

Chapter VI

Functionalization of Dendrimers with Crown Ethers

VI.1 Introduction

P. J. Flory first introduced the concept of highly branched-chain, three-dimensional macromolecules (known today as "dendrimers") in the early 1940s.¹⁻⁴ He demonstrated, by statistical theoretical means, that these unique macromolecular architectures were only evident after a certain extent of reaction of multifunctional monomers. The hypothetical polymer (**Figure VI-1**) was known as a "2,3,2,3,1,0 molecule," each number referring to the number of branch points in each generation.

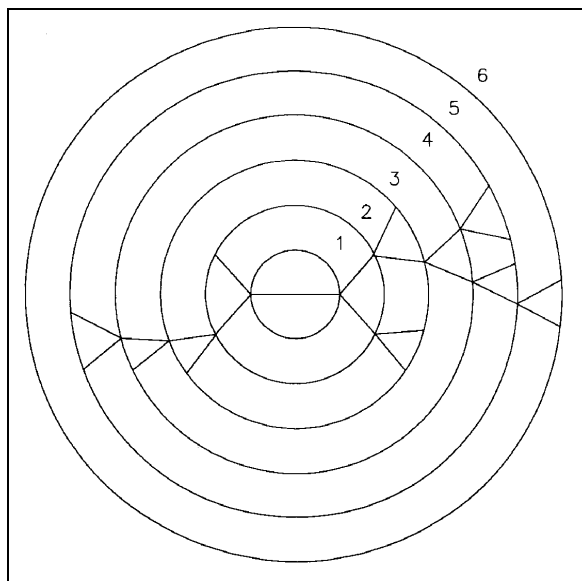


Figure VI-1. Flory's "2,3,2,3,1,0 molecule." A hypothetical "dendrimer."⁵

Flory's hypothetical concept became reality less than a decade later when he demonstrated in 1952⁶ that multifunctional monomers having two different functional groups (A and B, where A only reacts with B) could polymerize without forming a gel. The resulting highly branched polymers are today referred to as *hyperbranched polymers*.

Dendrimers are sometimes referred to as *hyperbranched polymers*, but they differ in that they must be synthesized in an iterative manner, whereby each successive layer, also known as a generation, is synthesized stepwise. A *hyperbranched polymer* is synthesized in a one step reaction, however.

It was not until 1978 when Flory's vision became a reality. Vögtle *et al.* first reported the synthesis of a dendrimer, then referred to a "cascade" molecule, via an iterative synthetic methodology.⁷ This event is considered to be the "birth of dendritic or 'cascade' chemistry."⁸ Several reviews concerning dendrimers have been published since its dawn and the reader is referred to these reviews for a more in depth understanding of this relatively new field.^{5,8-19}

The general synthetic approach to Vögtle's dendrimers has been named the *divergent* approach (**Figure VI-2**) since the successive generations are synthetically amplified from the core of the dendrimer. A core molecule (0th generation) possessing n reactive X groups is reacted with n equivalents of a multifunctional YZ_m monomer, where Y only reacts with X to give XY. This gives the 1st generation dendrimer having $n \times m$ end groups, i.e., $(XYZ_m)_n$. The endgroups of the first generation are then converted from "protected" Z to reactive X functionality. The multifunctional $(XYZ_m)_n$ monomer is reacted again to create the 2nd generation dendrimer. This cycle is repeated to build up higher generation dendrimers if needed. The main limitation of this method is that steric effects prevent the higher generations from being fully converted to the next generation, thus producing polydispersed samples, which are difficult to purify. Another limitation is the incomplete conversion of the Z groups to X groups which also leads to polydisperse samples.

An opposite approach was introduced by Hawker and Fréchet 12 years later, the *convergent* approach, whereby the dendrimers arms are synthesized first from the outside in and then these arms were attached to a core molecule (**Figure VI-2**).^{11,20,21} Here a focal molecule having an R group and nX functionalities is reacted with a multifunctional YZ_m monomer to give the 1st generation arm (also known as a "*dendron*") with $n \times m$ functional Z groups. The R group of the *dendron* is then converted to a Y group. Then m

dendrons are reacted with a core molecule having mX functional groups to give the 2nd generation dendrimer. This method is limited again by sterics as in the *convergent* approach particularly as the dendron gets larger. However, the *convergent* approach has an advantage over the divergent approach in that the number of coupling reactions required for each new generation is constant (at one); therefore, there are statistically fewer defects in the resulting dendrimers and they are often considered to be more homogeneously dispersed than the *divergent* dendrimers.¹⁸ Both methods described here, and depicted in **Figure VI-2**, result in the same dendrimer, demonstrating theoretically how the two seemingly different approaches can ultimately return the same product.

Since the concept of dendritic macromolecules became a reality numerous investigators have successfully synthesized a wide array of dendrimers having unique functionalities and properties. Most notable are Tomalia's poly(amidoamine) (PAMAM or "starburst") dendrimers^{22,23} (**VI-1**, 3rd generation) and the poly(propylene imine) dendrimers^{24,25} (**VI-2**, 5th generation) due to their commercial availability. Both dendrimers are made via the *divergent* approach. The research discussed in this chapter involves the functionalization of the poly(propylene imine) dendrimers with crown ethers.

The use of dendrimers in supramolecular chemistry was reviewed by Zeng and Zimmerman in 1997.¹⁸ The focus of the review was on 1) molecular recognition and 2) self-assembling systems. Dendrimers have been used in molecular recognition as receptors of substrates both in their "interior" cavities (via hydrophobic binding, hydrogen binding, metal-ligand coordination, and physical encapsulation) and their exterior surfaces (via electrostatic interactions and multiligation). Self-assembly systems using dendrimers have focused on dendritic amphiphiles, liquid crystals, hydrogen bonded supramolecular assemblies, metal coordinated self-assembled complexes and the self-assembly of mono- and multilayers.

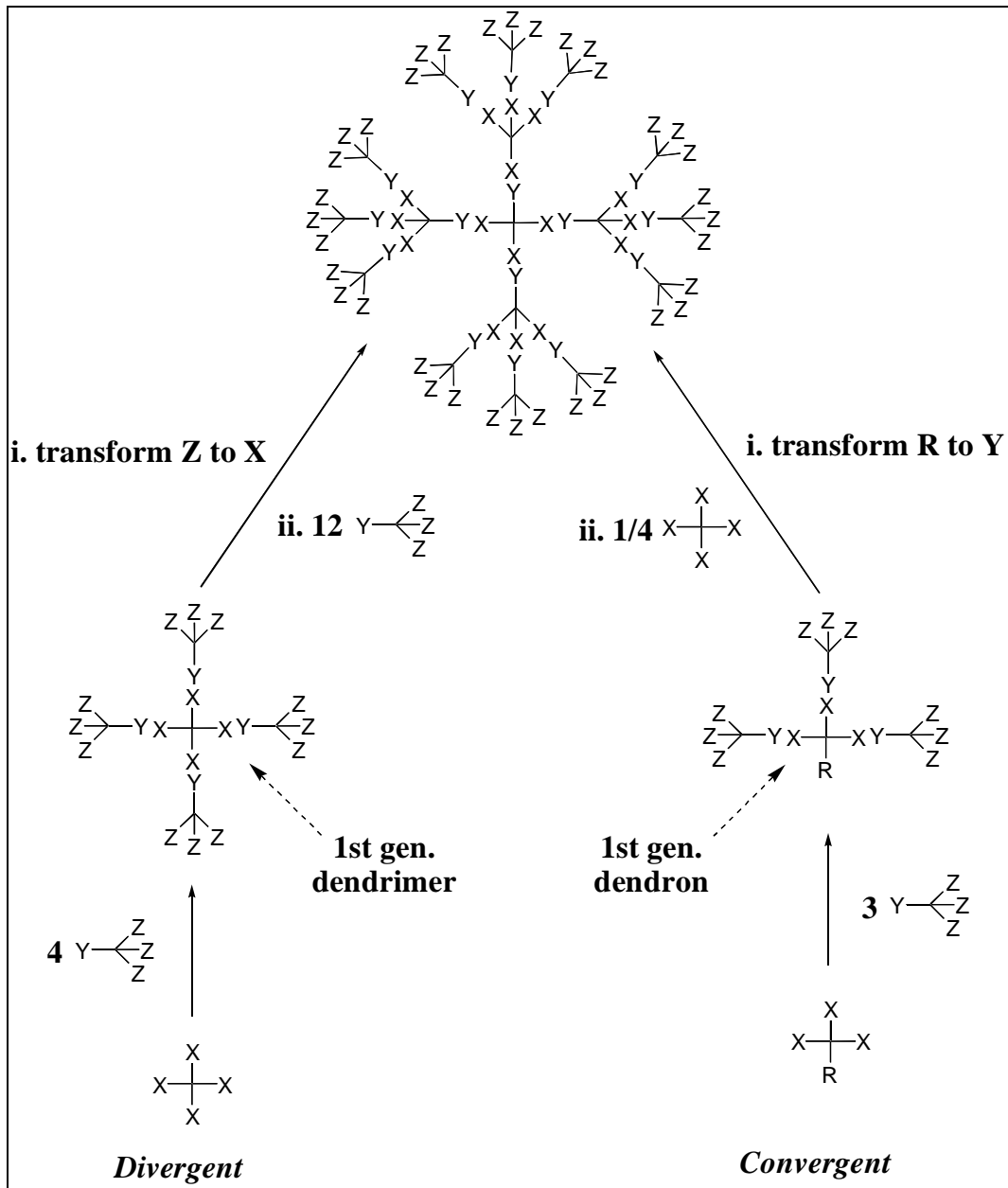
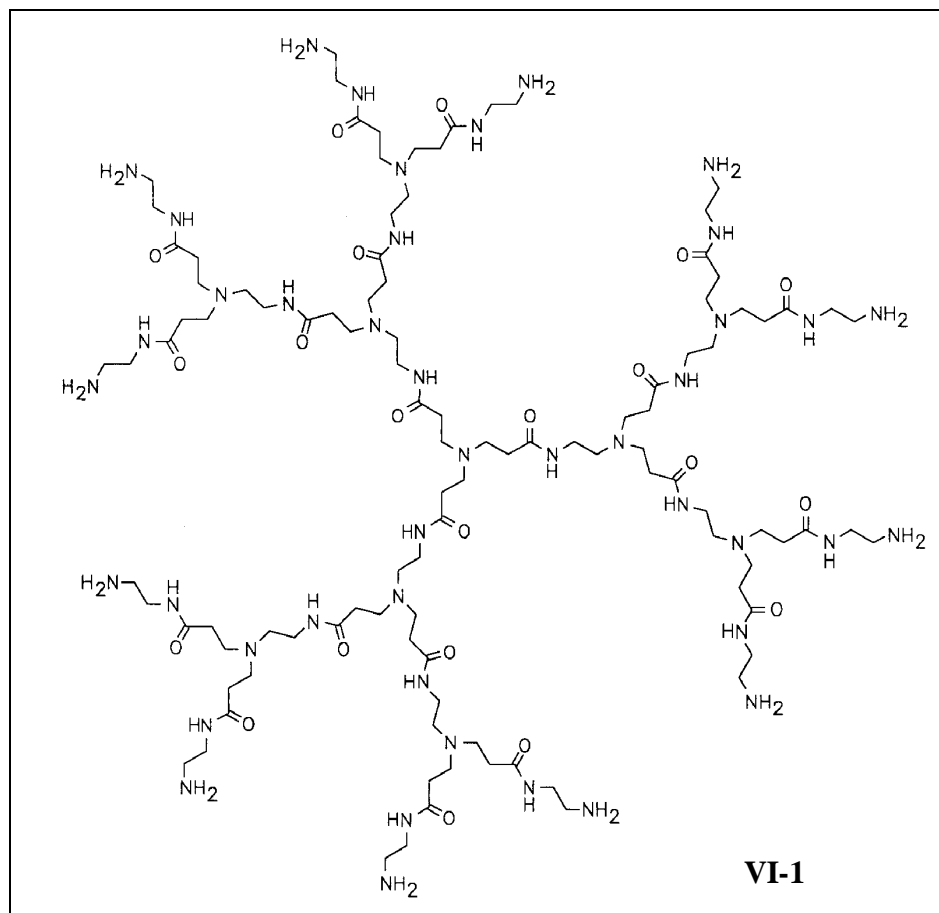
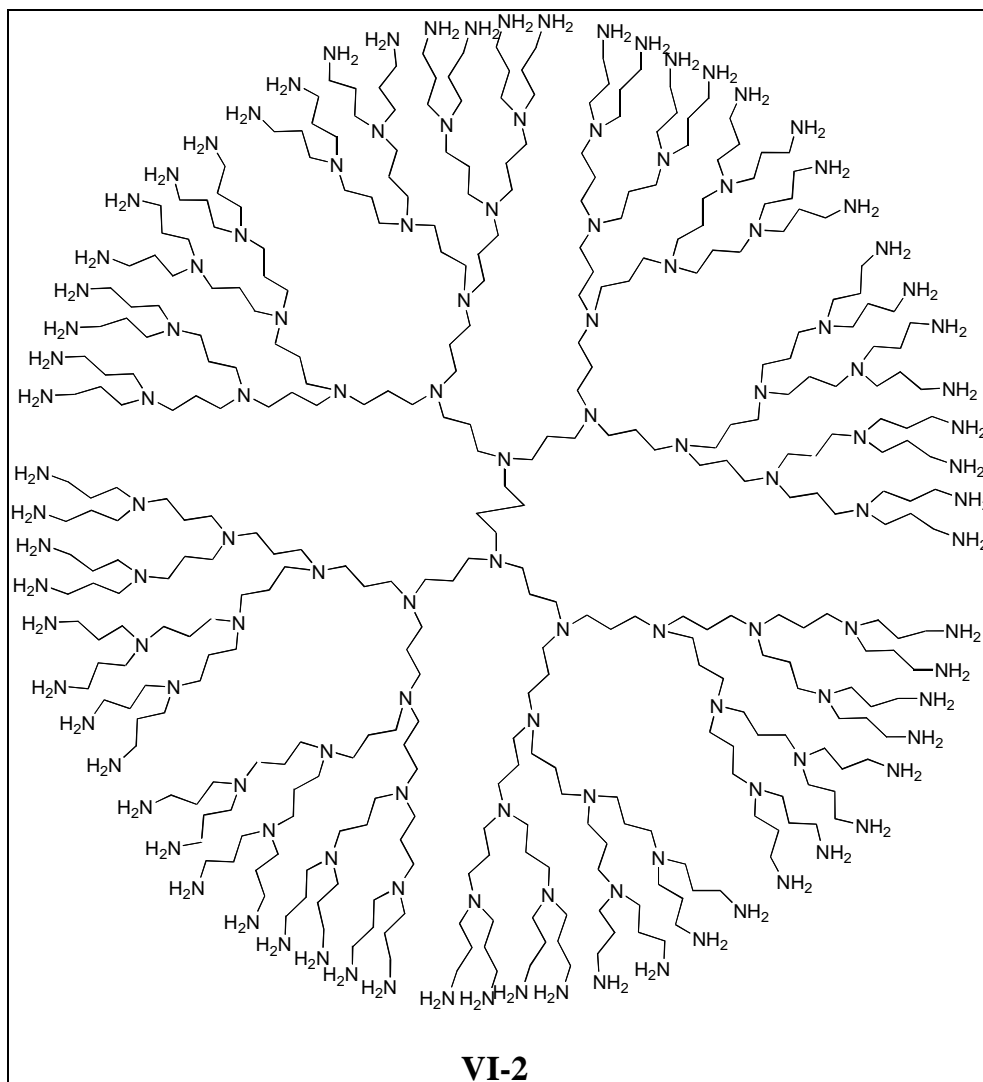


Figure VI-2. Divergent and convergent dendrimer approaches.



VI.1.2 Poly(propylene imine) Dendrimers

Currently the poly(propylene imine) dendrimers are commercially available from DSM in the Netherlands. They are synthesized via a procedure^{24,25} modified from Vögtle's original published method⁷ (**Figure VI-3**, steps **A** and **B**). Kilogram quantities are made by the repetitive addition of a primary amine to two equivalents of acrylonitrile (Michael addition, step **A Figure VI-3**), followed by hydrogenation of the nitrile end groups with Raney cobalt in a hydrogen atmosphere (step **B Figure VI-3**). Five repetitions gave **VI-2**.



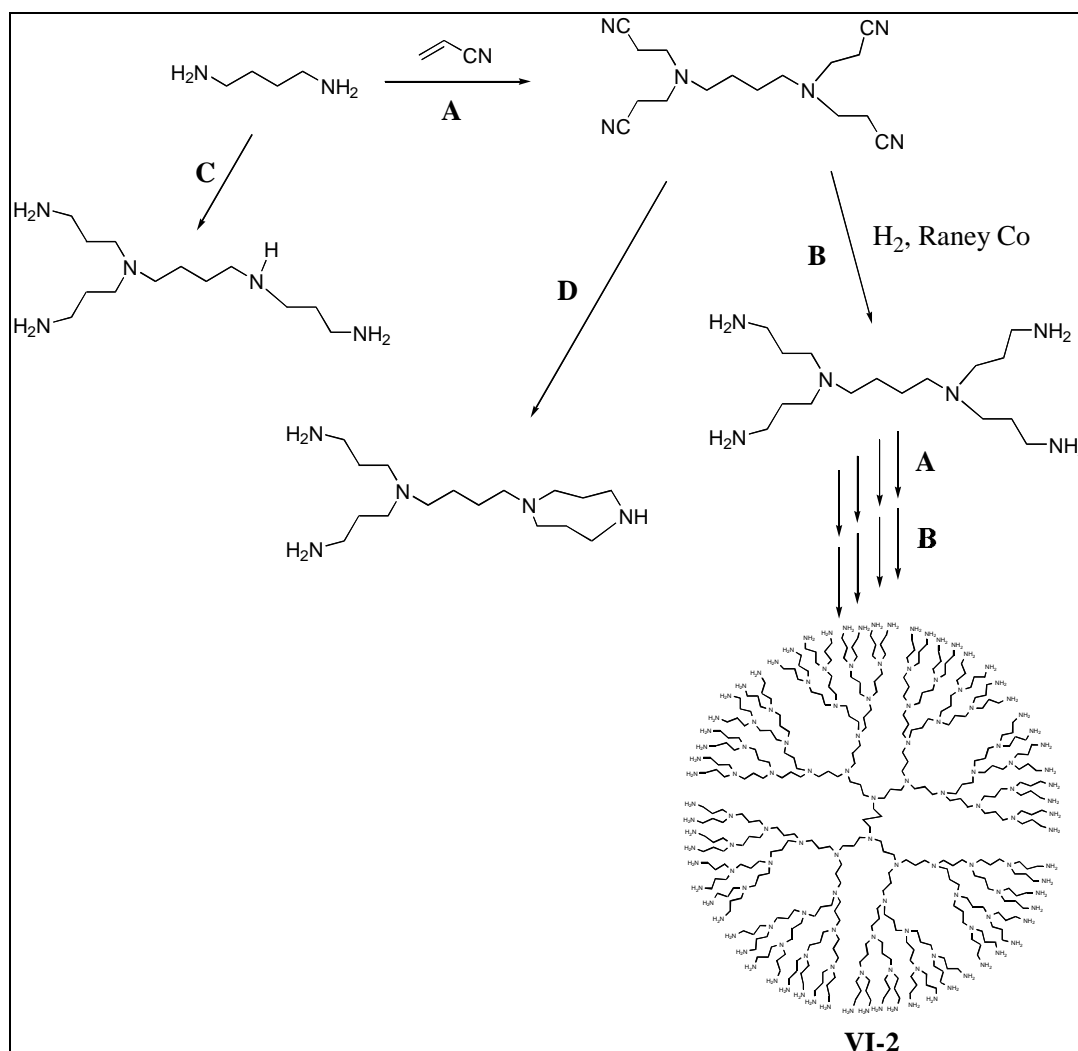
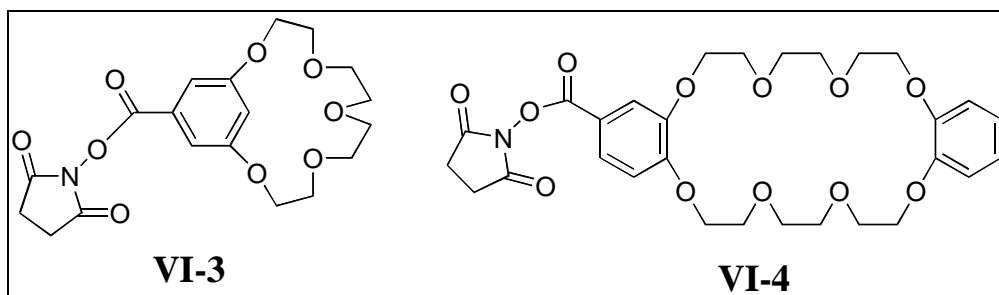


Figure VI-3. The synthesis of the poly(propylene imine) dendrimers (reactions **A** and **B**) and alternative, unwanted reactions **C** and **D** as discussed in the text.

Due to the divergent approach for the synthesis of the dendrimers there are defects in the resulting product.¹⁹ For example, if the selectivity of the reactions in **Figure VI-3** averaged 99.5% per reaction then the resulting 64 membered dendrimer **VI-2** would only be 29% defect free ($0.995^{248} = 0.288$). Therefore, it is important that the reader not assume that the dendrimers used here are monodispersed, nor are other dendrimers produced via the *divergent* method.¹⁹ A more detailed discussion of the defects present has been published.²⁶ Major defect reactions known thus far are paths **C**

and **D** in **Figure VI-3**. Path **C** illustrates a "missed" Michael addition (either by incomplete cyanoethylation or by a retro-Michael reaction) and path **D** illustrates unwanted cyclization reactions. Both paths result from propagation from one amine generation to the next.

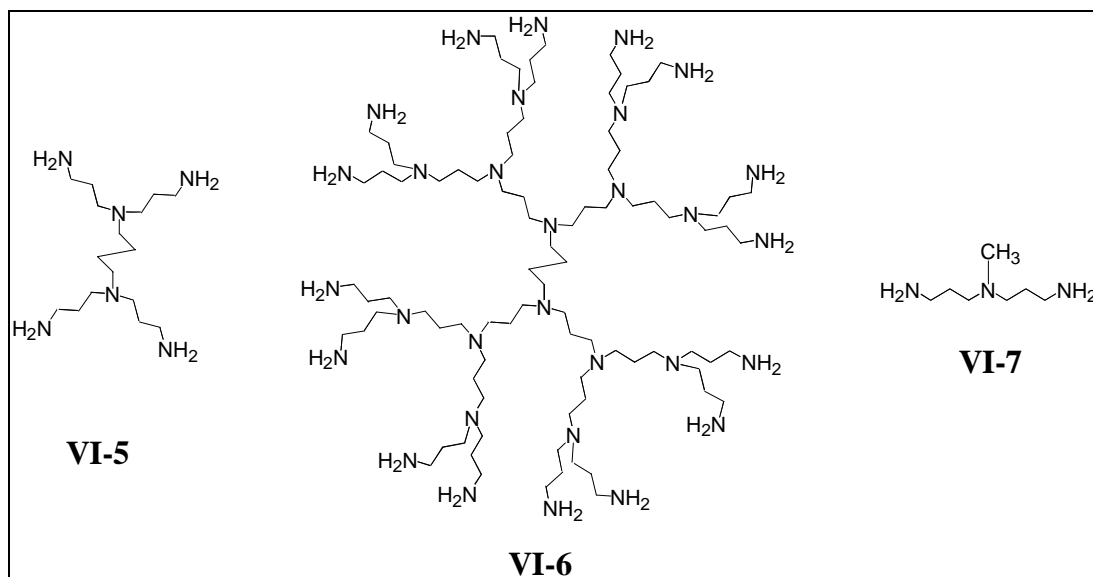
The conversion of the dendrimers' exterior primary amine groups requires a reaction that is quantitative to avoid more defects. Therefore, the succinimide esters of two crown ethers, **VI-3** and **VI-4**, were reacted with the primary amine groups of the dendrimers' surface. Reactions of succinimide esters with primary amines typically are quantitative and can be conducted at or below room temperature in nonpolar, aprotic solvents.²⁷



Throughout this chapter an abbreviation system was taken from the literature to simplify the discussion of the functionalized dendrimers. The abbreviation consists of three parts. The first part symbolizes the core starting diamine, which is abbreviated as DAB for diaminobutane. The second part is the phrase "*dendr*" implying that each nitrogen from that DAB core molecule out to, but not including, the surface of the dendrimer is a tertiary nitrogen having propyl groups as its substituents. The last part contains the number and type of end group on the dendrimer surface. As an example, **VI-2** is abbreviated as DAB-*dendr*-(NH₂)₆₄ which has 64 primary amine functionalities on its surface.

VI.2 Results and Discussion

The two crown ethers used to functionalize the 1st (**VI-5**), 3rd (**VI-6**), and 5th (**VI-2**) generation poly(propylene imine) dendrimers were the succinimide esters of 1,3-phenylene-16-crown-5 (**VI-3**) and dibenzo-24-crown-8 (**VI-4**). The syntheses of these compounds was described in **Chapter II**. To test the reactivity of the succinimide esters with the dendrimers both **VI-3** and **VI-4** were reacted with the diamine model compound *N*-methyl-*N*, *N*-bis(3-aminopropyl)amine (**VI-7**) to give the respective diamides. The succinimide esters were then reacted with the 1st, 3rd, and 5th generation dendrimers.



VI.2.1 Model Reactions

The model reactions involved stirring the succinimide ester and the model compound diamine **VI-7** overnight in either chloroform or dichloromethane. The reactivity of the 1,3-phenylene-16-crown-5 succinimide ester (**VI-3**) was first tested with the model compound diamine **VI-7** to give *N*-Methyl-*N*,*N'*-bis[*N*-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]amine (**VI-8**) (**Figure VI-4**). The product was isolated by first neutralizing the solution with NaOH and then washing first with

concentrated sodium bicarbonate and second water. The solvent was removed to give a slightly yellow viscous liquid. The ^1H , ^{13}C NMR, and COSY spectra (**Figures VI-5, VI-6, and VI-7** respectively) indicated that the product was formed and there were few impurities. Due to incomplete removal of the solvent the yield for the product was over 100%. **Figure VI-8** shows the electron ionization mass spectrum (EI-MS) of **VI-8**. The peak at 734.5 m/z corresponds to the desired product (**VI-8** + H^+) (calculated value is 734.3864 m/z). The peak at 1468.0 m/z corresponds to the doubly charged product ($2 \times [\text{VI-8} + \text{H}^+]$) (calculated value is 1468.7728 m/z). There is only a small peak for the sodium complex at 756.5 m/z (calculated value is 756.3683 m/z) which may indicate that the product (**VI-8**) did not retain sodium ions during the synthesis and purification.

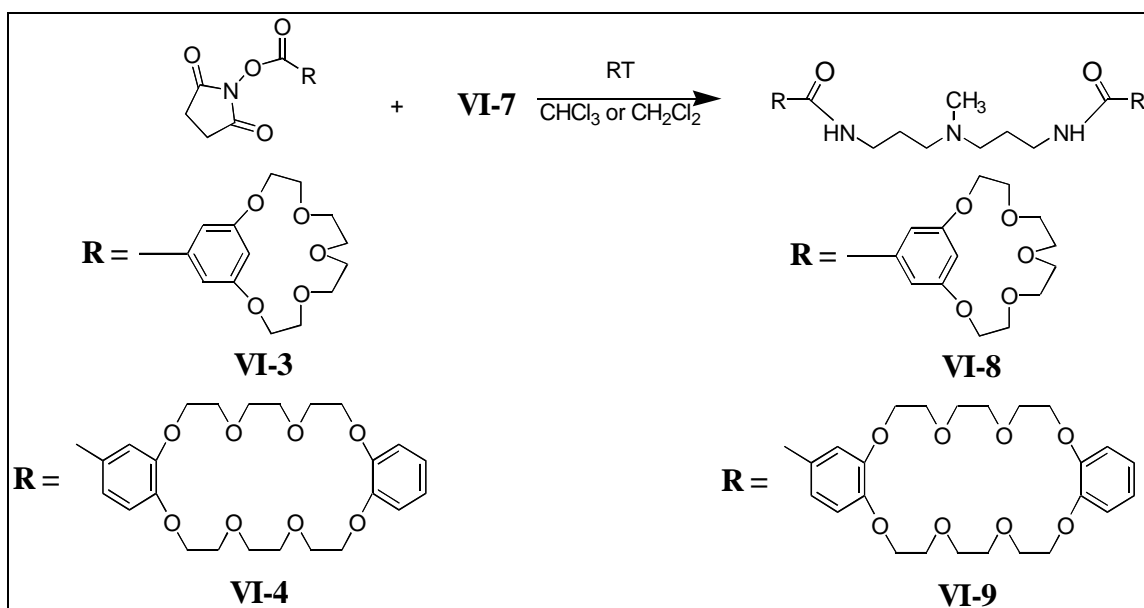


Figure VI-4. Synthesis of *N*-methyl-*N,N'*-bis[*N*-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]amine (**VI-8**) and *N*-methyl-*N,N'*-bis[*N*-(5-carboxy-dibenzo-24-crown-8)propylamino]amine (**VI-9**).

Although the reaction procedure was identical to that to the model reaction described above, complete conversion of the model compound **VI-7** to the difunctional 24-membered crown ether analog *N*-methyl-*N,N'*-bis[*N*-(5-carboxy-dibenzo-24-crown-8)propylamino]amine (**VI-9**) was not achieved (**Figure VI-4**). This was evident by the

^1H NMR of **VI-9** (Figure VI-9). There is a noticeable signal at 2.68 ppm, which corresponds to the methylene proton alpha to the terminal amine of the model compound diamine **VI-7**. There are also many unidentified peaks that are impurities. The observance of these peaks indicated that complete conversion was not achieved.

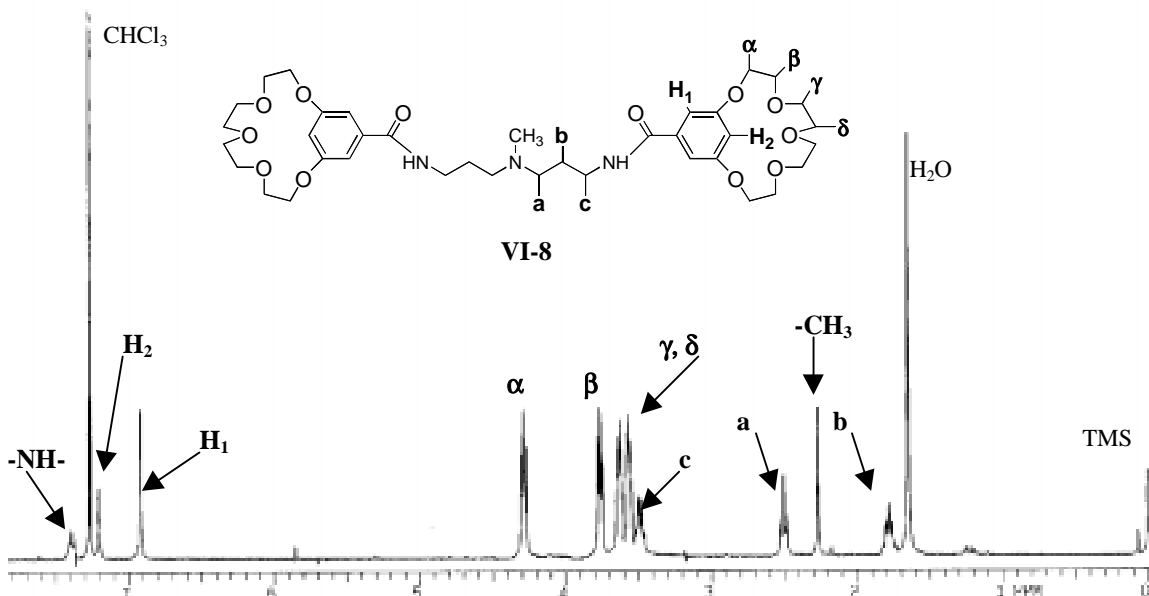


Figure VI-5. ^1H NMR (300 MHz, CDCl_3 , ambient T) of *N*-methyl-*N,N'*-bis[*N*-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]amine (**VI-8**).

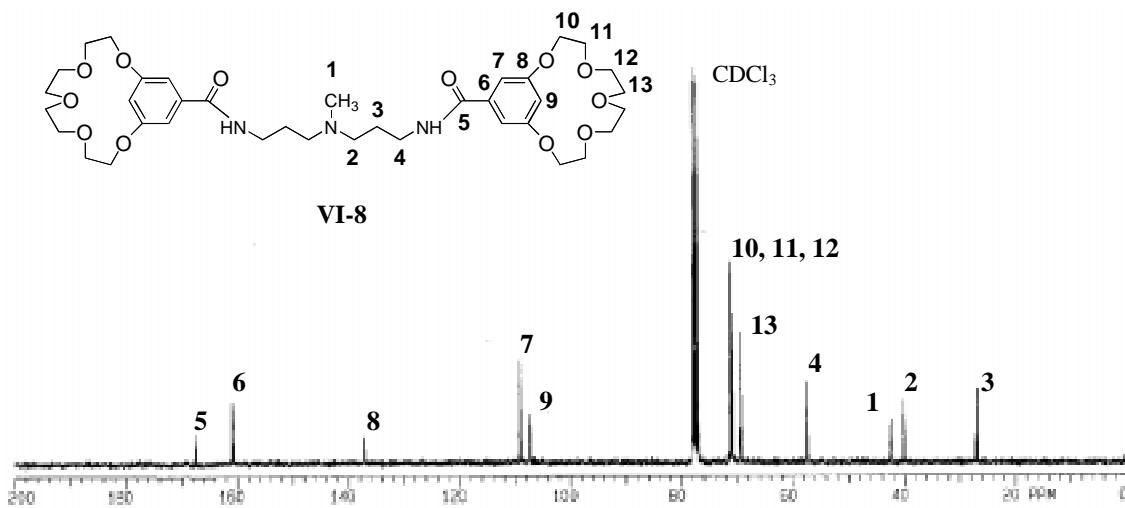


Figure VI-6. ^{13}C NMR (75 MHz, CDCl_3 , ambient T) of *N*-methyl-*N,N'*-bis[*N*-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]amine (**VI-8**).

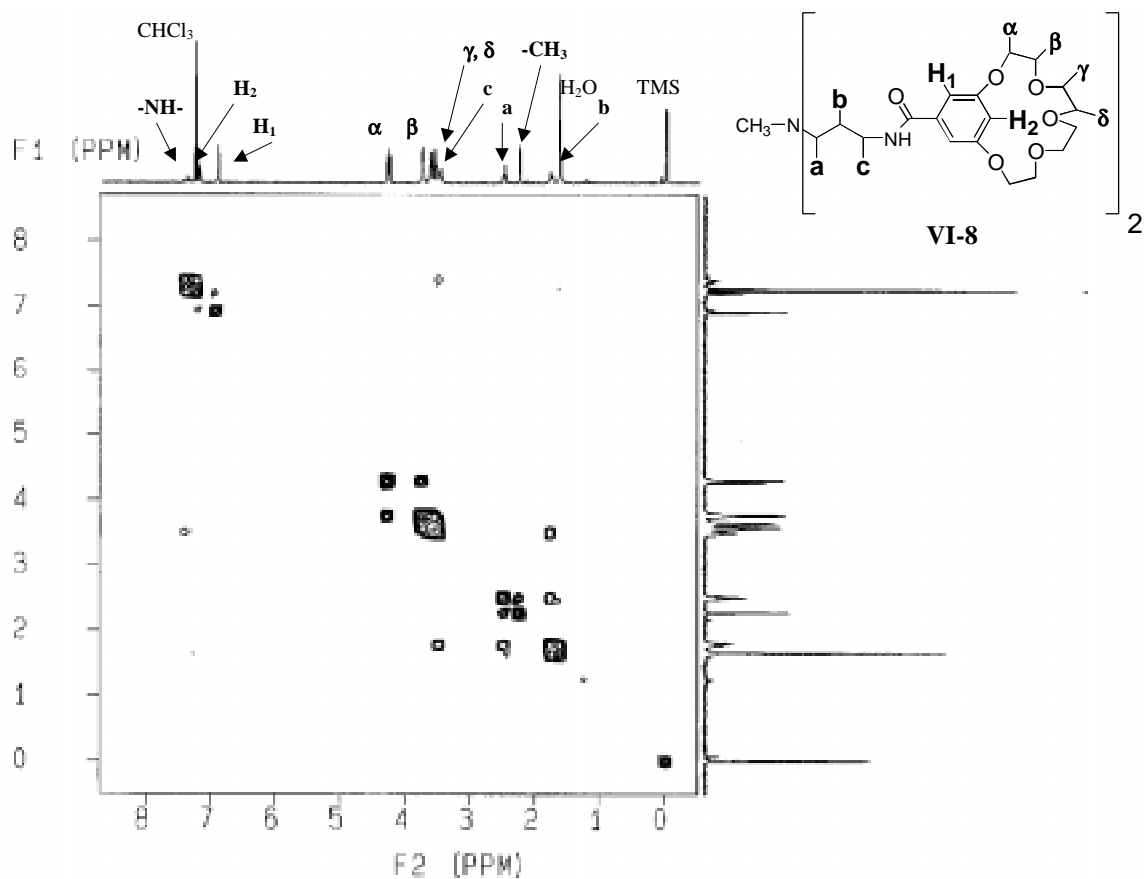


Figure VI-7. 2D COSY NMR (300 MHz, CDCl₃, ambient T) of *N*-methyl-*N,N'*-bis[*N*-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]amine (VI-8). Correlations (not shown): a) -NH- + c, b) H₁ + H₂, c) α + β, d) c + b, e) -CH₃ + a, f) a + b.

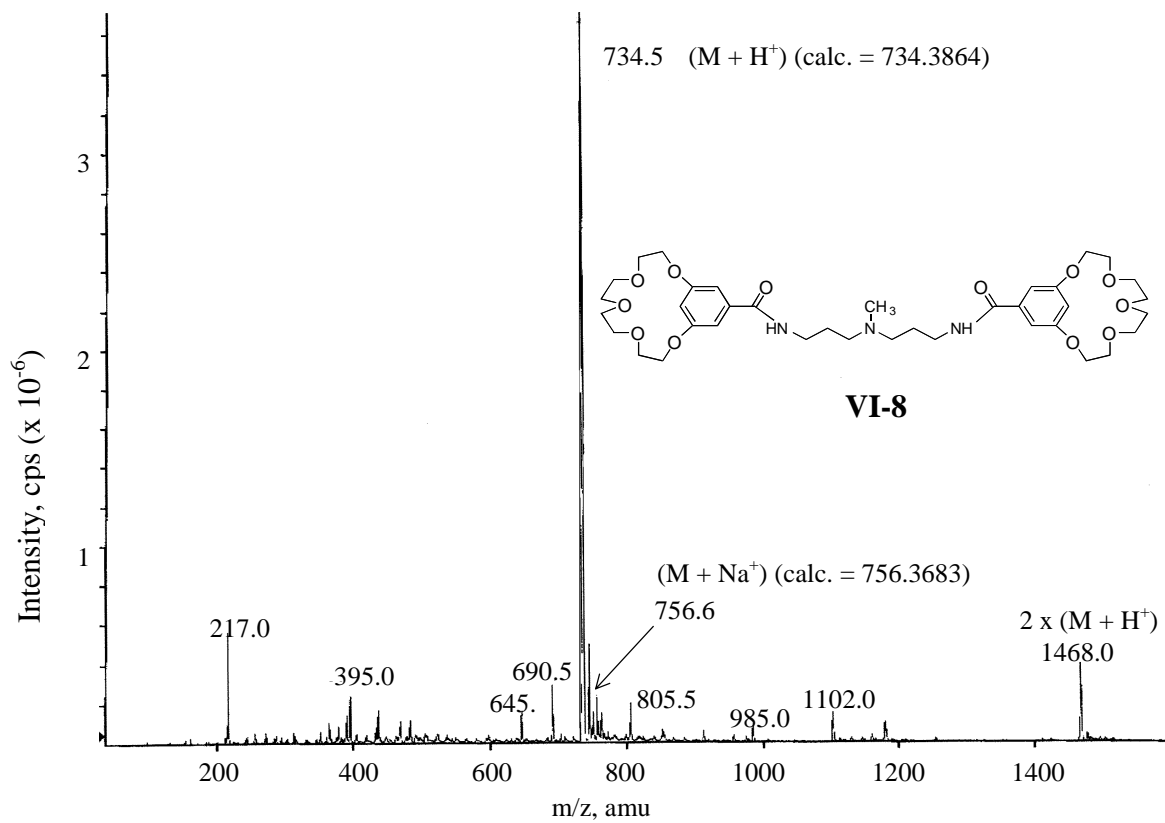


Figure VI-8. EI-MS of *N*-methyl-*N,N'*-bis[*N*-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]amine (**VI-8**).

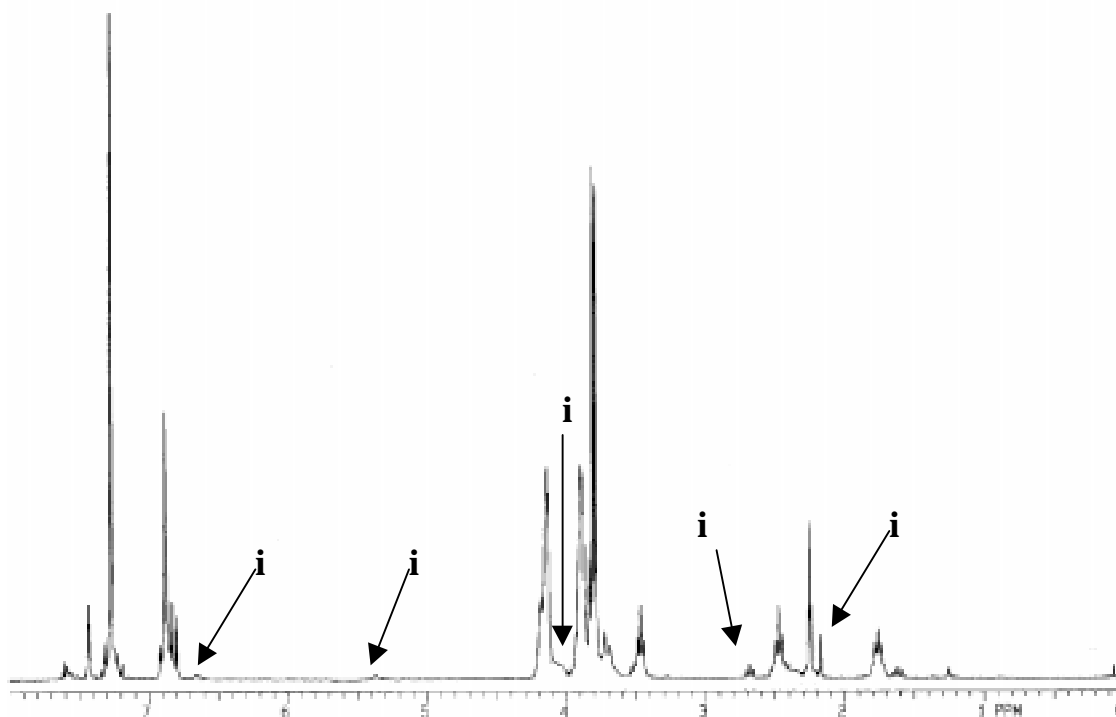


Figure VI-9. ^1H NMR (300 MHz, CDCl_3 , ambient T) of *N*-methyl-*N,N'*-bis[*N*-(5-carboxy-dibenzo-24-crown-8)propylamino]amine (**VI-9**). Impurities (**i**) have been marked.

Based on the above results for the synthesis of the diamide crown ether **VI-9**, the reactivity of the 24-membered crown ethers with the poly(propylene imine) dendrimers must be increased by using a better leaving group. **Figure VI-10** shows a possible synthesis for the pentafluorophenyl (PFP) ester of dibenzo-24-crown-8 (**VI-10**). Meijer and co-workers have had better results with the PFP leaving group than with the succinimide leaving group when functionizing the surface of their poly(propylene imine) dendrimers.¹ Also, it has been demonstrated that PFP esters activate hindered acids effectively.²⁸ Therefore, it is believed that the PFP ester of dibenzo-24-crown-8 (**VI-10**) will give a quantitative yield when reacted with the diamine **VI-7** or the poly(propylene imine) dendrimers.

¹ Personal communication with Dr. E. W. Meijer, Eindhoven University of Technology, Netherlands.

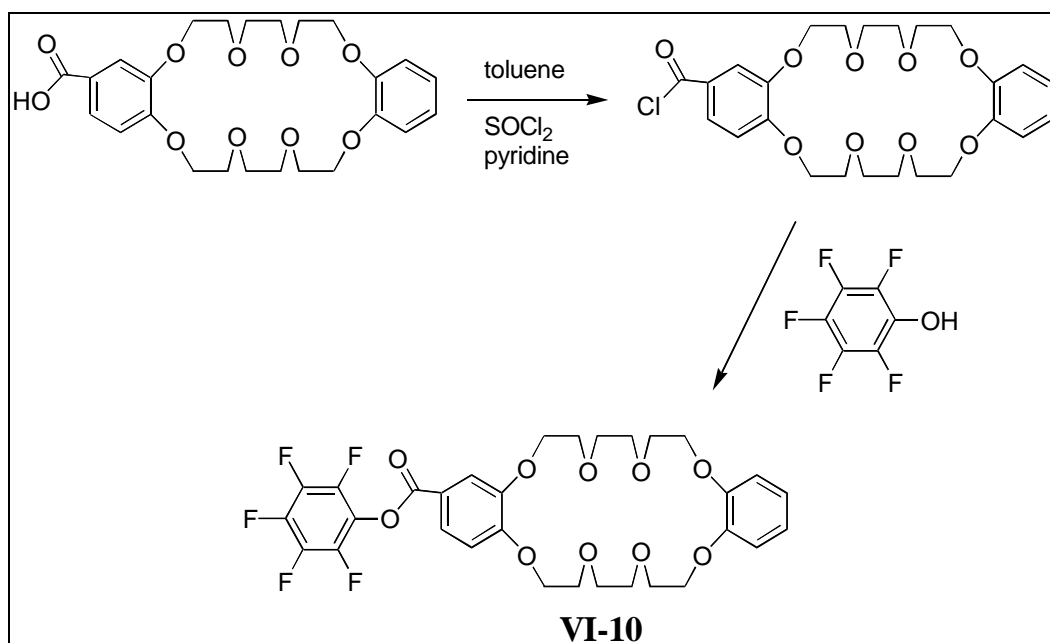


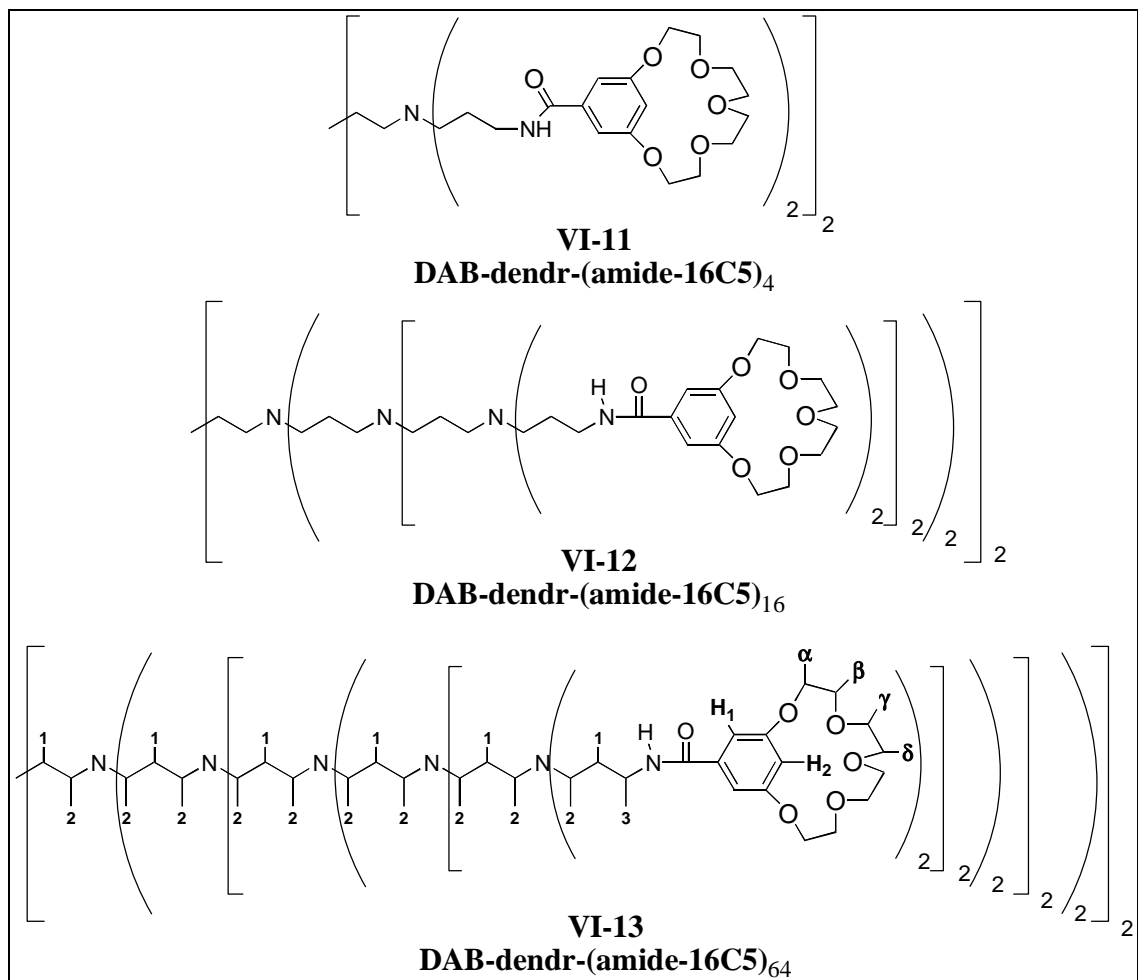
Figure VI-10. Proposed synthesis of the pentafluorobenzene ester of dibenzo-24-crown-8 (**VI-10**).

VI.2.2 Functionalization of Poly(propylene imine) Dendrimers with Crown Ethers

VI.2.2.1 1,3-Phenylene-16-crown-5 Functionalized Poly(propylene imine) Dendrimers

Encouraged by the successful quantitative conversion of the diamine **VI-7** to *N*-methyl-*N,N'*-bis[*N*-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]amine (**VI-8**), using the succinimide ester **VI-3**, identical reactions were conducted using the poly(propylene imine) dendrimers. The 1st (**VI-5**), 3rd (**VI-6**), and 5th (**VI-2**) generation poly(propylene imine) dendrimers were each converted to their respective 1,3-phenylene-16-crown-5 functionalized analogs (**VI-11**, DAB-*dendr*-(amide-16C5)₄; **VI-12**, DAB-*dendr*-(amide-16C5)₁₆; and **VI-13**, DAB-*dendr*-(amide-16C5)₆₄; respectively).

Upon work-up, complete removal of the solvent was only possible with the 5th generation crown ether functionalized dendrimer **VI-13**, DAB-*dendr*-(amide-16C5)₆₄. All of the products were glasses. The products were analyzed by both ¹H and ¹³C NMR. A representative ¹H NMR spectrum of the 5th generation dendrimer, **VI-13**, DAB-*dendr*-(amide-16C5)₆₄, is shown in **Figure VI-11**.



VI.2.2.1 Dibenzo-24-crown-8 Functionalized Poly(propylene imine) Dendrimers

In spite of the negative result for the conversion of the diamine **VI-7** to the bisamide-crown **VI-9**, the functionalization of the 1st generation poly(propylene imine) dendrimer with dibenzo-24-crown-8 was attempted. Again the reaction procedure was identical to that described above. However, when the resulting glassy product was analyzed by ¹H NMR signals were observed (~ 2.7 ppm) for the methylene protons alpha to the terminal primary amines of **VI-11**, DAB-dendr-(NH₂)₄, (**Figure VI-12**). There were also many unexplained peaks that were probably due to impurities. This observation

again supports the conclusion that a better leaving group is needed on dibenzo-24-crown-8 to fully convert the poly(propylene imine) dendrimers.

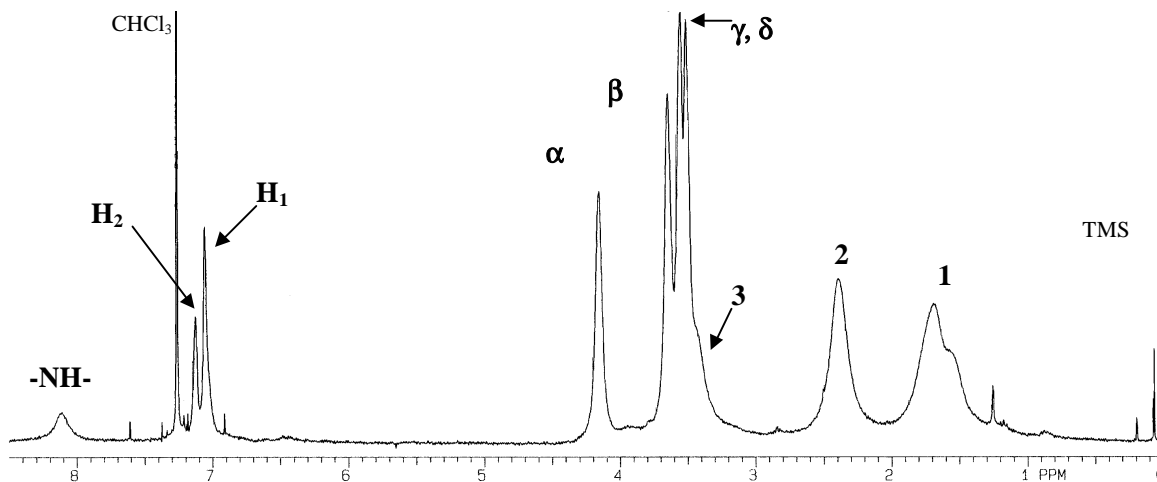


Figure VI-11. ¹H NMR (300 MHz, CDCl₃, ambient T) of **VI-13**, DAB-*dendr*-(amide-16C5)₆₄.

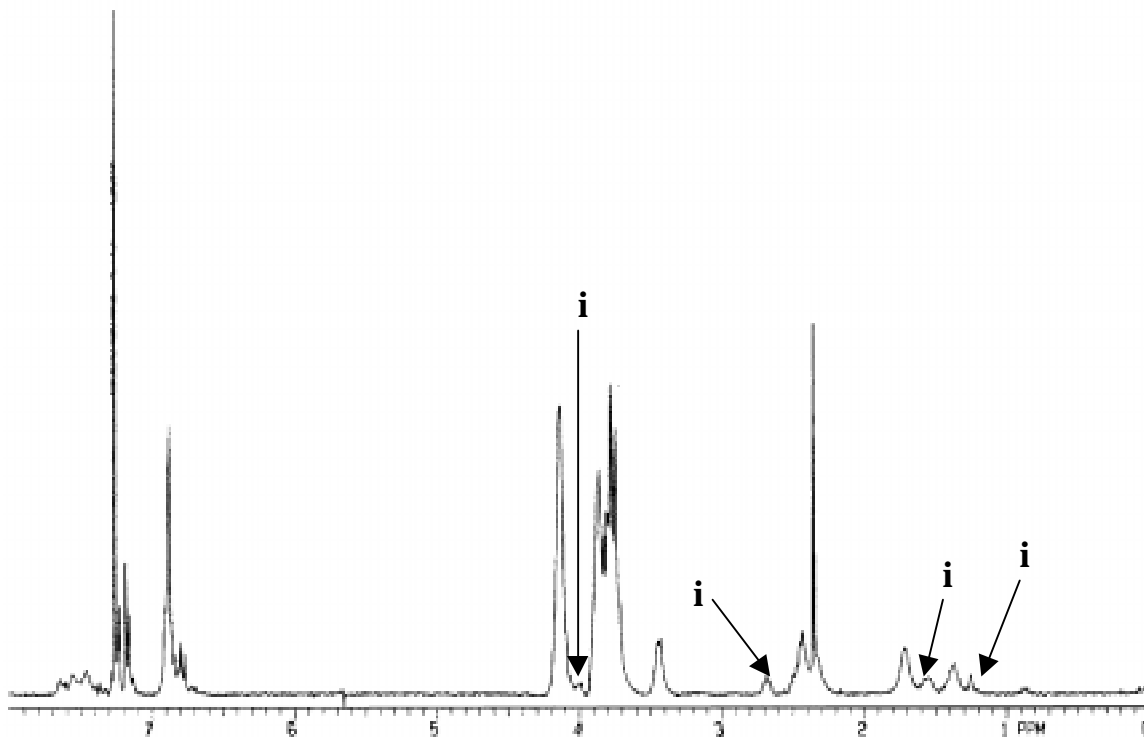


Figure VI-12. ¹H NMR (300 MHz, CDCl₃, ambient T) of product obtained from reaction of **VI-4** with **VI-11**, DAB-*dendr*-(NH₂)₄. Impurities (**i**) have been marked.

VI.3 Conclusions

The reactivity of the succinimide esters of 1,3-phenylene-16-crown-5 (**VI-3**) and dibenzo-24-crown-8 (**VI-4**) with the primary amine **VI-7** and the 1st, 3rd, and 5th generation poly(propylene imine) dendrimers was investigated. It was found that the 16-membered crown ether succinimide ester **VI-3** reacts quantitatively with the diamine model compound **VI-7**, but the 24-membered one (**VI-4**) does not. The same results were observed when both succinimide esters (**VI-3** and **VI-4**) were reacted with the poly(propylene imine) dendrimers. Therefore, only the 16-membered crown ether succinimide ester **VI-3** appears to be a suitable compound for the functionalization of the poly(propylene imine) dendrimers.

VI.4 Experimental

Chemical Reagents and Measurements

Poly(propylene imine) dendrimers were kindly provided by Dr. E. W. Meijer, Eindhoven University of Technology, Netherlands. Both succinimide esters **VI-3** and **VI-4** were synthesized and are described in **Chapter II**. *N*-methyl-*N,N'*-bis(3-aminopropyl)amine (**VI-7**) was used as received from Aldrich. All solvents were HPLC or GC grade. ¹H and ¹³C NMR spectra were obtained on a 300 MHz Varian Gemini spectrometer with tetramethylsilane as an internal standard. The following abbreviations have been used in describing NMR spectra: s (singlet), d (doublet), t (triplet), br s (broad singlet), and m (multiplet). EI-MS analyses were performed using the direct probe on the GCMS-QP5000.

1. *N*-Methyl-*N,N'*-bis[*N*-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]-amine (VI-8**).** *N*-methyl-*N,N'*-bis(3-aminopropyl)amine (**VI-7**, 19.0 mg, 0.133 mmol) was placed in a 50 mL single neck round bottom flask equipped with a magnetic stir bar. CH₂Cl₂ (~4-5 mL) was then added. The succinimide ester of 5-carboxy-1,3-phenylene-16-crown-5 (**VI-3**, 110 mg, 0.0268 mmol) was then added. The solution was stirred for 24 h. To the solution, ~4 ml of 1 M NaOH was added and the mixture was stirred for 1 h and transferred to a separatory funnel and the aqueous phase removed. The CH₂Cl₂ layer was then washed with a concentrated sodium bicarbonate solution followed by deionized H₂O. The CH₂Cl₂ was then removed by rotoevaporation to give an oil. Yield = 105 mg (~ 100 %). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.39 (2H, t, J = 4.2 Hz), 7.20 (2H, d, J = 2.1 Hz), 6.92 (4H, s), 4.29 (8H, t, J = 4.8 Hz), 3.76 (8H, t, J = 4.8 Hz), 3.60 (16H, m), 3.49 (4H, m), 2.50 (4H, t, J = 6.3 Hz), 2.27 (3H, s), 1.78 (4H, t, J = 6.3 Hz). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 167.6, 160.8, 137.1, 109.2, 107.4, 71.3, 71.2, 70.9, 69.4, 57.4, 42.4, 40.0, 27.0 (13 peaks as required). EI-MS (acetone): 734.5 m/z (**7** + H⁺) (calc. 734.3864 m/z), 1468.0 m/z (2 x [**7** + H⁺])(calc. 1468.7728 m/z).

2. Synthesis of Crown Ether Functionalized Dendrimers. The synthesis of the crown ether functionalized dendrimers was done using the same procedure used above for the synthesis of **VI-8**. **DAB-dendr-(amide-16C5)₄** Yield = 117 mg (~ 100 %). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.31 (H, m), 7.19 (4H, t, J = 2.1 Hz), 6.92 (8H, d, J = 3.0 Hz), 4.26 (16H, t, J = 4.8 Hz), 3.74 (16H, t, J = 4.8 Hz), 3.58 (32H, m), 3.45 (8H, m), 2.48 (8H, m), 2.39 (4H, br s), 1.71 (8H, t, J = 6.9 Hz), 1.40 (4H, br s). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 167.1, 160.3, 136.4, 108.7, 106.9, 70.7, 70.6, 70.3, 68.8, 53.9, 52.6, 39.3, 26.7, 24.8 (14 peaks as required). **DAB-dendr-(amide-16C5)₁₆** Yield = 108 mg (~ 100 %). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.78 (16H, br s), 7.17 (16H, s), 7.03 (32H, s), 4.22 (64H, br s), 3.58 (224H, m), 2.38 (84H, m), 1.55 (60H, m). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 167.2, 160.2, 136.3, 108.9, 107.1, 70.7, 70.6, 70.2, 68.8, 52.1, 39.1, 30.9, 26.8, 24.5. **DAB-dendr-(amide-16C5)₆₄** Yield = 86.5 mg (84.2 %). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 8.11 (64H, br s), 7.12 (64H, s), 7.06 (128H, s), 4.15 (256H, br s), 3.55 (896H, m), 2.39 (376H, br s), 1.60 (252H, br s). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 167.3, 160.2, 136.2, 109.1, 70.6, 70.2, 68.8, 54.3, 52.5, 40.6, 31.3, 25.4.

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