$^{-1}$. $^{13}$C NMR (CDCl$_3$): $\delta$ 7.14, 17.47, 21.30, 24.09, 26.30, 36.62, 40.78, 65.19, 68.44, 70.38, 71.00, 75.38, 97.85. MS: 609 (M + 1), 593 (80%, M – 15), 535, 520, 453, 395, 247, 173, 99 (100). The $^1$H NMR spectrum reveals distinctly the presence of a singlet at 0.82 ppm due to the methyl group on the triol core. A ratio of integrals can be obtained from the region due to the methylene and methyl group hydrogens of the ketal and that due to the methyl groups of the triol core and ketal. The observed value is 1.62 compared to a theoretical value of 1.78. The $^{13}$C NMR spectrum provides additional support to the validity of the assigned structure. The methyl group carbon and quarternary carbon of the triol core are readily discernible at 17.47 and 40.78 ppm. Confirmation of the structural assignment is provided by the mass spectral data. The total-ion chromatogram indicates that the material is of good purity.

**High-$R_f$ Component THE-DD(3).** These data should be interpreted in light of the presence of the known dimer impurity (see hydrolysis). $^1$H NMR (CDCl$_3$, 90 MHz): $\delta$ 0.80 and 0.89 (t, $J$ = 6 Hz, and s, overlapping, 12 H), 1.28 (s overlapping m, 24 H), 3.12–3.67 (m, 48 H). IR (KBr): 2860, 1450, 1370, 1250, 1200, 1150, 1020, 930, 885, 832, 700 cm$^{-1}$. $^{13}$C NMR (CDCl$_3$): $\delta$ 7.14, 17.27, 21.23, 24.09, 26.30, 36.62, 40.97, 65.19, 70.38, 70.58, 70.9, 73.76, 97.85. The $^1$H NMR spectra obtained for the higher $R_f$ component varied, depending upon the length of time the reactions were allowed to run. This point becomes apparent when one compares the spectrum of a sample isolated after a 100-h reaction and that from a 170-h reaction; although the methyl singlet of the core is clearly present at 0.89 ppm in the former, the spectrum of the latter reveals no discernible singlet in the same region. A similar trend is noted in the $^{13}$C NMR spectra; the ratio of the intensity of the resonance of the methyl group of the triol core (17.3 ppm) to the methyl resonance of the ketal moiety (7.14 ppm) is 1:3 for the 100-h reaction, while it is 5:9 for the 170-h reaction. The mass spectrum of scans 126–135 summed shows a prominent molecular ion peak at $m/e$ 491, which is 16 mass units below a smaller M + 1 peak at 507, suggesting the presence of an impurity of MW 506. Only a small amount of the trisalkylated compound is visible at $m/e$ 837. The mass spectrum of scans 199–204 summed, however, clearly corresponds to THE-DD(3). These data provide compelling evidence for the presence of an impurity, namely HMEDD dimer.

**Hydrolysis of THE-DD(3) to THE-OH(6).** A 1.0-g sample of the third 860-mL fraction was combined with 5% aqueous HCl (10 mL) and stirred at room temperature for 19 h. The resulting clear colorless solution was quenched by the addition of solid potassium carbonate and concentrated in vacuo to afford an oily white solid. This material was stirred with THF (40 mL) for $^1/_2$ h, filtered through a cone of sodium sulfate, and concentrated in vacuo to afford 0.86 g of yellow oil. The $^1$H NMR and $^{13}$C NMR spectra of this material showed mostly the presence of HMEDD dimer.

**Acknowledgment.** A.B.P. and H.K.H. acknowledge Dow Chemical Co., Midland, MI, for generous financial support, Dr. P. Owen for valuable discussions, Dr. G. Kallos for the mass spectra, and Dr. L. R. Wilson for the size exclusion chromatography measurements.

**Registry No.** HTBO, 72252-47-2; PE-BO(4), 104583-57-5; PE-OH(12), 6363-97-9; PE-Tos(12), 110614-84-1; PE-Br(12), 110637-30-4; PE-BO(12), 110637-31-5; PE-OH(36), 110614-85-2; PE-Tos(36), 110717-76-5; PE-Br(36), 110637-32-6; PE-BO(36), 110717-75-4; PE-OH(108), 110717-73-2; HMEDD, 20761-68-6; HMEDD-Cl, 110614-86-3; THE, 77-85-0; THE-DD(2), 110614-87-4; THE-DD(3), 110614-88-5; HMEDD-dimer, 110614-89-6; THE-OH(6), 110614-90-9; PE, 115-77-5; PE-Br(4), 3229-00-3; O(CH$_2$CH$_2$Cl)$_2$, 111-44-4.

**Supplementary Material Available:** $^{13}$C NMR data on all products and $^{13}$C NMR spectra for the second generation intermediates (2 pages). Ordering information is given on any current masthead page.