TU/e EINDHOVEN UNIVERSITY OF TECHNOLOGY

New molecular architectures based on dendrimers

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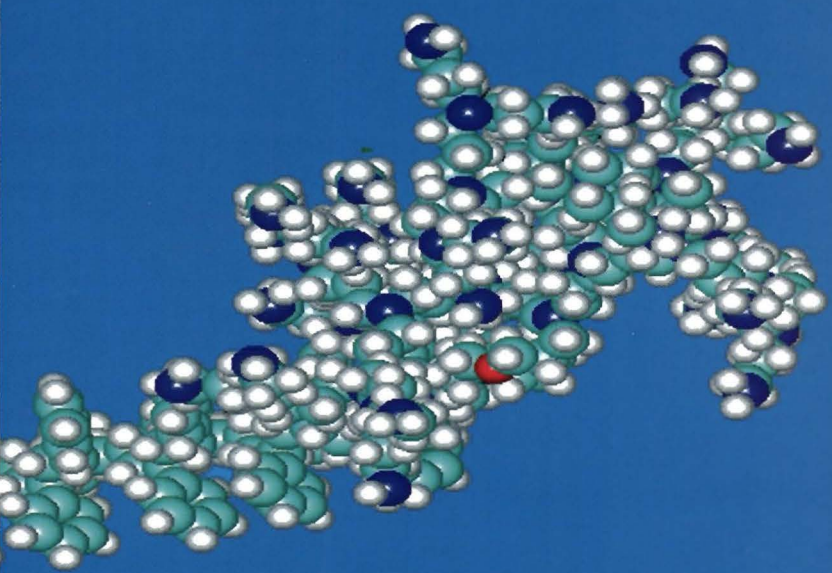
New Molecular Architectures Based on Dendrimers



Jan C.M.van Hest

New Molecular Architectures Based on Dendrimers

New Molecular Architectures Based on Dendrimers

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Technische Universiteit Eindhoven, op gezag van de Rector Magnificus, prof.dr. J.H. van Lint, voor een commissie aangewezen door het College van Dekanen in het openbaar te verdedigen op donderdag 14 maart 1996 om 16.00 uur

door

Jan Cornelis Maria van Hest

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druk: wibro dissertatiedrukkerij, helmond

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Chapter 1

General introduction

1.1 Introduction

Chemists have always been challenged by exploring new areas in their research. The traditional chemical disciplines, as for example colloid, organic and inorganic chemistry have been investigated in great detail. Research has, however, been quite monodisciplinary, which has resulted in gaps between the traditional fields of chemistry. These areas have now attracted an increasing number of scientists, and a cooperation between different disciplines seems to be the next step in the development of chemistry.

One of the areas that has gained interest, but is still hardly explored, is the field between organic and polymer chemistry. For the organic chemist, the covalent bond is not the only subject of interest anymore. It has become the aim of a large number of scientists to build up larger structures, based on non-covalent interactions, in a well-defined manner. Nature is in most cases the source of inspiration. Supramolecular chemistry implies that the border of organic chemistry is crossed in the direction of polymer science. A result of the increased complexity of the newly developed structures is that characterization is not possible anymore with classical organic chemistry techniques.

In polymer chemistry, on the other hand, a development is going on toward better control over polymer properties as chain length, molecular weight distribution, functionality and tacticity. The study of well-defined compounds can for example give a better insight into the structure-property relationships of polymers and can contribute in tuning material properties. A more detailed knowledge of organic chemistry is for this development a prerequisite.

The recently developed dendrimers perfectly fit in between organic and polymer chemistry. From an organic chemistry point of view dendrimers are versatile multifunctional materials; supramolecular chemists regard them as attractive building blocks for nanosized architectures, due to their shape and size. Considered as a well-defined globular polymer,

new topologies will arise from the combination with linear polymers, which can help the polymer chemist to obtain a better understanding of structure-property relations.

In this chapter a brief introduction to dendrimers is followed by a more detailed literature survey of the use of dendrimers in supramolecular and polymer chemistry, and their application as amphiphiles. At the end of the chapter the targets of this thesis will be discussed.

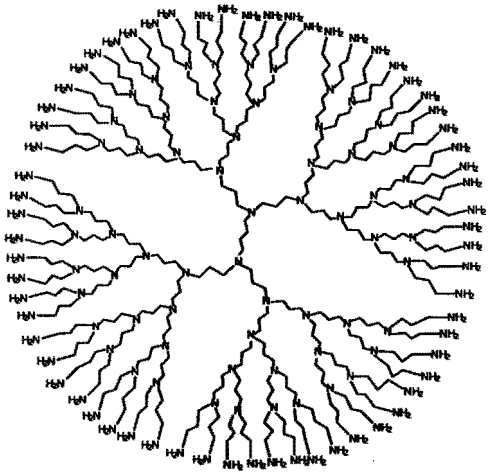


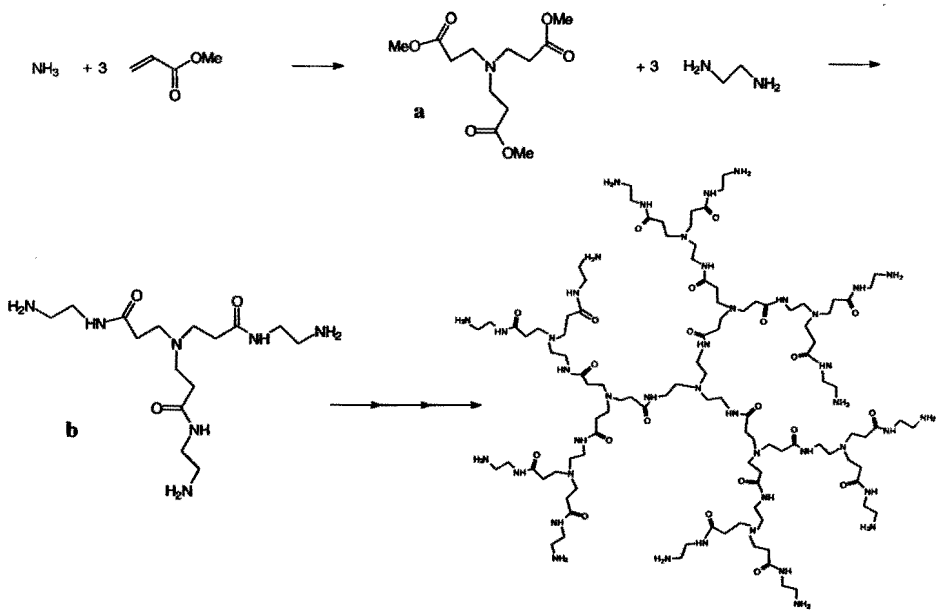
Figure 1.1: *The poly(propylene imine) dendrimer, a well-defined, highly branched structure*[7].

1.2 Dendrimers

It has been fifty years ago that dendrimers and hyperbranched structures were described for the first time by Flory and Stockmayer[1] in treatises, based on the infinite network theory. It lasted until 1978 before the first real chemical example of a dendrimer was reported by Vögtle[2]. In the last decade, after the publications in 1985 of Newkome and Tomalia[3], the area has been expanding exponentially. An increasing number of researchers has become fascinated by dendrimers and has entered this field, which now is regarded as one of the focal points in materials science[4].

Dendrimers are described as well-defined, highly branched molecules, that emanate from a central core. Because of a step-by-step synthesis, full control over size, shape and functionality can be obtained. This preparation technique distinguishes dendrimers from the related family of hyperbranched polymers[5], which are prepared by a one-pot polymerization of AB_x type of monomers. The ease of preparation of hyperbranched structures compensates in some cases the moderate loss of control over properties[6], when compared to dendrimers.

In general, there are two different routes toward dendritic structures: the divergent synthesis, as applied by e.g. Tomalia, Newkome and Meijer[7], and the convergent approach, developed by Fréchet and Neenan[8]. In the divergent approach, a repetition of a reaction sequence is used, which results in the introduction of branching points and a multiplication of the end groups (scheme 1.1). The synthesis starts at the core of the molecule. After every reaction sequence, the following generation is obtained and the number of reactions onto one molecule is multiplied. This approach, therefore, demands types of reactions that can proceed with very high selectivity and yield.



Scheme 1.1: *Divergent approach, as performed by Tomalia for the synthesis of PAMAM-dendrimers: a) generation 0.5; b) generation 1*[4a].

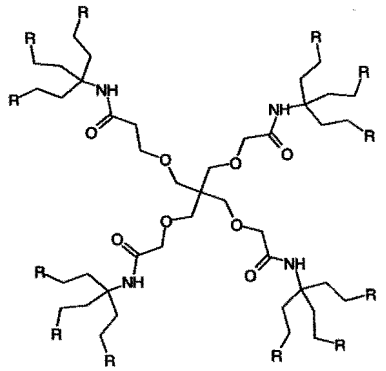
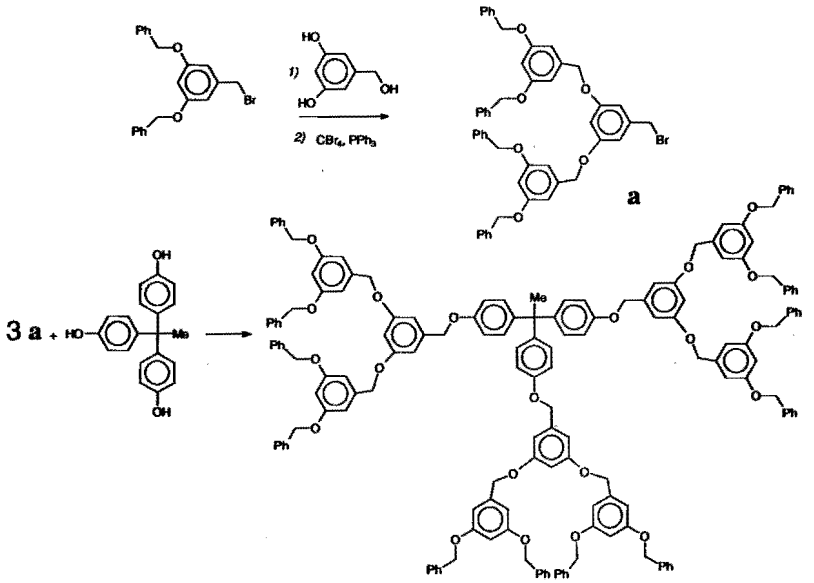


Figure 1.2: *First generation arborol; a): R = COOH, b) R = CH_2-NH_2, c) R = CH_2-OH*[38e].

The convergent route starts at the periphery of the dendritic structure. Wedges are synthesized, which are coupled in the last reaction step at the core molecule (scheme 1.2). The number of reactions per reaction step remains in this case constant.

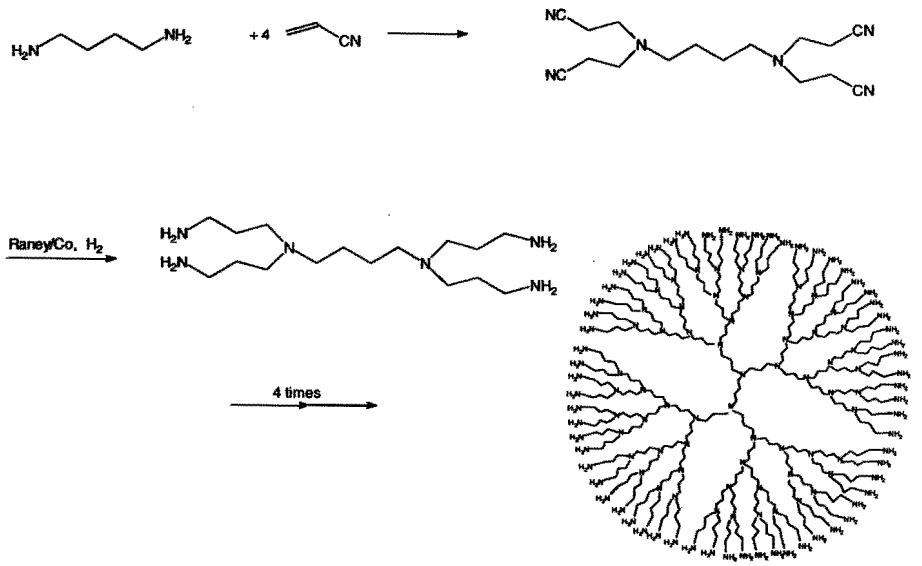


Scheme 1.2: *Convergent approach of Fréchet. Compound a is a second generation polyether dendritic wedge (G[2]-Br)*[8a].

The convergent method is considered as the organic chemistry approach toward dendrimers, whereas the divergent route can be regarded as the polymer chemistry equivalent. Dendrimers are therefore described as molecules in between organic and polymer chemistry, with regard to size and monodispersity of the end products. A broad variety of different synthetic routes has now been developed, resulting in e.g. silicon[9b-g], phosphorus[9h-i] and organometal-based structures[9i-n].

1.3 Large scale synthesis

Until recently, one of the problems concerning dendrimers was the small scale on which they could be synthesized. Property and application investigations were therefore strongly hampered. Nowadays, two dendrimer systems have become commercially available[10], of which the poly(propylene imine) dendrimers, developed at DSM, can even be scaled up to multikilogram quantities (scheme 1.3).



Scheme 1.3: *DSM-route toward poly(propylene imine) dendrimers. The end product is a fifth generation dendrimer with 64 primary amine end groups (DAB-dendr-$(NH_2)_{64}$)*[7].

The reaction scheme used consists of a double Michael addition with acrylonitrile onto primary amines, followed by Raney/Co catalyzed hydrogenation of the nitriles to the corresponding amines. This method, concurrently developed by Mühlhaupt et al.[11], is an adaptation of the Vögtle dendrimer approach of 1978. The use of cheap, readily accessible starting materials, in combination with a reaction sequence that after thorough optimization can easily be scaled up, makes this a commercially attractive process.

The poly(propylene imine) dendrimers have common dendritic properties: beyond a certain generation, –for the poly(propylene imines) this is the fourth generation DAB-*dendr*-$(NH_2)_{32}$[7b]–, the structures adopt a spherelike shape. This can be noticed from the fact that the intrinsic viscosity goes through a maximum by increasing molecular weight (figure 1.3). The dendritic, globular shape can, therefore, be utilized effectively for the fifth generation DAB-*dendr*-$(NH_2)_{64}$.

Every dendrimer has its limits of growth. From a certain generation on, the periphery is densely packed with end groups and a complete branching reaction isn't possible anymore. For the poly(propylene imines) this limit is calculated to occur for the cyanoethylation of

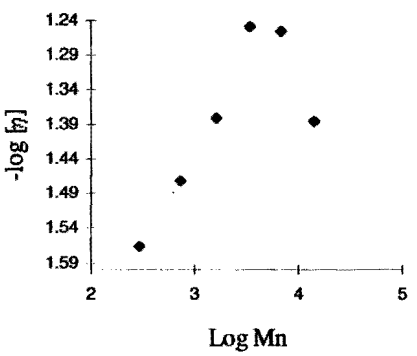


Figure 1.3: *Intrinsic viscosity versus molecular weight of the DAB-dendr-$(CN)_x$ series.*

DAB-*dendr*-$(NH_2)_{256}$. The density distribution within a dendrimer is subject of discussion. De Gennes[12] predicts an increasing density profile, going to the periphery of the structures. Lescanec's model[13] states that the highest density can be found in the interior of the dendrimer. For the poly(propylene imines) it seems to be that there is a density fluctuation inside the dendrimer, and that the truth is somewhere in between both models[14].

A property that distinguishes the poly(propylene imines) from most other dendrimers, is their hydrophilicity, which makes the amine-functionalized structures miscible with water

Table 1.1: diameters of DAB-*dendr*-$(CN)_x$ and DAB-*dendr*-$(NH_2)_x$[14]

DAB-*dendr*-$(NH_2)_x$	Radius (Å)	DAB-*dendr*-$(CN)_x$	Radius (Å)
4	4.4		
8	6.9	8	6.0
16	9.3	16	8.0
32	11.6	32	10.1
64	13.9	64	12.2

in all ratios. The diameter of the poly(propylene imines) varies from 9 to 28 Å (table 1.1), going from the first to the fifth generation. With these structures the nanoscopic chemistry region is therefore entered.

Their multifunctionality makes dendrimers also very interesting molecules from an organic chemists point of view. A broad range of modification reactions has been performed onto the poly(propylene imines)[15,19,42c]. It is demonstrated that simple quantitative reactions are best suited to obtain fully modified structures.

The development of large scale dendrimer syntheses marks a shift of interest in dendrimer research in the past four years. Not merely synthetic procedures are important, but the dendritic properties and applications have become intensively studied. Chiral dendrimers[16], liquid crystalline structures[17], dendrimers with catalytic sites[18] and the dendritic box[19] are just a few examples of the broad development[20] that has taken place. In this introduction three subjects that are of interest for this thesis, will be reviewed in more detail, namely new molecular architectures, based on the combination of polymers and dendrimers, micellar properties of dendrimers, and the role of dendrimers in supramolecular chemistry.

1.4 Dendrimers and supramolecular chemistry

The well-defined nanometer-sized shape of dendrimers has intrigued researchers to apply these structures as building blocks for supramolecular chemistry. Tomalia[21] even

compares dendrimers of different generations with different elements of the periodic table. Although this seems to be a little exaggerated, combining dendrimers of different sizes in a superstructure can lead to systems that resemble CPK-molecular models. However, at this moment only a few examples are known of the use of dendrimers in non-covalently bound structures.

Watanabe and Regen[22] have shown that it is possible to build up dendritic multilayers with amine-functionalized PAMAM-dendrimers. A monolayer is adsorbed onto a Pt^{2+} bearing surface. This monolayer is coated with K_2PtCl_4 and the following dendritic layer can be built up. These multilayers have been studied with XPS and AFM and applications have been proposed as well-defined phases for gel-electrophoresis.

One of the earlier examples of supramolecular organization of dendrimers is given by Newkome[23]. The arborol of figure 1.4 forms a gel in water, due to the lipophilic interaction of the alkyne parts of the molecules. The gel is made up of single-stranded, rodlike structures. No helical morphology can be observed. Applications which are thought of, are the creation of lipophilic domains for performing reactions or for enclosure of organic molecules. Grubbs[24] has already used the lipophilic dendritic environment for this purpose. He has performed an emulsion polymerization of styrene, vinyl acetate, methyl acrylate and acrylonitrile inside a PAMAM-dendrimer. Only for styrene a demixing occurs of the formed polymer and dendrimer. The other hybrid materials can't be separated by extraction.

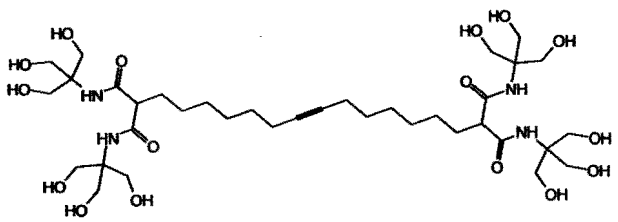


Figure 1.4: *Arborol structure, capable of gelation in water*[23].

Newkome[25] has connected two of his dendrimers by non-covalent bonding *via* a terpyridine-ruthenium-complex (figure 1.5), in a so-called key and lock principle. He has used a variety of different generations and has studied them with NMR, MALDI-TOF and cyclic voltammetry.

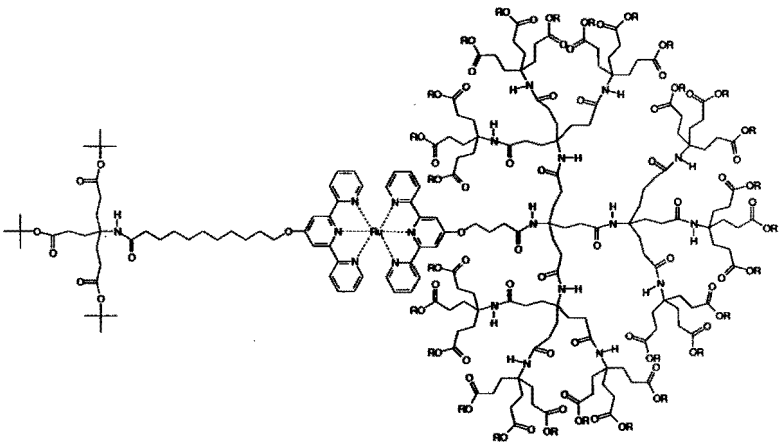


Figure 1.5: *Key and lock principle of Newkome*[25].

The building blocks themselves can be well characterized, but the complex itself, using dendrimers of the second and third generation, proves to be instable under MALDI-TOF analysis conditions. Cyclic voltammetric measurements of the different complexes show that with increasing generation the oxidation of the ruthenium-complex becomes irreversible.

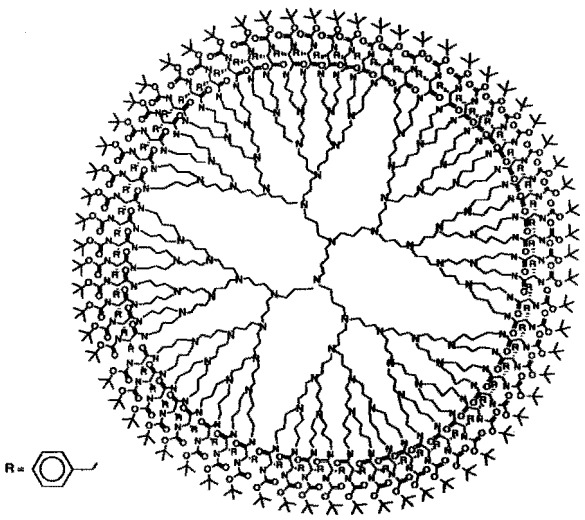


Figure 1.6: *The dendritic box*[19,26].

A final example of supramolecular complexes made up out of dendrimers, is the dendritic box (figure 1.6)[19,26]. By performing an amidation reaction with the active ester of N-*t*-Boc protected L-phenylalanine onto DAB-*dendr*-$(NH_2)_{64}$, a solid shell is built around the dendrimer. Molecules that are inside the dendrimer at the time that the shell is constructed, and that are large enough, are physically encapsulated and can only be released by removal of the shell. It is possible to lock in an integer number of guests: four molecules with a size comparable to Bengal Rose are enclosed. By partial removal of the shell, selective liberation of smaller guests is possible. The dendritic box can be regarded as a threedimensional equivalent of a crown ether, and has the ability of enclosing polar organic molecules and making them compatible with apolar environments.

Research in the area of dendrimers and supramolecular chemistry has only just started, and already has excited researchers about the great possibilities of using these well-defined macromolecules for building up nanoscopic architectures. This can be a direction to which dendrimer chemistry will be focused in the near future.

1.5 Polymers and dendrimers

New, interesting architectures can be obtained when linear polymer chains are combined with dendrimers. There are three general approaches described in literature: a) polymers with dendritic side chains, b) block copolymers of linear polymers and dendrimers and c) the use of linear polymers as dendritic building blocks. These three classes will be discussed in this paragraph.

Dendritic side chain polymers

When dendritic side chains are introduced along a polymer backbone, rodlike topologies are formed, instead of globularly shaped dendrimers. These new topologies can have their advantages, because the globular symmetry has disappeared, and rodlike dendrimers can therefore be used in applications where anisotropy is an important feature, as for example liquid crystalline materials.

The first report of dendritic side chain polymers was made by Tomalia in 1990[4a]. In his review paper he describes the use of linear poly(ethylene imine) as core molecule,

containing 300 to 400 functionalities. Rodlike dendrimers with a high aspect ratio are observed for the third and fourth dendrimer generation. Unfortunately, experimental details about this procedure have never been published.

Recently, Schlüter[27] has described the use of the rigid rod polymer poly([1.1.1]-propellane) as backbone for the synthesis of cylindrical dendrimers. The backbone contains MOM-protected hydroxyl-functions, which after deprotection can be coupled with Fréchet-type of dendritic wedges. Only some preliminary results have been published. For the second generation dendrimers a coverage of only 50-60% can be achieved. This seems to be caused by the coupling reaction and not by steric hindrance.

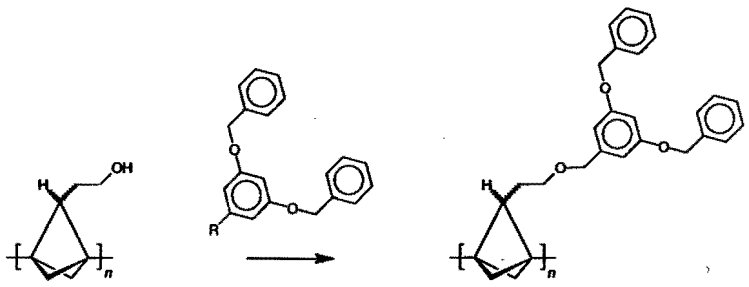


Figure 1.7: *[1.1.1]-Propellane-based dendrimers*[27].

Instead of performing a dendrimer synthesis onto a polymer, it is also possible to (co)polymerize dendritic macromonomers. The first example was given by Hawker[28], who copolymerized styrene with a macromonomer, containing a fourth generation polyether dendritic wedge. No difficulties were found in incorporating up to 40 w% of macromonomer into the polymer. However, due to the large difference in molecular weight between the used monomers, 40 w% is still rather low on a molar base.

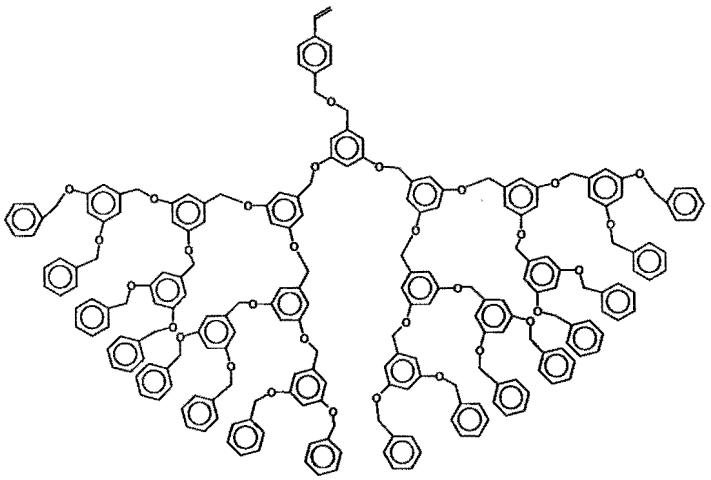


Figure 1.8: *Dendritic macromonomer: fourth generation Fréchet-type dendrimer [G-4]*[28].

A dense packing of dendritic side chains along the backbone will therefore not occur, and no cylindrical topology is to be expected. Ritter[29] homopolymerized dendritic monomers (figure 1.9 a,b and c) with chiral groups. The products showed an ill-defined, broad molecular weight distribution by comparing mass spectrometry and GPC techniques.

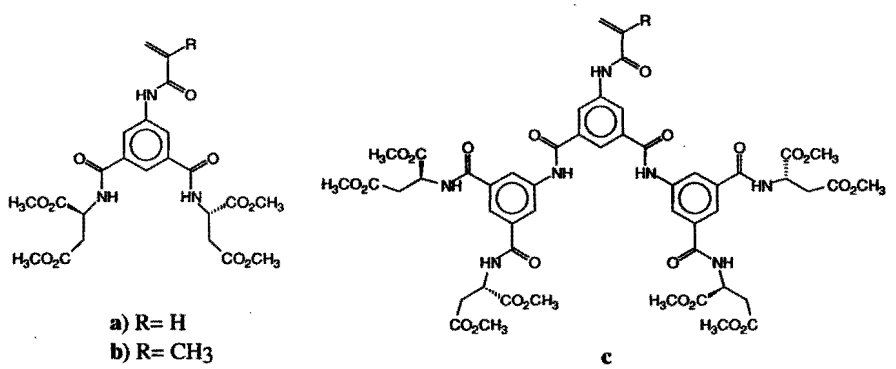


Figure 1.9: *Dendritic monomers, as developed by Ritter*[29].

The route to cylindrical dendrimers proves to be a challenging and difficult one. A dense packing of dendritic wedges along the backbone causes steric hindrance in polymerization processes, and well-defined characterization of the products also seems to be a problem.

b) Hybrid linear-dendritic block copolymers

There are two ways to prepare block copolymers out of linear and dendritic structures. The first method consists of building up one block onto the other. Gitsov[30] has elegantly used a dendritic polyether wedge as initiator for the polymerization of ε-caprolactone. This system works very well; block copolymers with narrow molecular weight distributions are obtained, and the initiator efficiency seems to be close to 100%. The bulky dendrimer furthermore has the advantage of temporarily shielding off the active centers and preventing backbiting reactions. Chapman[31] works the other way around: he builds up a poly(lysine) dendrimer *via* a divergent synthesis onto a poly(ethylene oxide) chain. Because of the large difference in polarity between both blocks, amphiphilic behavior of these so-called hydraamphiphiles is observed. These structures aggregate in water, and a CMC can be determined of about 10^{-4} mol/l. The lipophilic dye orange-T shows an enhanced solubility in water in the presence of this block copolymer.

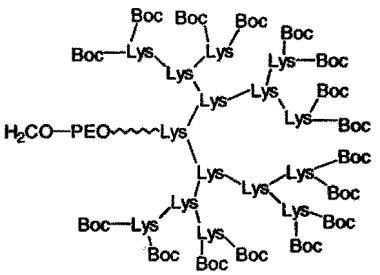


Figure 1.10: *Hydraamphiphiles*[31].

The second way of preparing block copolymers consists of a direct coupling of a linear polymer to a dendrimer, and is studied in great detail by Fréchet et al.[32]. The best examined combinations are the polyether dendrimer-poly(ethylene oxide) (PEO) block copolymers. Diblock copolymers, telechelics and alternating block copolymers have been prepared in high yields. Two coupling techniques are applied: the first method uses a methyl ester function of the dendrimer for the coupling with the hydroxy end group of the PEO chain. This reaction proceeds in the melt at 0.03 mm Hg, with the addition of Co(II) acetate tetrahydrate. The second preparation method comprises a Williamson synthesis, in which a benzylbromide-functionalized dendrimer is coupled to the alkoxide of PEO, in acetone at reflux temperatures, using K_2CO_3/18-crown-6. The bulky dendrimer doesn't disturb the coupling. For ABA block copolymers the reaction rate even increases with increasing generation when the second dendrimer has to be coupled to the PEO, probably due to improved solubility of the PEO block.

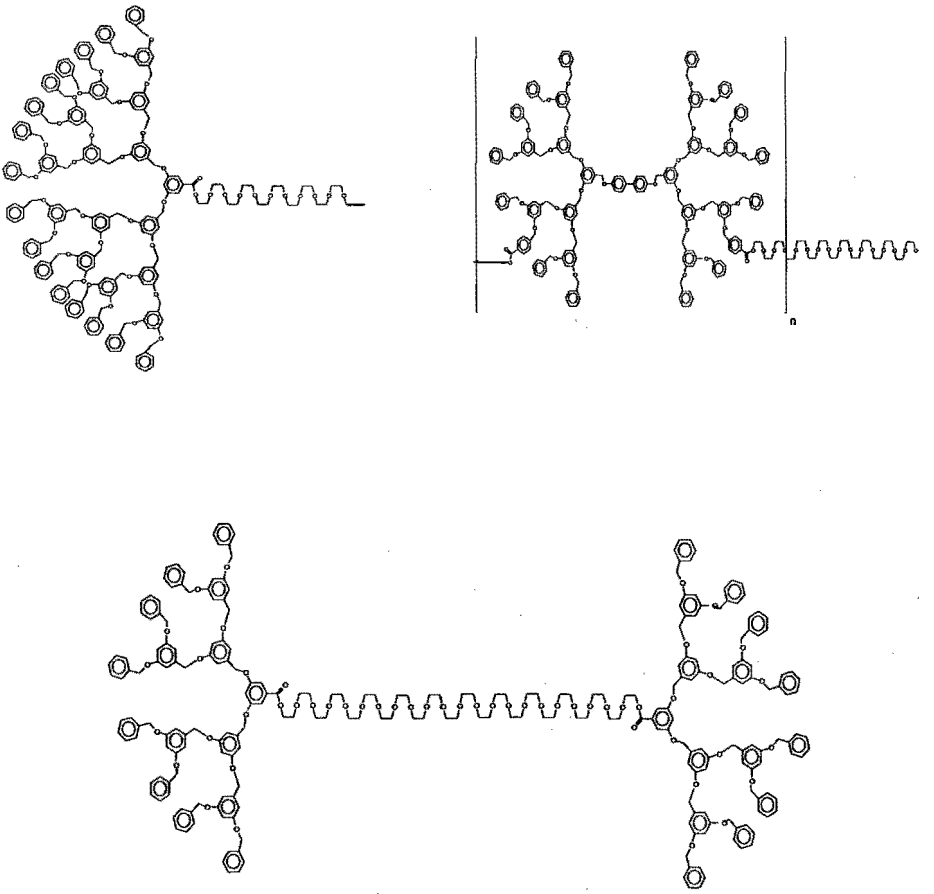


Figure 1.11: *PEO-dendrimer block copolymers*[32].

Thermal analysis of ABA block copolymers, in which A stands for a polyether dendrimer of the fourth generation, shows that when the dendrimer is in excess, the blocks mix, whereas when the linear PEO is in excess, phase separation occurs due to crystallization of PEO. Solubility behavior of AB block copolymers is studied in water/MeOH, which is a solvent for PEO and a non-solvent for the dendrimer. When the PEO block is long enough, solubilization of the entire molecule is possible, probably due to the formation of unimolecular micellar structures. For ABA type of block copolymers an optimal balance is required between dendrimer size and PEO chain length to obtain soluble structures in

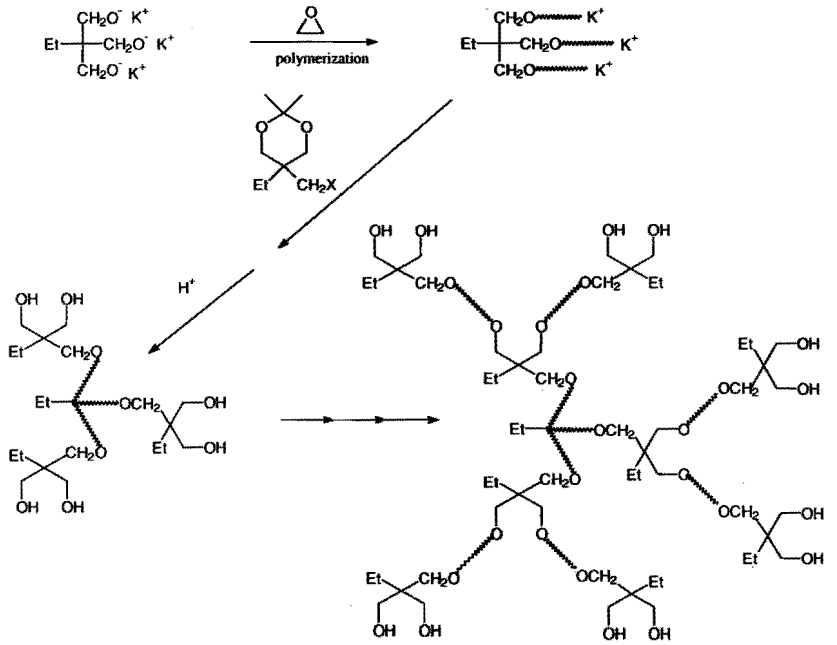
water/MeOH. With size exclusion chromatography (SEC) two signals are observed for ABA block copolymers. This result is ascribed to the formation of stable multimolecular micelles. In THF no aggregation can be observed. The interactions of these block copolymers with solvent is also noticed from different solid state morphologies of films cast from different solvents.

Instead of PEO also polystyrene is used as linear part in di- and triblock copolymers[33]. The preparation consists in both cases of an end-cap reaction of living polystyryl anions with a dendrimer with a bromide function. In case of the triblock system, the difunctional living polymer is first end-capped with 1,1-diphenyl ethylene to make the anion less nucleophilic, before quenching is performed with the dendritic bromide. For these structures remarkable SEC behavior is observed, because the M_n of the polystyrene homopolymer doesn't differ from the M_n of the triblock copolymer. This indicates that the universal calibration curve can't be applied for this type of hybrid block copolymers.

The incorporation of dendrimers into block copolymers is possible *via* a variety of techniques. The combination of globularly shaped structures with linear ones can give rise to new architectures. Until now, the first results indicate that by varying chain length and dendrimer size, properties of the structures can be influenced tremendously. Interesting applications can be expected from this new class of block copolymers in the area of emulsifiers and stabilizers of two-phase systems and polymer blends.

c) Linear polymers as dendritic building blocks

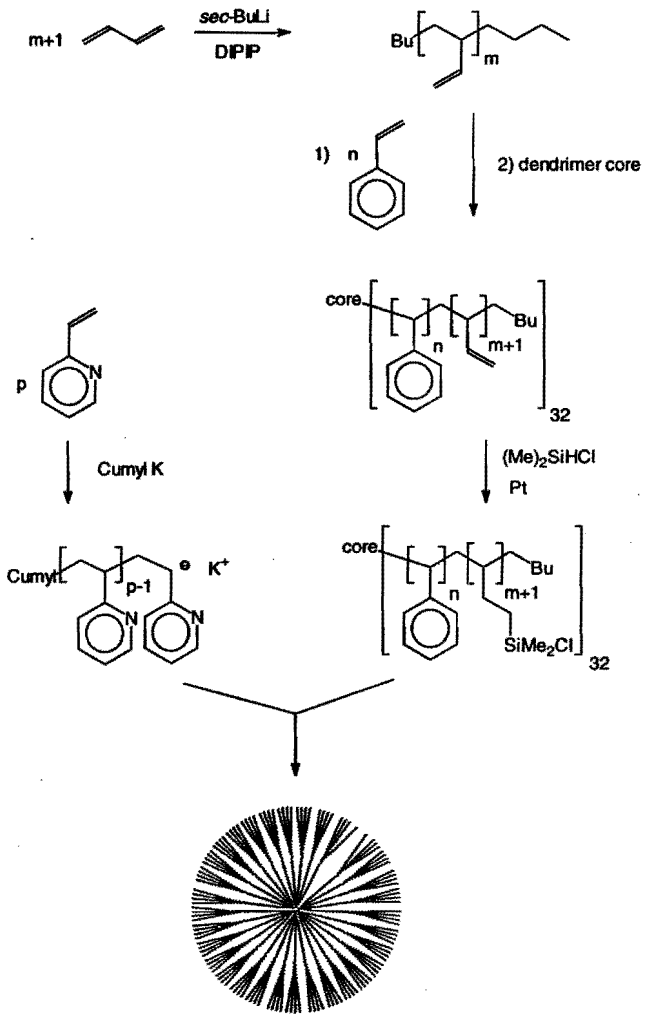
The use of linear polymers as building blocks in dendrimers is an area of research hardly explored. In literature only one true example can be found. Six[34] has reported PEO-dendrimers up to the third generation. The synthesis is depicted in scheme 1.4.



Scheme 1.4: *Reaction route to PEO-dendrimers. -X stands for -Cl, -I or -OTs*[34].

Using a trialkoxide as initiator for the polymerization of ethylene oxide, a three-arm polymer is obtained. Endcapping with the ketal, followed by deprotection of the alcohol groups, results in a doubling of the number of end group functionalities, and a second polymerization can be performed. The first generation three-armed star can be characterized without difficulty. The second and third generations, however, are more troublesome: linear polymers are found as impurity and, due to the structural branching, molecular weight determination is ambiguous.

Another example that is related to the incorporation of linear polymers into dendrimers is the umbrella block copolymer as synthesized by Roovers[35] (scheme 1.5).



Scheme 1.5: *Reaction route to umbrella block copolymers*[35].

Polymerization of butadiene in the presence of dipiperidino ethane results in living poly(vinyl ethylene), on which a block of polystyrene is grown. The living polystyryl chains are end-capped by a carbosilane dendrimer with 32 end groups. The vinyl groups are hydrosilylated, and used as end-capper for living poly(2-vinyl pyridine), resulting in the desired architecture.

Problems occur in fully modifying the dendrimer, and only 25 out of 32 end groups have reacted. Stability of the living polymers used is a second problem.

Examples of the use of linear polymers in hyperbranched structures are found in the work of Tomalia and Möller[36]. These so-called combburst or arborescent graft polymers of Tomalia are prepared by the attack of the living chain end of cationically polymerized poly(ethyloxazoline) onto the secondary amines of a linear poly(ethylene imine) chain. After the conversion of the poly(ethyloxazoline) side chains in poly(ethylene imines), this grafting reaction can be repeated and a hyperbranched, high molecular weight material is obtained. Möller uses living polystyrene, prepared by anionic polymerization, for his graft reaction onto chloromethylated polystyrene. The second step is the chloromethylation of the side chains, which makes the construction of a hyperbranched material possible.

In the near future probably more examples are to be expected in this field, because the advantages of these structures compared to other dendrimers, are their size enlargement and their closer resemblance with star-shaped and branched polymers. Their synthesis and characterization will however be even more cumbersome than for the earlier mentioned combinations of polymers and dendrimers.

1.6 Micellar behavior of dendrimers

Amphiphilicity is one of the best studied properties of dendrimers and has been already partly discussed in the previous paragraph for polymer-dendrimer hybrid block copolymers. In this paragraph comparison studies of dendrimers with other systems will be described with regard to amphiphilicity. The surface activity of a hydroxyl-functionalized polyether dendrimer and polystyrene with a hydroxy end group have been compared at the air/water interface[37]. Both systems show a similar dependence of the pressure isotherms on molecular weight.

The topology with which dendrimers are most often compared, however, is the globular micellar structure. Both dendrimers and micelles in most of the cases have globular shapes and a difference in polarity between interior and periphery. A dendrimer can be regarded as a covalently bound micelle, with the advantage of stability and the absence of a CMC. The first to recognize this similarity with micelles was Newkome[3], who in 1985

already proposed the micellar application of dendrimers. In a number of papers[38] he describes the synthesis of water-soluble micellanoates, alkyl-dendrimers with carboxylate end goups (figure 1.12).

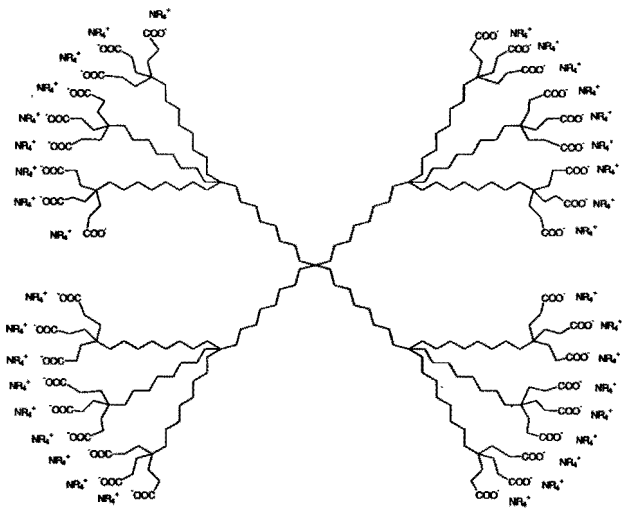


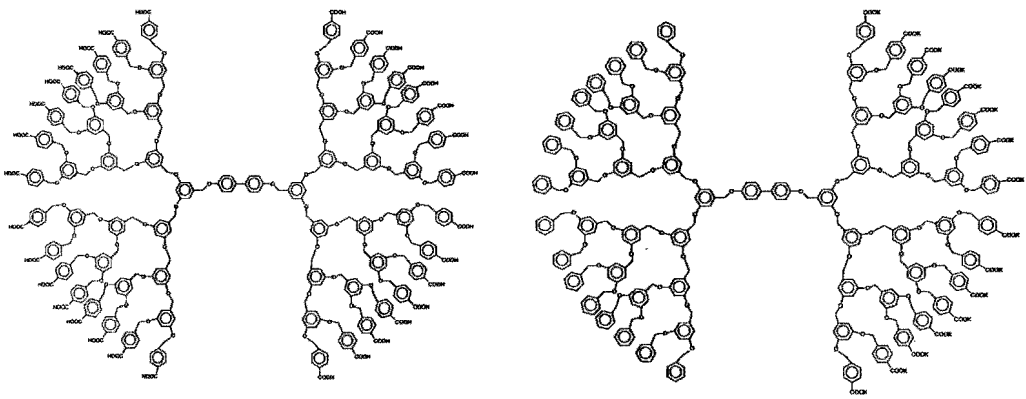
Figure 1.12: [8^2-3]- *micellanoate of Newkome*[38].

Proof of micellar behavior is obtained by solubilization experiments with a variety of probes. Chlorotetracycline only shows fluorescence in aqueous solution in the presence of the [8^2-3] micellanoate. Phenol blue and pinacyanol chloride show a shift in λ_{max}, which is characteristic for solubilization in micelles, when the micellanoate is added. A CMC can not be detected, and has therefore to be smaller than $4 \cdot 10^{-7}$ M. For other types of dendrimers, with basic, neutral and acidic end groups (figure 1.2, compounds a, b and c), the pH-dependence of the hydrodynamic radius is determined with DOSY measurements. As expected, a decrease in radius for the acid-functionalized and an increase for the basic dendrimer can be observed at lower pH; the neutral structure has a pH-independent behavior. Chemistry inside a precursor of a dendritic micelle has recently been reported: decaborane units have been coupled to alkyne moieties in the interior of the dendrimer.

Comparison has also been made between micelles and the PAMAM dendrimers[39]. From luminescence quenching studies of $Ru(phenanthrene)_3^{2+}$ and fluorescence studies of pyrene in the presence of different generations of carboxylate functionalized PAMAMs, it can

be concluded that from generation 3.5 on, dendrimers show similar behavior as micelles, whereas the lower generations are open structures and comparable to simple electrolyte solutions.

For Fréchet type of dendrimers[40], with the probe 4-N-methylamino-1-nitrobenzene covalently bound in the core of the molecule, a discontinuity is observed in the change of λ_{max}, going from generation 3 to 4. For the higher generations the probe is shielded off from the solvent and a microenvironment, comparable to the interior of micelles is formed.



a **b**

Figure 1.13: *Micellar, Fréchet type polyether dendrimers*[41].

Carboxyl-functionalized dendrimers (figure 1.13 **a** and **b**) have been prepared[41].The water solubility of **1.13a** increases tremendously when the acid functions are deprotonated. Compound **1.13b** proves to be insoluble in either CH_2Cl_2 and water, in which the parent dendrimer halves are soluble. By agitating this compound in a mixture of both solvents, a stable emulsion is formed, indicating the surface activity of **1.13b**. With **1.13a** solubilization experiments are performed, using as probes amongst others pyrene and 2,3,6,7-tetranitro fluorenone. An increase in solubility in water is found of a factor 58 for pyrene and even 265 for the fluorenone derivative. The strongly increased solubility is, besides the availiable apolar environment, explained by π-π interactions. A linear relationship is obtained for the concentration of pyrene versus the concentration of dendrimer. No CMC can be detected and solubilization already occurs at a dendrimer concentration of $5 \cdot 10^{-7}$ M. With this dendrimer it

is proven to be possible to extract pyrene from water and releasing it in an organic solvent. The dendrimer is recyclable during this process and this can open possiblities for using dendrimers as extracting agents.

One application that has proven to be successful for different types of dendrimers (PAMAMs, poly(propylene imines) and arborols), is dendritic electrokinetic chromatography[42]. For the PAMAMs only lower generations are studied and therefore the capacity factor of these systems is much smaller compared to SDS micelles. Separation of a mixture of aromatic compounds is possible and can be performed best for the carboxylate functionalized dendrimers at high pH. The acid-functionalized poly(propylene imine) DAB-*dendr*-$(COOH)_{64}$ shows a different separation pattern for a mixture of organic compounds, when compared to SDS-micelles.

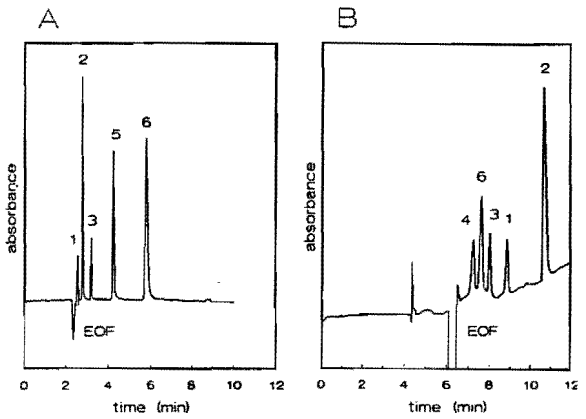


Figure 1.14: *Electrokinetic chromatograms of the separation of (1) hydroquinone, (2) resorcinol, (3) phenol, (4) benzyl alcohol, (5) o-cresol and (6) 2-xylenol in an electrolyte system containing (A) 0.05 M SDS, and (B) 0.002 M DAB-dendr-*$(COOH)_{64}$[42c].

This is also observed for the PAMAM-dendrimers and can be explained by a different interior of the SDS-micelles and the more hydrophilic dendrimers. For DAB-*dendr*-$(COOH)_{64}$ it is found that between pH 7-9 the structures resemble the mobility of SDS-micelles. The arborol system has been used to separate 4-hydroxybenzoate alkyl esters. With increasing generation elution times become longer and signals are broader.

As has become obvious, the amphiphilic properties of dendrimers have been studied extensively. Their resemblance with micelles has been proven with solubilization experiments. Their properties are dependent on generation and in most cases also on pH. Because of the absence of a CMC and the ability of solubilizing even at very low concentrations, dendrimers can have interesting future applications in colloid chemistry and physics.

1.7 Amphiphilicity

Amphiphilicity is a property observed for a large amount of materials. A lot of effort has been put into the understanding of aggregation and amphiphilic behavior of low molecular weight surfactants, polysoaps and amphiphilic block copolymers[43]. Due to the complexity of the amphiphile systems, however, general theories are still under development. It is also very difficult to apply for example theoretical models for surfactants onto polymeric systems. The difference in size and shape is in many cases too big. Furthermore polymer systems are often less well-defined than surfactants.

It is recognized that one of the ways to obtain a better understanding of general amphiphilic features, is the synthesis of new structures. Menger[44] states that: "Experimental work on micellar structure has now plateaued. Simply put, it is becoming more and more difficult to extract fundamentally new structural information on [sic] conventional systems. Two strategies are available to counter this problem: (a) one can develop new instrumentation (..) and (b) one can synthesize new surfactants, especially ones with unusual structural elements (..)". In the area between organic and polymer chemistry, there is a need for well-defined amphiphile systems. As is shown in the previous paragraph, dendrimers seem to be one class of compounds that can be excellently used for this purpose.

1.8 Scope of the thesis

The aim of this thesis is to use the unique properties of dendrimers, in particular the poly(propylene imines), for the construction of new molecular architectures. When a poly(propylene imine) dendrimer is connected to an apolar polystyrene chain, a new type of

amphiphilic molecules is prepared. These structures resemble traditional amphiphilic block copolymers with respect to size, but show similarity with low molecular weight surfactants, regarding geometry. The versatility of these molecules is located in the dendritic head group, of which size and polarity can be varied. It is these kind of structures that can contribute to a better understanding of amphiphilic and aggregation behavior.

Amphiphilicity is also the key-word for the second molecular architecture. By constructing an apolar alkyl shell around a poly(propylene imine) dendrimer, an inverted unimolecular micelle is obtained. These molecules are particularly interesting because of the absence of a CMC, and applications are to be found in host-guest chemistry.

The concept of the dendritic box is a versatile one. Up to now, guests that are locked in are completely encapsulated. The next step in the development is a structure of which both guest and box determine the topology. This can be achieved by locking in end groups of polystyrene chains, thereby binding the chains to the dendrimer. This new method of constructing star polymers, entirely based on mechanical locking, can result in a new building concept in supramolecular chemistry.

The synthesis and characterization of well-defined polystyrene-poly(propylene imine) dendrimer diblock copolymers is the subject of chapters 2 to 4. Chapter 2 deals with the preparation of a well-defined polystyrene core molecule, *via* the anionic polymerization technique. Several end-cap and functionalization methods are discussed. An indirect modification procedure results in primary amine-functionalized polystyrene, which can be used to build up a poly(propylene imine) dendrimer. The application of this divergent dendrimer synthesis onto polystyrene is the subject of chapter 3. A 10-step procedure is required to build up a block copolymer with a dendrimer structure with 32 primary amine end groups. The amphiphilic and aggregation behavior of this new series of block copolymers is discussed. In chapter 4 two modification reactions are performed onto the block copolymers of the previous chapter. Acid hydrolysis of the nitrile intermediates leads to pH-dependent, acid-functionalized structures. Methylation of the amine derivatives results in a polycationic dendritic compound. The effect of both modifications on amphiphilicity is described.

In chapter 5 the modification reactions of the poly(propylene imine) dendrimers with alkyl chains is investigated. The obtained structures show inverted unimolecular micellar

behavior. The compatibility of polar dyes with apolar solvents is strongly increased in the presence of the dendrimers.

Chapter 6 describes the approach toward a non-covalently bound polystyrene-dendrimer complex. The concept of physical encapsulation of guests in the dendritic box is used to lock in fluorescein groups that are linked *via* a spacer to a polystyrene chain. Complexes have been prepared, consisting of four polystyrene chains and one dendritic box, as based on UV-VIS and fluorescence measurements.

1.9 References and Notes

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Chapter 2

Anionic polymerization of styrene and the functionalization of polystyrene

Summary

The anionic polymerization technique was used to prepare well-defined amine-functionalized polystyrene (PS), which could be used as core molecule in the divergent poly(propylene imine) dendrimer synthesis. Using standard end-cap reactions with ethylene oxide and CO_2, the livingness of our polymerization system was confirmed. However, only with CO_2 it was possible to perform quantitative functionalization. Because direct amination procedures proved to be unsuccessful, an indirect amination route was developed. Cyanoethylation of PS-OH, followed by hydrogenation, resulted in the desired PS-NH_2 in high yields. The cyanoethylation step was a modification of a procedure developed by Percec[17] for nitrile-functionalized poly(isobutylene). PS-COOH itself was a versatile intermediate, not only in the reduction to PS-OH, but also in esterification and amidation reactions. Finally, a multifunctional core molecule was prepared, based on the end-cap reactions of polystyryl-lithium with a 1,1-diphenyl ethylene derivative. Although interesting behavior was observed, the desired high functionalization yields could not be obtained.

2.1 Introduction

For the preparation of polymer-dendrimer block copolymers, several methods can be applied[1], which have been reviewed in chapter one. Except for the preparation of hydraamphiphiles[1f] all of these routes are based on a one-step coupling procedure between

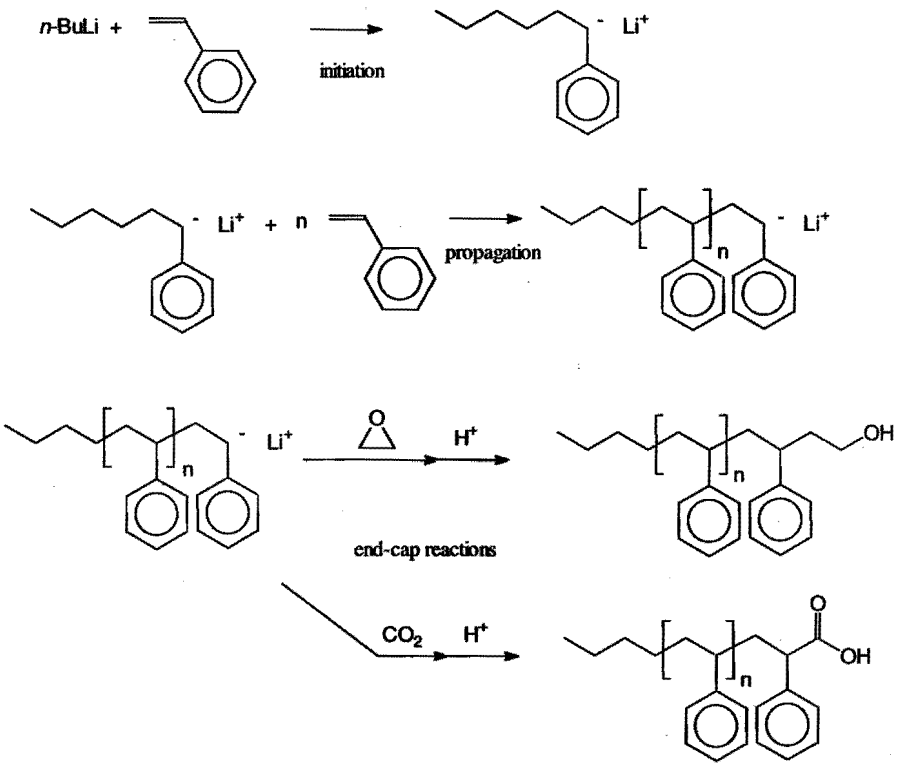
polymer and dendrimer. Because we are interested in polystyrene (PS) -poly(propylene imine) dendrimer diblock copolymers of all dendrimer generations, the most practical approach in our case is the multistep divergent dendrimer synthesis onto a PS-core molecule. Therefore, a method of preparation is required for well-defined amine-functionalized PS. Not only mono- but also multi-amine-functionalized PS is of interest. Though the latter is more difficult to obtain, it has the advantage, compared to mono-amine PS, of fewer dendrimer reaction steps onto PS, to achieve the same number of functional end groups. A polymerization method has to be chosen, therefore, which makes it possible to synthesize these desired core molecules.

In the field of polymer chemistry, research has been directed over the years toward control over polymerization. Polymers with a well-defined tacticity e.g. can be prepared using Ziegler-Natta or metallocene catalysts[2]. Control over molecular weight, polymer dispersity and end group functionalization has been the working area of the living ionic, and recently living radical, polymerization systems[3]. Of the different methods, the anionic polymerization has become the most fully developed and best understood technique[4] for the preparation of monodisperse polymers, and has even found commercial applications.

The anionic polymerization proceeds according to a 3-step process of initiation, propagation and termination. Strong bases as *n*-butyllithium and *sec*-butyllithium can be used as initiator. They react with monomers as styrene, butadiene and acrylates, that are capable of stabilizing the anionic charge, and can carry on the polymerization. Polymerizations are performed in non-protic solvents like cyclohexane or THF, and in an inert atmosphere or under high vacuum. When O_2, CO_2 and proton sources are excluded, termination doesn't take place and the growing chains stay active, or living. The molecular weight can be controlled by the ratio of monomer to initiator. The polymer dispersity follows a Poisson distribution, when care has been taken that initiation is fast compared to propagation. The living end groups can be modified by end-cap reactions, resulting in the introduction of functional end groups.

Although a lot of effort has been put in finding new end-cap reactions[4b,5], only two of them are widely used for PS, namely the introduction of a hydroxyl function with ethylene oxide[6] and a carboxylic acid end group with CO_2[7]. Very difficult are direct modifications toward halogen or primary amine chain ends[4b,8,14]. For the latter it is a prerequisite to protect

the primary amine function in order to prevent proton abstraction of the amine by the living ionic end group.



Scheme 2.1: *The process of anionic polymerization, including end-cap reactions with CO_2 and ethylene oxide.*

Recently several end-cap molecules have been described that seem to be promising[9]. Both Ueda and Peters report the use α–halo-ω-amino alkanes as effective end-cappers. In the case of the Ueda-system a silyl bridge is used as protective group (figure 2.1a), Peters applies an N-*bis*-trimethylsilyl group (figure 2.1b).

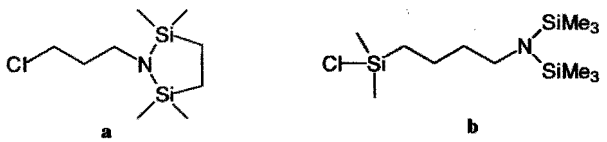


Figure 2.1: *a) 2,2,5,5-tetramethyl-1-(3-chloropropyl)-1-aza-2,5-disilacyclopentane; b) N,N-bis(trimethylsilyl) aminobutyl chlorodimethylsilane.*

Another versatile method of introducing a functional end group is based on the 1,1-diphenyl ethylene derivatives[10]. Only one molecule of 1,1-diphenyl ethylene is attached to the chain end, and a new, less reactive ionic end group is obtained. This reaction can be performed quantitatively, and is used in the synthesis of diblock copolymers, where the polymerization of the second block requires a less active ionic chain end. The phenyl rings offer the opportunity of introducing a broad range of functionalities and Quirk et al. have shown the possibility of modification with e.g. hydroxyl and aniline functions[11] (figure 2.2).

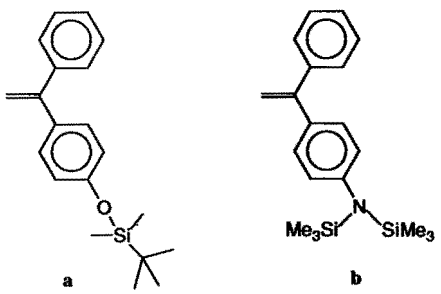


Figure 2.2:*a) 1-(4-t-butyldimethylsiloxyphenyl)-1-phenylethylene;b)1-[4-[N,N- bis(trimethylsilyl) amino]phenyl]-1-phenylethylene.*

In this chapter the synthesis of well-defined, functionalized PS is described *via* the anionic polymerization technique. This PS can be used as core molecule in the preparation of well-defined diblock copolymers of PS and poly(propylene imine) dendrimers. When PS is used as core molecule, it is necessary to introduce a primary amine end group. To achieve this goal, direct amination reactions were investigated. An indirect amination route was developed

starting from acid- or hydroxyl-functionalized PS. The last paragraph deals with the synthesis of a multifunctional core molecule, by end-cap reactions based on a 1,1-diphenyl ethylene derivative.

2.2 End-cap reactions with ethylene oxide and CO_2

A living polymerization has as requirement that the number of reactive end groups remains constant during and after reaction. One of the best ways to investigate the living nature of the polymerization is an end-cap reaction with quantitative functionalization as a result. Two standard methods, modification with ethylene oxide and CO_2 give the opportunity of investigating the polymerization system and introducing a functional end group. After confirmation of the living character, new end-cap molecules can be tested on their functionalization capabilities.

The following polymerization set-up was used: glassware was dried under vacuum and rinsed with predried argon. Toluene was used as solvent, with 0.6 vol% of THF added to deaggregate *n*-butyllithium, which was used as initiator. Styrene was used as monomer, and the polymerizations were performed under argon atmosphere. Several end-cap procedures were investigated with ethylene oxide: *i*) ethylene oxide was introduced as a gas without drying, *ii*) it was titrated with 1.6 M *n*-butyllithium, distilled and siphoned into the system, *iii*) a stock solution was made of ethylene oxide (distilled over CaH_2, titrated with 1.6 M *n*-butyllithium and redistilled) in toluene, of which 4 equivalents of ethylene oxide were injected into the system. The results are presented in table 2.1. The degree of functionalization was determined by a column chromatographic separation of PS and PS-OH. No quantitative modifications were obtained.

Table 2.1: End-cap reactions performed with ethylene oxide

Method	THF (vol%)	M_n (kg/mol)	M_w/M_n	% OH
i	0.6	5.05	1.05	70
ii	0.6	3.13	1.09	30
iii	0.6	3.33	1.03	50
i	0	2.86	1.06	50
i[a]	0	3.18	1.07	70

[a] *reaction performed in pure cyclohexane.*

The livingness of the polymerization was checked by titration of the polystyryl anion solution with *n*-butanol, which showed a constant number of active end groups for a period from 15 minutes to more than 2 hours after initiation. End-cap procedures with CO_2 according to literature[7], in which a 25 vol% THF solution was added to the reaction system before end-capping with CO_2, showed on TLC the formation of dimeric product, as a result of reaction of two ionic polystyryl chain ends with the same CO_2-molecule (figure 2.3).

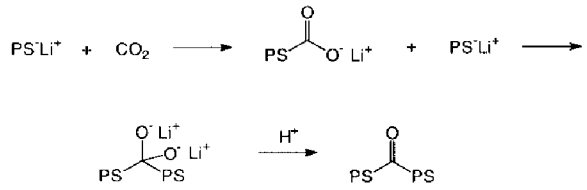


Figure 2.3: *Dimer adduct formation during end-cap reaction with CO_2.*

Siphoning the reaction mixture into a THF solution, saturated with CO_2 made it possible to obtain >95% to quantitative functionalization degrees, on basis of column chromatographic separation of functionalized and non-functionalized PS, and ^{1}H-NMR. No dimeric products were obtained using this procedure. This end-cap procedure was not only performed on 20 gram-scale but also on 100 gram-scale. Therefore, a new polymerization set-

up was built (picture 2.1). In this case styrene and cyclohexane were purified using column chromatographic techniques. A 2.5 bar purified N_2 atmosphere was applied. *sec*-Butyllithium was used as initiator instead of *n*-butyllithium. The change to *sec*-butyllithium for this scaled-up process was a result of the amounts of initiator used. It wasn't possible to inject 20 ml of initiator instantaneously, and the longer initiation period resulted in a broader MWD. This problem could be solved by preventing the use of THF. Without THF the propagation rate was lower. *n*-Butyllithium could not be used, however, because of the hexameric aggregation form in which this molecule is present in non-polar solvents without THF. This aggregation also results in broadening of the MWD. With *sec*-butyllithium this problem didn't occur. The end-cap procedure with CO_2 remained the same. High functionalization degrees, and narrow MWD's (1.05) were obtained over a molecular weight range of 1500-20.000 g/mol.

The lack of quantitative functionalization with ethylene oxide is remarkable. It can't be an effect of the non-livingness of the polymerization. Titration indicates a constant number of active end groups over a broad period of time, and end-cap reactions with CO_2, using the same polymerization set-up, are successful. An impurity in ethylene oxide can also be ruled out, because of the extensive drying procedures, without any improvement. Also the fact that with isoprene it was possible to perform a quantitative end-cap reaction with ethylene oxide in the same experimental set-up and using ethylene oxide from the same source, contradicts the presence of an impurity[12]. No effect can be noticed from varying end-cap temperature and solvent, or time between initiation and termination, therefore there is no evidence for the existence of an equilibrium between functionalized and non-functionalized chains. Because of the possibility of separation of PS and PS-OH by column chromatography, this end-cap procedure still can be used in obtaining the desired functionalized PS.

End-capping with CO_2 results in quantitatively functionalized PS (PS-COOH), but only when literature procedures are not followed. Because of aggregation of polystyryl-ionic chain ends in solution, a termolecular reaction between CO_2 and two chain ends becomes a serious problem. This aggregation phenomenon has been well recognized in literature[13] and is

partly responsible for the stability of the living polymer solution. A fast exchange between free and aggregated ions makes it possible to obtain well-defined, monodisperse PS. This equilibrium can be shifted by adding a decomplexing solvent as THF to the mixture. However, even addition of 25 vol% THF to the mixture doesn't prevent the formation of dimeric products. The only method that is successful, is siphoning the reaction mixture into a THF solution, saturated with CO_2; the large excess of THF and CO_2 reduces the chance of a termolecular reaction. End-capping with CO_2 has advantages over end-cap reactions with ethylene oxide. First the functionalization degree is much higher. Furthermore the carboxylic acid function is a versatile group that makes it possible to perform a broad range of modification reactions onto PS. Finally, CO_2 is less toxic than ethylene oxide. This is of special importance for scaling up the anionic polymerization set-up.

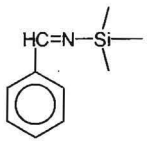
Now that we have the anionic polymerization techniques for polystyrene available, we can investigate the possibilities of introducing a primary amine functionality at the polymer chain end.

2.3 Synthesis of amine-functionalized PS *via* an indirect method

The most direct way to prepare amine-functionalized PS is by a termination reaction of living polystyryl anion with an end-cap molecule that contains a (protected) amine function. However, not many quantitative examples are known from literature. We have investigated two end-cap molecules that should result in a direct introduction of a primary amine end group. N-trimethylsilylbenzaldimine (**2.3**) has been described in literature by two different groups[14,15], and is therefore one of the better studied amine end-cappers. In this case the amine function is protected by the trimethylsilyl group, which can be easily removed under acidic conditions after reaction. The other examined molecule, N-*t*-butoxy-carboxyloxy-(Boc) aziridine (**2.4**), is the amine analogue of ethylene oxide[16]. The reactivity is located in the ring strain, and the amine-function is protected by the Boc-group. The *t*-butyl moiety of the protecting group should prevent attack of the anion at the carbonyl function.

Picture 2.1: *Large scale anionic polymerization set-up.*

The Boc-group is easily removed after reaction, either by employing heat or under acidic conditions.



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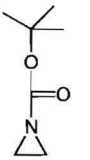


2.4

Figure 2.4: ***2.3****: N-trimethylsilylbenzaldimine;* ***2.4****: N-t-butoxy carboxyloxy aziridine.*

It proved to be, however, not possible to introduce a primary amine function with one of these end-cap molecules. Before investigating direct amination in greater detail[9], we first performed the double Michael addition of methyl acrylate onto the model compound α-methyl benzylamine, which resembled the end group of PS after direct amination, to check its reactivity (figure 2.5). Only when protic solvents as MeOH and Lewis acids as LiCl were used, the reaction could be performed quantitatively. Under conditions more suitable for PS, the reaction was far from complete. The sterically hindered core molecule obtained after

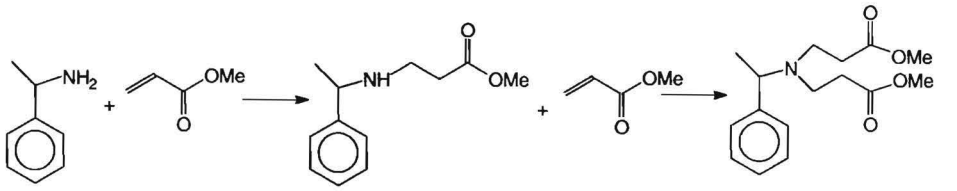
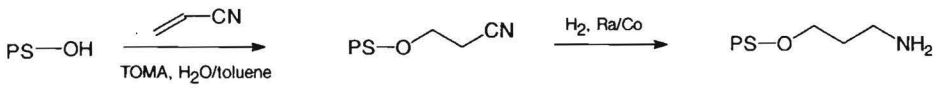


Figure 2.5: *The double Michael addition of methyl acrylate onto α-methyl benzylamine.*

direct amination is therefore less desired, and we have not investigated direct amination procedures in more detail.

To circumvent problems as mentioned for the direct introduction of a primary amine function, we have chosen to use a standard functionalization method and to develop an indirect amination procedure, which is presented in scheme 2.2. Starting from hydroxyl-functionalized PS (PS-OH), a cyanoethylation with acrylonitrile was performed, followed by hydrogenation of the nitrile to a primary amine. The cyanoethylation step in this reaction scheme is a modification of the method developed by Percec for the preparation of nitrile-functionalized poly(isobutylene)[17]. The end-cap reaction toward PS-OH as well as the cyanoethylation have been reported to proceed quantitatively. When the hydrogenation reaction can also be performed without any problems, this indirect approach is an interesting alternative for the direct amination procedures mentioned before.



Scheme 2.2: *Reaction route toward primary amine functionalized PS.*

To investigate the scope of the reaction sequence, polystyrene samples of different molecular weights were prepared, using the end-cap method with ethylene oxide. Instead of hydroxyl-functionalized PS, prepared by this method (PS_A-OH), PS-COOH could be used as starting material as well. The acid function, introduced by end-capping with CO_2, could be reduced with $LiAlH_4$ to alcohol-functionalized PS (PS_B-OH). This reduction was performed quantitatively on polystyrene-acid of M_n varying from 1.5 to $6.0 \cdot 10^3$ g/mol. Data of preparations of both PS_A-OH and PS_B-OH are shown in table 2.2.

Cyanoethylation reactions were performed in a two-phase system of toluene/$NaOH_{(aq)}$, to which a phase-transfer catalyst was added. Toluene was necessary to solubilize PS and the combination of NaOH and phase-transfer catalyst made it possible to introduce a base in the organic phase, that was strong enough to catalyze the Michael addition of acrylonitrile onto

Table 2.2: Hydroxyl-functionalized PS

PS[a]	M_n (g/mol)	M_w/M_n	%COOH[b]	% OH[c]
I	$3.00 \cdot 10^3$	1.04	-	50
II	$5.05 \cdot 10^3$	1.05	-	59
III	$8.07 \cdot 10^3$	1.07	-	53
IV	$3.2 \cdot 10^3$	1.05	>95	99[d]

[a] I-III are prepared by termination with ethylene oxide, IV is obtained by end-cap reaction with CO_2, followed by reduction; [b] determined by TLC and ^{1}H-NMR; [c] percentage determined by column chromatographic separation of PS and PS-OH; [d] based on TLC, relative to the acid function.

the alcohol function. Cyanoethylation reactions were quantitative in 30 minutes time for all tested molecular weights and for both types of PS-OH (table 2.3).

Table 2.3: Cyanoethylation and hydrogenation results of PS-OH

PS	PS-CN yield (%)	PS-NH_2 yield (%)
I	91	89
II	92	92
III	94	100
IV	83	93

Of key importance in this reaction was the use of the combination of NaOH and the phase transfer catalyst trioctyl methyl ammonium chloride (TOMA). Experiments with other base systems such as the organic base DBU, which made it possible to have a homogeneous reaction system, Lewatite resin, which was very successful in catalyzing the cyanoethylation of alcohol-functionalized poly(ethylene oxide), or the phase-transfer catalyst tetra butyl ammonium hydroxide (TBAH) showed very slow and no quantitative reaction (table 2.4). The method based on TOMA was rather robust. The excess of acrylonitrile or the amounts of TOMA and NaOH could be varied over a broad range without changing the reactivity or yield

of the reaction. Only when more than 40 equivalents of NaOH were added, dicyanoethyl ether became a significant by-product and the yield was lowered to 80 %.

A problem occurred during the work-up of the reaction mixture. When the mixture was concentrated before precipitation, polystyrene with M_n = $8 \cdot 10^3$ g/mol showed considerable retro-Michael reaction. By adjusting the procedure and precipitating the mixture directly into methanol, no traces of retro-Michael reaction could be detected. At this point separation of PS, PS-OH and PS-CN was very well possible using flash chromatography.

Table 2.4: Cyanoethylation experiments of PS_A-OH ($3.0 \cdot 10^3$ g/mol)

Base system	Base (moleq)	acrylonitrile (moleq)	Temp (°C)	reaction time (min)	yield (%)
Lewatite resin	0.6 grameq	350	45	2 d	-
DBU	1.1	180	25	8 d	40
DBU	4	20	45	8 d	40
TBAH	1	20	25	1 d	80-90
TOMA/NaOH	1/4	25	25	10	100
TOMA/NaOH	1/2.7	4.5	25	10	95
TOMA/NaOH	1/4	4.5	45	10	90
TOMA/NaOH	0.4/3	24	25	10	95
TOMA/NaOH	0.5/1.2	4.5	25	60	>95
TOMA/NaOH	10/40	4.5	25	10	80

The extent of reaction could easily be followed with TLC, whereas IR, ^{1}H-NMR and ^{13}C-NMR spectra gave unambiguous evidence of the formation of PS-CN, even for the higher molecular weight polystyrenes.

The hydrogenation procedure of the nitrile function to a primary amine was a modification of the method described for the poly (propylene imine) dendrimer synthesis[18]. Modifications that had to be made were a change of solvent to toluene/CH_3OH 3/1 v/v to dissolve polystyrene, and the application of longer reaction times. The use of NH_3 was crucial

for a successful hydrogenation. Without NH_3 yields after work up didn't exceed 50%, whereas with NH_3 yields > 90% could be obtained. NH_3 also had a positive effect on the reaction rate. The disappearance of the CN signal in IR was a suitable method to follow the hydrogenation reaction. The position of the CN peak at 2252 cm^{-1} was even visible for molecular weights up to $20 \cdot 10^3$ g/mol of polystyrene. The primary amine stretch vibration was somewhat obscured by the H_2O absorption band, but was still visible for PS-NH_2 of M_n = $3 \cdot 10^3$ g/mol. TLC also proved to be a method with which the reaction could be followed. ^{1}H-NMR and ^{13}C-NMR excluded side reactions and the combination of these techniques made it possible to identify the reaction product as PS-NH_2. A purification procedure wasn't necessary. The only loss of material was a result of some adsorption of polymer onto the catalyst. Yields of the hydrogenation reaction therefore amounted to 90% (table 2.3).

Because of the low end-cap yields with ethylene oxide, the two-step synthesis to the alcohol *via* end-capping with CO_2, followed by reduction of the acid, becomes an attractive route. The reduction step can be performed quantitatively and, especially when PS-OH is required at large scale, it is safer to work with CO_2 than with ethylene oxide.

The choice of the base system for the cyanoethylation reaction is not straightforward. The difference in reactivity of polyethylene oxide and polystyrene toward acrylonitrile in the presence of Lewatite resin can be explained by a large difference in polarity of both polymers: the alcohol-functionality of PS is too much shielded by the PS-chain. The applied organic base, DBU, on the other hand, isn't strong enough for deprotonation of the alcohol. TOMA, as a phase-transfer catalyst, is able to introduce sufficient OH^- in the chemical environment of the hydroxyl function of polystyrene to obtain the alkoxide form, and makes the Michael reaction possible. The choice of phase-transfer catalyst (PTC) is also critical, as can be shown from the lower modification results with TBAH. An explanation can be the lower availability of OH^- in this case. Cyanoethylation of a polymeric alcohol has earlier been described for polyisobutylene[17]. Also in this case a PTC (Triton B) was necessary to give quantitative results. Although longer reaction times are reported for the cyanoethylation of polyisobutylene, it is not clear whether this results from a significant difference in reactivity.

In our group the same system as described in this chapter has been used for PPE[19], thereby showing the versatility of the developed method.

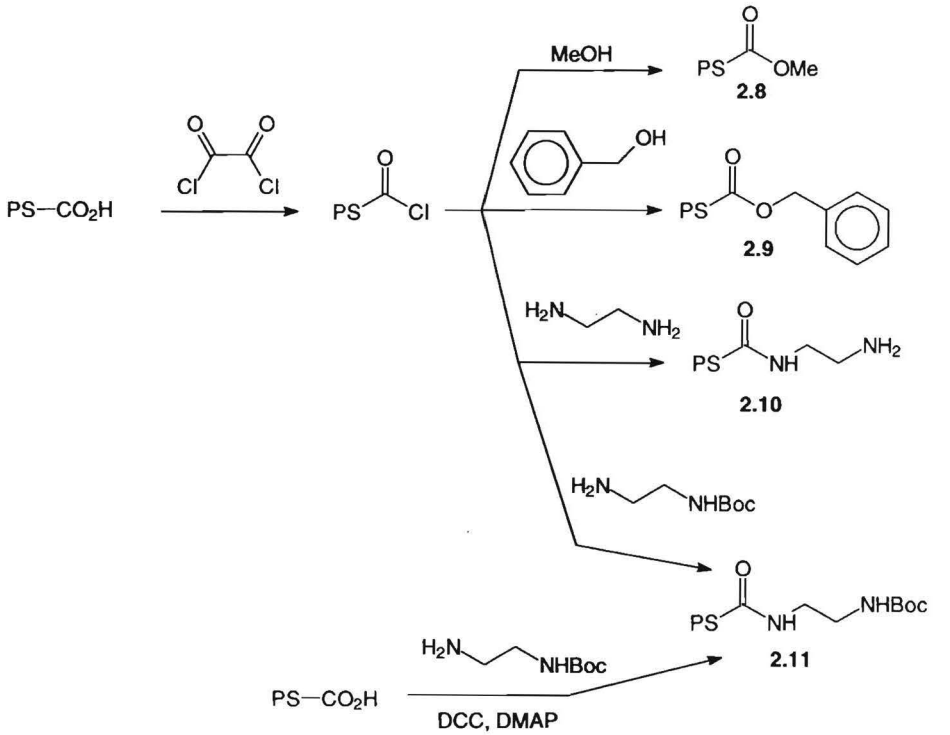
NH_3 plays a crucial role in the hydrogenation of the nitrile function. It causes a fast exchange of nitrile and amine end groups on the catalyst, thereby increasing the availability of the active sites and enhancing the reaction rate. This desorption also results in higher yields after work up, because a smaller amount of polymer remains attached at the catalyst surface. Furthermore, NH_3 prevents undesired coupling reactions between intermediate secondary amines and PS-NH_2.

After optimization of this three- or four-step procedure, an interesting indirect route has been developed toward primary amine functionalized PS. Also the intermediate acid, alcohol and nitrile can be used for a variety of reactions onto PS. Therefore this method can be seen as a good alternative for direct amination procedures.

2.4 Modifications of PS-COOH

PS-COOH is not only suitable as starting material for the indirect amination procedure by the reduction of PS-COOH to PS-OH. It's a potentially versatile molecule, that can be used in amidation and esterification reactions. In this paragraph four modification reactions of PS-COOH are described (Scheme 2.3). Polymers **2.8**, **2.9** and **2.10** were prepared by precipitating the acid chloride of PS in an excess of MeOH, benzyl alcohol and ethylenediamine, respectively. Precipitation, normally, should result in a bad interaction between reagents and would therefore prevent modification, as is indeed the case for the precipitation of PS-COCl in H_2O. However, TLC, IR and NMR showed quantitative functionalization toward **2.8** and **2.9**. With the bifunctional molecule ethylenediamine a small amount (5%) of PS-dimer was formed. To circumvent this problem, the mono-Boc protected form of ethylenediamine was used. In this case, however, no excess of reagent could be applied and the reaction was carried out equimolarly. Reactions had to be performed in a polar solvent as DMF to get a quantitative reaction. In CH_2Cl_2 no reaction could be detected. Coupling using DCC also proved to be quantitative for the preparation of **2.11**. NMR-

characterization of **2.11** was difficult, because of the broad proton signals and the fact that with ^{13}C-NMR an overlap occurred of the significant carbon signals with the signals of the PS-chain. Deprotection of the Boc-group with trifluoroacetic acid resulted in a change from $R_f = 0.4$ to $R_f = 0.2$ on TLC (eluent CH_2Cl_2/MeOH 99/1 v/v) and a positive ninhydrin test. Subsequent acetylation with acetic anhydride could be performed quantitatively, based on



Scheme 2.3: *Modifications of PS-COOH.*

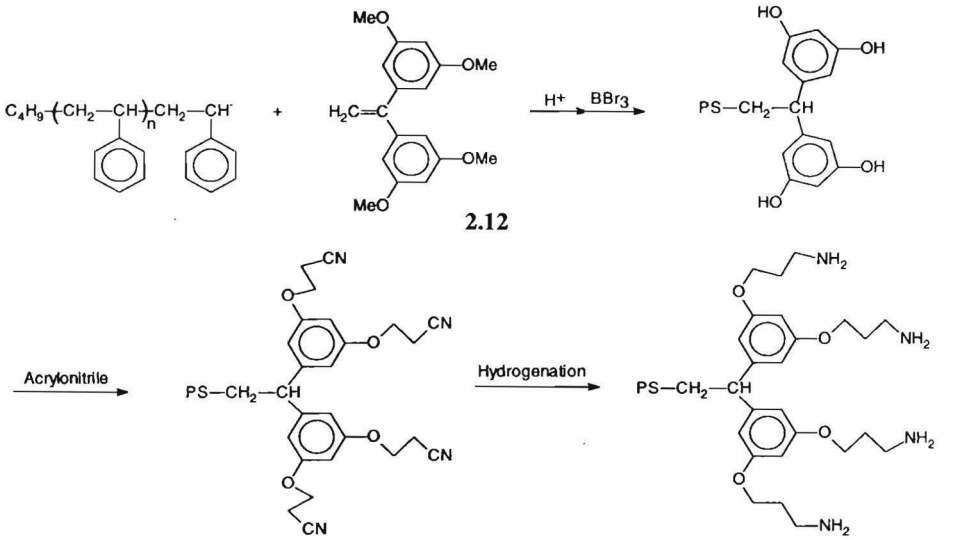
TLC-tests and a negative ninhydrin result. Unfortunately, also in this case, NMR could not give ultimate evidence.

Precipitation of the PSCOCl in an excess of alcohol or amine is a very efficient and simple method of modifying PS-COOH. Only in the case of bifunctional molecules as ethylenediamine some dimer formation also occurs. This is a result of aggregation of the polar COCl head groups, and is comparable to the problems of the CO_2 end-capping reaction (§2.2).

Another polarity effect can be found in the equimolar reactions toward **2.11**. In an apolar solvent the PS-end groups are not available and no reaction occurs. Therefore DMF has to be used as solvent. With equimolar reactions no difference can be noticed between DCC and COCl coupling methods. The characterization problem of **2.11** with NMR can be a result of hydrogen bonding between the introduced amide functions. Broadening of proton signals attached to a PS-chain is a well-known phenomenon. The deprotection and acetylation reactions however, give sufficient supporting evidence to confirm the success of the reaction.

2.5 Synthetic approaches toward multifunctional core-molecules

The versatile end-cap reaction based on 1,1-diphenyl ethylene derivatives has been used to introduce a variety of monofunctional and difunctional endgroups[10,11,20]. It was our aim to use this procedure for the synthesis of multifunctional PS core-molecules. Therefore the derivative 1,1-*bis*-(3,5-dimethoxyphenyl) ethylene (**2.12**) was investigated. The OMe-groups of **2.12** can be regarded as precursors for primary amines according to scheme 2.4. The influence of the position of the functional groups along the phenyl rings on the reactivity of 1,1-diphenyl ethylene was studied in detail by Busson and Van Beylen[21]. They investigated the Hammett relation of the reaction of living polystyryl anion with a series of 1,1-diphenyl ethylene derivatives. The reactivity of these derivatives was positively influenced with electron-donating groups (e.g. OMe) in the meta position. The derivative **2.12** proposed here, should therefore react more easily with polystyryl lithium than 1,1-diphenyl ethylene. In this paragraph we describe the synthesis of the end-capper **2.12**, as well as its potential as starting material for multifunctional PS.



Scheme 2.4: *Proposed synthetic route toward tetraamino PS via 1,1-bis(3,5-dimethoxy-phenyl) ethylene.*

Tetramethoxy-diphenyl ethylene **2.12** was synthesized by a Grignard reaction of 2 equivalents of 1-chloro-3,5-dimethoxy benzene onto ethyl acetate, followed by dehydration. The product could easily be purified by column chromatography and recrystallization. The yield of the reaction was rather poor. The possibility of demethylation of **2.12** by BBr_3 was investigated according to literature procedures[22]; 1,1-*bis*(3,5-dihydroxy phenyl) ethylene (**2.13**), however, was only obtained in low yield. A significant by-product was formed, that could be characterized with NMR as the dimer of **2.13** 1,1,3-*tris* (3,5-dihydroxyphenyl)-3-methyl-6,8-dihydroxy indane (**2.14**). By means of a deuteration

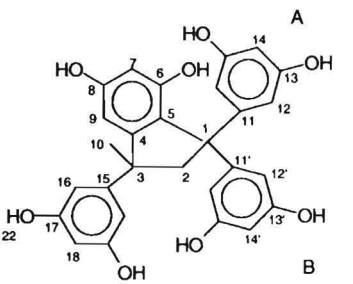
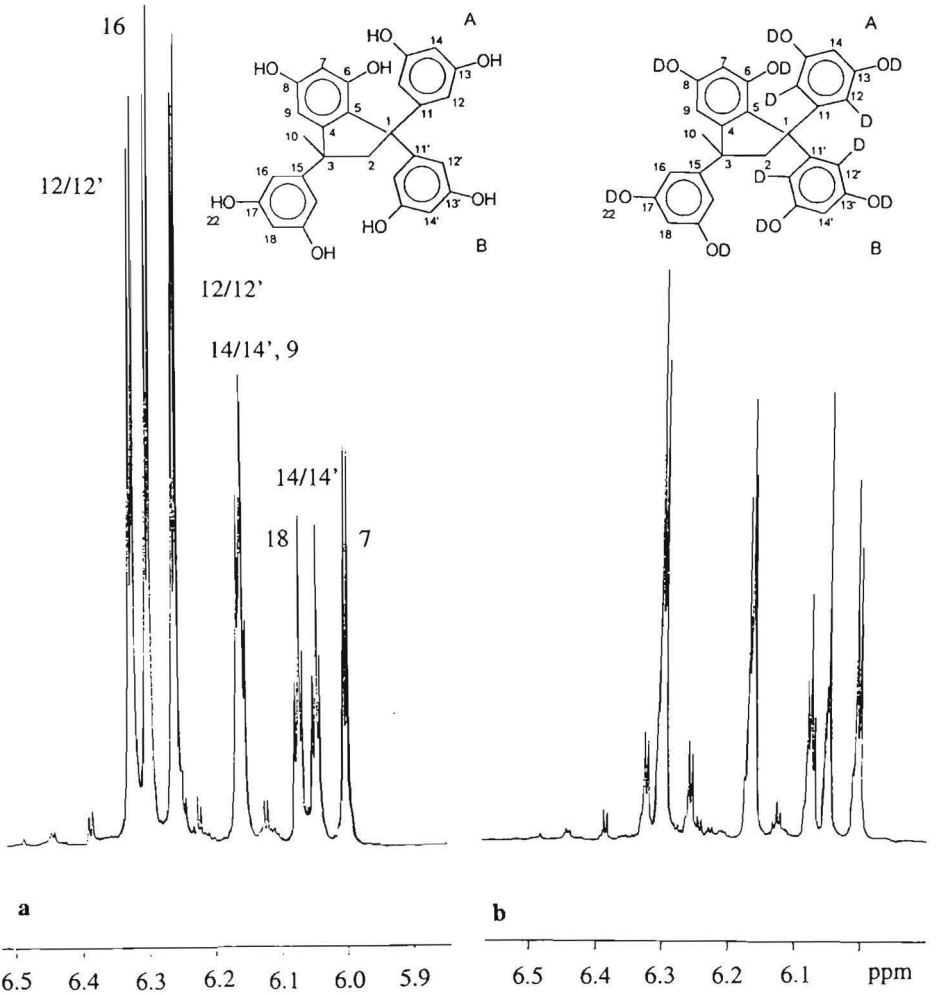


Figure 2.6: *1,1,3-tris(3,5-dihydroxy-phenyl) -3-methyl-6,8-dihydroxy indane (2.14).*

experiment it was possible to ascribe in more detail the aryl signals of this structure in ^{1}H-NMR. After storage in CD_3OD for 3 months, it was found that the protons H^{12} and $H^{12'}$ were exchanged for D. This was clearly visible in the ^{1}H-NMR spectrum, where a decrease was



Picture 2.2: *a) ^{1}H-NMR aromatic region of **2.14** before deuteration; b) ^{1}H-NMR aromatic region of **2.14** after deuteration.*

observed for 2 of the 3 doublets, accompanied with a change from triplet to singulet for the H^{14} and $H^{14'}$ resonances (picture 2.2).

A model reaction was performed between a slight excess of *n*-butyl lithium and **2.12**. 1,1-*bis*-(3,5-dimethoxy phenyl) hexane (**2.15**) was formed quantitatively. Demethylation of **2.15** with BBr_3 didn't give any problems: in high yield (80%) 1,1-*bis*-(3,5-dihydroxy phenyl) hexane (**2.16**) could be isolated. Cyanoethylation attempts of **2.16** were not successful.

Several end-cap reactions were performed with **2.12**, and functionalized product (PS-$(OMe)_4$, **2.17**) was obtained, however not in quantitative yields. Functionalized and non-functionalized PS could be separated by column chromatography.

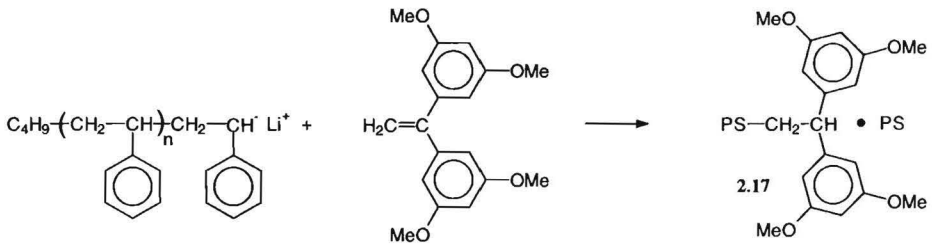


Figure 2.7: *End-cap reaction with tetramethoxy-diphenyl ethylene.*

^{1}H-NMR characterization of **2.17** showed a remarkable OMe-signal. This signal was a complex multiplet and had an integral value that corresponded with 6 instead of 12 protons. The shape of the multiplet remained the same even at elevated temperatures and in different deuterated solvents. GPC in $CHCl_3$ and THF gave M_n values that were the same for unfunctionalized PS and **2.17**, HPLC and TLC of strongly diluted samples of **2.17** all showed one signal. Demethylation of **2.17** however resulted in 2 products, which were separated with column chromatography in a 1/1 ratio, and that could be identified as non-functionalized PS and PS with 4 phenol functions (PS-$(OH)_4$, **2.18**).

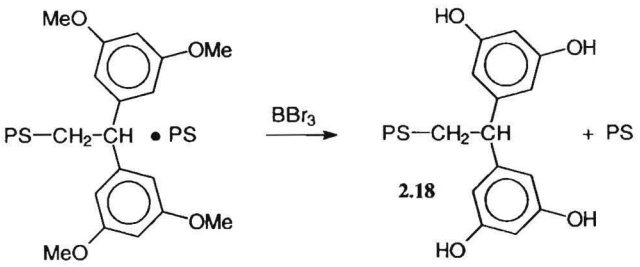


Figure 2.8: *Demethylation of tetramethoxy-functionalized PS.*

The low yields of the synthesis of **2.12** are a result of the fact that a Grignard reagent has to be prepared of 1-chloro-3,5-dimethoxybenzene instead of the bromo-derivative, because the latter isn't commercially available. Demethylation of **2.12** proceeds, but traces of acid (HBr) lead to the formation of a dimer by a cyclization reaction and electrophilic aromatic substitution. This reaction is known for α-methylstyrene and 1,1-diphenyl ethylene in the presence of electrophilic metal complexes[23]. The deuteration experiment validates the synthesis of **2.14**. The exclusive deuteration of the A and B rings of the system (figure 2.6) can be explained by an intramolecular mechanism. The OH-groups of the A-ring are located in the vicinity of the ortho-protons of the B-ring, and vice versa. In a deuterated solvent a D-H exchange can occur between these protons and the slightly acidic OD-group. This is not the case for the other 2 rings, for which it is necessary to have an intermolecular exchange. The problem of this cyclization reaction is circumvented by preparing the butyl adduct of **2.12**: **2.15**. With this reaction it is also shown that **2.12** can react quantitatively with an organolithium compound. After the disappearance of the vinyl bond, the demethylation proceeds without any problems. The next step in the reaction scheme toward an amine functionalized molecule, cyanoethylation of the phenols, doesn't occur at all. This is probably due to the lowered reactivity of this type of phenol in the Michael reaction.

The end-cap reaction with **2.12** doesn't proceed quantitatively. An explanation can be the small scale at which the reactions have been performed. The quantitative formation of **2.15** indicates that no side reactions occur, and that quantitative functionalization should be

possible. In ^{1}H-NMR, the OMe signal has a peculiar multiplet form, that isn't altered at different temperatures or with different solvents. The tacticity of the polystyrene backbone is therefore responsible for this phenomenon, that causes also the broadening of e.g. the C<u>H</u>$_2$-OH signal of **2.1**. The integral of the OMe signal is significantly too small. An explanation can be found in the demethylation of **2.17**, which results in 2 products: non-functionalized PS and **2.18**. From the model study of the demethylation of **2.15**, it is found that this reaction proceeds without any side reactions. A chemical reaction that leads to removal of the diphenyl group can be ruled out. The appearance of non-functionalized PS can therefore be a result of a decomplexation of **2.17** and PS by demethylation. This complex should be formed during anionic polymerization.

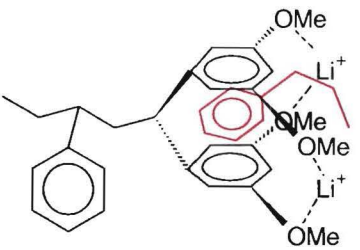


Figure 2.9: *Schematic presentation of π-π stacking during anionic polymerization.*

Aggregated ion pairs of polystyryl lithium can lead to a situation that after end-capping of one polystyryl chain, another chain becomes entrapped by the ionic interactions and the complex formation between Li^+ and the OMe-groups, which are known to have a strong complexating ability[24]. This trapped polystyryl chain can't react anymore with **2.12**. After termination of the reaction, electronic interactions have disappeared. The reason the complex stays intact can be that the unfunctionalized chain is stacked between the 2 aryls of the endgroup of **2.17**.

The complex should have, if stable, an M_n twice the value of the unfunctionalized PS. This is, however, not the case with GPC in $CHCl_3$ and in THF. With HPLC and TLC experiments of diluted samples no decomplexation can be observed. Therefore, GPC and HPLC are contradictory to the other observations and absolute proof for the existence of the PS-complex is lacking. The fact that with demethylation half of the end-capped PS is

obtained in the unfunctionalized form, in combination with the cyanoethylation problems of **2.16**, makes this route undesirable for the preparation of a multifunctional core molecule.

2.6 Conclusions

With our anionic polymerization set-up it is possible to prepare well-defined PS of molecular weights varying from 1.5 to $20 \cdot 10^3$ g/mol. In our hands end-cap reactions with ethylene oxide don't exceed 70% functionalization degree. Quantitative functionalization to PS-COOH is possible using CO_2 as end-cap molecule. PS-COOH is a versatile reagent. It can easily be amidated or esterified and is also quantitatively reduced to the corresponding alcohol. Direct introduction of a primary amine function by end-cap reactions with N-trimethylsilyl-benzaldimine (**2.3**) or N-*t*-butoxycarboxyloxy aziridine (**2.4**) proves to be unsuccessful. Literature procedures are in all of the examined cases not as straightforward as reported, and have to be examined carefully. Therefore an indirect amination procedure has been developed with PS-OH as starting material, consisting of a cyanoethylation step with acrylonitrile, followed by Raney/Co catalyzed hydrogenation. Because both steps can be performed in high yields, this synthetic approach is a good alternative for direct amination procedures. The preparation of multi-functional PS, *via* end-cap reaction with 1,1-*bis*-(3,5-dimethoxyphenyl) ethylene (**2.12**) is unsuccessful due to complex formation during end-capping.

2.7 Experimental

General procedure

^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Bruker AM-400 spectrometer at 400.13 and 100.62 MHz respectively. All δ values were given in ppm downfield from tetramethylsilane. Infrared samples were prepared according the KBr-technique and were measured on a Perkin Elmer 1605 FT. GPC analyses were performed on a Waters 590 GPC, using a PL-GEL 352 column and THF as eluent, and with a Spectra physics GPC, with Viscotek H502 and Shodex RI71 detectors, equipped with 2 PL-GEL mixed-C 30 cm columns, and using $CHCl_3$ as

eluent. TLC was performed with Merck 60 F_{254} silica gel plates and compounds were visualized with I_2 vapors or under UV light (λ=254 nm). Column chromatography was performed with Merck silica gel 60, 70-230 mesh ASTM. Flash chromatography was performed with Merck silica gel 60, 230-400 mesh ASTM.

Glassware was kept in a stove at 150 °C before use, except for the synthesis of **2.4-2.7**. A Parr reactor, type 4561 (300 ml), equipped with 4642 controller was used for the hydrogenation reactions. THF p.a. was distilled from Na/benzophenone, DMF was distilled and stored on molecular sieves (3Å). Toluene p.a. used for the synthesis of **2.3** was stored on CaH_2. CH_2Cl_2 used for the acid chloride syntheses (**2.8-2.11**) was of p.a. quality. All other solvents (p.a. quality) and reagents were used without further purification, except for CH_2Cl_2 (chemical purity), *n*-hexane (distilled before use) and methanol used for precipitations (technical grade). Raney Cobalt (Grace) was kindly provided by DSM.

Anionic polymerization, laboratory scale (20 gram)

Glassware used for the anionic polymerization was kept in a stove at 150 °C before use. argon 5.0 was predried over molecular sieves (3Å), followed by a drying column containing a solution of styrene (2 ml) and 1.6 M *n*-butyllithium (20 ml) in toluene (150 ml). Toluene was predried on CaH_2 under argon atmosphere. THF was heated under reflux over Na/benzophenone under argon prior to use. Styrene was distilled over CaH_2 and stored under argon at 4 °C. Fluorene was recrystallized from toluene/methanol (1/9 v/v). 9-Fluorenyl-lithium was prepared by addition of 7 ml 1.6 M *n*-butyllithium to a solution of 6.6 g fluorene in 150 ml toluene. After stirring for 3 days a yellow suspension of 9-fluorenyl-lithium in toluene was obtained. Technical grade methanol was used for precipitation. CO_2 4.6 (Hoek Loos) and ethylene oxide 3.0 (Hoek Loos) were used. Other materials were used as purchased.

Anionic polymerization, large scale synthesis (100 gram)

A 1.5 l BEP 280 Büchi glass reactor was used for the large scale anionic polymerization. The reactor was evacuated at 60°C and purged with nitrogen prior to use. Reactions were carried out under 2.5 bar N_2 pressure. Nitrogen was purified over a column filled with activated BTS-catalyst to remove O_2, followed by a molecular sieves (3Å) column to remove traces of H_2O. Styrene was purified at -18°C over a column filled with Al_2O_3 granulates, and stored in a storage vessel under nitrogen pressure at 4°C. Cyclohexane was purified over a molecular sieves (3Å) column and stored in a storage vessel under nitrogen pressure. *sec*-Butyl-lithium (1.3 M solution in cyclohexane/*n*-hexane 92/8 v/v) and CO_2 were used as purchased. Other solvents used were purified as described for the lab scale synthesis.

Anionic polymerization, end-cap reaction with ethylene oxide: PS_A-OH (2.1)

Anionic polymerizations were carried out under argon atmosphere. The polymerization system was dried by heating under vacuum and was purged several times with argon. A mixture of toluene (150 ml) and THF (1 ml) was used as solvent and was titrated in the polymerization system at 40 °C with a solution consisting of toluene (30 ml), styrene (0.8 ml) and 1.6 M *n*-butyllithium (2 ml), until a yellow color was sustained for more than 30 minutes.

Freshly distilled styrene (ca. 20 g) was dried with a suspension of 9-fluorenyllithium in toluene and was redistilled. The styrene was siphoned into the reaction system, after this was cooled to 4 °C. Titration with the previously described titration solution was carefully carried out, until a yellow color was sustained for 15 minutes. The appropriate amount of 1.6 M *n*-butyllithium was injected and the system was allowed to heat up to 40 °C. After an hour the reaction was terminated by addition of ethylene oxide. Several purification methods were used for ethylene oxide. *i*) Ethylene oxide was introduced as a gas without drying, *ii*) it was titrated with 1.6 M *n*-butyllithium, distilled and siphoned into the system, *iii*) a stock solution was made of ethylene oxide (distilled over CaH_2, titrated with 1.6 M n-butyllithium and redistilled) in toluene, of which 4 equivalents of ethylene oxide were injected into the system.

After the end-cap reaction, a few drops of acidified methanol were added and polystyrene was precipitated in a tenfold excess of methanol. Polystyrene was filtered, washed and dried *in vacuo* at 60 °C.

The polystyrene samples were characterized by ^{1}H-NMR, ^{13}C-NMR, GPC, IR and TLC. Functionalization yields were reached up to 70 %. Flash chromatography (eluent *n*-hexane/CH_2Cl_2 7/3 v/v) could be used to separate hydroxyl-functionalized from non-functionalized polystyrene.

^{1}H-NMR ($CDCl_3$): δ 0.73-1.22 (9H, Bu-$(CH_2$-$CHPh)_n$), 1.22 -1.71 ($(C\underline{H}_2$-$CHPh)_n$), 1.71-2.35 ($(CH_2$-$C\underline{H}Ph)_n$), 3.25 -3.43 (br, s, -$C\underline{H}_2$-OH), 6.28-7.25 ($(CH_2$-$CH\underline{Ph})_n$) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.0 ($\underline{C}H_3$-CH_2-CH_2CH_2-$(CH_2$-$CHPh)_n$), 22.5 (CH_3-$\underline{C}H_2$-CH_2-CH_2-$(CH_2$-$CHPh)_n$), 26.9 (CH_3-CH_2-$\underline{C}H_2$-CH_2-$(CH_2$-$CHPh)_n$), 27.0 ($(CH_2$-$CHPh)_n$-$\underline{C}H_2$), 31.8 (CH_3-CH_2-CH_2-$\underline{C}H_2$-$(CH_2$-$CHPh)_n$), 40.3 (br, (CH_2-$\underline{C}HPh)_n$), 40.0-46.5 (br, ($\underline{C}H_2$-$CHPh)_n$), 61.0 (-$\underline{C}H_2$-OH), 124.1-127.0 (br, CH_2-$CH\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-$CH\underline{Ph}_{ortho+meta}$), 145.1-146.5 (br, CH_2-$CH\underline{Ph}_{ipso}$) ppm.

Polystyryl anion titration

17.5 g (0.17 mmol) styrene was polymerized using 5.0 ml 1.6 M *n*-butyllithium according to the previously described procedure. After 15, 45, 75 and 150 minutes 5 ml of the polymer solution was taken out of the system, using a syringe that was first rinsed three times with polymer solution. The 5 ml solution was injected into a 25 ml 1-neck round-bottom flask equipped with magnetic stirrer and septum. A solution of 1.00 ml *n*-butanol in 200 ml toluene (0.055 M) was added until total decolorization occurred. All titrations were executed in duplo. For all decolorizations 2.7 ± 0.2 ml titration solution was needed. Titration of a sample after 5 days of reaction still needed 2.1 ml of solution. GPC of the resulting polymer showed $M_n = 2.7 \cdot 10^3$ g/mol and MWD = 1.11.

Anionic polymerization, end-cap reaction with CO_2: PS-COOH (2.2)

Anionic polymerizations were carried out according to the previously described procedure. The following method was used for the end-cap reaction with CO_2. A 5-neck 500-ml round-bottom flask, equipped with magnetic stirrer, argon inlet and outlet, CO_2 inlet, THF inlet and septum, was dried and 250 ml THF was freshly distilled into the flask. After cooling the flask in an ice bath, the THF was saturated with CO_2 during 15 minutes. By applying argon pressure the contents of the polymerization vessel were siphoned into the THF. The solution was neutralized with acidified methanol, concentrated and precipitated in a tenfold excess of methanol. Yields obtained after precipitation, filtration and drying *in vacuo* at 60°C were >90%, COOH-functionalization yields >95%.

^{1}H-NMR ($CDCl_3$): δ 0.73-1.22 (9H, Bu-(CH_2-CHPh)$_n$), 1.22 -1.71 ((CH_2-CHPh)$_n$), 1.71-2.35 ((CH_2-CHPh)$_n$), 3.00-3.30 (br, 1H, (CH_2-CHPh)$_{n-1}$-CH_2-CHPh-COOH), 6.28-7.25 ((CH_2-CHPh)$_n$) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.0 (CH_3-CH_2-CH_2CH_2-(CH_2-CHPh)$_n$), 22.5 (CH_3-CH_2-CH_2-CH_2-(CH_2-CHPh)$_n$), 26.9 (CH_3-CH_2-CH_2-CH_2-(CH_2-CHPh)$_n$), 31.8 (CH_3-CH_2-CH_2-CH_2-(CH_2-CHPh)$_n$), 40.3 (br, (CH_2-CHPh)$_n$), 40.0-46.5 (br, (CH_2-CHPh)$_n$), 49.5 ((CH_2-CHPh)$_{n-1}$-CH_2-CHPh-COOH), 124.1-127.0 (br, CH_2-CHPh$_{para}$), 127.0-129.5 (br, CH_2-CHPh$_{ortho+meta}$), 145.1-146.5 (br, CH_2-CHPh$_{ipso}$). 178.8-179.8 (br, (CH_2-CHPh)$_{n-1}$-CH_2-CHPh- COOH) ppm.

IR: $\nu_{C=O}$ 1706 cm^{-1}.

Anionic polymerization, large scale synthesis: PS-COOH (2.2a)

Cyclohexane was siphoned from the storage vessel into the reactor applying N_2 pressure. The reactor was cooled to 10°C. A weighed amount of styrene was siphoned in according to the same procedure.

The solution was mechanically stirred at 800 rpm. Next the appropiate amount of *sec*-butyllithium was added, using a syringe. After addition, the temperature was raised to 60°C and reaction was continued for 2 hours.

A 5-neck 2-l round-bottom flask, equipped with magnetic stirrer, argon inlet and outlet, CO_2 inlet, THF inlet and a sealed reactor connection tube, was dried according to the procedure described for the lab scale polymerization. 500 ml THF was freshly distilled into the flask. After cooling the flask in an ice bath, the THF was saturated with CO_2, disconnected from the argon system and THF distillation apparatus and connected *via* the tube to the polymerization reactor. Under nitrogen pressure the contents of the polymerization vessel was siphoned into the THF. The solution was neutralized with acidified methanol, concentrated and precipitated in a tenfold excess of methanol. Yields obtained after decanting and drying *in vacuo* at 60°C were >90%, COOH-functionalization yields >95%.

^{1}H-NMR ($CDCl_3$): δ 0.54-0.78 (br, 6H, CH_3-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 0.78-2.44 (CH_3-CH_2-CH(CH_3)-(CH_2-CHPh)$_{n-1}$-CH_2-CHPh-COOH), 3.00-3.30 (br, 1H; (CH_2-CHPh)$_{n-1}$-CH_2-CHPh-COOH), 6.25-7.32 (CH_2-CHPh) ppm.

^{13}C-NMR ($CDCl_3$): δ 11.0-11.4 (m, CH_3-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 18.5-19.8 (m, CH_3-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 28.7-30.4 (m, CH_3-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 31.5 (CH_3-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 40.8 (CH_3-CH_2-CH(CH_3)-(CH_2-CHPh)$_{n-1}$), 40.3-46.7 (br, CH_3-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 49.5 (CH_3-CH_2-CH(CH_3)-(CH_2-CHPh)$_{n-1}$-CH_2-CHPh-COOH), 124.1-127.0 (br, CH_2-CHPh_{para}), 127.0-129.5 (br, CH_2-CH$Ph_{ortho+meta}$), 145.1-146.5 (br, CH_2-CHPh_{ipso}), 178.8-179.8 (br, (CH_2-CHPh)$_{n-1}$-CH_2-CHPh- COOH) ppm.

IR: $\nu_{C=O}$ 1706 cm^{-1}.

N-trimethylsilylbenzaldimine (2.3)

2.3 was synthesized according to the procedure described by C. Krüger et al. and U Wannagat et al.[15]. To 55 g (0.34 mol) hexamethyldisilazane 13.0 g (0.33 mol) $NaNH_2$ (50 w% in toluene) was added and heated under reflux under argon atmosphere for 28 hours. After filtration and evaporation of the solvent, 55.7 g (0.30 mol, yield = 91.4%) Na-*bis*-trimethylsilylamide was obtained (^{1}H-NMR (toluene-d_8): δ 0.1 (s, Si-(CH_3)$_3$)) ppm. 36.5 g (0.2 mol) of Na-*bis*-trimethylsilylamide was dissolved in 200 ml toluene. In a 3-neck 500-ml round-bottom flask, equipped with condenser and dropping funnel, 21.2 g (0.2 mol) benzaldehyde was added dropwise. The yellow reaction mixture was stirred for 4 hours at 70 °C under argon atmosphere, followed by 3 hour heating under reflux. The mixture

was filtrated under nitrogen atmosphere. The filtrate was repeatedly distilled. Some impurities were still present, amounting to 10%. Yield was 58%.

^{1}H-NMR ($CDCl_3$): δ 0.25 (s, 9H, Si-($C\underline{H}_3$)$_3$), 7.45-7.8 (m, 5H, $\underline{Ph}$), 9.0 (s, 1H, $\underline{H}$C-Ph) ppm.

^{13}C-NMR ($CDCl_3$): δ 0.78 (Si-($\underline{C}H_3$)$_3$), 129.0, 129.2, 131.9 ($\underline{Ph}_{ortho,\ meta,\ para}$), 139.7 ($\underline{Ph}_{ipso}$), 168.5 ($\underline{C}$=N) ppm.

End-cap reactions were performed with **2.3**. The same anionic polymerization method was used as described for **2.1**. 5 equivalents of **2.3** were injected. Direct decolorization was observed. After work-up of the reaction mixture, no functionalization could be detected with ^{1}H-NMR and TLC (eluent: $CHCl_3$).

Michael addition of methyl acrylate onto α-methyl benzylamine

To 2.9 g (33 mmol) of methyl acrylate in a 100 ml 1-neck round-bottom flask a solution of 1 g (8.15 mmol) α-methyl benzylamine in 10 ml MeOH and 0.7 g (16.4 mmol) LiCl were added. The reaction mixture was stirred for 10 days under N_2-atmosphere at room temperature. The reaction was followed with ^{1}H-NMR and TLC (eluent: $CHCl_3$/MeOH 2/3 v/v, R_f mono-adduct: 0.69; R_f di-adduct: 0.96). After evaporation of solvent and excess methyl acrylate, the product was purified by column chromatography (eluent CH_2Cl_2/MeOH 99/1 v/v) and was obtained as a yellow oil.

^{1}H-NMR: (CD_3OD): δ 1.33 (d, 3H, $C\underline{H}_3$-CH), 2.4 (t, 4H, $C\underline{H}_2$-C=O), 2.7, 2.82 (m, 4H, N-$C\underline{H}_2$), 3.6 (s, 6H, $OC\underline{H}_3$), 3.84 (q, 1H, CH_3-$C\underline{H}$), 7.25 (m, 5H, $\underline{Ph}$) ppm.

N-*t*-Boc-aziridine (2.4)

2.4 was synthesized by reaction between aziridine and Boc-anhydride, in analogy with the preparation described by Beak et al.[16c]. Aziridine was prepared according to the procedure described by W.A. Reeves et al.[16b]. 2.45 g NaOH, dissolved in 15 ml H_2O was placed in a 500 ml 3-neck round-bottom flask, equipped with distillation setup and dropping funnel. 50 g (0.35 mol) 2-aminoethyl hydrogen sulfate, dissolved in 214 ml H_2O and 50 g NaOH, was added dropwise to the NaOH-solution. The mixture was heated (bp =104-109°C) and distilled at such a rate that the volume in the flask remained constant. The distillate was treated with 140 g NaOH. The separated organic layer was distilled, resulting in 6.1 g (η=40%) pure aziridine. (^{1}H-NMR ($CDCl_3$): δ -0.1 (s, 1H, N$\underline{H}$), 1.55 (s, 4H, $C\underline{H}_2$), (DMSO-d_6): δ 0.8 (s, 1H, N$\underline{H}$), 1.40 (s, 4H, $C\underline{H}_2$); ^{13}C-NMR (DMSO-d_6): δ 17.4 ($\underline{C}H_2$)) ppm.

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Chapter 3

Polystyrene - poly(propylene imine) dendrimers, a new class of amphiphiles

Summary

A new class of amphiphilic macromolecules has successfully been synthesized by combining well-defined polystyrene (PS) with poly(propylene imine) dendrimers. Five different generations, from PS-dendr-NH_2 up to PS-dendr-$(NH_2)_{32}$ were prepared in yields of 70 to 90%. The molecular structure of the block copolymers was analyzed in detail, with NMR-, IR- and electrospray mass spectroscopy. Using conductivity measurements and monolayer pressure-area isotherm determinations, we observed generation dependent amphiphilic behavior. Dynamic light scattering and transmission electron microscopy showed that in aqueous phases, PS-dendr-$(NH_2)_{32}$ forms spherical micelles, PS-dendr-$(NH_2)_{16}$ micellar rods and PS-dendr-$(NH_2)_8$ vesicular structures. The lower generations showed inverted micellar behavior. The observed effect of amphiphile geometry on aggregation behavior is in qualitative agreement with the theory of Israelachvili. The amphiphiles presented here are similar in shape but different in size as compared with traditional surfactants, while similar in size but different in shape as compared with traditional block copolymers.

3.1 Introduction

The synthesis and characterization of new amphiphilic structures is one of the most daring and promising approaches toward a better understanding of the structure-property relation of amphiphiles[1]. Historically, the field has been subdivided into traditional

surfactants and amphiphilic block copolymers. Both classes have been subject of extensive studies[2,3,4], but a detailed comparison between both to understand the effect of increasing size and shape on aggregation has not really been possible, because of the distinct differences in the polar segments. The low molecular weight surfactants have a compact polar head group, whereas the block copolymers known thus far have linear, extendible polar chains.

Recently, dendrimers, which are well-defined highly branched macromolecules that emanate from a central core, have gained a growing scientific interest[5]. These spherical structures have been proposed as precise nanoscopic building blocks[6]. New architectures have been synthesized[7], including unimolecular micelles and structures containing dendrimers and linear macromolecules[8] (figure 3.1). Chapman et al.[9] presented hydraamphiphiles that consist of a dendrimer as the apolar and a poly(ethylene oxide) chain as the polar part (figure 3.2).

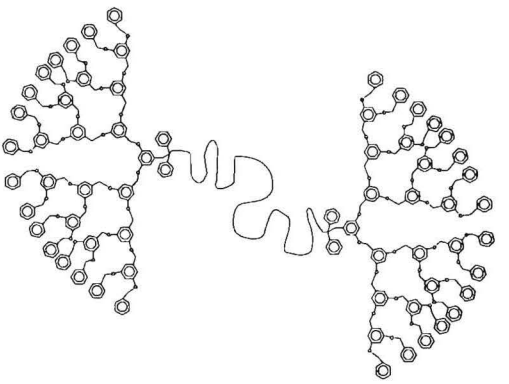


Figure 3.1: *Polyether-dendrimer-Polystyrene triblock copolymer*[8e].

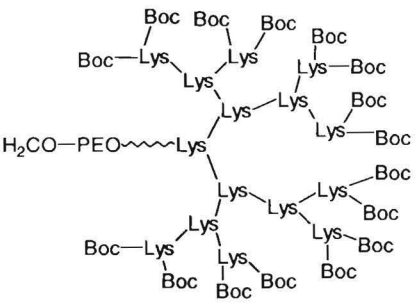


Figure 3.2: *Hydraamphiphiles*[9].

The amphiphilic polymers as described by Zhong and Eisenberg[10] can be regarded as the first approach toward polystyrene (PS)-dendrimer structures with variable polar head group size. Poly(propylene imine) dendrimers represent a special class of very hydrophilic dendrimers[11]. These spherelike structures with diameters of 1 to 4 nm are synthesized by a

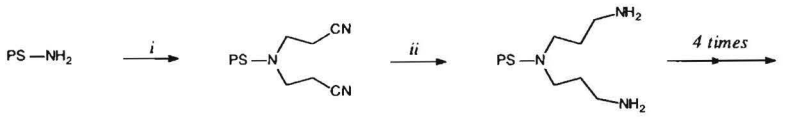
reaction sequence of two steps: a double cyanoethylation of primary amines with acrylonitrile, followed by Raney-Cobalt hydrogenation of the nitriles to primary amines. The combination of hydrophilicity and a highly branched structure makes these dendrimers very interesting building blocks to be used as polar part in amphiphilic block copolymers. In this chapter the synthesis and characterization is described of a well-defined class of hybrid PS-dendrimer block copolymers of which the head group size is varied. The structures presented here can be seen as a new type of amphiphiles in between the traditional organic surfactants and amphiphilic block copolymers, with the size of the latter and the shape of the first.

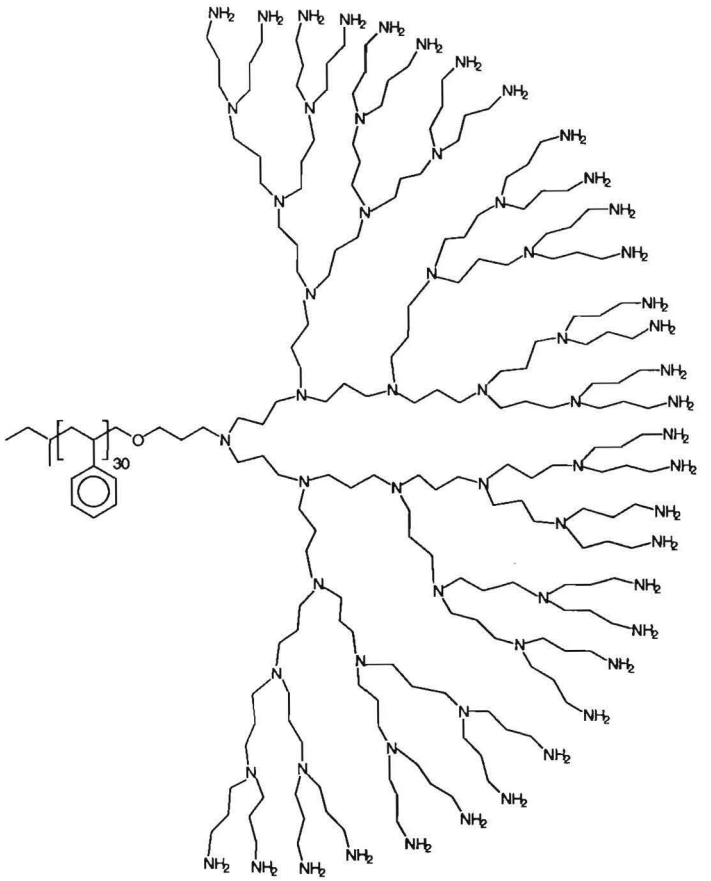
3.2 Synthesis of PS-*dendr*-$(NH_2)_n$ with n=1–32 and PS-*dendr*-$(CN)_n$ with n=2–32

To obtain PS-poly(propylene imine) block copolymers, the divergent dendrimer synthesis was performed onto a primary amine functionalized PS-core molecule, as is depicted in scheme 3.1. This core molecule was prepared *via* an indirect amination procedure of PS-COOH (§ 2.4), that was itself synthesized using the large scale anionic polymerization set-up (§ 2.2). The reaction sequence, consisting of a double Michale addition of acrylonitrile onto primary amines, followed by Raney/Co catalyzed heterogeneous hydrogenation of the nitriles to amines, has proven to be a very efficient and simple procedure to prepare dendrimers on a large scale, when 1,4-diaminobutane is used as core molecule. The change from 1,4-diaminobutane to PS, in combination with the developing amphiphilic character of the intermediates, required adjustment and optimization of both cyanoethylation and hydrogenation steps of the dendrimer reaction sequence, compared to the DSM-route. For the cyanoethylation, the choice of solvent combination was of considerable importance. The first reaction step toward PS-*dendr*-$(CN)_2$ was possible in acrylonitrile as reactive solvent, the other reactions had to be performed in a heterogeneous system of toluene/water. Acetic acid was used as catalyst in all cases. To obtain stable emulsions, the water to toluene ratio had to be adjusted for each cyanoethylation step.

Hydrogenations were performed under conditions that were similar to the DSM-route, using 80 bar H_2-pressure and Raney-Cobalt as catalyst. However, also in this case solvent had

to be changed to a toluene/MeOH 3/1 v/v mixture in order to dissolve the products. Furthermore, the addition of NH_3 was of utmost importance. Without NH_3 it was impossible





Scheme 3.1: *Synthetic route toward PS-dendr-$(NH_2)_{32}$: (i) Cyanoethylation with acrylonitrile in water/toluene, catalyzed by acetic acid; (ii) and hydrogenation at 80 bar H_2-pressure, with Raney-Cobalt as catalyst.*

to fully hydrogenate even PS-*dendr*-$(CN)_4$. Side reactions as intramolecular bridging between a primary amine and an imine function took place, and the yields after work-up were drastically decreased when no NH_3 was used. NH_3 made it possible to circumvent these problems and even increased the reaction rate. When hydrogenations were performed on small scale (< 1 g), serious cobalt contamination and carbamate formation were observed. Performing the work-up under N_2-atmosphere could prevent the latter problem. When the reactions were performed on larger scale (> 5 g) both problems didn't occur anymore. All nitrile and amine products, with the exception of PS-*dendr*-$(NH_2)_{32}$, could be purified by precipitation techniques. The polarity of the medium that was used for precipitation had to be increased with increasing generation, from MeOH to ammonia. PS-*dendr*-$(NH_2)_{32}$ was too polar to be precipitated even in ammonia. Column-chromatographic purification of the nitrile intermediates was possible up to PS-*dendr*-$(CN)_{16}$. With this technique, side products as for example poly(acrylonitrile) and acetylated PS-NH_2 could easily be removed. All of the products were obtained in good yields after work-up (table 3.1).

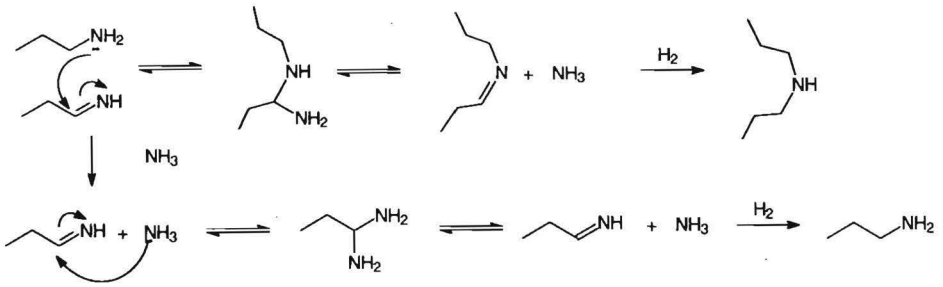
Table 3.1: Yields and calculated molecular masses of the PS-poly(propylene imine) block copolymers

Product	M_n (kg/mol)	Yield after work-up (%)
PS-*dendr*-$(CN)_2$	3.35	97
PS-*dendr*-$(NH_2)_2$	3.36	90
PS-*dendr*-$(CN)_4$	3.57	70*
PS-*dendr*-$(NH_2)_4$	3.60	90
PS-*dendr*-$(CN)_8$	4.0	75
PS-*dendr*-$(NH_2)_8$	4.02	85
PS-*dendr*-$(CN)_{16}$	4.9	93
PS-*dendr*-$(NH_2)_{16}$	4.97	93
PS-*dendr*-$(CN)_{32}$	6.5	80
PS-*dendr*-$(NH_2)_{32}$	6.6	64

* *Product purified by column chromatography*

The cyanoethylation experiments demonstrate the development of amphiphilicity of the molecules. Because the Michael addition is performed at the interface of the water/toluene mixture, stability of the emulsion is important. The increasing polarity of the dendrimer with increasing generation makes it necessary to add more water to the system. During reaction, it is difficult to follow the cyanoethylation, either with TLC or with spectroscopic techniques. This is a result of the formation of protonated dendritic structures, due to the presence of HOAc. Optimization of the reaction time is therefore difficult to achieve. Column chromatography makes it possible to separate a number of side products from the desired dendritic structures. The difference in polarity between amine- and nitrile-functionalized dendrimers is large, and incompletely cyanoethylated structures can therefore be removed. However, it is not possible to remove side products of which e.g. 1 of the 16 amine functions hasn't reacted. After optimization, the cyanoethylation reactions can be performed quantitatively, and column chromatographic purifications are therefore most of the time not necessary.

The role of NH_3 during hydrogenation is a crucial but also a fairly well-known one[12]. One of the major side reactions that can occur, is the intramolecular bridging reaction between an imine and a primary amine function, with the release of NH_3. NH_3 is thought to compete with the primary amines in attack on the intermediate imine. The attack of NH_3 leads to the formation of the desired amine.



Scheme 3.2: *Mechanism of intramolecular bridging, and the role of NH_3.*

NH_3 also promotes desorption of the primary amines from the catalyst surface. This causes a lower loss in the work-up procedure and an enhanced reaction rate. Especially in the case of

the hydrogenations, the scale of reaction is important. Precipitation and filtration techniques can be performed more effectively, with as a result that cobalt is removed and carbamate formation can be prevented. The hydrogenation step is most difficult to control in the reaction sequence and can give rise to the formation of byproducts. These byproducts can't be separated from the desired product with column chromatography, because of the high polarity of both materials. Using the multistep divergent dendrimer synthesis it is therefore almost impossible to prevent any formation of side products or to isolate the pure product. The divergent synthesis can in this respect be regarded as the polymeric approach toward dendrimers. On the other hand, to obtain the end product a 13 step synthesis had to be performed onto a polymer in a well-defined manner. This makes this procedure also an unprecedented effort in the area of polymer modification reactions.

3.3 Characterization of PS-*dendr*-$(NH_2)_n$ with n=1–32 and PS-*dendr*-$(CN)_n$ with n=2–32

The process of hydrogenation could be excellently followed using IR-spectroscopy. The disappearance of the CN-stretch vibration around 2245 cm^{-1} was used as indication for the end of the reaction. Only in the case of the preparation of PS-*dendr*-$(NH_2)_{32}$, even after several hydrogenation attempts, the CN-signal didn't completely disappear; this signal was estimated to be less than 3% of the starting stretch vibration. Besides IR-spectroscopy, all products were characterized with ^{1}H-NMR and ^{13}C-NMR-spectroscopy. With both techniques positive structural identification was achieved. With ^{13}C-NMR, it was possible to analyze the structures in great detail, as is shown in figure 3.3 for PS-*dendr*-$(CN)_{16}$. All of the signals present in the spectrum could be assigned. It was possible to discern between the different dendritic layers of the molecules, as was clearly noticed for the resonances of the carbons next to the tertiary amines (around 50 ppm) and the carbons in between the tertiary amines (around 25 ppm). Even single carbons were visible (C^3 and C^4). The signals of the carbon atoms next to the ether function (C^1 and C^2) were much broader, due to the effect of tacticity of the polymer backbone. The signals that are not numbered in the ^{13}C-NMR spectrum

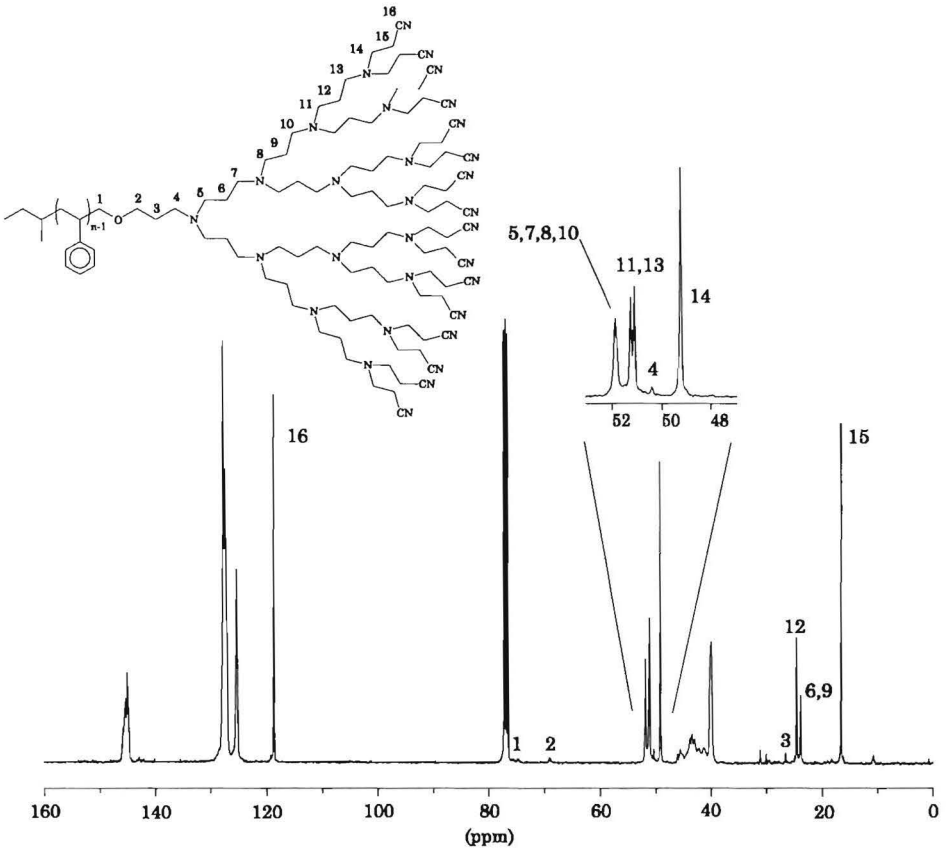


Figure 3.3: *^{13}C-NMR spectrum of PS-dendr-$(CN)_{16}$ in $CDCl_3$.*

originate from the *sec*-butyl group. All of the other ^{13}C-NMR spectra could be assigned likewise, only for PS-*dendr*-$(NH_2)_{32}$ solubility problems occurred, and characterization with NMR became very difficult. In this case, only the PS-chains were visible in $CDCl_3$. After storage of the PS-*dendr*-$(NH_2)_{32}$ foam for 2 months, the product had become insoluble, even in DMSO. After an extraction process with water and toluene a product was obtained that was soluble in organic phases. Again, however, characterization with $CDCl_3$ only showed PS, and other solvents used gave ambiguous results. In the case of PS-*dendr*-$(NH_2)_8$ a few very small additional peaks (<5%) were visible with ^{13}C-NMR, which possibly could be related to a side

product. Electrospray mass spectrometry was performed on PS-*dendr*-$(NH_2)_8$ (figure 3.4), and showed a small imperfection of the dendrimer head group (peaks at 956.3 and 982.6). The 'dispersity' of the dendrimer block is, however, of a totally different order than the dispersity of the well-defined PS-chain. Due to the MWD of PS, which is 1.04, at least 18 different PS-oligomers are detected, from 813.5 to 1229.9.This spectrum is obtained from a non-optimized reaction. Analysis of optimized samples should even give better results.

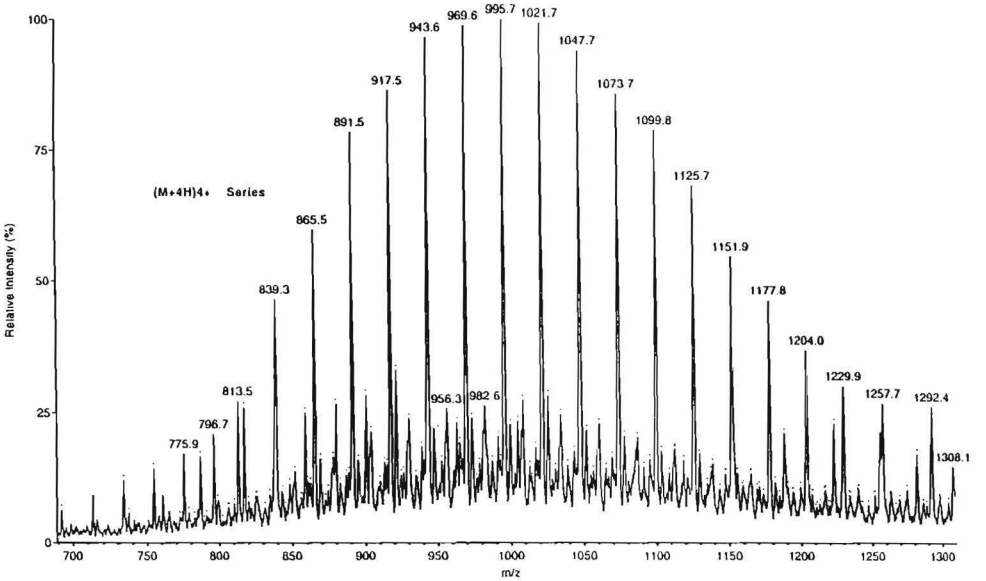


Figure 3.4: *Electrospray mass spectrum of PS-dendr-*$(NH_2)_8$*. The correct mass can be calculated by multiplication of the values with 4 and substraction of 4.*

Although electrospray mass spectrometry is a very powerful and absolute technique to analyze the synthesized products, it is also a quite complex characterization method, still under development. Especially sample preparation and interface techniques need meticulous optimization in order to measure samples satisfactorly. Characterization with NMR-spectroscopy is therefore still the most used technique. With this analysis method no

imperfections can be detected for the nitrile intermediates and the stratified structure of the dendrimers becomes perfectly clear. An approximation of the resolution of ^{13}C-NMR is given by the fact that O-CH_2-CH_2-$\underline{C}H_2$-N is visible; the limit of detection is below 5%. One very important aspect of NMR-characterization is that every intermediate has to be fully characterized. The very small impurities or side products that were noticed for PS-*dendr*-$(NH_2)_8$ aren't visible anymore for the higher generations. Due to the symmetry of the dendrimers, these imperfections are camouflaged, because the chemical environments of the imperfections and the correct structure become almost identical. The preparation of PS-*dendr*-$(NH_2)_{32}$ proves to be a reaction at the limits of the synthetic possibilities. From IR-spectroscopy it can be concluded that approximately 1 of 32 nitrile functions hasn't been hydrogenated. The NMR characterization difficulties are partly a result of the amphiphilic character; the dendrimer head groups are aggregated in and shielded from deuterated solvents as $CDCl_3$. Storage of PS-*dendr*-$(NH_2)_{32}$ as a solid gives rise to an intermolecular bridging process, that results in an insoluble material. Although this process isn't observed for the other generations, it is sometimes noticed for the poly(propylene imine) dendrimers[13]. However, samples that were freshly prepared from PS-*dendr*-$(NH_2)_{32}$ for aggregation and amphiphile behavior (§ 3.4) weren't affected by intermolecular bridging and their properties are hardly influenced by the probably incompletely hydrogenated structures. From the characterization results it can be concluded that our aim: obtaining a well-defined series of polystyrene-poly(propylene imine) dendrimer diblock copolymers has been accomplished quite successfully, and has brought us to the limits of the present synthetic and characterization possibilities.

3.4 Amphiphilic behavior of PS-*dendr*-$(NH_2)_n$

The development of amphiphilic and aggregation behavior as a function of dendrimer generation of PS-*dendr*-$(NH_2)_n$ was studied with 4 different techniques: the amphiphilic character at a toluene/water interface was investigated with conductivity measurements, and at a water/air interface with monolayer experiments. Dynamic light scattering (DLS) and

transmission electron microscopy (TEM) were used to examine the aggregates formed by the different generations in aqueous solutions.

3.4.1 Conductivity measurements

To a stirred $3 \cdot 10^{-4}$ mol/l dispersion of PS-*dendr*-$(NH_2)_n$ in a 0.01 M KCl solution, a $3 \cdot 10^{-4}$ M amphiphile solution in toluene was added dropwise. By measuring the conductivity of the system as a function of the ratio toluene/water, it could be estimated whether toluene or water was the continuous phase. At the point where the conductivity dropped to zero, the phase inversion point was reached and toluene became dispersing phase. The effect of dendrimer generation on the position of this inversion point was investigated with PS-*dendr*-$(NH_2)_n$ with n=2–16. PS-*dendr*-$(NH_2)_{32}$ could not be measured in the same manner, because this product proved to be insoluble in toluene. The results are depicted in figure 3.5.

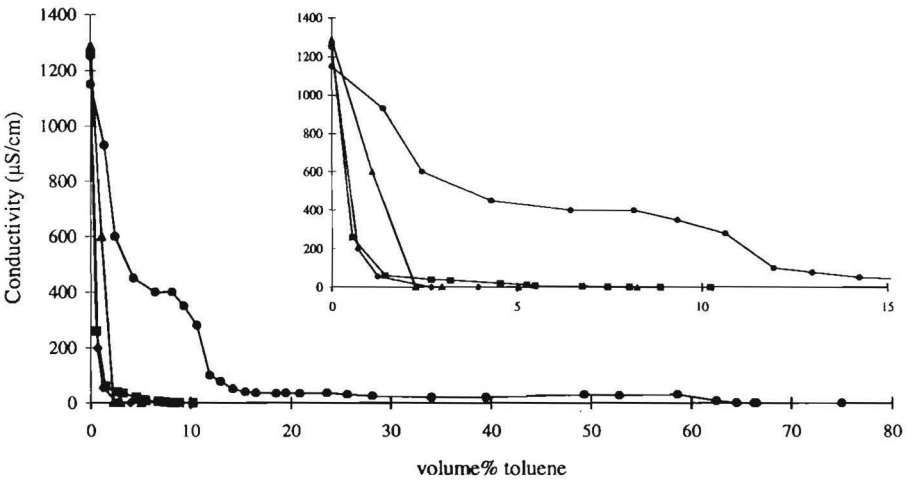


Figure 3.5: *Conductivity measurements of toluene/water systems in the presence of PS-dendr-$(NH_2)_n$, (Δ: n=2, □: n=4, ◊: n=8, ○: n=16). The insert is an enlargement of the 0 to 15 vol% area.*

The conductivity measurements show a distinct difference between PS-*dendr*-$(NH_2)_{16}$ and the lower generations. For PS-*dendr*-$(NH_2)_n$ with n = 2–8 there is a strong tendency of stabilizing toluene as continuous phase. PS-*dendr*-$(NH_2)_2$ even showed a remarkable phase inversion at 2 vol% of toluene. This can be explained by the fact that PS is the dominant part in the amphiphilic structure and, according to the empirical rules of Bancroft[14] the organic phase as continuous phase is preferred. PS-*dendr*-$(NH_2)_{16}$ is a much more balanced amphiphile and is therefore equally capable of stabilizing toluene as well as water as dispersing phase.

3.4.2 Monolayer experiments

Amphiphilic behavior at an air/water interface was studied using monolayer experiments. By dissolving the amphiphiles in a volatile apolar solvent, and spreading it on a water subphase in between 2 moveable barriers, monomolecular layers are obtained. By

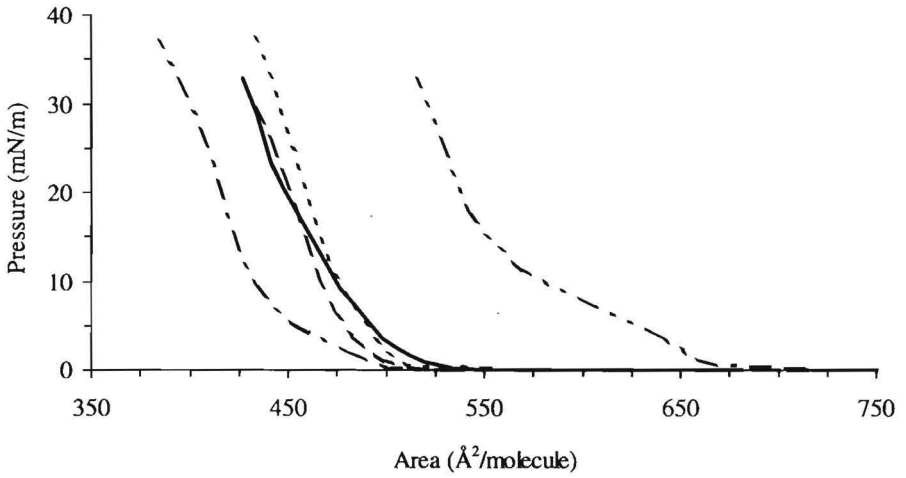


Figure 3.6: *Pressure-area isotherms;* —— *PS-NH₂;* — — *PS-dendr-(NH₂)₂;* — — *PS dendr-(NH₂)₄;* —— — *PS-dendr-(NH₂)₈ ;* —— — —*PS-dendr-(NH₂)₁₆.*

diminishing the area between the barriers, phase transitions can occur from the two-dimensional 'gaseous' state through liquid-like, to condensed or solid state situations. In the latter case the molecules are densely packed and highly ordered. These phase transitions can be investigated by measuring the surface pressure as a function of area between the barriers. Extrapolation of the solid state curve to the intercept with the X-axis gives an estimate of the head group dimensions of the amphiphiles. Surface pressure-area isotherms were recorded for PS-*dendr*-$(NH_2)_n$ with n=1–16. The formed monolayers were also investigated with a Brewster angle microscope (BAM)[15], which made it possible to investigate the type of structures that are formed in the monolayer. The results are shown in figure 3.6 and table 3.2.

Table 3.2: Head group dimensions derived from monolayer experiments

Product	Head group area (Å^2)	Head group diameter (Å)
PS-*dendr*-$(NH_2)_8$	440	23.7
PS-*dendr*-$(NH_2)_{16}$	570	26.9

The development of amphiphilic character is also noticed from the monolayer experiments. Only for PS-*dendr*-$(NH_2)_n$ with n = 8 and 16, a normal pressure-area isotherm is obtained, which shows a transition from gaseous through the liquid to the solid like state. For these 2 generations an estimation of head group dimensions is possible. The lower generations all show the same type of curves and directly go to solid state behavior. In these cases solid PS-films are formed, that, at the point of increase of surface pressure, collide and cover the total area between the barriers. With BAM these colliding plateaus were also observed. These films are formed because of the dominance of the PS-chain interactions over the dendrimer head group interactions. The areas per molecule that can be estimated are more determined by PS than by the dendrimer head group. This explains that for PS-*dendr*-$(NH_2)_8$ a lower value is found for the pressure-area isotherm. This is the first generation for which the influence of the head group on the behavior at the air/water interface has to be taken into account.

3.4.3 Dynamic Light Scattering

DLS measurements were performed for PS-*dendr*-$(NH_2)_4$ in toluene and for PS-*dendr*-$(NH_2)_n$, with n= 8 to 32 in water. Concentrations of all of the aggregates were $3 \cdot 10^{-4}$ mol/l. For the aqueous aggregates turbid systems were obtained, except for PS-*dendr*-$(NH_2)_{32}$. PS-*dendr*-$(NH_2)_4$ showed single particle behavior in toluene. A hydrodynamic radius of 3.4 nm could therefore be estimated. The aqueous aggregates were much more difficult to interpret. For PS-*dendr*-$(NH_2)_{16}$ complicated structures were observed that could be identified as large threadlike structures with a hydrodynamic radius of 120 nm. This type of aggregation remained unchanged even after extreme dilution. The other structures, however, showed so much clustering of the aggregates that no particle dimensions could be estimated. Dilution of the samples couldn't improve the experiments.

Clustering occurs when the dendritic head groups are directed toward the periphery of the aggregates, where they are able of forming electrostatic interactions. These interactions are also noticed for the normal poly(propylene imine) dendrimers[16]. The fact that even after extreme dilution the aggregates and clusters remain intact, means that these intermolecular interactions are very strong. They can only be supppressed by modification of the dendrimers (Chapter 5) or by inverted micellar behavior. This is the case for PS-*dendr*-$(NH_2)_4$ in toluene. Single particle behavior points in the direction of inverted micellar structures, in which case the head groups are shielded off from the environment by the PS-chains. The hydrodynamic radius of 3.4 nm can be related to the core of the inverted micellar structure. The outer parts of the PS-chains are less limited in their dynamic behavior and have a low scattering intensity in toluene. They are therefore not observed with DLS.

3.4.4 Transmission electron microscopy studies

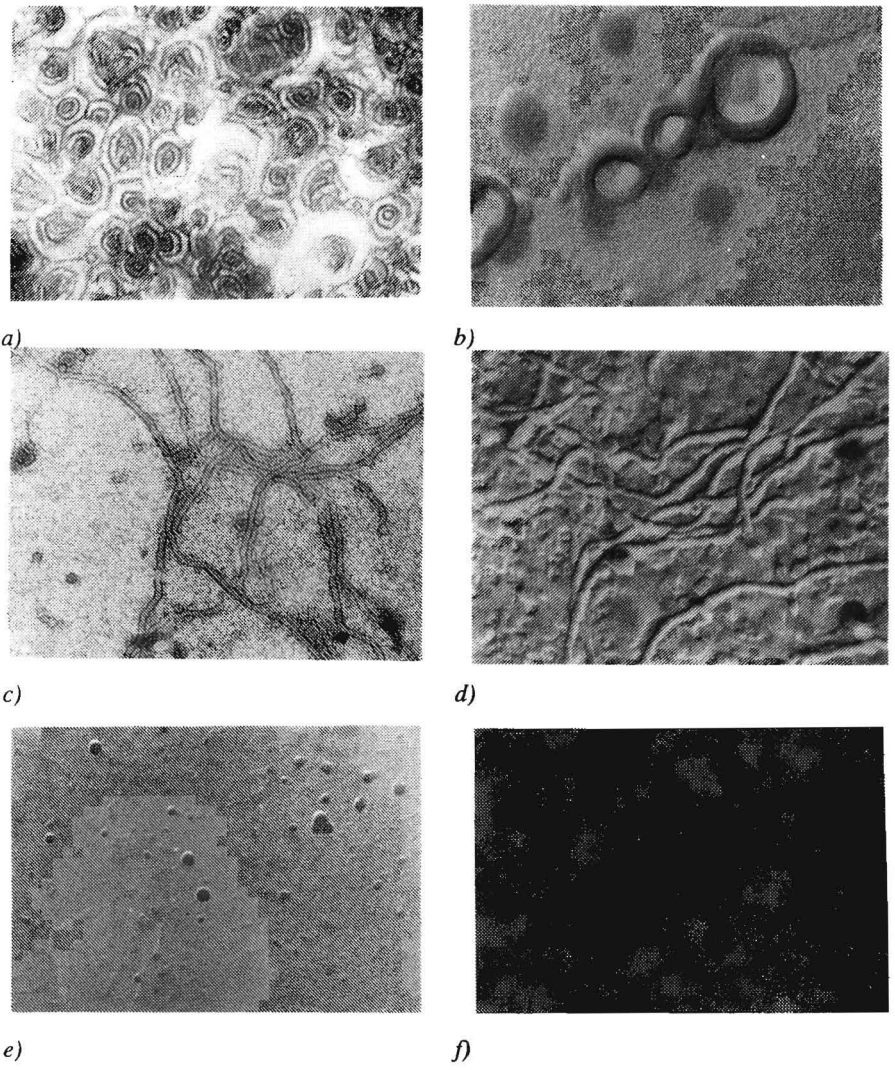
Aqueous aggregates of PS-*dendr*-$(NH_2)_n$ with n = 8, 16, 32 ($3 \cdot 10^{-4}$ mol/l) were studied with three different TEM techniques: negative staining with uranyl acetate, Pt-shading and freeze fracture. All three techniques gave consistent results (picture 3.1): in case of PS-

dendr-$(NH_2)_8$ flexible bilayers were formed[17], PS-*dendr*-$(NH_2)_{16}$ showed rodlike micelles with a diameter of 12 nm, and PS-*dendr*-$(NH_2)_{32}$ gave spherical micelles with diameters between 10–20 nm. For this last sample no freeze fracture results could be obtained. Acidification of PS-*dendr*-$(NH_2)_8$ from pH = 7 to pH = 1 didn't influence the aggregation type. Also after 4 weeks the same aggregates were still observed for PS-*dendr*-$(NH_2)_8$.

The observed diameters of rodlike and spherical micelles are in the same order of magnitude as can be expected from a bilayer of the diblock copolymers. With respect to clustering and stability of aggregates TEM is consistent with the DLS-measurements. The stability of the aggregates formed is remarkable: spherical micelles can be made visible with the TEM-techniques used[18]. The well-known transition behavior for simple amphiphiles[2a] from micellar cylinders toward micelles upon dilution is in this case not observed. The aggregates formed of PS-*dendr*-$(NH_2)_8$ are shown to be stable in time, for at least a month. This structure also shows pH-independent behavior. This can be explained by the fact that at pH = 7 the primary amines are already partly protonated, so that a change to lower pH doesn't have a drastic effect on head group charge and size.

3.4.5 Discussion

The results obtained with both TEM and DLS are in perfect qualitative agreement with the theory of Israelachvili[3,19] about surfactant assembly. He describes, using the packing parameter $P = V/(a_0 \cdot l_0)$, in which V = apolar chain volume, a_0 = head group area and l_0 = chain length, that the geometry of the amphiphile determines what kind of aggregates is formed. Starting with a small head group, compared to the chain, inverted micelles are to be expected.



Picture 3.1: *a) PS-dendr-$(NH_2)_8$, negative staining, x107,000; b) Pt-shadowing vesicular structures, x84,000; c) PS-dendr-$(NH_2)_{16}$, negative staining, x84,000; d) freeze fracture micellar rods, x84,000; (e) PS-dendr-$(NH_2)_{32}$, Pt-shadowing, x24,400; f) negative staining spherical micelles.*

With increasing head group size, aggregates change from planar bilayers, through vesicles, rodlike micelles to spherical micelles. This process is exactly what is observed going from PS-*dendr*-$(NH_2)_4$ to PS-*dendr*-$(NH_2)_{32}$. Changing head group size and not the chemical nature of the amphiphilic structures is only possible using dendrimers and results in proof for Israelachvili's theory of shape-dependent aggregation behavior. A model for traditional surfactants is now qualitatively applicable for this special kind of amphiphilic block copolymers.

For a quantitative comparison with the theory of Israelachvili, knowledge of dendrimer head group size, chain length and volume are necessary. The head group areas, determined with the monolayer techniques, are known for PS-*dendr*-$(NH_2)_n$ with n = 8, 16. The volume of the chain can be estimated from the Van der Waals volume of a styrene unit (53 cm^3/mol)[20]. For 30 units this results in a volume of 1897.5 cm^3/mol. From these values the packing parameter P can be calculated, using 6 nm as chain length (estimated from the TEM-pictures). Using preset values of P, the corresponding l_0 can be calculated (table 3.3).

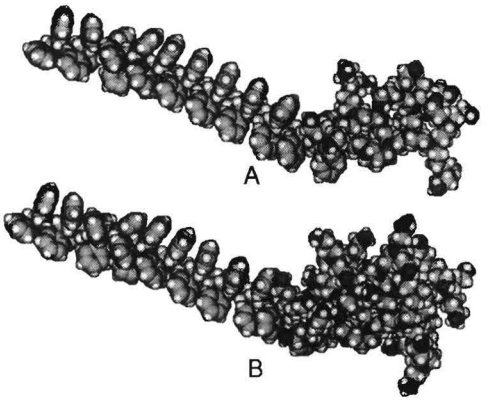
Table 3.3: Quantitative validation of the theory of Israelachvili

Product	$P_{Israelachvili}$	l_0, calculated[a] (Å)	P, calculated[b]
PS-*dendr*-$(NH_2)_8$	0.50–1.00	7.2–14	0.12
PS-*dendr*-$(NH_2)_{16}$	0.33–0.50	11.1–17	0.09

[a] Calculated with V=1897.5 cm^3/mol; [b] Calculated with l_0= 6nm.

Both methods show a large discrepancy between what is calculated and what is expected, based on theory. An explanation can be that for block copolymers this theory is oversimplified and corrections have to be made for the strongly differing entropic factors when polymers are compared with small organic molecules. The fact that a perfect qualitative agreement is found, proves however that the basic theoretical ideas of Israelachvili's model are correct and universally applicable.

By comparing the polystyrene-poly(propylene imine) dendrimer amphiphiles with low molecular weight surfactants and traditional amphiphilic block copolymers, it becomes clear that our structures combine properties of both. A shared feature with surfactants is the ability of changing the type of aggregation by adjusting amphiphile geometry. For surfactants this is a well-known phenomenon, and forms the basis of Israelachvilis theory[19].



Picture 3.2: *a) PS-dendr-$(NH_2)_{16}$ and b) PS-dendr-$(NH_2)_{32}$. These molecular modelling representations, prepared by Quanta-CharMM, illustrate the effect of varying dendrimer generation on molecular shape.*

Changes in aggregation type can also be induced by solubilization[21], varying the concentration[22] or changing the ratio of mixed systems[23]. For amphiphilic block copolymers the possibilities are much more restricted. The main aggregation form is the spherical micelle, whereas some anomalous behavior is reported that leads to metastable wormlike micelles[24] or ellipsoidal structures[25]. For PS-PEO-PS triblock copolymers a change from spherical to rodlike micelles on increasing the temperature is reported[26].Using polymerizable surfactants or polymers with amphiphilic side chains it is possible to obtain a broader variety of aggregation types[27]. However, this is a different class of amphiphiles, for which the aggregate consists mostly out of one polymer, and of which the composition is less well-

defined. Variation of aggregation within a series of block copolymers is observed for twodimensional self-assembly of a polystyrene-peralkylated poly(vinyl pyridine) block copolymer[28]. On addition of polystyrene homopolymer different structures, varying from rings to sphercial micelles, were observed. Varying the ratio of block lengths of a polystyrene-polyisoprene diblock copolymer resulted in the solid phase in different agggregation types, from lamellar structures to the so-called ordered bicontinuous double diamond morphology[29]. Changing three-dimensional solvated aggregates by tuning the geometry, as observed for our structures however, is a new feature for block copolymers.
An advantage that our systems share with block copolymers is the stability of the aggregates formed. The strong interactions between the polymers in the core of the structure[30] makes it possible to observe micelles with TEM[18] and GPC[31]. The very low deaggregation rate was also observed by Riess et al. for block copolymers used in emulsion polymerization[32]. For our structures, stability is also proven by the techniques mentioned above and by the fact that on dilution no change occurs in aggregation type. This also points in the direction of low CMC-values, comparable to traditional block copolymer systems. Our systems are therefore very interesting to be used as stabilizers for vesicle and emulsion polymerization.

Polystyrene-poly(propylene imine) dendrimers can furthermore contribute to a better understanding of aggregation behavior of amphiphilic block copolymers, because the polar part of our molecules is as well-defined as a polymer can be, and heterogeneity of the structures, that sometimes can affect amphiphilic behavior[33], is diminished strongly.

3.5 Conclusions

It is possible to prepare a new series of amphiphilic diblock copolymers by a divergent poly(propylene imine) dendrimer synthesis onto a primary amine functionalized polystyrene core molecule. Every intermediate of this 10-step reaction procedure can be characterized in great detail. Study of the behavior of these amphiphiles at toluene/water and air/water interfaces clearly demonstrates the development of amphiphilicity with increasing generation. The change of aggregation type from inverted micellar structures for PS-*dendr*-$(NH_2)_4$,

through vesicles, rodlike micelles to spherical micelles for PS-*dendr*-$(NH_2)_{32}$ is in qualitative agreement with the theory of Israelachvili concerning surfactant assembly. The amphiphiles described in this chapter are similar in shape but different in size as compared with traditional surfactants, while similar in size but different in shape as compared with traditional block copolymers. This new class of amphiphiles can therefore contribute to a better understanding of the relation between molecular structure and amphiphilic properties. Furthermore, the versatility of these block copolymer systems makes it possible that they can be applied as stabilizer for microemulsions, vesicle and emulsion polymerization.

3.6 Experimental

General procedures

For a general section concerning purification of solvents and spectroscopic and chromatographic techniques: see chapter 2.

DSC-measurements were performed on a Perkin Elmer TAC 7/DX, with a heating rate of 40°C /min.

Monolayer experiments were performed on a thermostated, home-built trough (140x210 mm, University of Nijmegen). The surface pressure was measured using Wilhelmy plates mounted on a Trans-Tek transducer (Connecticut USA). The surface of compressed monolayers was studied with a Brewster angle microscope (NFT BAM-1), equipped with a 10 mW He-Ne laser with a beam diameter of 0.68 mm, operating at 632.8 nm. Reflections were detected using a CCD camera. On the subphase (Milli-Q water) 50-150 µl of a solution of the amphiphiles in $CHCl_3$ was spread and allowed to evaporate. The rate of compression was 7.0 cm^2/min.

Conductivity measurements were performed in a heterogeneous toluene/water system, with a CDM 83 conductivity meter, and a Philips conductivity cell PW9550. The cell constant was 0.872 cm^{-1}, and was calibrated with 0.1 M and 0.01 M KCl solutions. Measurements were performed at room temperature. 20 ml of a 0.01 M KCl solution in which $3.3 \cdot 10^{-4}$ mol/l amphiphile was dispersed was starting point of the measurements. To this mixture a $3.3 \cdot 10^{-4}$M amphiphile solution in toluene was added dropwise. The conductivity was measured continuously.

TEM-samples were prepared by the following procedure: the amphiphiles were dissolved in 2 ml toluene or tetrahydrofuran. After addition of 25 ml of water, the organic solvents were evaporated

and stable aggregates of $3 \cdot 10^{-4}$ mol/l were formed. A droplet of the sample was placed on a Cu-grid, covered with formvar, and allowed to dry for 1 minute, after which the droplet was removed. Negative staining was performed by addition of a droplet of a 2 w% uranyl acetate solution during 15 seconds. Pt-shaded samples were prepared by covering the dried sample with Pt using a Balzers Sputter unit. Freeze fractured samples were prepared by addition of a droplet of the amphiphile dispersion onto a golden microscope grid (150 mesh), placed between 2 copper plates and fixated in supercooled liquid pentane. Sample holders were placed in a Balzers freeze etching system BAF 400 D at 10^{-7} Torr and heated to -105 °C. After fracturing, the samples were etched for 1 min. (ΔT 20°C), shaded with Pt (layer thickness 2 nm) and covered with carbon (layer thickness 20 nm). Replicas were allowed to heat up to room temperature and left on 20% chromic acid for 16 h. After rinsing with water they were allowed to dry. All samples were studied using a Philips TEM 201 (60 kV).

Dynamic light scattering was performed at DSM-Research, Geleen, using a ALV/SP-86 goniometer, equipped with a Spectra Physics 2000 Ar^+-laser (514.5 nm, 300 mW). A Glan-Thompson prism was used for detection of the vertically polarized scattered light. The intensity-auto correlation functions were determined with an ALV-5000 multibit correlator. Aqueous aggregates were prepared according to the method described for the TEM samples.

Electrospray mass spectra were recorded on an API 300 MS/MS Perkin Elmer sciex mass spectrometer, with a mass range of 3000. Compounds were dissolved at concentrations of 150 ppm in 50% MeOH/ 50% THF, and 0.1% HCOOH was added. The sample solution was delivered directly to the ES-MS by a Harvard syringe pump at a flow rate of 5 µl/min. The mass spectrometer was used in a positive ion mode by applying to the capillary a voltage of 5.5 kV, while the orifice was set at 35 V. Mass spectra were collected in full scan mode, scanning over $30 < m/z > 2500$ in 25 s. Dry air was used as nebulizer gas at a flow rate of 1.04 l/min. Nitrogen was used as drying bath gas at a flow rate of 0.63 l/min. Electrospray data were deconvoluted by the Bio-reconstruct program.

Dendrimer synthesis

A Parr reactor, type 4561 (300 ml), equipped with 4642 controller was used for the hydrogenation reactions. All solvents (p.a. quality) and reagents were used without further purification, except for dichloromethane (chemical purity), *n*-hexane (distilled before use) and methanol used for precipitations (technical grade). Raney cobalt (Grace) was kindly provided by DSM. PS-NH_2 (M_n=3.26·10^3 g/mol, M_w/M_n =1.05) was prepared according to the procedure described in chapter 2,

using the large scale anionic polymerization set-up, the CO_2 end-cap method and the indirect amination route.

PS-*dendr*-$(CN)_2$ (3.1)

To a solution of 49.28 g of PS-NH_2 in 100 ml toluene 10.95 g HOAc (11 moleq.), 50 ml water and 100 ml acrylonitrile were added. The mixture was heated under reflux during 24 hours and the solution was evaporated *in vacuo*. The crude solid was dissolved in CH_2Cl_2 and the solution was again evaporated *in vacuo* to remove residual HOAc. The product was taken up in THF and precipitated in a tenfold excess of a mixture of methanol and a few drops of ammonia. After filtration and drying *in vacuo* (60°C) 49.33 g (97%) of dinitrile **3.1** was obtained.

DSC: Tg = 79.3°C.

^{1}H-NMR ($CDCl_3$) δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-$CH(C\underline{H}_3)$-$(CH_2$-$CHPh)_n$), 0.78-2.44 (CH_3-$C\underline{H}_2$-$C\underline{H}(CH_3)$-$(C\underline{H}_2$-$C\underline{H}Ph)_{n-1}$-$C\underline{H}_2$-CHPh-CH_2-O-CH_2-$C\underline{H}_2$-CH_2-N), 2.16 (4H, N-CH_2-$\underline{C}H_2$-CN), 2.30 (2H, O-CH_2-CH_2-$C\underline{H}_2$-N), 2.66 (4H, N-$C\underline{H}_2$-CH_2-CN), 3.10-3.48 (br, 4H, CH_2-CHPh-$C\underline{H}_2$-O-$C\underline{H}_2$-CH_2-CH_2-N), 6.25-7.32 ($(CH_2$-$CH\underline{Ph})_n$) ppm.

^{13}C- NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 18.0 (N-CH_2-$\underline{C}H_2$-CN), 18.5-19.8 (br, CH_3-CH_2-$CH(\underline{C}H_3)$-$(CH_2$-$CHPh)_n$), 27.5 (N-CH_2-$\underline{C}H_2$-CH_2-N), 28.7-30.4 (br, CH_3-$\underline{C}H_2$-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 31.5 (CH_3-CH_2-$\underline{C}H(CH_3)$-$(CH_2$-$CHPh)_n$), 40.3 (CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$\underline{C}HPh)_n$), 40.0-46.5 (br, CH_3-CH_2-$CH(CH_3)$-$(\underline{C}H_2$-$CHPh)_n$), 49.5 (O-CH_2-CH_2-$\underline{C}H_2$-N), 49.9 (N-$\underline{C}H_2$-CH_2-CN), 67.0-67.6 (br, $(CH_2$-$CHPh)_n$-CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 75.0-76.5 (br, $(CH_2$-$CHPh)_n$-$\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 118.7 (2C, $\underline{C}N$), 124.1-127.0 (br, CH_2-$CH\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-$CH\underline{Ph}_{ortho+meta}$), 145.1-146.5 (br, CH_2-$CH\underline{Ph}_{ipso}$) ppm.

IR: ν_{CN} 2246 cm^{-1}; 3025, 2923.7, 1943.3, 1872.1, 1803.7, 1744.2, 1664.9, 1601.0, 1492.9, 1451.9, 1372.8, 1116.3, 1028.4, 906.5, 756.7, 699.1, 539.4 cm^{-1}.

PS-*dendr*-$(NH_2)_2$ (3.2)

Dinitrile **3.1** (25.00 g, M_n=3.35·10^3 g/mol) was dissolved in a mixture of toluene/methanol 3/1 v/v and transferred into the Parr-reactor vessel. 9 g Raney/cobalt catalyst suspension in water was decanted, rinsed with methanol (3 times) and toluene (1 time) and added to the substrate using the toluene/methanol 3/1 v/v mixture. Next the total volume was brought to 225 ml. After closing the reactor, the solution was purged 3 times with H_2. 35 g NH_3 was added to the system. The reaction mixture was mechanically stirred during 24 hours at 50°C and 80 bar H_2 pressure. The hydrogenation

could be followed accurately by the decrease of the CN stretch vibration in the IR spectrum. After cooling and releasing pressure the catalyst was filtered off on a glass filter over a layer of diatomaceous earth. After evaporation of the solvent the product was taken up in THF and precipitated in a tenfold excess of H_2O. After precipitating in H_2O the product was free of carbamate. After filtration and drying *in vacuo* at 60°C 22.45 g of product was obtained (89%). The purity was confirmed by TLC, IR, ^{1}H-NMR and ^{13}C-NMR.

DSC: Tg = 77.9°C.

^{1}H-NMR ($CDCl_3$) δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-$CH(C\underline{H}_3)$-$(CH_2$-$CHPh)_n$), 0.78-2.44 (CH_3-$C\underline{H}_2$-$C\underline{H}(CH_3)$-$(C\underline{H}_2$-$C\underline{H}Ph)_{n-1}$-$C\underline{H}_2$-CHPh-CH_2-O-CH_2-$C\underline{H}_2$-CH_2-N + N-CH_2-$C\underline{H}_2$-CH_2-N), 2.32-2.50 (6H, O-CH_2-CH_2-$C\underline{H}_2$-N + N-$C\underline{H}_2$-CH_2-CH_2-NH_2), 2.67 (4H, N-CH_2-CH_2-$C\underline{H}_2$-NH_2), 3.10-3.48 (br, 4H, CH_2-CHPh-$C\underline{H}_2$-O-$C\underline{H}_2$-CH_2-CH_2-N), 6.25-7.32 ($(CH_2$-$C\underline{H}Ph)_n$) ppm.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 18.4-19.9 (br, CH_3-CH_2-$CH(\underline{C}H_3)$-$(CH_2$-$CHPh)_n$), 25.6 (O-CH_2-$\underline{C}H_2$-CH_2-N), 29.9 (N-CH_2-CH_2-CH_2-NH_2), 28.7-30.4 (br, CH_3-$\underline{C}H_2$-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 30.9 (N-CH_2-$\underline{C}H_2$-CH_2-NH_2), 31.4 (CH_3-CH_2-$\underline{C}H(CH_3)$-$(CH_2$-$CHPh)_n$), 40.4 (CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$\underline{C}HPh)_n$), 40.7 (N-CH_2-CH_2-$\underline{C}H_2$-NH_2), 40.0-46.4 (br, CH_3-CH_2-$CH(CH_3)$-$(\underline{C}H_2$-$CHPh)_n$), 50.5 (O-CH_2-CH_2-$\underline{C}H_2$-N), 51.8 (N-$\underline{C}H_2$-CH_2-CH_2-NH_2), 68.6-69.0 (br, $(CH_2$-$CHPh)_n$-CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 75.0-76.4 (br, $(CH_2$-$CHPh)_n$-$\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 124.1-127.0 (br, CH_2-$C\underline{H}Ph_{para}$), 127.0-129.5 (br, CH_2-$C\underline{H}Ph_{ortho+meta}$), 145.1-146.5(br, CH_2-$C\underline{H}Ph_{ipso}$) ppm.

IR: ν_{NH}: 3436.3, 3382.2 cm^{-1}.

PS-*dendr*-$(CN)_4$ (3.3)

To a solution of diamine **3.2** (28.80 g, M_n=3.36·10^3 g/mol) in 200 ml toluene 6.0 g HOAc (11 moleq.), 100 ml water and 100 ml acrylonitrile were added. The mixture was heated under reflux during 65 hours. After work up an impurity was detected on TLC and ^{1}H NMR. The resulting product was purified using flash chromatography. By elution with CH_2Cl_2 all impurities were removed. Eluting with 3% MeOH in CH_2Cl_2 gave the desired pure tetranitrile **3.3** (22.89 g, 80%).

DSC: Tg = 74.9°C.

^{1}H-NMR ($CDCl_3$) δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-$CH(C\underline{H}_3)$-$(CH_2$-$CHPh)_n$), 0.78-2.74 (CH_3-$C\underline{H}_2$-$C\underline{H}(CH_3)$-$(C\underline{H}_2$-$C\underline{H}Ph)_n$-CH_2-O-CH_2-CH_2-CH_2-N), 1.55-1.62 (br, 6H, O-CH_2-$C\underline{H}_2$-CH_2-N + N-CH_2-$C\underline{H}_2$-CH_2-N), 2.35-2.42 (br, 6H, O-CH_2-CH_2-$C\underline{H}_2$-N + N-CH_2-CH_2-$C\underline{H}_2$-N), 2.41 (t, J = 6.6 Hz, 8H,

N-CH_2-$C\underline{H}_2$-CN), 2.53 (t, J =6.7 Hz, 4H, N-$C\underline{H}_2$-CH_2-CH_2-N), 2.75-2.85 (br, 8H, N-$C\underline{H}_2$-CH_2-CN), 3.11-3.45 (br, 4H, CH_2-CHPh-$C\underline{H}_2$-O-$C\underline{H}_2$-CH_2-CH_2-N), 6.25-7.32 ((CH_2-$C\underline{H}$Ph)$_n$) ppm.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 16.9 (N-CH_2-$\underline{C}H_2$-CN), 18.5-19.8 (br, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 24.9 (N-CH_2-$\underline{C}H_2$-CH_2-N), 26.9 (O-CH_2-$\underline{C}H_2$-CH_2-N), 28.7-30.4 (br, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 31.5 (CH_3-CH_2-$\underline{C}$H(CH_3)-(CH_2-CHPh)$_n$), 40.3 (CH_3-CH_2-CH(CH_3)-(CH_2-$\underline{C}$HPh)$_n$), 40.0-46.5 (br, CH_3-CH_2-CH(CH_3)-($\underline{C}H_2$-CHPh)$_n$), 49.5 (N-$\underline{C}H_2$-CH_2-CN), 50.3 (O-CH_2-CH_2-$\underline{C}H_2$-N), 51.3/51.5 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 67.9-68.7 (br, (CH_2-CHPh)$_n$-CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 75.0-76.5 (br, (CH_2-CHPh)$_n$-$\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 118.7 (CN), 124.1-127.0 (br, CH_2-CH$\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-CH$\underline{Ph}_{ortho+meta}$), 145.1-146.5 (br, CH_2-CH$\underline{Ph}_{ipso}$) ppm.

IR: ν_{CN} 2245 cm^{-1}.

PS-*dendr*-(NH_2)$_4$ (3.4)

Tetranitrile **3.3** (19,80 g, M_n=3.57·10^3 g/mol) was hydrogenated during 24 hours according to the procedure described for the synthesis of **3.2**. 12 g catalyst and 30 g NH_3 were used. Tetraamine **3.4** (17.75 g, **90%**) was obtained after taking up the crude solid in THF and precipitating in H_2O.

DSC: Tg = 72.7°C.

^{1}H-NMR ($CDCl_3$) δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-CH($C\underline{H}_3$)-(CH_2-CHPh)$_n$), 0.78-2.44 (CH_3-$C\underline{H}_2$-$C\underline{H}$(CH_3)-($C\underline{H}_2$-$C\underline{H}$Ph)$_{n-1}$-$C\underline{H}_2$-CHPh-CH_2-O), 1.60-1.70 (br, 14H, O-CH_2-$C\underline{H}_2$-CH_2-N + N-CH_2-$C\underline{H}_2$-CH_2-N), 2.25-2.38 (br, 10H, O-CH_2-CH_2-$C\underline{H}_2$-N + N-$C\underline{H}_2$-CH_2-$C\underline{H}_2$-N), 2.42 (t, J = 6.7 Hz, 8H, N-$C\underline{H}_2$-CH_2-CH_2-NH_2), 2.70 (t, J = 6.7 Hz, 8H, N-CH_2-CH_2-$\underline{C}H_2$-NH_2), 3.10-3.48 (br, 4H, CH_2-CHPh-$C\underline{H}_2$-O-$C\underline{H}_2$-CH_2-CH_2-N), 6.25-7.32 ((CH_2-$C\underline{H}$Ph)$_n$) ppm.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 18.4-19.9 (br, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 24.5 (N-CH_2-$\underline{C}H_2$-CH_2-N), 27.0 (O-CH_2-$\underline{C}H_2$-CH_2-N), 28.7-30.4 (br, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 30.9 (N-CH_2-$\underline{C}H_2$-CH_2-NH_2), 31.4 (CH_3-CH_2-$\underline{C}$H(CH_3)-(CH_2-CHPh)$_n$), 40.4 (CH_3-CH_2-CH(CH_3)-(CH_2-$\underline{C}$HPh)$_n$), 40.7 (N-CH_2-CH_2-$\underline{C}H_2$-NH_2), 40.0-46.4 (br, CH_3-CH_2-CH(CH_3)-($\underline{C}H_2$-CHPh)$_n$), 50.9 (O-CH_2-CH_2-$\underline{C}H_2$-N), 51.8 (N-$\underline{C}H_2$-CH_2-CH_2-NH_2), 52.2 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 69.0-69.4 (br, (CH_2-CHPh)$_n$-CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 75.0-76.4 (br, (CH_2-CHPh)$_n$-$\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 124.1-127.0 (br, CH_2-CH$\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-CH$\underline{Ph}_{ortho+meta}$), 145.1-146.5 (br, CH_2-CH$\underline{Ph}_{ipso}$) ppm.

IR: ν_{NH} 3436.3, 3378.7 cm^{-1}.

PS-*dendr*-$(CN)_8$ (3.5)

To a solution of tetraamine **3.4** (17.00 g, M_n=3.60·10^3 g/mol) in 170 ml toluene 2.0 g HOAc (11 moleq.), 85 ml water and 60 ml acrylonitrile were added. The mixture was heated under reflux during 48 hours. The solution was evaporated *in vacuo*. The crude solid was dissolved in CH_2Cl_2 and the solution was again evaporated *in vacuo* to remove residual HOAc. The product was taken up in THF and precipitated in a tenfold excess of a mixture of methanol and ammonia (9/1 v/v). After filtration and drying *in vacuo* (60°C) 14.0 g (75%) of octanitrile **3.5** was obtained.

DSC: Tg = 61.7°C.

^{1}H-NMR ($CDCl_3$) δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-$CH(C\underline{H}_3)$-$(CH_2$-$CHPh)_n$), 0.78-2.74 (CH_3-$C\underline{H}_2$-$C\underline{H}(CH_3)$-$(C\underline{H}_2$-$C\underline{H}Ph)_n$-CH_2-O-CH_2-CH_2-CH_2-N), 1.60 (s, 12H, N-CH_2-$C\underline{H}_2$-CH_2-N) 2.37 (br, 14H, O-CH_2-CH_2-$C\underline{H}_2$-N + N-CH_2-CH_2-$C\underline{H}_2$-N), 2.43 (t, *J* = 6.6 Hz, 16H, N-CH_2-$C\underline{H}_2$-CN), 2.53 (t, *J* = 6.7 Hz, 12H, N-$C\underline{H}_2$-CH_2-CH_2-N), 2.80 (t, *J* = 6.6 Hz, 16H, N-$C\underline{H}_2$-CH_2-CN), 3.13-3.45 (br, 4H, CH_2-CHPh-$C\underline{H}_2$-O-$C\underline{H}_2$-CH_2-CH_2-N), 6.25-7.32 ($(CH_2$-$C\underline{H}Ph)_n$) ppm.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 17.0 (N-CH_2-$\underline{C}H_2$-CN), 18.8-20.0 (br, CH_3-CH_2-$CH(\underline{C}H_3)$-$(CH_2$-$CHPh)_n$), 24.6 (N-CH_2-$\underline{C}H_2$-CH_2-N), 25.1 (N-CH_2-$\underline{C}H_2$-CH_2-N), 27.2 (CH_2-$\underline{C}H_2$-CH_2-N), 28.3-30.6 (br, CH_3-$\underline{C}H_2$-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 31.6 (CH_3-CH_2-$\underline{C}H(CH_3)$-$(CH_2$-$CHPh)_n$), 40.4 (CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$\underline{C}HPh)_n$), 40.2-47.0 (br, CH_3-CH_2-$CH(CH_3)$-$(\underline{C}H_2$-$CHPh)_n$), 49.6 (N-$\underline{C}H_2$-CH_2-CN), 50.9 (O-CH_2-CH_2-$\underline{C}H_2$-N), 51.5/51.7 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 52.2/52.4 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 69.6-69.2 (br, $(CH_2$-$CHPh)_n$-CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 75.2-76.2 (br, $(CH_2$-$CHPh)_n$-$\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 119.1 (8C, $\underline{C}N$), 125.2-127.0 (br, CH_2-$CH\underline{Ph}_{para}$), 127.1-130.0 (br, CH_2-$CH\underline{Ph}_{ortho+meta}$), 145.1-146.6 (br, CH_2-$CH\underline{Ph}_{ipso}$) ppm.

IR: ν_{CN} 2247 cm^{-1}.

PS-*dendr*-$(NH_2)_8$ (3.6)

Octanitrile **3.5** (12,50 g, M_n=4.00·10^3 g/mol) was hydrogenated during 26 hours according to the procedure described for the synthesis of **3.2**, using 160 ml solvent, 7.9 g catalyst and 15.6 g NH_3. Octaamine **3.6** (11.94 g, 95%) was obtained after taking up the crude solid in THF and precipitating in ammonia. The product was carbamate free.

DSC: Tg = 73.6°C.

^{1}H-NMR ($CDCl_3$) δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-$CH(C\underline{H}_3)$-$(CH_2$-$CHPh)_n$), 0.78-2.44 (CH_3-$C\underline{H}_2$-$C\underline{H}(CH_3)$-$(C\underline{H}_2$-$C\underline{H}Ph)_{n-1}$-$C\underline{H}_2$-CHPh-CH_2-O), 1.55-1.65 (br, 30H, O-CH_2-$C\underline{H}_2$-CH_2-N + N-CH_2-$C\underline{H}_2$-

CH_2-N), 2.25-2.41 (br, 26H, O-CH_2-CH_2-C$\underline{H_2}$-N + N-C$\underline{H_2}$-CH_2-C$\underline{H_2}$-N), 2.45 (t, J = 6.7 Hz, 16H, N-$\underline{C}H_2$-CH_2-CH_2-NH_2), 2.72 (t, J = 6.7 Hz, 16H, N-CH_2-CH_2-$\underline{C}H_2$-NH_2), 3.10-3.48 (br, 4H, CH_2-CHPh-C$\underline{H_2}$-O-C$\underline{H_2}$-CH_2-CH_2-N), 6.25-7.32 ((CH$_2$-CH$\underline{Ph}$)$_n$) ppm.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 18.4-19.9 (br, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 24.4 (N-CH_2-$\underline{C}H_2$-CH_2-N), 28.1 (O-CH_2-$\underline{C}H_2$-CH_2-N), 28.7-30.4 (br, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 30.5 (N-CH_2-$\underline{C}H_2$-CH_2-NH_2), 31.4 (CH_3-CH_2-$\underline{C}H$(CH_3)-(CH_2-CHPh)$_n$), 40.4 (CH_3-CH_2-CH(CH_3)-(CH_2-$\underline{C}$HPh)$_n$), 40.5 (N-CH_2-CH_2-$\underline{C}H_2$-NH_2), 40.0-46.4 (br, CH_3-CH_2-CH(CH_3)-($\underline{C}H_2$-CHPh)$_n$), 50.7 (O-CH_2-CH_2-$\underline{C}H_2$-N), 51.8 (N-$\underline{C}H_2$-CH_2-CH_2-NH_2), 52.2 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 69.0-69.4 (br, (CH_2-CHPh)$_n$-CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 75.0-76.4 (br, (CH_2-CHPh)$_n$-$\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 124.1-127.0 (br, CH_2-CH$\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-CH$\underline{Ph}_{ortho+meta}$), 145.1-146.5(br, CH_2-CH$\underline{Ph}_{ipso}$) ppm.

IR: ν_{N-H} 3375 / 3289 cm^{-1}.

PS-*dendr*-(CN)$_{16}$ (3.7)

To a solution of octaamine **3.6** (11.25 g, M_n=4.02·10^3 g/mol) in 100 ml toluene 1.8 g HOAc (11 moleq.), 100 ml water and 60 ml acrylonitrile were added to obtain a stable emulsion. The mixture was heated under reflux during 30 hours. The solution was evaporated *in vacuo*. The crude solid was dissolved in CH_2Cl_2 and the solution was again evaporated to remove residual HOAc. The product was taken up in THF and precipitated in a tenfold excess of H_2O. After filtration and drying *in vacuo* (60°C) 12.75 g (93%) of hexadecanitrile **3.7** was obtained.

DSC: Tg = -26.3 and 65.5°C.

^{1}H-NMR ($CDCl_3$) δ 0.54-0.78 (br, 6H, $\underline{C}H_3$-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 0.78-2.74 (CH_3-$\underline{C}H_2$-$\underline{C}H$(CH_3)-($\underline{C}H_2$-$\underline{C}$HPh)$_n$-CH_2-O-CH_2-CH_2-CH_2-N), 1.52-1.62 (br, 26H, N-CH_2-$\underline{C}H_2$-CH_2-N), 2.25-2,41 (br, 30H, O-CH_2-CH_2-C$\underline{H_2}$-N + N-CH_2-CH_2-C$\underline{H_2}$-N), 2.45 (t, J = 6.6 Hz, 32H, N-CH_2-C$\underline{H_2}$-CN), 2.54 (t, J = 6.7 Hz, 28H, N-C$\underline{H_2}$-CH_2-CH_2-N), 2.82 (t, J = 6.6 Hz 32H, N-C$\underline{H_2}$-CH_2-CN), 3.13-3.45 (br, 4H, CH_2-CHPh-C$\underline{H_2}$-O-C$\underline{H_2}$-CH_2-CH_2-N), 6.25-7.32 ((CH$_2$-CH$\underline{Ph}$)$_n$) ppm.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 16.6 (N-CH_2-$\underline{C}H_2$-CN), 18.8-20.0 (br, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 23.9 (N-CH_2-$\underline{C}H_2$-CH_2-N), 24.6 (N-CH_2-$\underline{C}H_2$-CH_2-N), 26.6 (O-CH_2-$\underline{C}H_2$-CH_2-N), 28.1-30.2 (br, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 31.3 (CH_3-CH_2-$\underline{C}H$(CH_3)-(CH_2-CHPh)$_n$), 40.1 (CH_3-CH_2-CH(CH_3)-(CH_2-$\underline{C}$HPh)$_n$), 39.8-46.6 (br, CH_3-CH_2-CH(CH_3)-($\underline{C}H_2$-CHPh)$_n$), 49.2 (N-$\underline{C}H_2$-CH_2-CN), 50.4 (O-CH_2-CH_2-$\underline{C}H_2$-N), 51.1/51.3 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 51.9 (N-$\underline{C}H_2$-CH_2-CH_2-N), 69.2-69.6 (br, (CH_2-CHPh)$_n$-CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 75.2-76.2 (br,

$(CH_2\text{-}CHPh)_n\text{-}\underline{C}H_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}N$), 118.7 (16C, $\underline{C}N$), 125.2-127.0 (br, $CH_2\text{-}CH\underline{Ph}_{para}$), 127.1-130.0 (br, $CH_2\text{-}CH\underline{Ph}_{ortho+meta}$), 145.1-146.6 (br, $CH_2\text{-}CH\underline{Ph}_{ipso}$) ppm.

IR: ν_{CN} 2246 cm^{-1}; 1657.9, 1640.5 cm^{-1}.

PS-*dendr*-$(NH_2)_{16}$ (3.8)

Hexadecanitrile **3.7** (10.75 g, M_n=4.9·10^3 g/mol) was hydrogenated during 50 hours according to the procedure described for the synthesis of **3.2**, using as solvent 160 ml toluene/MeOH = 2/1 v/v, 10.9 g catalyst and 25 g NH_3. Hexadecaamine **3.8** (10.00 g, 93%) was obtained after taking up the crude solid in THF and precipitating in ammonia.

DSC: Tg = -10.2 and 77.6°C.

^{1}H-NMR ($CDCl_3$) δ 0.54-0.78 (br, 6H, $C\underline{H}_3\text{-}CH_2\text{-}CH(C\underline{H}_3)\text{-}(CH_2\text{-}CHPh)_n$), 0.78-2.44 ($CH_3\text{-}C\underline{H}_2\text{-}C\underline{H}(CH_3)\text{-}(C\underline{H}_2\text{-}C\underline{H}Ph)_{n-1}\text{-}C\underline{H}_2\text{-}CHPh\text{-}CH_2\text{-}O$), 1.52-1.62 (br, 62H, $O\text{-}CH_2\text{-}C\underline{H}_2\text{-}CH_2\text{-}N$ + $N\text{-}CH_2\text{-}C\underline{H}_2\text{-}CH_2\text{-}N$), 2.30-2.41 (br, 58H, $O\text{-}CH_2\text{-}CH_2\text{-}C\underline{H}_2\text{-}N$ + $N\text{-}C\underline{H}_2\text{-}CH_2\text{-}C\underline{H}_2\text{-}N$), 2.45 (t, J = 6.7 Hz, 32H, $N\text{-}\underline{C}H_2\text{-}CH_2\text{-}CH_2\text{-}NH_2$), 2.72 (t, J = 6.7 Hz, 32H, $N\text{-}CH_2\text{-}CH_2\text{-}\underline{C}H_2\text{-}NH_2$), 3.10-3.48 (br, 4H, $CH_2\text{-}CHPh\text{-}C\underline{H}_2\text{-}O\text{-}C\underline{H}_2\text{-}CH_2\text{-}CH_2\text{-}N$), 6.25-7.32 ($(CH_2\text{-}C\underline{H}Ph)_n$).

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3\text{-}CH_2\text{-}CH(CH_3)\text{-}(CH_2\text{-}CHPh)_n$), 18.4-19.9 (br, $CH_3\text{-}CH_2\text{-}CH(\underline{C}H_3)\text{-}(CH_2\text{-}CHPh)_n$), 24.4 ($N\text{-}CH_2\text{-}\underline{C}H_2\text{-}CH_2\text{-}N$), 28.1 ($O\text{-}CH_2\text{-}\underline{C}H_2\text{-}CH_2\text{-}N$), 28.7-30.4 (br, $CH_3\text{-}\underline{C}H_2\text{-}CH(CH_3)\text{-}(CH_2\text{-}CHPh)_n$), 30.8 ($N\text{-}CH_2\text{-}\underline{C}H_2\text{-}CH_2\text{-}NH_2$), 31.4 ($CH_3\text{-}CH_2\text{-}\underline{C}H(CH_3)\text{-}(CH_2\text{-}CHPh)_n$), 40.4 ($CH_3\text{-}CH_2\text{-}CH(CH_3)\text{-}(CH_2\text{-}\underline{C}HPh)_n$), 40.5 ($N\text{-}CH_2\text{-}CH_2\text{-}\underline{C}H_2\text{-}NH_2$), 40.0-46.4 (br, $CH_3\text{-}CH_2\text{-}CH(CH_3)\text{-}(\underline{C}H_2\text{-}CHPh)_n$), 51.5 ($N\text{-}CH_2\text{-}CH_2\text{-}\underline{C}H_2\text{-}NH_2$), 50.0-53.0 (br, $N\text{-}\underline{C}H_2\text{-}CH_2\text{-}\underline{C}H_2\text{-}N$), 68.0-69.0 (br, $(CH_2\text{-}CHPh)_n\text{-}CH_2\text{-}O\text{-}\underline{C}H_2\text{-}CH_2\text{-}CH_2\text{-}N$), 75.0-76.4 (br, $(\underline{C}H_2\text{-}CHPh)_n\text{-}\underline{C}H_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}N$), 124.1-127.0 (br, $CH_2\text{-}CH\underline{Ph}_{para}$), 127.0-129.5 (br, $CH_2\text{-}CH\underline{Ph}_{ortho+meta}$), 145.1-146.5(br, $CH_2\text{-}CH\underline{Ph}_{ipso}$).

IR: $\nu_{N\text{-}H}$ 3362 / 3286 cm^{-1}.

PS-*dendr*-$(CN)_{32}$ (3.9)

To a solution of hexadecaamine **3.8** (9.50 g, M_n=5.0·10^3 g/mol) in 200 ml toluene 1.3 g HOAc (11 moleq.), 200 ml water and 100 ml acrylonitrile were added to obtain a stable emulsion. The mixture was heated under reflux during 64 hours. The solution was evaporated *in vacuo*. The crude solid was dissolved in CH_2Cl_2 and the solution was again evaporated *in vacuo* to remove residual HOAc. The product was taken up in THF and precipitated in a tenfold excess of ammonia. After filtration and drying *in vacuo* (60°C) 9.22 g (80%) of 32-nitrile **3.9** was obtained.

DSC: Tg = -23.8 and 59.9°C.

^{1}H-NMR ($CDCl_3$) δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-$CH(C\underline{H}_3)$-$(CH_2$-$CHPh)_n$), 0.78-2.74 (CH_3-$C\underline{H}_2$-$C\underline{H}(CH_3)$-$(C\underline{H}_2$-$C\underline{H}Ph)_n$-CH_2-O-CH_2-CH_2-CH_2-N), 1.52-1.68 (br, 60H, N-CH_2-$C\underline{H}_2$-CH_2-N), 2.30-2,62 (br, 122H, O-CH_2-CH_2-$C\underline{H}_2$-N + N-CH_2-CH_2-$C\underline{H}_2$-N), 2.45 (t, *J* = 6.6 Hz, 64H, N-CH_2-$C\underline{H}_2$-CN), 2.82 (t, *J* = 6.6 Hz, 64H, N-$C\underline{H}_2$-CH_2-CN), 3.13-3.45 (br, 4H, CH_2-CHPh-$C\underline{H}_2$-O-$C\underline{H}_2$-CH_2-CH_2-N), 6.25-7.32 ((CH_2-$C\underline{H}Ph)_n$) ppm.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 16.8 (N-CH_2-$\underline{C}H_2$-CN), 18.8-20.0 (br, CH_3-CH_2-$CH(\underline{C}H_3)$-$(CH_2$-$CHPh)_n$), 23.7 (N-CH_2-$\underline{C}H_2$-CH_2-N), 24.6 (N-CH_2-$\underline{C}H_2$-CH_2-N), 26.5 (O-CH_2-$\underline{C}H_2$-CH_2-N), 28.1-30.2 (br, CH_3-$\underline{C}H_2$-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 31.3 (CH_3-CH_2-$\underline{C}H(CH_3)$-$(CH_2$-$CHPh)_n$), 40.1 (CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$\underline{C}HPh)_n$), 39.8-46.6 (br, CH_3-CH_2-$CH(CH_3)$-$(\underline{C}H_2$-$CHPh)_n$), 49.0 (N-$\underline{C}H_2$-CH_2-CN), 52.0-50.4 (br, O-CH_2-CH_2-$\underline{C}H_2$-N, N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 69.6-69.2 (br, $(CH_2$-$CHPh)_n$-CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 75.2-76.2 (br, $(CH_2$-$CHPh)_n$-$\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 118.7 (CN), 125.2-127.0 (br, CH_2-$CH\underline{Ph}_{para}$), 127.1-130.0 (br, CH_2-$CH\underline{Ph}_{ortho+meta}$), 145.1-146.6 (br, CH_2-$CH\underline{Ph}_{ipso}$) ppm.

IR: ν_{CN} 2246 cm^{-1}; 1667.9 cm^{-1}.

PS-*dendr*-$(NH_2)_{32}$ (3.10)

Dotriacontanitrile **3.9** (7.72 g, M_n=6.50·10^3 g/mol) was hydrogenated according to the procedure described for the synthesis of **3.2** using 8.0 g catalyst and 19.8 g NH_3. Reaction was performed during 72 hours in 160 ml solvent (toluene/MeOH = 1/1 v/v). After this time no further decrease of the CN-stretch vibration ($\nu_{C\equiv N}$) in the IR-spectrum could be detected. After work-up reaction was prolonged under identical circumstances (i.e. adding the same quantities of solvents and reactants) for 72 hours. After this time again no further decrease of the CN-stretch vibration could be detected. After work-up reaction was prolonged under identical circumstances for another 26 hours. After evaporation 5.05 g (64%) of 32-amine **3.10** was obtained. Precipitation in ammonia was not possible due to the amphiphilic character of **3.10**. Direct structural evidence via ^{1}H NMR and ^{13}C NMR was not possible due to carbamate formation.

IR: $\nu_{N\text{-}H}$ 3362 / 3281 cm^{-1}.

3.7 References and Notes

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Chapter 4

Modifications of polystyrene-poly(propylene imine) diblock copolymers

Summary

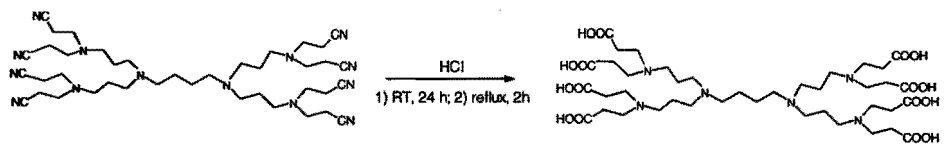
In this chapter the effect of two types of dendrimer modification on amphiphilic behavior of the polystyrene (PS)-poly(propylene imine) block copolymers is described. Acid hydrolysis of PS-dendr-$(CN)_n$ with n = 2–32 resulted in acid end group functionalized dendrimers in high yields. By methylation of the amine-terminated diblock copolymers (PS-dendr-$(NH_2)_n$ with n = 1–16), polycationic structures were obtained, of which all primary and tertiary amines were quaternized. Aggregation behavior was clearly demonstrated for both modified block copolymers with ^{13}C-NMR spectroscopy. Dynamic light scattering and transmission electron microscopy were hampered by strong clustering between the aggregates. With conductivity measurements it could be determined that PS-dendr-$(COOH)_n$ showed pH-dependent amphiphilic behavior; at high and low pH the structures showed an increased ability for stabilizing water as continuous phase. A comparable increase in polarity was observed for the methylated structures. Using these modifications, it is therefore possible to influence the polar character of PS-poly(propylene imine) block copolymers, which makes them a very versatile new class of amphiphiles.

4.1 Introduction

The generation dependency of amphiphilic and aggregation behavior of the polystyrene (PS) - poly(propylene imine) dendrimer diblock copolymers has clearly been demonstrated in chapter 3. The versatility of these amphiphilic block copolymers, however, is not only due to changing

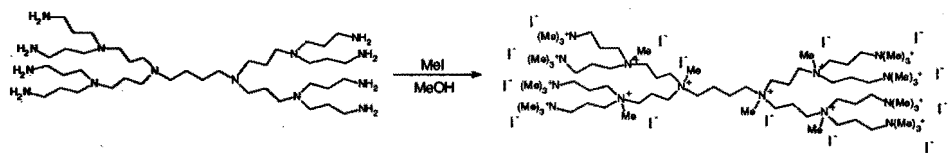
head group size, but the chemical structure of the poly(propylene imines) also offers the possibility of changing the polarity of the head group. Already a large variety of modification reactions has been investigated for DAB-*dendr*-$(NH_2)_n$ and DAB-*dendr*-$(CN)_n$[1]. A choice was made for simple, well-defined chemistry, that was known to proceed quantitatively. Even with this kind of chemistry, difficulties were sometimes encountered[2], due to the complex dendritic structure. Two types of reactions, that can be performed without any problems, are also very interesting for the amphiphilic block copolymers.

Acid hydrolysis of the nitrile intermediates[3] results in a dendritic structure with carboxylic acid end groups. The reaction is performed in concentrated hydrochloric acid, by stirring for 24 h at room temperature, followed by heating under reflux for an additional 2 h. The modified dendrimer has an ambivalent character, based on the basic interior tertiary amines and the carboxylic acids at the periphery. This can give rise to interesting, but also complex, pH-dependent structural changes, varying from a fully protonated, polycationic structure at low pH, to a deprotonated polyanionic system at high pH. In between these limits a point can be reached for which the total net charge will equal zero.



Scheme 4.1: *Acid hydrolysis of DAB-dendr-(CN)$_8$.*

Quaternization with MeI of the amine-functionalized dendrimers is a second quantitative reaction that has been studied extensively[4]. In this case the primary as well as the tertiary amines become methylated. This modification is therefore a powerful tool in eliminating pH effects. The presence of a large amount of cationic charges onto the dendritic head group, in combination with the bulky I^- counterions, results in a significant increase in polarity and size of the dendritic structure.



Scheme 4.2: *Quaternization of DAB-dendr-(NH$_2$)$_8$.*

In this chapter the application of both reactions is described for the modification of PS-dendrimer block copolymers. The acid derivatives are interesting, because their amphiphilic behavior can possibly be regulated by adjustment of pH. Quaternization should also have a pronounced effect, because of the increase in polarity and head group size of the amphiphiles. The effect of head group modification on amphiphilic behavior is studied with conductivity measurements, whereas aggregation phenomena are observed with ^{13}C-NMR spectroscopy, dynamic light scattering and transmission electron microscopy.

4.2 Synthesis of modified PS-dendrimer block copolymers

Although both acid hydrolysis and quaternization have been performed quantitatively for the poly(propylene imine) dendrimers, the change to PS as core molecule could introduce synthetic problems. In case of the acid hydrolysis, no homogeneous reaction system can be obtained in an aqueous HCl-solution. For the quaternization reaction the availability of all tertiary and primary amines can be questioned in the presence of the PS-chain. Also work-up procedures have to be adjusted. In this paragraph the modified reaction procedures are described for acid hydrolysis (§ 4.2.1) and quaternization (§ 4.2.2).

4.2.1 Synthesis and characterization of PS-*dendr*-$(COOH)_n$

The acid hydrolysis of PS-*dendr*-$(CN)_n$ to PS-*dendr*-$(COOH)_n$ with n = 1–32 (figure 4.1) was performed in a heterogeneous reaction mixture of toluene/concentrated hydrochloric acid, in a two-step procedure. This procedure was developed to exclude acid-catalyzed retro-Michael reaction. First the mixture was stirred for 24 hours at room temperature, followed by 2 hours heating under reflux. Using this reaction process, the PS-*dendr*-$(CN)_n$ with n = 2–32 series was quantitatively hydrolyzed to the desired acid-functionalized dendrimers. The two-phase system at the beginning of the reaction changed into a stable emulsion at the end. Purification proved to be tedious. The work-up procedure used for the DAB-*dendr*-$(COOH)_n$ series, which included washing with dry acetone, was used for the higher generations of amphiphiles, (PS-*dendr*-$(COOH)_n$ with n = 8–32). PS-*dendr*-$(COOH)_n$ with n = 2,4 were

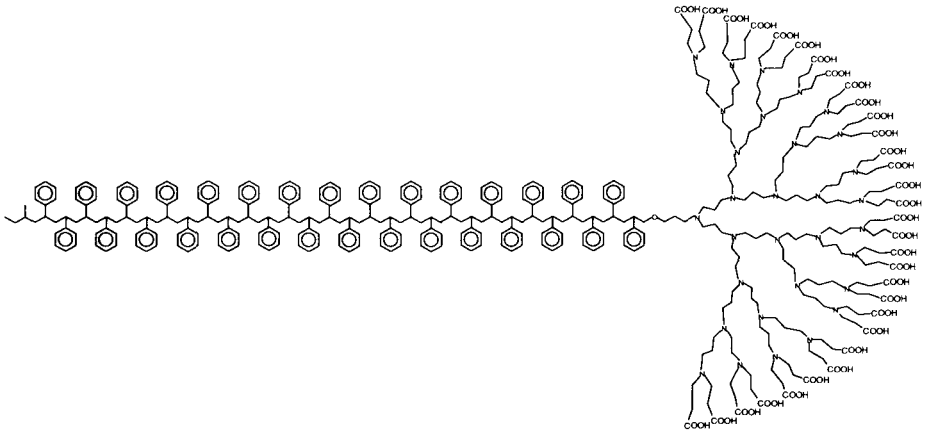


Figure 4.1: *PS-dendr-(COOH)$_{32}$.*

purified by precipitation in water, since these products were soluble in acetone. Dialysis of the products was impossible, due to the too large pore width of the available dialysis membrane, and the poor solubility of the products in either acetone, CH_2Cl_2 or water. All products were obtained as HCl salts in high yields after work-up (table 4.1). Characterization was possible with ^{13}C-NMR-spectroscopy in DMSO-d_6 (figure 4.2) . ^{1}H-NMR showed broad signals, of which no real quantitative information could be obtained. IR-spectroscopy was very useful for confirmation of the hydrolysis of the nitriles, by a complete disappearance of the CN-stretch vibration and the rise of a carboxylic signal. It was impossible to hydrolyze PS-CN when the same procedure was used as for the rest of the series. When this reaction system was used, no reaction occurred at all. The hydrolysis of PS-CN was further investigated using THF instead of toluene, or applying a basic hydrolysis method with toluene/NaOH (20 w% aqueous solution) and TOMA as phase transfer catalyst. In both cases considerable retro Michael reactions occurred and no desired product was formed.

The adjustment of the acid hydrolysis medium from HCl (33% aqueous solution) in the case of the traditional poly(propylene imines), to a toluene/concentrated hydrochloric acid mixture is a result of the change from 1,4-diaminobutane to PS as core molecule. Addition of toluene is required to dissolve the PS-part of the block copolymer, and the dendritic head group has to be located at the HCl-toluene interface, in order to hydrolyze the nitriles. In case of PS-CN, the dendritic part is not polar enough, and therefore this product can't get into contact with

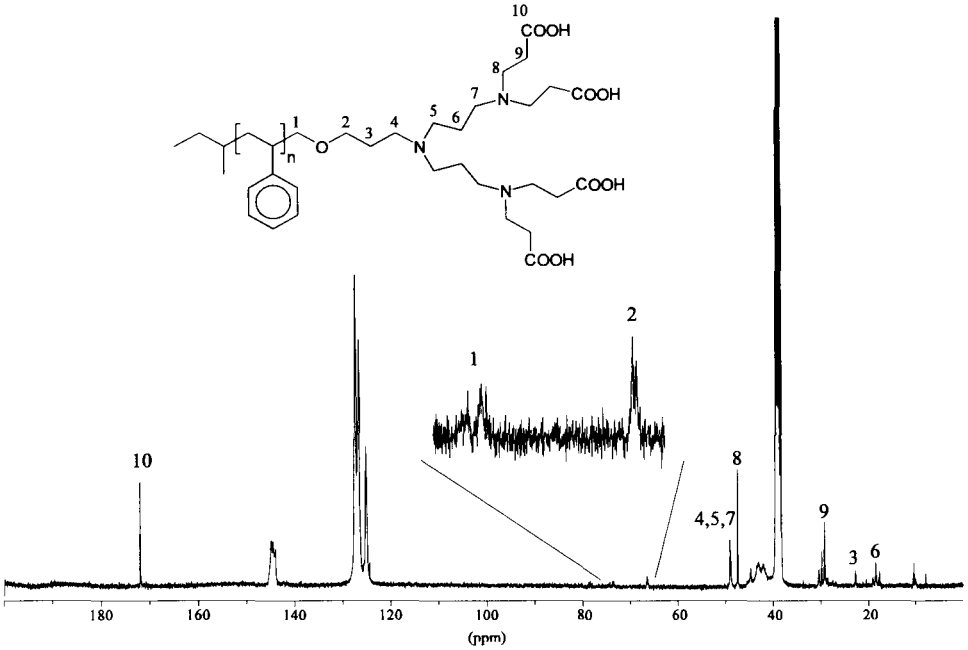


Figure 4.2: *^{13}C-NMR spectrum of PS-dendr-(COOH)$_4$ in DMSO-d$_6$.*

the acid, and isn't hydrolyzed. Using THF instead of toluene makes a better miscibility possible between organic and aqueous phase. A better contact is also achieved using the basic heterogeneous system, which already proved to be successful as described in chapter 2. Both alternatives, however, favor the undesired retro-Michael side reaction. This reaction is known to proceed especially easily for addition products to alcohols[5]. This is much less the case for the amine addition products. To prevent acid-catalyzed retro-Michael reactions for the higher generations, a two-step procedure is used. First the amide is synthesized at room temperature. This is then hydrolyzed at elevated temperatures to the desired acids, without the chance of retro-Michael reactions. The ease of hydrolysis is clearly demonstrated. By modification of one nitrile, the obtained product is even more amphiphilic and therefore will facilitate the hydrolysis of the residual nitriles. The obtained fully hydrolyzed structure has a more pronounced amphiphilic behavior than the nitrile compound, as can be noticed from the fact that a stable emulsion is formed at the end of reaction.

Table 4.1: Yields after work-up of PS-*dendr*-$(COOH)_n$ and characterization with ^{13}C-NMR in different deuterated solvents

product	yield (%)	$CDCl_3$	DMSO-d_6	D_2O/NaOD
PS-*dendr*-$(COOH)_2$	95	+	+	-
PS-*dendr*-$(COOH)_4$	93	p	+	-
PS-*dendr*-$(COOH)_8$	85	p	+	d
PS-*dendr*-$(COOH)_{16}$	98	p	+	d
PS-*dendr*-$(COOH)_{32}$	94	-	+	d

+: full characterization, p: only polystyrene-block visible, d: only dendrimer-block visible,
-: no characterization possible.

Characterization with the spectroscopic techniques used, shows unambiguously that all of the nitriles are converted into acids. The reaction itself doesn't give problems, purification however, is difficult. These amphiphilic structures are fully protonated, and the best way of removal of the excess HCl is by dialysis, until a zwitterionic equilibrium point is reached. Already for the DAB-*dendr*-$(COOH)_n$ series it is demonstrated that this procedure is time consuming[6]. The low solubility of the amphiphiles, in combination with the possibility that the lower generations can pass through the dialysis membrane, leaves us with no other possibility than using the fully protonated structures.

4.2.2. Synthesis and characterization of PS-*dendr*-$(NMe_3^+)_n \cdot (2n-1)\ I^-$

Methylation of PS-*dendr*-$(NH_2)_n$ to PS-*dendr*-$(NMe_3^+)_n \cdot (2n-1)\ I^-$ was performed for the n = 1–32 series (figure 4.3). A mixture of CH_2Cl_2 and MeOH was used as solvent, and a large excess of MeI was added. The reaction was heated under reflux. Reaction times increased with increasing generation from 4 to 10 days. Purifications were performed by filtration, followed by washing procedures with dry acetone, to remove residual salts.

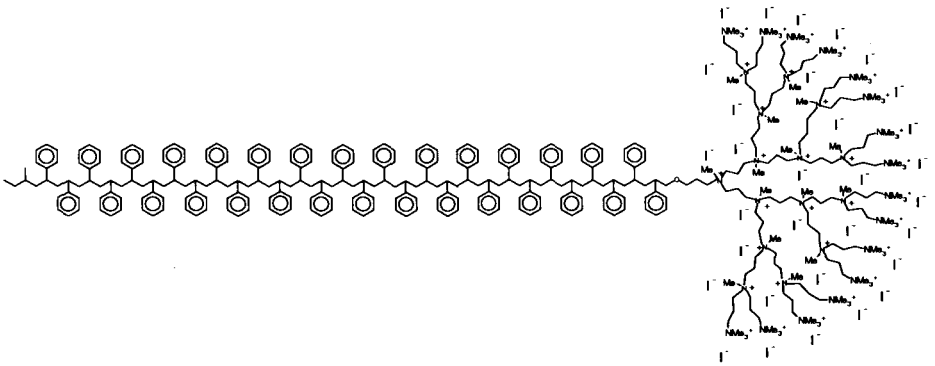


Figure 4.3: *PS-dendr-$(NMe_3^+)_{16}$· 31 I^-.*

The pure products were obtained in good yields and characterized with ^{13}C-NMR and ^{1}H-NMR spectroscopy in DMSO-d_6, except for PS-*dendr*-$(NMe_3^+)_{32}$ · 63 I^-, which showed severe solubility problems and could therefore not be analyzed (table 4.2). For this type of reaction IR-spectroscopy didn't supply useful information.

Table 4.2: Yields after work-up of PS-*dendr*-($NMe_3^+)_n$ ·2n-1 I^- and characterization with ^{13}C-NMR in different deuterated solvents

product (·2n-1 I^-)	yield (%)	$CDCl_3$	DMSO-d_6	D_2O
PS-*dendr*-NMe_3^+	99	+	+	-
PS-*dendr*-($NMe_3^+)_2$	95	+	+	-
PS-*dendr*-($NMe_3^+)_4$	90	p	+	d
PS-*dendr*-($NMe_3^+)_8$	75	p	+	d
PS-*dendr*-($NMe_3^+)_{16}$	67	p	+	d

+: full characterization, p: only polystyrene-block visible, d: only dendrimer-block visible,
-: no characterization possible.

An adaptation in the preparation of PS-*dendr*-$(NMe_3^+)_n$ ·2n-1 I^-, in comparison with the methylation of the DAB-*dendr*-$(NH_2)_n$ series, is the addition of CH_2Cl_2 for a better solubility of PS-*dendr*-$(NH_2)_n$. This doesn't seem to have a great effect on reaction. In contrast to the acid hydrolysis, the higher generations are more difficult to modify. It, however, still is remarkable that all primary and tertiary amines can be methylated, even for the higher generations, as

becomes clear from NMR-spectroscopy. This can be a result of the use of a soft base counterion as I^- instead of hard bases as for example triflate. Purification is again the most difficult step in the preparation procedure. Filtration and washing with acetone results in removal of the bulk of NaI salts. Because this work-up procedure proved to be successful for the DAB-*dendr*-$(NMe_3^+)_n$ ·2n-1 I^- series, it is assumed that this is also the case for the amphiphilic structures. It is however, very difficult to know if all of the salt is removed.

4.3 Amphiphilic and aggregation behavior

4.3.1 PS-*dendr*-$(COOH)_n$

Aggregates of PS-*dendr*-$(COOH)_n$ (n = 2–32) were investigated with ^{13}C-NMR spectroscopy in $NaOD/D_2O$, DMSO-d_6 and $CDCl_3$. Aqueous samples for transmission electron microscopy (TEM) and dynamic light scattering (DLS) (n = 8–32) were prepared with concentrations of $3 \cdot 10^{-4}$ mol/l at pH=12. The results of the ^{13}C-NMR investigations are presented in table 4.1. DLS and TEM measurements were strongly hampered by clustering of the amphiphilic aggregates. Only for PS-*dendr*-$(COOH)_8$ individual aggregates could be recognized, and were identified as curved, wormlike micellar structures (picture 4.1). However, also for this sample a large amount of clustering was observed as is shown in picture 4.2.

Picture 4.1: *TEM-picture of PS-dendr-$(COOH)_8$, prepared by Pt-shading technique. The used enlargement was x23,000.*

The results of the ^{13}C-NMR measurements clearly indicate the development of amphiphilic character of this series of modified block copolymers. Only the low generations can be fully characterized in $CDCl_3$. Aggregation behavior begins at PS-*dendr*-$(COOH)_4$, for which the dendritic head group is not visible anymore due to clustering. The dendritic parts are shielded off from the solvent, and therefore long relaxation times result in broad peaks that

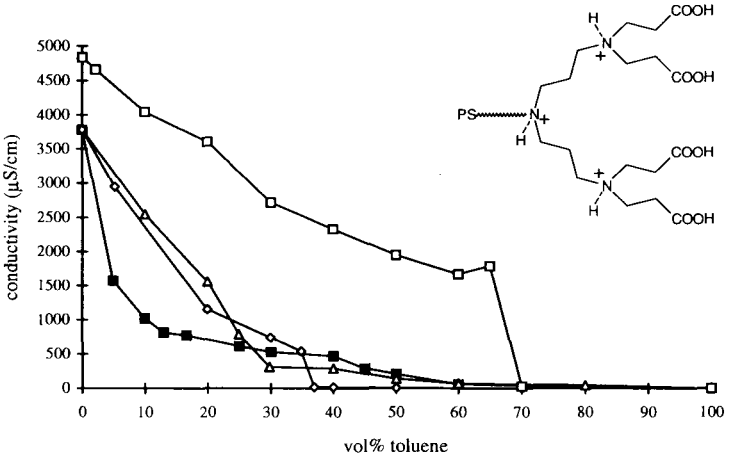
Picture 4.2: *TEM-picture of PS-dendr-$(COOH)_8$, prepared by negative staining. The used enlargement was x84,000.*

make identification impossible. The same effect, but then for the PS-parts, is shown for the higher generation amphiphiles PS-*dendr*-$(COOH)_8$ in D_2O/NaOD. Now only the dendrimer parts are visible. A comparable behavior of selective visibility of parts of block copolymers due to aggregation has earlier been reported by Spevácek and Gitsov[7]. The characterization problems with TEM and DLS, arising from clustering of aggregates are already observed for the PS-*dendr*-$(NH_2)_n$ series and also known for DAB-*dendr*-$(NH_2)_n$, and are due to strong electrostatic interactions. PS-*dendr*-$(COOH)_8$, the only structure that can be identified with TEM, shows a behavior in-between the vesicular structures of PS-*dendr*-$(NH_2)_8$ and the rodlike micelles of PS-*dendr*-$(NH_2)_{16}$.

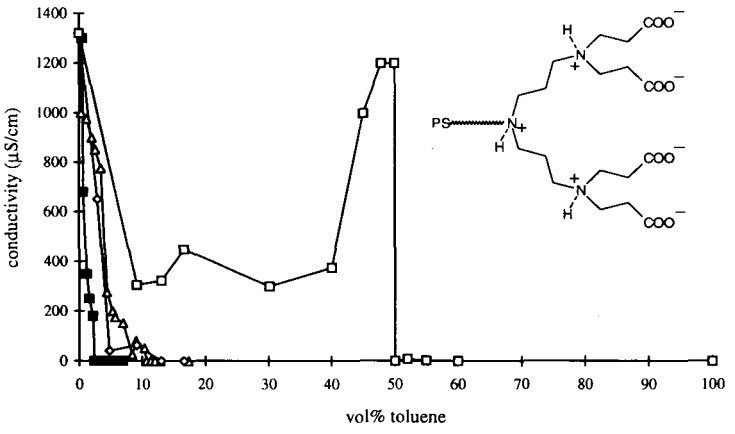
Amphiphilic behavior of PS-*dendr*-$(COOH)_n$ with n = 2–32 was studied with conductivity measurements. The influence of pH on amphiphilicity was tested for the acid derivatives at three different pH's, in 0.01 M HCl (pH = 1.9, measured for PS-*dendr*-$(COOH)_{16}$), in 0.01 M KCl (pH = 3.5) and in 0.01 M KOH (pH = 9.1). The concentration of amphiphiles used was $3 \cdot 10^{-4}$ mo/l, the ratio of toluene and electrolyte was varied discontinuously, in a batchwise manner. The results are depicted in figure 4.4. PS-*dendr*-$(COOH)_{32}$ is left out of the figure, because this structure didn't show amphiphilic behavior and a dilution curve was measured instead.

The change of pH has a distinct effect on the amphiphilic behavior of PS-*dendr*-$(COOH)_n$, with n = 2–8. The ability of stabilizing water as continuous phase is tremendously increased for pH = 1.9 and 9.1. The PS-*dendr*-$(COOH)_n$ series in 0.01 M KCl shows a behavior that resembles the PS-*dendr*-$(NH_2)_n$ system (figure 3.5).

4.4a



4.4b



4.4c

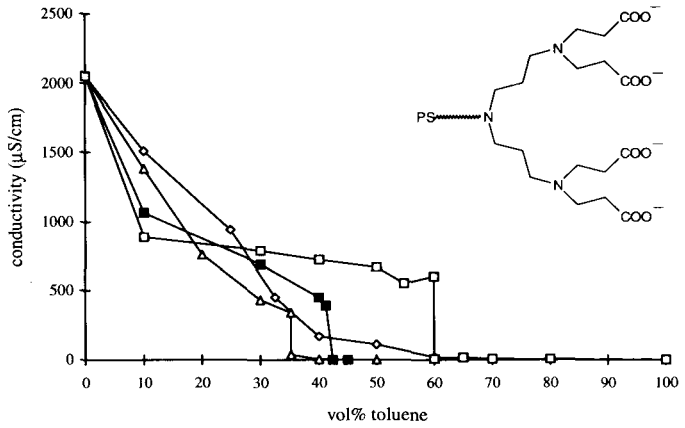


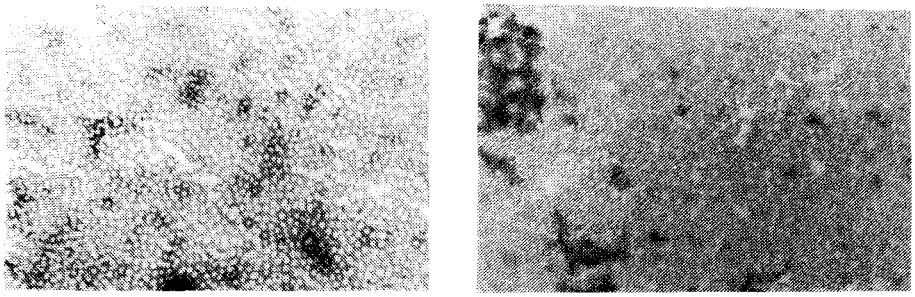
Figure 4.4: *Conductivity measurements of PS-dendr-(COOH)$_n$ in toluene/water emulsions at different pH, as a result of different electrolytes used: a) 0.01 M HCl; b) 0.01 M KCl; c) 0.01 M KOH.* ■*: PS-dendr-(COOH)$_2$;* Δ*: PS-dendr-(COOH)$_4$;*◊*: PS-dendr-(COOH)$_8$* □*: PS-dendr-(COOH)$_{16}$.*

PS-*dendr*-(COOH)$_n$ in 0.01 M KCl still has a pH = 3.5. This results from the fact that the HCl-salts of the acid series were used. A H^+/K^+ exchange lowers the pH. The overall net charge of the system, however, seems to be comparable to the PS-*dendr*-$(NH_2)_n$ series. PS-*dendr*-$(COOH)_{16}$ is less influenced by a change in pH, probably due to the already more balanced amphiphilic character of this molecule. The remarkable upswing in conductivity of PS-*dendr*-$(COOH)_{16}$ in figure 4.4b is accompanied by a strong viscosity increase of the system. The conductivity increase can therefore be explained by difficulties in mixing the viscous foam with a lamellar structure, which allows conductivity paths to sustain.

4.3.2 PS-*dendr*-$(NMe_3^+)_n \cdot(2n\text{-}1)\ I^-$

The PS-*dendr*-$(NMe_3^+)_n \cdot(2n\text{-}1)\ I^-$ series was studied with the same techniques, except for DLS, as the acid derivatives. The results of the ^{13}C-NMR investigations are presented in table 4.2. The same ^{13}C-NMR behavior is observed for PS-*dendr*-$(NMe_3^+)_n \cdot(2n\text{-}1)\ I^-$ as for the acid derivatives, and can therefore be explained in the same way. However, the onset of clustering begins for these modified structures already at n = 4.

TEM measurements were performed on PS-*dendr*-$(NMe_3^+)_n$ ·(2n-1) I^- with n = 4 and 8, with sample concentrations of $3 \cdot 10^{-4}$ mol/l. Again clustering was obtained, but now in a regular form, and both structures could be characterized as nanofoams[8] (picture 4.3).



a b

Picture 4.3: *TEM-picture of a) PS-dendr-$(NMe_3^+)_4$ · 7 I^- enlargement x 84,000 and b) PS-dendr-$(NMe_3^+)_8$ · 15 I^- enlargement x 56,000.*

These nanofoam structures are unexpected and show once more the versatility of these amphiphiles, for which modifications can lead to totally different aggregation types. The

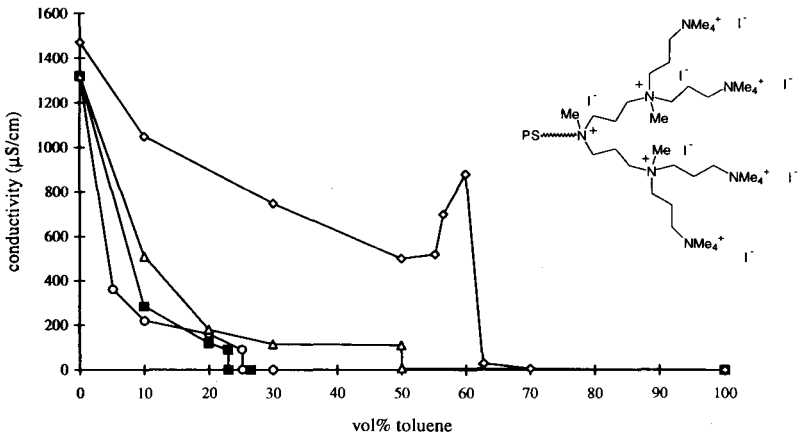


Figure 4.5: *Conductivity measurements of PS-dendr-($Nme_3^+)_n$·(2n-1) I^- in toluene/water emulsions with 0.01 M KCl used as electrolyte. ○: PS-dendr-$NMe_3^+ \cdot I^-$;*
■: PS-dendr-$(NMe_3^+)_2$·3 I^-; Δ: PS-dendr-($NMe_3^+)_4$·7 I^-; ◊: PS-dendr-($NMe_3^+)_8$·15 I^-.

nanofoams are however too irregular to obtain more detailed information from these pictures. This is due to the preparation technique used for TEM. More information can be obtained when AFM investigations are made, so that height and width of the foam structures can be accurately estimated.

Conductivity measurements were performed in the same way as the acid derivatives on PS-*dendr*-$(NMe_3^+)_n \cdot (2n-1)\ I^-$ in 0.01 M KCl electrolyte (figure 4.5). PS-*dendr*-$(NMe_3^+)_{16} \cdot 31\ I^-$ could not be measured accurately, and is therefore left out of the figure. The observed behavior shows a strong resemblance with the acid series measured at high and low pH. The onset of viscosity increase takes place in this case for n = 8.

4.4 Discussion

From all of the characterization techniques on both modified amphiphiles it has become clear that addition of charge onto the dendritic head group has a tremendous effect on the amphiphilic behavior of the block copolymers. The polarity of the head groups increases, which can be noticed from the larger amount of clustering, compared to the amine series, and the observed aggregation phenomena in ^{13}C-NMR. Also the greater ease with which the lower generations tend to stabilize water as continuous phase is partly a result of the increased polarity. A second effect is that the head group also becomes larger, due to electrostatic repulsions. The change in amphiphile geometry, due to the larger head group, results in an aggregation behavior of PS-*dendr*-$(COOH)_8$ which is in between the strucures observed for PS-*dendr*-$(NH_2)_8$ and PS-*dendr*-$(NH_2)_{16}$. This is again in agreement with Israelachvili's theory. The fact that the conductivity behavior of PS-*dendr*-$(COOH)_{16}$ is hardly influenced by charge, also indicates that shape of the molecules is of importance. The rodlike shape of this structure doesn't change so much that different amphiphilic behavior can be observed. The effect of charge on head group size is in line with Newkome's observations of a sharp increase of dendritic diameter due to repulsive interactions, for spherical, acid end group functionalized dendrimers[9]. Also modelling studies, performed by DSM-Research[10], on the effect of charge on the size of poly(propylene imine) dendrimers show the same results. Methylation proves to have a stronger effect on polarity and head group size than acid hydrolysis. This is shown by the fact that the head group of PS-*dendr*-$(NMe_3^+)_4 \cdot 7\ I^-$ already can be investigated in D_2O, one generation earlier than is the case for the acid structures. A similar effect is noticed for the

conductivity measurements for PS-*dendr*-$(NMe_3^+)_8 \cdot 15\ I^-$, which are comparable with PS-*dendr*-$(COOH)_{16}$.

Clustering of charged species is a phenomenon often observed, but hardly understood. This is partly due to the complexity of the investigated systems, which consist of a mixture of compounds as solvent, (poly)ions and counterions. In case of block copolymer systems the number of data available is furthermore limited, because of the difficulty of preparing well-defined polymer structures.

For surfactant systems lower consolute behavior is sometimes observed. This behavior is the spontaneous demixing of micellar solutions into dilute and concentrated conjugate phases with increasing temperature. Demixing is a result of interactions between the charged species. The nature of the attractive potential is not discussed. Quaternary ammonium salts, with different alkyl chain lengths attached to the ammonium group, are examples of these types of surfactants[11].

For block copolymers of polystyrene-poly(methacrylic acid) specific interactions are reported between the poly(methacrylic acid) chains[12]. Deprotonated and, therefore, highly charged systems lead to the formation of organized structures in solution. Also in the solid phase association of poly(methacrylic acid) chains occurs, which leads to the formation of a cylindrical type of morphology[13]. The degree of organization increases with increasing polarity. Dynamic light scattering studies of poly(styrene sulphonate) and poly(methacrylic acid)[14] show two dynamic modes, with characteristic times: a slow and a fast mode. The latter one is understood as a coupled diffusion of polyions and counterions. The slow mode, which is even described as 'mysterious', finds its origin in the formation of multichain domains. Therefore, an attractive force has to be present, that is electrostatic of nature. On dilution, the ordered structures tend to disappear.

An explanation for the phenomena described above is given by Ise[15], based on model studies on charged latex particles, for which also clustering is observed. Ise states that the reason for clustering is the fact that equally charged particles attract each other *via* their counterions. The Coulomb interaction exceeds the Coulomb repulsion, as is for example also the case in a NaCl crystal. The amount of clustering increases with increasing charge of the systems. For our structures, results are in close agreement with the abovementioned observations. In our case, however, no decrease in clustering is observed on dilution, which means that interactions are very strong.

4.5 Conclusions

Modification by acid hydrolysis of PS-*dendr*-$(CN)_n$ with n = 2–32 and methylation reactions on PS-*dendr*-$(NH_2)_n$ with n = 1–16 results in good yields in PS-*dendr*-$(COOH)_n$ and PS-*dendr*-$(NMe_3)^+_n \cdot(2n-1)\ I^-$, respectively. The PS-*dendr*-$(COOH)_n$ series shows a pH-dependent amphiphilic behavior. At high and low pH a strong increase in polarity is observed with ^{13}C-NMR spectroscopy, conductivity measurements and DLS. Increase of head group size by electrostatic repulsions is shown by TEM. Around the isoelectric point, the acids are comparable in their behavior with the amine-series. The PS-*dendr*-$(NMe_3)^+_n \cdot(2n-1)\ I^-$ series has an amphiphilic behavior that is similar to the acid series at extreme pH. The effects are, however, more outspoken, for both increase in polarity and increase in head group size. Head group modification of the amphiphilic block copolymers provides us with a powerful tool in changing and tuning amphiphilic properties, which makes this new class of amphiphiles very promising molecules for a large variety of surfactant applications.

4.6 Experimental

General procedures

For a general section concerning purification of solvents and spectroscopic and chromatographic techniques: see chapter 2. For the TEM-and dynamic light scattering measurements: see chapter 3.

Conductivity measurements were performed in a heterogeneous toluene/water system, with a CDM 83 conductivity meter, using a Philips conductivity cell PW9550. The cell constant was 0.872 cm^{-1}, and was calibrated with 0.1 M and 0.01 M KCl solutions. Measurements were performed at room temperature. For PS-*dendr*-$(COOH)_n$ 3 different electrolytes were used: 0.01 M KCl (pH = 3.5), 0.01 M KOH (pH = 9.1) and 0.01 M HCl (pH = 1.9). The pH values were measured for PS-*dendr*-$(COOH)_{16}$. For PS-*dendr*-$(NMe_3^+)_n$ a 0.01 M KCl solution was used. The conductivity measurements were performed in a batchwise manner: $3.3 \cdot 10^{-4}$ mol/l amphiphile was dispersed in a toluene/electrolyte mixture with a total volume of 23 ml. The ratio of toluene and electrolyte was varied. The conductivity was measured after 2 minutes equilibration time, after which a stable conductivity value was obtained.

Attempted synthesis of PS-COOH via hydrolysis of PS-CN

i) PS-CN (**2.6**) (0.50 g; M_n=3.2·10^3 g/mol) was dissolved in a mixture of 5 ml toluene and 5 ml concentrated hydrochloric acid. After vigorous stirring for about 24 hours at room temperature, the reaction mixture was heated under reflux during two hours. After evaporating the solution *in vacuo*, the product was taken up in THF and precipitated in H_2O. From characterization with ^{1}H-NMR, IR and TLC it became clear that no reaction had taken place and PS-CN was obtained.

ii) **2.6** (0.50 g; M_n=3.2·10^3 g/mol) was dissolved in a mixture of 5 ml toluene and 5 ml 25w% NaOH-solution. An equimolar amount of TOMA was added to this solution. After vigorous stirring of the solution for about 24 hours at room temperature, the reaction mixture was heated under reflux during two hours. After evaporating the solution *in vacuo*, taking up the product in THF and precipitating in H_2O, PS-OH (**2.5**) was obtained. This product was characterized with TLC and IR.

iii) **2.6** (0.50 g; M_n=3.2·10^3 g/mol) was dissolved in a mixture of 5 ml THF and 5 ml concentrated hydrochloric acid. The reaction mixture was vigorously stirred for about 24 hours at room temperature. After evaporating the solution *in vacuo*, the product was taken up in THF and precipitated in H_2O. With ^{1}H-NMR, IR and TLC two products (PS-CN and PS-OH) could be characterized in almost equivalent amounts.

PS-*dendr*-(COOH)$_2$ (4.1)

Dinitrile **3.1** (0.50 g; M_n=3.35·10^3 g/mol) was dissolved in a mixture of 5 ml toluene and 5 ml concentrated hydrochloric acid. After vigorous stirring for about 24 hours at room temperature, the reaction mixture was heated under reflux during 2 hours. After evaporating the solution and drying *in vacuo* (60°C) 0.48 g (95%) diacid **4.1** was obtained.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 18.5-19.8 (br, CH_3-CH_2-$CH(\underline{C}H_3)$-$(CH_2$-$CHPh)_n$), 23.5 (O-CH_2-$\underline{C}H_2$-CH_2-N), 27.5 (N-CH_2-$\underline{C}H_2$-COOH), 28.7-30.4 (br, CH_3-$\underline{C}H_2$-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 31.5 (CH_3-CH_2-$\underline{C}H(CH_3)$-$(CH_2$-$CHPh)_n$), 40.0-46.7 (br, $(\underline{C}H_2$-$\underline{C}HPh)_n$), 48.0 (N-$\underline{C}H_2$-CH_2-COOH), 49.9 (N-$\underline{C}H_2$-CH_2-CN), 50.0 (O-CH_2-CH_2-$\underline{C}H_2$-N), 67.0-67.6 (br, $(CH_2$-$CHPh)_n$-CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 74.5-76.5 (br, ($\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 124.1-127.0 (br, CH_2-$CH\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-$CH\underline{Ph}_{ortho+meta}$), 145.1-146.5 (br, CH_2-$CH\underline{Ph}_{ipso}$), 167.5 ($\underline{C}$OOH) ppm.

IR: ν_{CO} 1732.8 cm^{-1}; $\nu_{O\text{-}H}$ 3354cm^{-1}.

PS-*dendr*-(COOH)$_4$ (4.2)

Tetranitrile **3.3** (0.50 g; M_n=3,57·10^3 g/mol) was hydrolyzed according to the procedure described for the preparation of **4.1**. 0.49 g of **4.2** was obtained (93% yield).

^{13}C-NMR (DMSO-d_6) δ 10.0-10.6 (br, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$),17.8-18.0 (N-CH_2-$\underline{C}H_2$-CH_2-N), 18.3-19.2 (br, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 22.8 (O-CH_2-$\underline{C}H_2$-CH_2-N), 27.6 (N-CH_2-$\underline{C}H_2$-COOH), 28.6-30.0 (br, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 30.5 (CH_3-CH_2-$\underline{C}H$(CH_3)-(CH_2-CHPh)$_n$), 40.0-46.7 (($\underline{C}H_2$-$\underline{C}$HPh)$_n$), 47.7 (N-$\underline{C}H_2$-CH_2-COOH), 49.0-49.1 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 66.4-66.6 (CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 73.7-75.0 ($\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 125.2-131.8 (br, CH_2-CH$\underline{Ph}_{ortho,meta+para}$), 143.0-146.9 (br, CH_2-CH$\underline{Ph}_{ipso}$), 172.0 ($\underline{C}$OOH) ppm.

IR: $\nu_{C=O}$ 1706 cm^{-1}.

PS-*dendr*-(COOH)$_8$ (4.3)

Octranitrile **3.5** (0.50 g; $M_n = 4.00 \cdot 10^3$ g/mol) was dissolved in a mixture of 5 ml toluene and 5 ml concentrated hydrochloric acid. After vigorous stirring for about 24 hours at room temperature, the reaction mixture was heated under reflux during 2 hours. After evaporating the solution *in vacuo*, the product was washed several times with dry acetone. After drying *in vacuo* (60°C) 0.45 g (85%) octaacid **4.3** was obtained.

^{13}C-NMR (DMSO-d_6) δ 10.8-11.0 (br, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$),17.6 (N-CH_2-$\underline{C}H_2$-CH_2-N), 18.5-19.8 (br, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 23.4 (O-CH_2-$\underline{C}H_2$-CH_2-N), 27.5 (N-CH_2-$\underline{C}H_2$-COOH), 28.7-30.4 (br, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 31.0 (CH_3-CH_2-$\underline{C}H$(CH_3)-(CH_2-CHPh)$_n$), 40.0-46.7 (($\underline{C}H_2$-$\underline{C}$HPh)$_n$), 47.9 (N-$\underline{C}H_2$-CH_2-COOH), 49.1 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 50.2 (O-CH_2-CH_2-$\underline{C}H_2$-N), 67.0 (CH_2-O-$\underline{C}H_2$-CH_2-CH_2-N), 73.9-75.4 ($\underline{C}H_2$-O-CH_2-CH_2-CH_2-N), 125.2-131.8 (br, CH_2-CH$\underline{Ph}_{ortho,meta+para}$), 143.0-146.9 (br, CH_2-CH$\underline{Ph}_{ipso}$), 171.6 ($\underline{C}$OOH) ppm.

IR: $\nu_{C=O}$ 1706 cm^{-1}.

PS-*dendr*-(COOH)$_{16}$ (4.4)

Hexadecanitrile **3.7** (0.50 g; $M_n = 4.90 \cdot 10^3$ g/mol) was hydrolyzed according to the procedure described for the preparation of **4.3**. 0.57 g (98%) of **4.4** was obtained.

^{13}C-NMR (DMSO-d_6) δ 17.7 (O-CH_2-$\underline{C}H_2$-CH_2-N; N-CH_2-$\underline{C}H_2$-CH_2-N), 28.5 (N-CH_2-$\underline{C}H_2$-COOH), 48.1 (N-$\underline{C}H_2$-CH_2-COOH), 49.2 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 120.3-130.0 (br, CH_2-CH$\underline{Ph}_{ortho,meta+para}$), 142.6-148.0 (br, CH_2-CH$\underline{Ph}_{ipso}$), 171.6 ($\underline{C}$OOH) ppm.

IR: $\nu_{C=O}$ 1706 cm^{-1}; ν_{O-H} 2500-3600 cm^{-1}.

PS-*dendr*-(COOH)$_{32}$ (4.5)

Dotriacontanitrile **3.9** (1.00 g; $M_n = 6.50 \cdot 10^3$ g/mol) was hydrolyzed according to the procedure described for the preparation of **4.3**. 1.19 g (94%) of **4.5** was obtained.

^{13}C-NMR (DMSO-d_6) δ 17.8 (N-CH_2-$\underline{C}H_2$-CH_2-N), 28.6 (N-CH_2-$\underline{C}H_2$-COOH), 48.1 (N-$\underline{C}H_2$-CH_2-COOH), 49.3 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 125.3-129.0 (CH_2-CH$\underline{Ph}_{ortho,meta+para}$), 144.5-147.0 ($CH_2$-CH$\underline{Ph}_{ipso}$), 171.6 (COOH) ppm.

^{13}C-NMR (D_2O/NaOD) δ 25.0 (O-CH_2-$\underline{C}H_2$-CH_2-N; N-CH_2-$\underline{C}H_2$-CH_2-N), 36.7 (N-CH_2-$\underline{C}H_2$-COO^-), 52.0 (N-$\underline{C}H_2$-CH_2-COO^-), 53.5 (N-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-N), 183.9 ($\underline{C}OO^-$) ppm.

IR: $\nu_{C=O}$ 1706 cm^{-1} ; ν_{O-H} 2500-3600 cm^{-1}.

PS-NMe_3^+ (4.6)

To a solution of amine **2.7** (0.45 g, $M_n = 2.79 \cdot 10^3$ g/mol) in a mixture of 5 ml CH_2Cl_2 and 3 ml MeOH 1.45 g MeI (60 moleq.) and 0.060 g $NaHCO_3$ (4 moleq.) were added. The mixture was heated at 65°C during 4 days. After evaporation of the solution *in vacuo*, the crude solid was dissolved in $CHCl_3$. Removal of residual salts was possible by filtration. After evaporation of the clear solution and drying *in vacuo* (60°C) 0.47 g (99%) of **4.6** was obtained as a yellow foam.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 18.5-21.0 (br, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 23.6 (O-CH_2-$\underline{C}H_2$-CH_2-$^+N(CH_3)_3$), 28.0-30.5 (br, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 31.5 (CH_3-CH_2-$\underline{C}H$(CH_3)-(CH_2-CHPh)$_n$), 40.3 ((CH_2-$\underline{C}$HPh)$_n$), 40.0-46.8 (($\underline{C}H_2$-CHPh)$_n$), 53.5 (O-CH_2-CH_2-CH_2-$^+N(\underline{C}H_3)_3$), 64.9 (O-CH_2-CH_2-$\underline{C}H_2$-$^+N(CH_3)_3$), 65.9-66.3 (O-$\underline{C}H_2$-CH_2-CH_2-$^+N(CH_3)_3$), 74.9-76.7 ($\underline{C}H_2$-O-CH_2-CH_2-CH_2-$^+N(CH_3)_3$), 125.4-127.0 (br, CH_2-CH$\underline{Ph}_{para}$), 127.0-130.0 (br, CH_2-CH$\underline{Ph}_{ortho+meta}$), 144.5-146.5 (br, CH_2-CH$\underline{Ph}_{ipso}$) ppm.

PS-*dendr*-(NMe_3^+)$_2$ (4.7)

To a solution of diamine **3.2** (0.30 g, $M_n = 2.96 \cdot 10^3$ g/mol) in a mixture of 5 ml CH_2Cl_2 and 3 ml MeOH 2.01 g MeI (140 moleq.) and 0.070 g $NaHCO_3$ (8 moleq.) were added. The mixture was heated at 65°C during 4 days. The solution was evaporated *in vacuo*. The crude solid was dissolved in $CHCl_3$. Removal of residual salts was possible by filtration. After evaporation of the clear solution and drying *in vacuo* (60°C) 0.33 g (95%) of **4.7** was obtained as a pale yellow solid.

^{13}C-NMR ($CDCl_3$) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 18.9 ($^+N(CH_3)$-CH_2-$\underline{C}H_2$-CH_2-$^+N(CH_3)_3$), 18.5-21.0 (br, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 23.4 (O-CH_2-$\underline{C}H_2$-CH_2-$^+N(CH_3)_3$), 28.0-30.5 (br, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 31.5 (CH_3-CH_2-$\underline{C}H$(CH_3)-(CH_2-CHPh)$_n$), 40.3 ((CH_2-$\underline{C}$HPh)$_n$), 40.0-46.8 (($\underline{C}H_2$-CHPh)$_n$), 50.4 ($^+N(\underline{C}H_3)$), 54.7 ($^+N(\underline{C}H_3)_3$), 57.2 (O-CH_2-CH_2-$\underline{C}H_2$-$^+N(CH_3)$; $^+N(CH_3)$-$\underline{C}H_2$-CH_2-CH_2-$^+N(CH_3)_3$, 62.2 ($^+N(CH_3)$-CH_2-CH_2-$\underline{C}H_2$-$^+N(CH_3)_3$), 65.9-66.3 (CH_2-O-$\underline{C}H_2$-CH_2-CH_2-$^+N(CH_3)$), 74.9-76.7 ($\underline{C}H_2$-O-CH_2-CH_2-CH_2-$^+N(CH_3)$), 125.4-127.0 (br, CH_2-CH$\underline{Ph}_{para}$), 127.0-130.0 (br, CH_2- CH$\underline{Ph}_{ortho+meta}$), 144.5-146.5 (br, CH_2-CH$\underline{Ph}_{ipso}$) ppm.

PS-*dendr*-(NMe_3^+)$_4$ (4.8)

To a solution of tetraamine **3.4** (0.33 g, $M_n = 3.19 \cdot 10^3$ g/mol) in a mixture of 5 ml CH_2Cl_2 and 3 ml MeOH 3.67 g MeI (250 moleq.) and 0.14 g $NaHCO_3$ (16 moleq.) were added. The mixture was heated at 65°C during 4 days. After work-up the reaction proved to be not complete and was prolonged under identical circumstances (i.e. addition of the same quantities of solvents and reagents) for another 6 days. The solution was evaporated *in vacuo*. The crude solid was dissolved in $CHCl_3$. Removal of residual salts was possible by filtration. After evaporation of the clear solution and drying *in vacuo* (60°C) 0.40 g (95%) of **4.8** was obtained as a pale yellow solid.

^{13}C-NMR (DMSO-d_6) δ 11.0-11.4 (br, $\underline{C}H_3$-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 17.0 ($^+N(CH_3)$-CH_2-$\underline{C}H_2$-CH_2-$^+N(CH_3)$), 18.0 ($^+N(CH_3)$-CH_2-$\underline{C}H_2$-CH_2-$^+N(CH_3)_3$), 18.5-21.0 (br, CH_3-CH_2-$CH(\underline{C}H_3)$-$(CH_2$-$CHPh)_n$), 22.0 (O-CH_2-$\underline{C}H_2$-CH_2-$^+N(CH_3)$, 28.0-30.5 (br, CH_3-$\underline{C}H_2$-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 31.5 (CH_3-CH_2-$\underline{C}H(CH_3)$-$(CH_2$-$CHPh)_n$), 40.3 ((CH_2-$\underline{C}HPh)_n$), 40.0-46.8 (($\underline{C}H_2$-$CHPh)_n$), 50.3 (O-CH_2-CH_2-CH_2-$^+N(\underline{C}H_3)$), 50.8 ($^+N(\underline{C}H_3)$-CH_2-CH_2-CH_2-$^+N(CH_3)_3$), 53.3 ($^+N(\underline{C}H_3)_3$), 62.4 (CH_2-O-CH_2-CH_2-$\underline{C}H_2$-$^+N(CH_3)$), 62.8 ($^+N(CH_3)$-$\underline{C}H_2$-CH_2-CH_2-$^+N(CH_3)$; $^+N(CH_3)$-$\underline{C}H_2$-CH_2-CH_2-$^+N(CH_3)_3$), 61.9 ($^+N(CH_3)$-CH_2-CH_2-$\underline{C}H_2$-$^+N(CH_3)_3$), 65.9-66.3 (CH_2-O-$\underline{C}H_2$-CH_2-CH_2-$^+N(CH_3)$), 74.9-76.7 ($\underline{C}H_2$-O-CH_2-CH_2-CH_2-$^+N(CH_3)$), 125.4-127.0 (br, CH_2-$CH\underline{Ph}_{para}$), 127.0-130.0 (br, CH_2- $CH\underline{Ph}_{ortho+meta}$), 144.5-146.5 (br, CH_2-$CH\underline{Ph}_{ipso}$) ppm.

PS-*dendr*-(NMe_3^+)$_8$ (4.9)

To a solution of octaamine **3.6** (0.20 g, $M_n = 4.02 \cdot 10^3$ g/mol) in a mixture of 5 ml CH_2Cl_2 and 5 ml MeOH 3.53 g MeI (500 moleq.) and 0.13 g $NaHCO_3$ (32 moleq.) were added. The mixture was heated at 65°C during 4 days. After work-up reaction still was not complete and was prolonged under identical circumstances (i.e. addition of the same quantities of solvents and reagents) for another 6 days. The solution was evaporated *in vacuo*. The crude solid was washed several times with dry acetone to remove residual salts. After drying *in vacuo* (60°C) 0.23 g (75%) of **4.9** was obtained as a pale yellow solid.

^{13}C-NMR (DMSO-d_6) δ 16.0 ($^+N(CH_3)$-CH_2-$\underline{C}H_2$-CH_2-$^+N(CH_3)$), 18.0 ($^+N(CH_3)$-CH_2-$\underline{C}H_2$-CH_2-$^+N(CH_3)_3$), 18.5-21.0 (br, CH_3-CH_2-$CH(\underline{C}H_3)$-$(CH_2$-$CHPh)_n$), 22.0 (O-CH_2-$\underline{C}H_2$-CH_2-$^+N(CH_3)$, 28.0-30.5 (br, CH_3-$\underline{C}H_2$-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 31.5 (CH_3-CH_2-$\underline{C}H(CH_3)$-$(CH_2$-$CHPh)_n$), 40.3 ((CH_2-$\underline{C}HPh)_n$), 40.0-46.8 (($\underline{C}H_2$-$CHPh)_n$), 49.6 ($^+N(\underline{C}H_3)$), 53.6 ($^+N(\underline{C}H_3)_3$), 57.9 (O-CH_2-CH_2-$\underline{C}H_2$-$^+N(CH_3)$; $^+N(CH_3)$-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-$^+N(CH_3)$; $^+N(CH_3)$-$\underline{C}H_2$-CH_2-CH_2-$^+N(CH_3)_3$), 61.9 ($^+N(CH_3)$-CH_2-CH_2-$\underline{C}H_2$-$^+N(CH_3)_3$), 125.4-127.0 (br, CH_2-$CH\underline{Ph}_{para}$), 127.0-130.0 (br, CH_2- $CH\underline{Ph}_{ortho+meta}$), 144.5-146.5 (br, CH_2-$CH\underline{Ph}_{ipso}$) ppm.

PS-*dendr*-(NMe_3^+)$_{16}$ (4.10)

To a solution of hexadecaamine **3.8** (0.050 g, $M_n = 4.97 \cdot 10^3$ g/mol) in a mixture of 5 ml CH_2Cl_2 and 5 ml MeOH 1.18 g MeI (250 moleq.) and 0.022 g $NaHCO_3$ (32 moleq.) were added. The mixture was heated at 65°C during 10 days. The solution was evaporated *in vacuo*. The crude solid was washed several times with dry acetone to remove residual salts. After drying *in vacuo* (60°C) 0.052 g (67%) of **4.10** was obtained as a pale yellow solid.

^{13}C-NMR (DMSO-d_6) δ 17.4 ($^+$N(CH_3)-CH_2-$\underline{C}H_2$-CH_2-$^+$N(CH_3)), 18.0 ($^+$N(CH_3)-CH_2-$\underline{C}H_2$-CH_2-$^+$N(CH_3)$_3$), 18.5-21.0 (br, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 22.0 (O-CH_2-$\underline{C}H_2$-CH_2-$^+$N(CH_3), 28.0-30.5 (br, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 31.5 (CH_3-CH_2-$\underline{C}H$(CH_3)-(CH_2-CHPh)$_n$), 40.3 ((CH_2-$\underline{C}$HPh)$_n$), 40.0-46.8 (($\underline{C}H_2$-CHPh)$_n$), 49.6 ($^+$N($\underline{C}H_3$)), 53.6 ($^+$N($\underline{C}H_3$)$_3$), 58.5 (O-CH_2-CH_2-$\underline{C}H_2$-$^+$N(CH_3); $^+$N(CH_3)-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-$^+$N(CH_3); $^+$N(CH_3)-$\underline{C}H_2$-CH_2-CH_2-$^+$N(CH_3)$_3$), 61.9 ($^+$N(CH_3)-CH_2-CH_2-$\underline{C}H_2$-$^+$N(CH_3)$_3$), 125.4-127.0 (br, CH_2-C$\underline{H}$Ph$_{para}$), 127.0-130.0 (br, CH_2- C$\underline{H}$Ph$_{ortho+meta}$), 144.5-146.5 (br, CH_2-C$\underline{Ph}_{ipso}$) ppm.

Attempted synthesis of PS-*dendr*-(NMe_3^+)$_{32}$ (4.11)

To a solution of PS-*dendr*-(NH_2)$_{32}$ (**3.10**, 0.50 g, $M_n = 6.60 \cdot 10^3$ g/mol) in a mixture of 5 ml CH_2Cl_2 and 5 ml MeOH 5.30 g MeI (500 moleq.) and 0.32 g $NaHCO_3$ (64 moleq.) was added. The mixture was heated at 65°C during 10 days. The solution was evaporated *in vacuo*. The crude solid was washed several times with dry acetone to remove residual salts. After drying *in vacuo* (60°C) a pale yellow solid was obtained. Quantitative characterization with ^{1}H-NMR and ^{13}C-NMR proved to be impossible, because this product could not properly be dissolved.

4.7 References and Notes

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Chapter 5
Alkyl-modified dendrimers

Summary

Inverted unimolecular dendritic micelles of different generations and with different alkyl chain lengths were prepared by the reaction of alkylacid chlorides with poly(propylene imine) dendrimers. An extreme autoacceleration effect was observed during the reaction of alkylacid chlorides with an excess of dendrimer, which resulted in 2 structures: fully modified and totally unreacted dendrimers. The development of dendritic character, going from low to higher generations, was clearly noticed with ^{1}H-NMR spectroscopy by the change from predominantly inter- to intramolecular hydrogen bonding. DSC showed that phase transitions of the structures were determined by the length of the alkyl chain, except for DAB-dendr-(alkylamide)$_4$, which showed melting points similar to the corresponding alkylamides. With DAB-dendr-(alkylamide)$_{8,64}$ it was possible to physically encapsulate the hydrophilic dye Bengal Rose. The host-guest system obtained was useful for improving the compatibility of this dye with apolar materials.

5.1 Introduction

In chapter 3 and 4 the use of dendrimers as polar head group in amphiphilic block copolymers is described. By varying charge and size of the dendrimers, amphiphilic and aggregation behavior can be tuned and a variety of micellar structures is obtained. Dendrimers *themselves* can sometimes be regarded as amphiphilic structures as well. Already in 1985, Newkome[1] proposed the use of dendrimers as unimolecular micelles. He synthesized hydrophobic alkyl-dendrimers with carboxylate endgroups, the so-called micellanoates. By inclusion of lipophilic guests as chlorotetracycline and pinacyanol chloride in the core of the

dendrimer it was proven that these structures can act as unimolecular micelles[1b-d]. Research has recently been directed toward chemistry inside the dendritic micelle[1e].

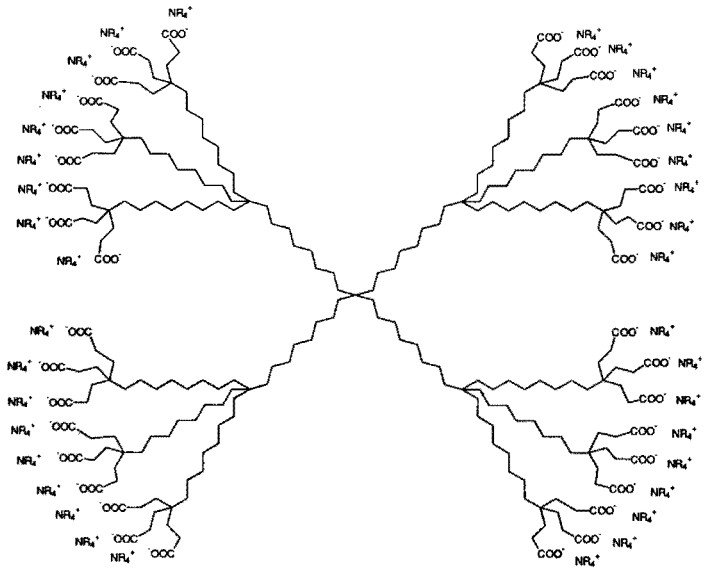


Figure 5.1: *[8^2-3] Micellanoate: a unimolecular micelle.*

The concept of the dendrimer as micelle has also been studied by Tomalia and Fréchet, who have shown enhanced solubility of apolar molecules in a polar environment by the use of dendrimers[2a,b]. One of the applications that seems to be promising is the use of these unimolecular micelles in electrokinetic capillary chromatography[2c-f]. In all of the cases mentioned thus far, dendrimers are regarded as regular unimolecular micelles, because they consist of an apolar core and a polar shell. Functionalization of the endgroups of hydrophilic dendrimers can lead to systems with a shell that is less polar than the dendritic core. When poly(propylene imine) dendrimers[3] are modified with alkyl chains, an inverted micellar structure is obtained, because the core of the dendrimer remains polar, due to the presence of inner tertiary amines. Very recently Tomalia has reported a similar modification for the PAMAM dendrimers[4].

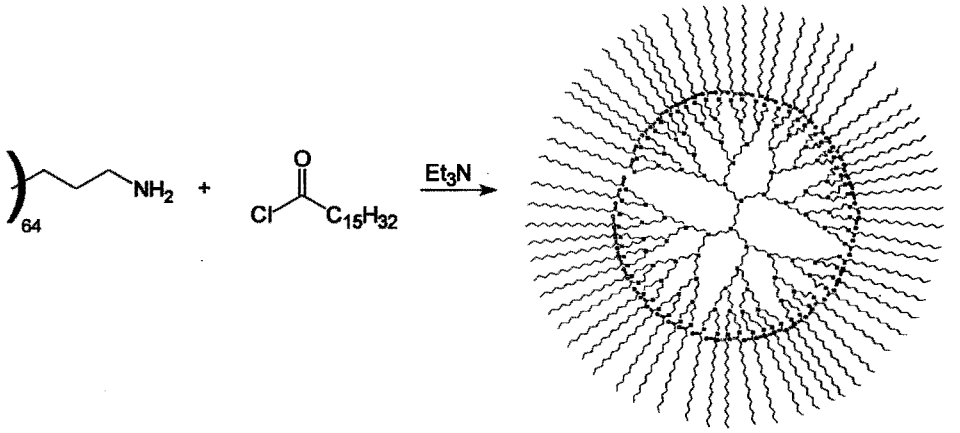
The guest-host properties of these modified dendritic molecules can show a resemblance with classical complexating agents as crown ethers, cryptands and calixarenes[5]. These systems all enhance the solubility of polar ionic compounds in an apolar environment.

However, with the inverted unimolecular micelles it should be possible to extend the solubility improvement to larger molecules, due to the fact that the cavities inside a dendrimer are larger than for the earlier mentioned host-systems[6].

Besides as unimolecular micelles, this type of modified dendrimers can also be considered as "hairy spheres", in analogy with the "hairy rods"[7]. It is known that the latter compounds can form mesophases after disentanglement of the alkyl chains, by alignment of the rods. It is interesting to investigate what kind of thermal properties can be found for hairy spheres, which in principle should lack anisotropy in their mesophases, due to the symmetry of the dendritic structures. In this chapter the synthesis of alkyl-modified dendrimers is described. The effect of generation and alkyl chain length on properties as dendritic character, phase transitions and guest-host complexation is discussed.

5.2 Synthesis of alkyl-modified dendrimers

Five different generations of poly(propylene imines), with 4 to 64 primary amine end groups (DAB-*dendr*-$(NH_2)_x$, with x=4–64) were used as starting materials for the synthesis of the alkyl-modified structures. The modification consisted of the conversion of the primary amines into amides through reaction with a small excess (1.1 eq. to 1.2 eq. for the higher generations) of acid chlorides in THF, in the presence of triethylamine as external base (scheme 5.1).



Scheme 5.1: *Synthesis of DAB-dendr-(palmitoyl)$_{64}$*

The use of alkanoic acids in combination with a coupling agent as DCC, resulted in the introduction of an impurity that could not be removed afterwards, and therefore this

method was rejected. Caproyl- (C5-tail), decanoyl- (C9) and palmitoyl- (C15) acid chlorides were used for the entire dendrimer series. DAB-*dendr*-$(NH_2)_{64}$ was also modified with undecanoyl (C10), lauroyl (C11), tridecanoyl (C12), myristoyl (C13) and pentadecanoyl (C14) chains. In these cases no excess acid chloride was used. The corresponding products could be obtained in reasonable yields (table 5.1), and were characterized by ^{1}H-NMR, ^{13}C-NMR and IR-spectroscopy. Special attention had to be paid to the purification of the alkyl-functionalized dendrimers. Every chain length required a different work-up procedure. The caproyl series was deprotonated and purified from unreacted acid and ammonium salt by heating under reflux in a Na_2CO_3 solution. This method was also used for the C10-C12 series; for these systems partially reacted dendrimer was present, but this could easily be

Table 5.1: Yields after work-up of the reactions of DAB-*dendr*-$(NH_2)_x$ with the corresponding acid chlorides

	x=4 (%)	x=8 (%)	x=16 (%)	x=32 (%)	x=64 (%)
Caproyl chloride (C5)[a]	67	50	59	77	51
Decanoyl chloride (C9)[a]	68	65	54	56	60
Palmitoyl chloride (C15)[a]	64	76	82	72	56

	C10[a] (%)	C11[a] (%)	C12[a] (%)	C13[a] (%)	C14[a] (%)
DAB-*dendr*-$(NH_2)_{64}$	98.9	90	80.8	69.5	57.5

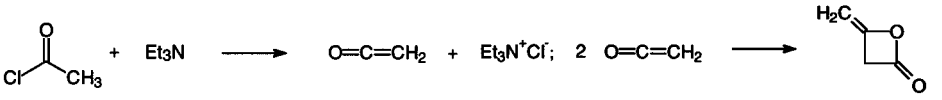
[a] The given C values represent the number of carbon atoms in the aliphatic tail.

removed, because it was still soluble in water. For the decanoyl series, this procedure had to be followed by precipitation of the compound from ethanol by addition of water, to remove decanoic acid. The C13, C14 and palmitoyl series were purified first by washing with diethyl ether to remove, if present, excess alkanoyl chloride and acid, followed by heating under reflux in a Na_2CO_3 solution.

The preparation and work-up of alkylamide dendrimers is performed simply and efficiently when acid chloride derivatives are used. The release of HCl during reaction can partially be neutralized by Et_3N. However, the strongly basic tertiary amines of the dendrimers are also partially protonated. Therefore the treatment with Na_2CO_3 is a prerequisite. There is no relation between yield after work-up and generation or alkyl chain

length for the modified dendrimers. Only for the C10 to C12 systems a higher yield is obtained. This can be explained by the fact that no free acid is present in these systems. Therefore, a washing procedure with organic solvent isn't necessary. An excess of acid furthermore can cause a reduction of the yield, due to solubilization of the dendrimers by the unreacted acids in aqueous solution, as is probably the case for the caproyl series.

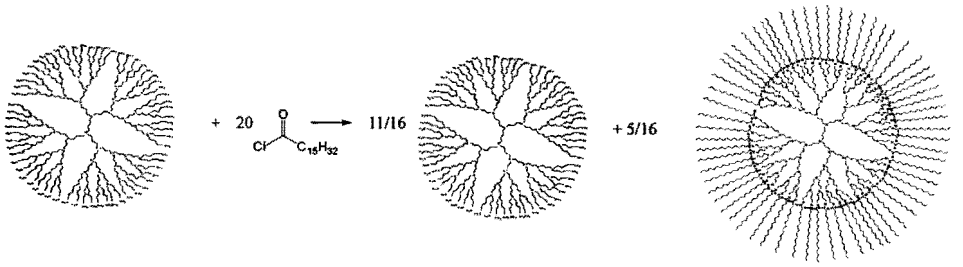
Partially modified dendrimers could be prepared by reaction of DAB-*dendr*-$(NH_2)_{64}$ with 21 equivalents of pivaloylchloride (table 5.2). The functionalization degree, however, was considerably lower than expected from the ratio between dendrimer and acid chloride. This is not caused by steric hindrance, because it proved to be possible to prepare fully modified DAB-*dendr*-(pivaloyl)$_{64}$. It is possible that during work-up, and especially during dialysis, a fractionation has occurred, resulting in loss of the fraction with a higher functionalization degree. The use of acetyl chloride in the partial modification reaction, resulted in an insoluble product that could not be characterized. The insoluble reaction product can be explained by the formation of ketene from the reaction of acetyl chloride with Et_3N, which dimerizes to vinylbutyrolactone[8] (scheme 5.2). This lactone can give rise to crosslinking reactions between amines of different dendrimers.



Scheme 5.2: *Lactone formation caused by reaction between Et_3N and acetylchoride.*

When the long chain palmitoyl- and oleyl chloride were reacted with an excess DAB-*dendr*-$(NH_2)_{64}$, however, a two-phase system was formed that was separated by centrifugation in an aqueous fraction and a water-insoluble product (scheme 5.3, table 5.2). The latter proved to be completely modified dendrimer, whereas in the water layer fully unreacted dendrimer was present. A mass balance over both products was in accordance with this observed phenomenon (table 5.3).

The modification reactions with the alkyl chains show an extraordinary result: only fully unreacted and fully reacted dendrimers are formed. This is an indication for an extreme autoacceleration effect, or strong neighbouring group participation. When one alkyl chain is attached to the dendrimer, the reactivity toward the next acid chloride increases tremendously



Scheme 5.3: *Reaction between palmitoyl chloride and an excess of DAB-dendr-$(NH_2)_{64}$.*

Table 5.2: Partial modification of DAB-*dendr*-$(NH_2)_{64}$

acid chloride	eq. acid chloride	prod. water phase (x)[a]	prod. second phase (x)[a]
acetyl	21.5	-	-
pivaloyl[b]	20.6	13	-
palmitoyl[b]	21.9	0	64
oleyl	28.3	0	64
oleyl[c]	22.6	0	64
oleyl[d]	21.7	0	62-63

[a] x stands for the number of reacted amine end groups, determined with ^{1}H-NMR- spectroscopy; [b] samples were first dialyzed before centrifugation; [c] reaction in CH_2Cl_2; [d] a dilute solution of oleylchloride in THF was added.

Table 5.3: Mass balance of 3 reactions of 20 eq. oleylchloride with DAB-*dendr*-$(NH_2)_{64}$

water phase		second phase	
exp.[a](g)	calc.[b] (g)	exp.(g)	calc.[c] (g)
0.0717	0.0669	0.1405	0.1785
0.1285	0.1153	0.2046	0.2151
0.0807	0.686	0.1140	0.1201

[a] The water phase products contain $Et_3N \cdot HCl$ as impurity; [b] Expected mass for DAB-dendr-$(NH_2)_{64}$; [c] Expected mass for DAB-dendr-$(oleyl)_{64}$

and the dendrimer is modified to completion. There are related subjects: autocatalysis has been described e.g. in relation with self replication[9]. In these cases, however, the observed effects are relatively small. In polymer chemistry neighboring group assisted hydrolysis is known to proceed for the preparation of poly(vinyl alcohol) from poly(vinyl acetate)[10]. As far

as we know the extent of acceleration and discrimination in our case, however, is unprecedented and can have several reasons: after reaction with one alkyl chain an amphiphilic structure is obtained that has a higher affinity for the alkyl chlorides. Neighboring group participation can play a role. The presence of amide functions next to primary amines can result in an amide-supported amidation reaction, which for example explains the observed autocatalyic effect of Rebek et al.[9d]. Dendrimers also have a strong tendency to cluster. After reacting once with an alkyl chain their solubility can be increased and the degree of clustering is diminished. The alkyl chains themselves can be present in the form of micelles, resulting in high local concentrations of the reactive groups. This effect can be seen, though vaguely, when oleyl chlorides are added in diluted form. To obtain more detailed information of the mechanism of this autoaccelerating effect, more polar solvents can be used and less polar head groups as active esters can be applied.

From the autoacceleration experiments already one conclusion can be drawn, namely that the easiest way to prepare fully alkyl-modified dendrimers is to use an excess of DAB-*dendr*-$(NH_2)_{64}$.The only by-product obtained is then the unmodified dendrimer that can easily be removed by the work-up with a Na_2CO_3 solution, resulting therefore in high yields after work-up, as is the case for the C10-C12 series.

5.3 Physical properties of alkyl-modified dendrimers

Several characterization techniques were used to investigate the physical properties of the fully alkyl-modified dendrimers. ^{1}H-NMR spectroscopy was used to study the generation dependence of the position of the NHCO resonance (figure 5.2). A shift to lower fields was observed with increasing generation. For the low generations (DAB-*dendr*-(alkylamide)$_x$, with x = 4–16) also a concentration dependence of the NHCO position could be noticed, that was absent for the other two higher generations (DAB-*dendr*-(alkylamide)$_x$, with x = 32–64 (figure 5.3). The limited number of data points for DAB-*dendr*-(palmitoyl)$_{64}$ was a result of the low solubility of this material in $CDCl_3$.

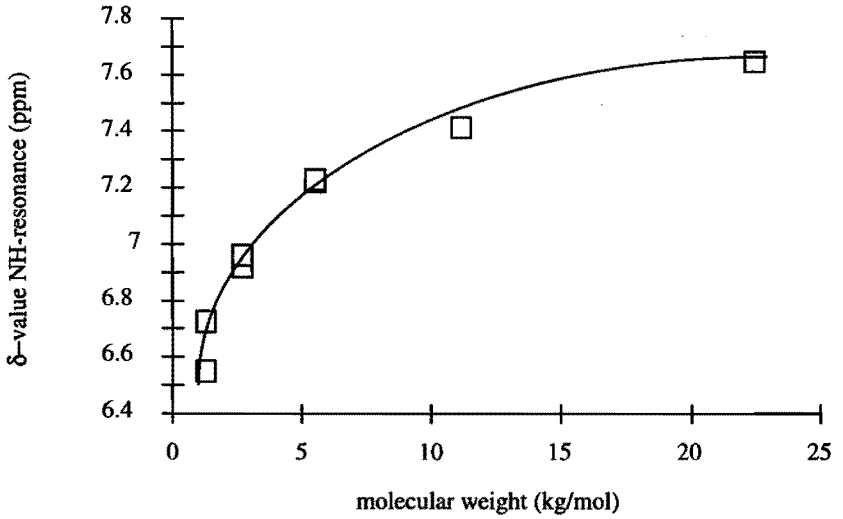


Figure 5.2: *Generation dependence of the NHCO resonance of the DAB-dendr-(palmitoyl)$_x$ series.*

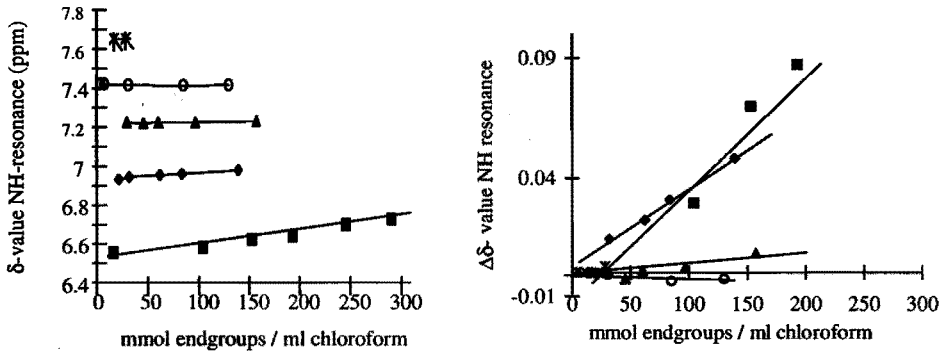


Figure 5.3: *Concentration dependence of the NHCO resonance of the DAB-dendr-(palmitoyl)$_x$ series; ■: DAB-dendr-(palmitoyl)$_4$, ◆: DAB-dendr-(palmitoyl)$_8$, ▲: DAB-dendr-(palmitoyl)$_{16}$, O: DAB-dendr-(palmitoyl)$_{32}$, ✳: DAB-dendr-(palmitoyl)$_{64}$.*

Differential scanning calorimetry (DSC) was performed to investigate the phase transitions of these materials. The caproyl-, decanoyl- and palmitoyl-modified first generation dendrimers showed melting points (96°C, 112°C and 116°C, respectively) that resembled the

melting points of the corresponding alkylamides. Phase transitions were observed for the higher generation caproyl (1±3 °C), decanoyl (44 ± 5°C) and palmitoyl (76± 5°C) dendrimers that were independent of the number of endgroups and fully determined by chain length (figure 5.4).The C9 to C15 series was used to investigate a possible occurrence of an odd-even effect on the phase transition temperature, as is observed e.g. for side chain liquid crystalline polymers[11]. For these systems it is found that, as a result of a better packing between chains with an even number than with an odd number of C-atoms, the even numbered chains have a higher phase transition temperature. In the case of the DAB-*dendr*-(alkylamide)$_{64}$, (C9-C15), the phase transition temperature was continuously increasing with increasing chain length and no odd-even behavior could be detected (figure 5.5). Furthermore, in all of the cases no mesophase was observed.

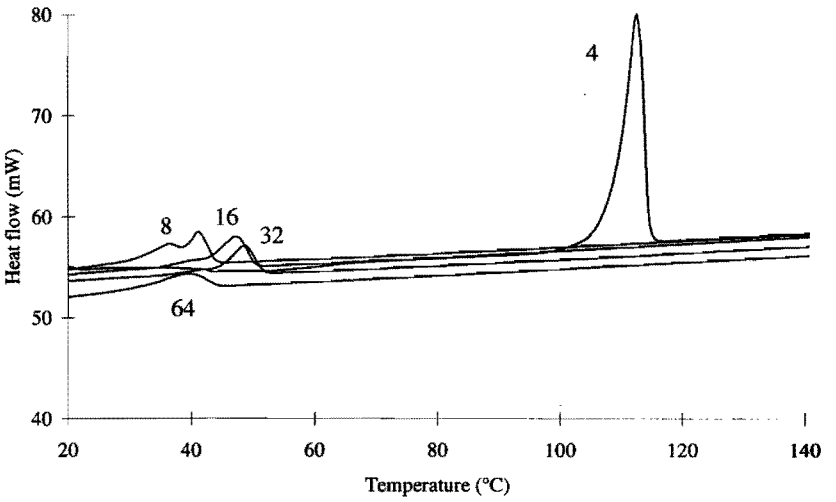


Figure 5.4: *DSC curves of the DAB-dendr-(decanoyl)$_x$ series.*

Dynamic light scattering showed single particle behavior with a hydrodynamic diameter of 2-3 nm for DAB-*dendr*-(palmitoyl)$_{64}$ in dichloromethane. Contradictory to other examined poly(propylene imine) based structures[12] no clustering was found. Evidence for an inverted micellar structure was obtained by ^{1}H-2D NOESY NMR spectroscopy. A sample of

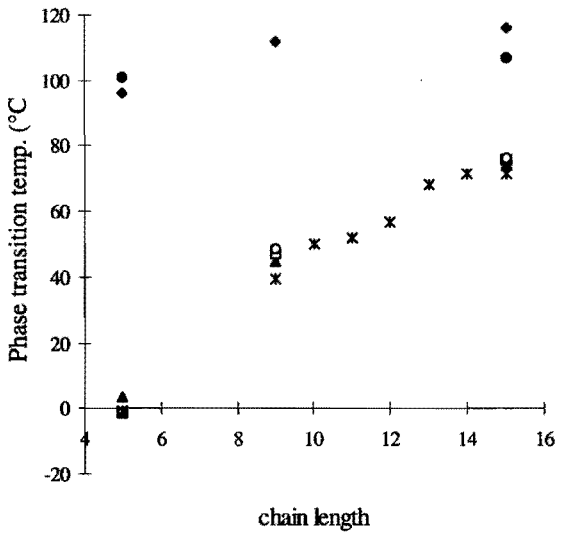


Figure 5.5: *Phase transition temperature as a function of alkyl chain length -NHCOC$_n$H$_{2n+2}$ and dendrimer generation; ●: alkylamide, ◆: DAB-dendr-(alkylamide)$_4$, ▲: DAB-dendr-(alkylamide)$_8$, □: DAB-dendr-(alkylamide)$_{16}$, ○: DAB-dendr-(alkylamide)$_{32}$, ✳: DAB-dendr-(alkylamide)$_{64}$.*

DAB-*dendr*-(palmitoyl)$_{64}$ containing water as well as toluene, only showed NOE interactions between water and the polar dendritic core. Toluene only had interactions with the alkyl chains. GPC of the alkyl-modified dendrimers in THF and in $CHCl_3$ proved to be unsuccessful. The only product that eluted was DAB-*dendr*-(alkylamide)$_4$, which showed a single narrow peak. An elution problem was also noticed for column chromatography and TLC, in which cases the dendrimers showed irreversible interactions with the stationary phase.

From the ^{1}H-NMR and DSC results it is clear that there is a development of dendritic character going from DAB-*dendr*-(alkylamide)$_4$ to DAB-*dendr*-(alkylamide)$_{64}$. The shift of the amide proton is a result of a change from predominantly intermolecular hydrogen bonding for the lower generations, to intramolecular hydrogen bonding for the higher generations

(figure 5.6). The intermolecular hydrogen bonding is affected by the concentration of the sample. The concentration-independent behavior of DAB-*dendr*-(alkanoyl)$_{32,64}$ indicates that these structures only have intramolecular amide interactions. The same amide behavior is also noticed for poly(propylene imine) dendrimers modified with *p*-dimethylamino benzoylchloride[13]. The fact that the amide functions are shielded for DAB-*dendr*-(palmitoyl)$_{64}$ is also confirmed with DLS, because in this case single particle behavior indicates that no electrostatic interactions are found between the dendrimers.

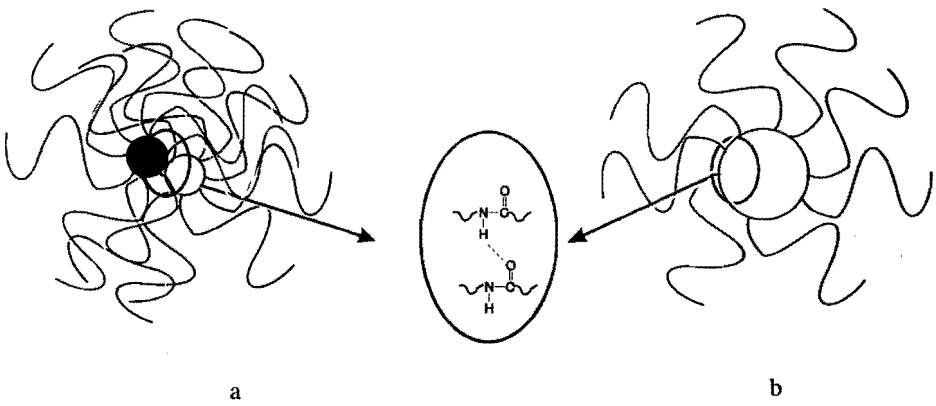


Figure 5.6: *a) intermolecular H-bond interactions; b) intramolecular H-bond interactions.*

The resemblance of the melting behavior of DAB-*dendr*-(alkylamide)$_4$ with the corresponding amides also shows that for this generation, contrary to the others, the amide functions are not shielded, and have strong intermolecular interactions. DAB-*dendr*-(alkylamide)$_4$ can therefore be seen as regular organic molecules. The phase transitions for the other generations, as observed with DSC, are determined by alkyl interactions, and are comparable to the observations made for alkanethiol stabilized gold clusters and poly(L-glutamates) with alkyl side chains[14]. An increase in phase transition temperature is noticed for longer alkyl chains. The multiple peaks at the phase transition region that are sometimes observed, may be due to different conformational changes of the alkyl chains and the dendritic core. Chains with odd or even numbers of C-atoms show the same packing properties. The dendritic core is unable to introduce an odd/even behavior, which is noticed for side chain liquid crystalline materials. GPC-behavior of these materials is quite extraordinary. The product that can have the strongest interactions, DAB-*dendr*-

(alkylamide)$_4$, is the only one that can be analyzed. The other systems tend to stick at the column packing. The nature of this phenomenon is unknown. The only possible interactions should be alkyl-chain interactions, and they can't be responsible for adsorption at the column material. An explanation can be that spherical dendritic structures remain in the small pores of these column materials and can't get out, due to extension of the alkyl arms.

5.4 Host-guest systems based on alkyl-modified dendrimers

An important application of inverted micellar structures is the solubilization of hydrophilic materials in an apolar environment, based on the host-guest principle. To investigate if the alkyl-modified dendrimers could be useful as dynamic hosts, attempts were made to incorporate the hydrophilic dye Bengal Rose into 6 different structures: DAB-*dendr*-(caproyl)$_{8,64}$, DAB-*dendr*-(decanoyl)$_{8,64}$ and DAB-*dendr*-(palmitoyl)$_{8,64}$ The dendrimers were therefore dissolved in ethanol in the presence of Bengal Rose, allowing the dye to enter the dendritic core. After stirring for 24 hours, the dendrimers were poured into acetonitrile, which is a non-solvent for the dendrimers and a solvent for Bengal Rose. Because of the collapse of the alkyl-chains, dye-molecules were trapped inside the dendrimer. Free Bengal Rose was removed by an extensive washing procedure with acetonitrile, until no coloration of solvent occurred anymore. The dendrimers with 64 endgroups were further purified by dialysis with water. The Bengal Rose loads were determined with UV-spectroscopy (table 5.4).

Table 5.4: Loads of Bengal Rose, physically encapsulated in alkyl-modified dendrimers

	n=8	n=64
DAB-*dendr*-(caproyl)$_n$	0.8	2.7
DAB-*dendr*-(decanoyl)$_n$	2.0	6.9
DAB-*dendr*-(palmitoyl)$_n$	0.5	2.2

With the trapped Bengal Rose it was possible to strongly improve its compatibility with *n*-hexane, compared to the free dye, which is insoluble in this apolar medium. The locked-in Bengal Rose could easily be liberated by addition of toluene, which is a solvent for the alkyl chains. Washing of this organic layer with water resulted in the complete removal of the dye. Although the results are still somewhat preliminary, an explanation for the difference

in load between the examined structures can be the following: variation of the alkyl chain length proves to have a twofold effect on the Bengal Rose load in the dendrimer. With increasing alkyl chain length, the barrier to enter the dendritic core is increased, but also the barrier to diffuse out of the system. With the caproyl chain, the latter determines the amount of Bengal Rose in the dendritic core, in the case of the palmitoyl modified dendrimers it is the former process that hinders a maximum load. With the decanoyl chain length an optimum is found between the two opposing processes and a higher load is reached. A comparison between the low generation and high generation of alkyl-modified dendrimers shows that the former have a strongly reduced ability to incorporate Bengal Rose, although also in these cases a significant amount of Bengal Rose can be detected. This can also be a result of a less extensive washing procedure, because of the inability to perform a dialysis with the low generation dendrimers.

Compared to the dendritic box[6], this new system is also capable of encapsulating and liberating guests. Instead of a chemical process, however, the polarity of the environment is in this case the tool for the physical entrapment of molecules in dendrimers. The compatibilization of polar dyes and apolar materials *via* the described host-guest system has the possibility of becoming an important application of dendrimers in the field of polymer processing.

5.5 Conclusions

The preparation of alkyl-modified dendrimers by the reaction of DAB-*dendr*-$(NH_2)_x$ with different alkanoyl chlorides proceeds in reasonable to good yields. Fully modified structures are always obtained, even when an excess of dendrimer is used. In this case besides the fully converted structures, only totally unreacted dendrimers are obtained, indicating a strong autoaccelaration effect. The development of dendritic character is observed with ^{1}H-NMR and DSC. The alkyl-modified dendrimers, as hairy spheres, don't show mesophasic structures or odd-even behavior. They can be considered as unimolecular inverted micelles and can excellently be used as dynamic hosts in host-guest systems, thereby enhancing the compatibility between polar guests and apolar environments.

5.6 Experimental

General procedures

For general procedures see chapter 2.

^{13}C-NMR measurements were recorded on a Varian Gemini 300, 75 MHz. All δ values were given in ppm downfield from tetramethylsilane. DSC measurements were performed on a Perkin-Elmer DSC7. A Homef LC-30 was used for centrifugation. Dialysis was performed with Visking dialysis tubing, size 2 inf dia 18/32" - 14.3 mm: 30M.

Poly(propylene imine) dendrimers were kindly provided by DSM and were stripped 3 times with toluene to remove residual H_2O. Alkanoic acids and acid chlorides were used as purchased. The number of equivalents used was corrected for the reported purity of the chemicals and is given in equivalents per functional dendrimer end group.

General procedure for the preparation of DAB-*dendr*-(caproyl)$_x$:

DAB-*dendr*-(caproyl)$_4$ (5.1)

To a solution of 1.02 g DAB-*dendr*-$(NH_2)_4$ (1 eq., 3.17 mmol) in 50 ml THF 5.14 g triethylamine and 2.05 g caproyl chloride (1.16 eq., 14.8 mmol) were added. After stirring for 20 hours at room temperature, the solvent was evaporated. To the reaction product a solution of 2 g Na_2CO_3 in 50 ml H_2O was added and the mixture was heated under reflux for 6 hours. The product was then extracted with 3 times 30 ml CH_2Cl_2. The combined fractions were washed with H_2O and dried over $MgSO_4$. The solvent was evaporated, **5.1** was dried *in vacuo* at 40°C and obtained as a yellow solid material (yield 67%).

DSC: melting point at 95.7 °C.

^{1}H-NMR ($CDCl_3$): δ 0.90 (12H, t, C$\underline{H}_3$), 1.20-1.70 (36H, m, C$\underline{H}_2$-CH$_3$ + CH$_2$-C$\underline{H}_2$-CH$_2$), 2.16 (8H, t, NHCO-C$\underline{H}_2$), 2.28-2.50 (12H, m, C$\underline{H}_2$-N-(CH$_2$)$_2$), 3.30 (8H, q, C$\underline{H}_2$-NHCO), 7.05 (4H, t, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 13.93 (C$\underline{H}_3$), 22.42 (C$\underline{H}_2$-CH$_3$), 25.00 (N-CH$_2$-C$\underline{H}_2$-CH$_2$-CH$_2$-N + N-CH$_2$-C$\underline{H}_2$-CH$_2$-N), 25.53 (NHCO-CH$_2$-C$\underline{H}_2$), 27.05 (N-CH$_2$-C$\underline{H}_2$-CH$_2$-NHCO), 31.53 (C$\underline{H}_2$-CH$_2$-CH$_3$), 36.77 (NHCO-C$\underline{H}_2$), 38.21 (C$\underline{H}_2$-NHCO), 52.03 (N-C$\underline{H}_2$-CH$_2$-CH$_2$-NHCO), 53.88 (N-C$\underline{H}_2$-CH$_2$-CH$_2$-C$\underline{H}_2$-N + N-C$\underline{H}_2$-CH$_2$-CH$_2$-N), 173.35 (NHC$\underline{O}$) ppm.

IR: amide N-H stretch 3277.9 cm^{-1}, sec. amide N-H stretch 3083.8 cm^{-1} ,

C-H sat. 2931.0 cm^{-1}, sec. amide C=O 1637.4 cm^{-1}, N-H bend 1560.0 cm^{-1}.

DAB-*dendr*-(caproyl)$_8$ (5.2)

A yellowish oil was obtained (yield 50%).

DSC: phase transition at 3.5 °C.

^{1}H-NMR ($CDCl_3$): δ 0.90 (24H, t, $C\underline{H}_3$), 1.22-1.70 (76H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2), 2.18 (16H, t, NHCO-$C\underline{H}_2$), 2.28-2.30 (36H, m, $C\underline{H}_2$-N-$(CH_2)_2$), 3.30 (16H, q, $C\underline{H}_2$-NHCO), 7.03 (8H, t, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 13.94 ($\underline{C}H_3$), 22.42 ($\underline{C}H_2$-CH_3), 24.75 (N-CH_2-$\underline{C}H_2$-CH_2-CH_2-N + N-CH_2-$\underline{C}H_2$-CH_2-N), 25.55 (NHCO-CH_2-$\underline{C}H_2$), 26.98 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 31.53 ($\underline{C}H_2$-CH_2-CH_3), 36.64 (NHCO-$\underline{C}H_2$), 37.93 ($\underline{C}H_2$-NHCO), 51.66 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.13 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.55 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3289.7 cm^{-1}, sec. amide N-H stretch 3081.0 cm^{-1} ,

C-H sat. 2929.6 cm^{-1}, sec. amide C=O 1644.1 cm^{-1}, N-H bend 1556.8 cm^{-1}.

DAB-*dendr*-(caproyl)$_{16}$ (5.3)

A yellowish oil was obtained (yield 59%).

DSC: phase transition at -1.5 °C.

^{1}H-NMR ($CDCl_3$): δ 0.90 (48H, t, $C\underline{H}_3$), 1.22-1.72 (156H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2), 2.18 (32H, t, NHCO-$C\underline{H}_2$), 2.40 (84H, m, $C\underline{H}_2$-N-$(CH_2)_2$), 3.30 (32H, br. q, $C\underline{H}_2$-NHCO), 7.15 (16H, t, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.00 ($\underline{C}H_3$), 22.47 ($\underline{C}H_2$-CH_3), 24.80 (N-CH_2-$\underline{C}H_2$-CH_2-CH_2-N + N-CH_2-$\underline{C}H_2$-CH_2-N), 25.62 (NHCO-CH_2-$\underline{C}H_2$), 27.08 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 31.58 ($\underline{C}H_2$-CH_2-CH_3), 36.64 (NHCO-$\underline{C}H_2$), 37.90 ($\underline{C}H_2$-NHCO), 51.62 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.23 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.65 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3291.4 cm^{-1}, sec. amide N-H stretch 3081.2 cm^{-1} ,

C-H sat. 2954.3 cm^{-1}, sec. amide C=O 1644.2 cm^{-1}, N-H bend 1555.5 cm^{-1}.

DAB-*dendr*-(caproyl)$_{32}$ (5.4)

A yellowish oil was obtained (yield 77%).

DSC: phase transition at -1.2 °C.

^{1}H-NMR ($CDCl_3$): δ 0.90 (96H, t, $C\underline{H}_3$), 1.20-1.80 (316H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2), 2.20 (64H, t, NHCO-$C\underline{H}_2$), 2.40 (180H, m, $C\underline{H}_2$-N-$(CH_2)_2$), 3.30 (64H, br. q., $C\underline{H}_2$-NHCO), 7.38 (32H, br. t, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 13.97 ($\underline{C}H_3$), 22.44 ($\underline{C}H_2$-CH_3), 24.77 (N-CH_2-$\underline{C}H_2$-CH_2-CH_2-N + N-CH_2-$\underline{C}H_2$-CH_2-N), 25.60 (NHCO-CH_2-$\underline{C}H_2$), 27.06 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 31.55 ($\underline{C}H_2$-CH_2-CH_3), 36.56 (NHCO-$\underline{C}H_2$), 37.79 ($\underline{C}H_2$-NHCO), 51.51 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.21 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.77 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3296.0 cm^{-1}, sec. amide N-H stretch 3083.6 cm^{-1} ,

C-H sat. 2921.2 cm^{-1}, sec. amide C=O 1655.7 cm^{-1}, N-H bend 1556.5 cm^{-1}.

DAB-*dendr*-(caproyl)$_{64}$ (5.5)

A yellowish oil was obtained (yield 51%).

DSC: phase transition at -1.0 °C.

^{1}H-NMR ($CDCl_3$): δ 0.90 (192H, t, CH_3), 1.20-1.75 (636H, m, CH_2-CH_3 + CH_2-CH_2-CH_2), 2.20 (128H, br. t, NHCO-CH2), 2.40 (372H, br. s, CH_2-N-$(CH_2)_2$), 3.28 (128H, br. s, CH_2-NHCO), 7.60 (64H, br. s,NHCO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.01 (CH_3), 22.47 (CH_2-CH_3), 24.96 (N-CH_2-CH_2-CH_2-CH_2-N + N-CH_2-CH_2-CH_2-N), 25.65 (NHCO-CH_2-CH_2), 27.09 (N-CH_2-CH_2-CH_2-NHCO), 31.39 (CH_2-CH_2-CH_3), 36.56 (NHCO-CH_2), 37.80 (CH_2-NHCO), 51.51 (N-CH_2-CH_2-CH_2-NHCO), 52.19 (N-CH_2-CH_2-CH_2-CH_2-N + N-CH_2-CH_2-CH_2-N), 173.84 (NHCO) ppm.

IR: amide N-H stretch 3292.8 cm^{-1}, sec. amide N-H stretch 3082.8 cm^{-1} ,

C-H sat. 2953.9 cm^{-1}, sec. amide C=O 1643.8 cm^{-1}, N-H bend 1549.8 cm^{-1}.

DAB-*dendr*-(decanoyl)$_4$ (5.6)

To a solution of 0.99 g DAB-*dendr*-$(NH_2)_4$ (1 eq., 3.08 mmol) in 50 ml THF 5.00 g triethylamine and 2.74 g decanoyl chloride (1.14 eq., 14.1 mmol) were added. After stirring for 20 hours at room temperature, the solvent was evaporated. To the reaction product 50 ml diethyl ether was added and the mixture was heated under reflux for 30 minutes. The mixture was then filtrated. To the residue a solution of 2 g Na_2CO_3 in 50 ml H_2O was added and heated under reflux for 6 hours. The product was filtrated, the residual product dried *in vacuo* at 40°C and **5.6** was obtained as a white/yellow solid material (yield 68%).

DSC: melting point at 112.5 °C.

^{1}H-NMR ($CDCl_3$): δ 0.87 (12H, t, CH_3), 1.18-1.62 (68H, m, CH_2-CH_3 + CH_2-CH_2-CH_2), 2.15 (8H, t, NHCO-CH_2), 2.32-2.45 (12H, m, CH_2-N-$(CH_2)_2$), 3.28 (8H, q, CH_2-NHCO), 6.55 (4H, t, NHCO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.05 (CH_3), 22.63 (CH_2-CH_3), 24.99 (N-CH_2-CH_2-CH_2-CH_2-N + N-CH_2-CH_2-CH_2-N), 25.87 (NHCO-CH_2-CH_2), 27.04 (N-CH_2-CH_2-CH_2-NHCO), 29.29- 29.41 (CH_2-$(CH_2)_n$-CH_2), 31.85 (CH_2-CH_2-CH_3), 36.80 (NHCO-CH_2), 38.15 (CH_2-NHCO), 51.95 (N-CH_2-CH_2-CH_2-NHCO), 53.84 (N-CH_2-CH_2-CH_2-CH_2-N + N-CH_2-CH_2-CH_2-N), 173.38 (NHCO) ppm.

IR: amide N-H stretch 3281.7 cm^{-1}, sec. amide N-H stretch 3085.5 cm^{-1} ,

C-H sat. 2918.9 cm^{-1}, sec. amide C=O 1637.1 cm^{-1}, N-H bend 1560.0 cm^{-1}.

General procedure for the preparation of DAB-*dendr*-(decanoyl)$_x$:

DAB-*dendr*-(decanoyl)$_8$ (5.7)

To a solution of 1.01 g DAB-*dendr*-(NH_2)$_8$ (1 eq., 1.25 mmol) in 50 ml THF 5.10 g triethylamine and 2.20 g decanoyl chloride (1.13 eq., 11.3 mmol) were added. After stirring for 20 hours at room temperature, the solvent was evaporated. To the reaction product a solution of 2 g Na_2CO_3 in 50 ml H_2O was added and the mixture was heated under reflux for 6 hours. The mixture was filtrated, the residue was dissolved in ethanol. The product was precipitated by addition of H_2O, decanted, dried *in vacuo* at 40°C and **5.7** was obtained as a white/yellow solid material (yield 65%).

DSC: phase transition at 44.7 °C.

^{1}H-NMR ($CDCl_3$): δ 0.89 (24H, t, C$\underline{H}_3$), 1.18- 1.70 (140H, m, C$\underline{H}_2$-CH_3 + CH_2-C$\underline{H}_2$-CH_2), 2.19 (16H, t, NHCO-C$\underline{H}_2$), 2.40 (36H, m, C$\underline{H}_2$-N-(CH_2)$_2$), 3.28 (16H, q, C$\underline{H}_2$-NHCO), 6.95 (8H, t, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.08 ($\underline{C}H_3$), 22.66 ($\underline{C}H_2$-CH_3), 24.85 (N-CH_2-$\underline{C}H_2$-CH_2-CH_2-N + N-CH_2-$\underline{C}H_2$-CH_2-N), 25.93 (NHCO-CH_2-$\underline{C}H_2$), 27.07 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.31- 29.53 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.88 ($\underline{C}H_2$-CH_2-CH_3), 36.73 (NHCO-$\underline{C}H_2$), 37.92 ($\underline{C}H_2$-NHCO), 51.63 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.20 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.58 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3301.0 cm^{-1}, C-H sat. 2921.8 cm^{-1}, sec. amide C=O 1636.9 cm^{-1}, N-H bend 1559.9 cm^{-1}.

DAB-*dendr*-(decanoyl)$_{16}$ (5.8)

The product was obtained as a white/yellow solid (yield 54%).

DSC: phase transition at 47.3 °C.

^{1}H-NMR ($CDCl_3$): δ 0.87 (48H, t, C$\underline{H}_3$), 1.18-1.70 (140H, m, C$\underline{H}_2$-CH_3 + CH_2-C$\underline{H}_2$-CH_2), 2.20 (32H, t, NHCO-C$\underline{H}_2$), 2.37 (84H, br. s, C$\underline{H}_2$-N-(CH_2)$_2$), 3.26 (32H, br. q, C$\underline{H}_2$-NHCO), 7.44 (16H, br. t,N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.09 ($\underline{C}H_3$), 22.67 ($\underline{C}H_2$-CH_3), 25.99 (NHCO-CH_2-$\underline{C}H_2$), 27.15 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.34- 29.48 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.90 ($\underline{C}H_2$-CH_2-CH_3), 36.63 (NHCO-$\underline{C}H_2$), 37.72 ($\underline{C}H_2$-NHCO), 51.44 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.26 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.82 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3311.8 cm^{-1}, C-H sat. 2921.8 cm^{-1}, sec. amide C=O 1636.6 cm^{-1}, N-H bend 1559.9 cm^{-1}.

DAB-*dendr*-(decanoyl)$_{32}$ (5.9)

The product was obtained as a white/yellow solid (yield 56%).

DSC: phase transition at 48.7 °C.

^{1}H-NMR ($CDCl_3$): δ 0.88 (96H, t, $C\underline{H}_3$), 1.20-1.73 (572H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2), 2.20 (64H, t, NHCO-$C\underline{H}_2$), 2.38 (180H, br.s, $C\underline{H}_2$-N-$(CH_2)_2$), 3.25 (64H, br. q, $C\underline{H}_2$-NHCO), 7.42 (32H, br. t, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.11 ($\underline{C}H_3$), 22.67 ($\underline{C}H_2$-CH_3), 25.99 (NHCO-CH_2-$\underline{C}H_2$), 27.08 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.35- 29.58 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.90 ($\underline{C}H_2$-CH_2-CH_3), 36.61 (NHCO-$\underline{C}H_2$), 37.70 ($\underline{C}H_2$-NHCO), 51.31 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.21 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.89 (N$\underline{H}\underline{C}$O) ppm.

IR: amide N-H stretch 3310.2 cm^{-1}, sec. amide N-H stretch 3079.6 cm^{-1} ,

C-H sat. 2922.1 cm^{-1}, sec. amide C=O 1636.5 cm^{-1}, N-H bend 1559.7 cm^{-1}.

DAB-*dendr*-(decanoyl)$_{64}$ (5.10)

The product was obtained as a white/yellow solid (yield 60%).

DSC: phase transition at 39.3 °C.

^{1}H-NMR ($CDCl_3$): δ 0.89 (192H, t, $C\underline{H}_3$), 1.19-1.71 (1148H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2), 2.22 (128H, t, NHCO-$C\underline{H}_2$), 2.40 (372H, m, $C\underline{H}_2$-N-$(CH_2)_2$), 3.28 (128H, br. s, $C\underline{H}_2$-NHCO), 7.66 (64H, br. s, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.13 ($\underline{C}H_3$), 22.69 ($\underline{C}H_2$-CH_3), 26.06 (NHCO-CH_2-$\underline{C}H_2$), 27.23 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.38- 29.58 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.93 ($\underline{C}H_2$-CH_2-CH_3), 36.61 (NHCO-$\underline{C}H_2$), 37.73 ($\underline{C}H_2$-NHCO), 51.32 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.32 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N) ppm.

IR: amide N-H stretch 3293.1 cm^{-1}, sec. amide N-H stretch 3080.6 cm^{-1} ,

C-H sat. 2924.5 cm^{-1}, sec. amide C=O 1642.3 cm^{-1}, N-H bend 1549.3 cm^{-1}.

General procedure for the preparation of DAB-*dendr*-(palmitoyl)$_x$:

DAB-*dendr*-(palmitoyl)$_4$ (5.11)

To a solution of 1.05 g DAB-*dendr*-$(NH_2)_4$ (1 eq., 2.26 mmol) in 50 ml THF 5.00 g triethylamine and 4.28 g palmitoyl chloride (1.10 eq., 14.3 mmol) were added. After stirring for 20 hours at room temperature, the solvent was evaporated. The mixture was dissolved in 50 ml diethyl ether, heated under reflux for 30 minutes and filtrated. To the residue a solution of 2 g Na_2CO_3 in 50 ml H_2O was added and the mixture was heated under reflux for 6 hours. The mixture was filtrated, the residue was dried *in vacuo* at 40°C and **5.11** was obtained as a white/yellow solid material (yield 64%).

DSC: melting point at 116.1 °C.

^{1}H-NMR ($CDCl_3$): δ 0.88 (12H, t, $C\underline{H}_3$), 1.18-1.62 (116H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2), 2.15 (8H, t, NHCO-$C\underline{H}_2$), 2.31-2.45 (12H, m, $C\underline{H}_2$-N-$(CH_2)_2$), 3.28 (8H, q, $C\underline{H}_2$-NHCO), 6.51 (4H, t, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.10 ($\underline{C}H_3$), 22.69 ($\underline{C}H_2$-CH_3), 25.05 (N-CH_2-$\underline{C}H_2$-CH_2-CH_2-N + N-CH_2-$\underline{C}H_2$-CH_2-N), 25.91 (NHCO-CH_2-$\underline{C}H_2$), 27.11 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.47- 29.71 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.93 ($\underline{C}H_2$-CH_2-CH_3), 36.85 (NHCO-$\underline{C}H_2$), 38.20 ($\underline{C}H_2$-NHCO), 52.00 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 53.90 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.39 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3319.2 cm^{-1}, sec. amide N-H stretch 3075.8 cm^{-1},

C-H sat. 2918.2 cm^{-1}, sec. amide C=O 1638.4 cm^{-1}, N-H bend 1549.1 cm^{-1}.

DAB-*dendr*-(palmitoyl)$_8$ (5.12)

The product was obtained as a yellow/white solid (yield 76%).

DSC: phase transition at 74.3 °C.

^{1}H-NMR ($CDCl_3$): δ 0.90 (24H, t, $C\underline{H}_3$), 1.18-1.75 (236H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2) , 2.17 (16H, t, NHCO-$C\underline{H}_2$), 2.40 (36H, m, $C\underline{H}_2$-N-(CH_2)$_2$), 3.28 (16H, q, $C\underline{H}_2$-NHCO), 6.95 (8H, t, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.10 ($\underline{C}H_3$), 22.69 ($\underline{C}H_2$-CH_3), 24.87 (N-CH_2-$\underline{C}H_2$-CH_2-CH_2-N + N-CH_2-$\underline{C}H_2$-CH_2-N), 25.96 (NHCO-CH_2-$\underline{C}H_2$), 27.09 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.37- 29.73 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.93 ($\underline{C}H_2$-CH_2-CH_3), 36.75 (NHCO-$\underline{C}H_2$), 37.93 ($\underline{C}H_2$-NHCO), 51.64 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.20 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.59 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3300.2 cm^{-1}, sec. amide N-H stretch 3083.8 cm^{-1},

C-H sat. 2918.1 cm^{-1}, sec. amide C=O 1638.9 cm^{-1}, N-H bend 1560.0 cm^{-1}.

DAB-*dendr*-(palmitoyl)$_{16}$ (5.13)

The product was obtained as a yellow/white solid (yield 82%).

DSC: phase transition at 75.7 °C.

^{1}H-NMR ($CDCl_3$): δ 0.88 (48H, t, $C\underline{H}_3$), 1.14-1.70 (476H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2), 2.16 (32H, t, NHCO-$C\underline{H}_2$), 2.36 (84H, m, $C\underline{H}_2$-N-(CH_2)$_2$), 3.25 (32H, br. q, $C\underline{H}_2$-NHCO), 7.26 (16H, br. t, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.08 ($\underline{C}H_3$), 22.66 ($\underline{C}H_2$-CH_3), 24.61 (N-CH_2-$\underline{C}H_2$-CH_2-CH_2-N + N-CH_2-$\underline{C}H_2$-CH_2-N), 25.96 (NHCO-CH_2-$\underline{C}H_2$), 27.06 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.34- 29.74 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.91 ($\underline{C}H_2$-CH_2-CH_3), 36.65 (NHCO-$\underline{C}H_2$), 37.78 ($\underline{C}H_2$-NHCO), 51.44 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.20 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.82 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3299.0 cm^{-1}, sec. amide N-H stretch 3092.7 cm^{-1},

C-H sat. 2918.5 cm^{-1}, sec. amide C=O 1636.9 cm^{-1}, N-H bend 1560.0 cm^{-1}.

DAB-*dendr*-(palmitoyl)$_{32}$ (5.14)

The product was obtained as a yellow/white solid (yield 72%).

DSC: phase transition at 76.3 °C.

^{1}H-NMR: ($CDCl_3$): δ 0.88 (96H, t, $C\underline{H}_3$), 1.20-1.70 (956H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2), 2.16 (64H, t, NHCO-$C\underline{H}_2$), 2.37 (180H, br. s, $C\underline{H}_2$-N-$(CH_2)_2$), 3.25 (64H, br. s, $C\underline{H}_2$-NHCO) , 7.42 (32H, br. s, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.09 ($\underline{C}H_3$), 22.68 ($\underline{C}H_2$-CH_3), 26.01 (NHCO-CH_2-$\underline{C}H_2$), 27.18 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.37- 29.75 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.92 ($\underline{C}H_2$-CH_2-CH_3), 36.64 (NHCO-$\underline{C}H_2$), 37.70 ($\underline{C}H_2$-NHCO), 51.39 , (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.27 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.86 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3300.4 cm^{-1}, sec. amide N-H stretch 3081.0 cm^{-1} ,

C-H sat. 2918.0 cm^{-1}, sec. amide C=O 1637.0 cm^{-1}, N-H bend 1560.0 cm^{-1}.

DAB-*dendr*-(palmitoyl)$_{64}$ (5.15)

The product was obtained as a yellow/white solid (yield 56%).

DSC: phase transition at 71.7 °C.

^{1}H-NMR ($CDCl_3$): δ 0.89 (192H, t, $C\underline{H}_3$), 1.20-1.75 (1916H, m, $C\underline{H}_2$-CH_3 + CH_2-$C\underline{H}_2$-CH_2), 2.19 (128H, br. s, NHCO-$C\underline{H}_2$), 2.38 (372H, br. s, $C\underline{H}_2$-N-$(CH_2)_2$), 3.25 (128H, br. s, $C\underline{H}_2$-NHCO), 7.64 (64H, br. s, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.09 ($\underline{C}H_3$), 22.68 ($\underline{C}H_2$-CH_3), 26.06 (NHCO-CH_2-$\underline{C}H_2$), 27.19 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.38- 29.77 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.93 ($\underline{C}H_2$-CH_2-CH_3), 36.59 (NHCO-$\underline{C}H_2$), 37.63 ($\underline{C}H_2$-NHCO), 51.34 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.20 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.98 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3299.8 cm^{-1}, sec. amide N-H stretch 3082.5 cm^{-1} ,

C-H sat. 2917.0 cm^{-1}, sec. amide C=O 1640.6 cm^{-1}, N-H bend 1552.2 cm^{-1}.

DAB-*dendr*-(undecanoyl)$_{64}$ (5.16)

0.47 g Undecanoic acid (2.5 mmol) was dissolved in 3 g thionyl chloride (25 mmol).

The solution was heated under reflux for 5 hours. The excess thionyl cloride was removed by evaporation, followed by stripping with *n*-hexane. Undecanoyl chloride was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$): δ 0.88 (3H, t, CH_2-$C\underline{H}_3$), 1.20 - 1.40 (14H, m, CH_2-($C\underline{H}_2$)$_n$-CH_2), 1.70 (2H, m, $C\underline{H}_2$-CH_2-CO-Cl), 2.86 (2H, t, $C\underline{H}_2$-CO-Cl) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.09 ($C\underline{H}_3$), 22.05 ($C\underline{H}_2$-CH_3), 25.04 ($\underline{C}H_2$-CH_2-CO-Cl), 28.41 - 29.45 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.84 ($\underline{C}H_2$-CH_2-CH_3), 47.10 ($\underline{C}H_2$-CO-Cl) ppm.

DAB-*dendr*-(undecanoyl)$_{64}$ was prepared according to the method described for **5.1**. Instead of an excess acid chloride an equimolar amount was used and isolation was achieved directly by filtration instead of first extraction with CH_2Cl_2. **5.16** was obtained as a white/yellow solid (yield 99%).

DSC: phase transition at 49.9 °C.

^{1}H-NMR ($CDCl_3$): δ 0.80 (192H, t, C$\underline{H}_3$), 1.10-1.62 (1276H, m, C$\underline{H}_2$-CH$_3$ + CH$_2$-C$\underline{H}_2$-CH$_2$), 2.05-2.43 (500H, m, NHCO-C$\underline{H}_2$+ C$\underline{H}_2$-N-(CH$_2$)$_2$), 3.17 (128H, br. s,C$\underline{H}_2$-NHCO), 7.50 (64H, br. s, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.12 (C$\underline{H}_3$), 22.68 (C$\underline{H}_2$-CH$_3$), 26.03 (NHCO-CH$_2$-C$\underline{H}_2$), 27.80 (N-CH$_2$-C$\underline{H}_2$-CH$_2$-NHCO), 29.37- 29.67 (CH$_2$-(C$\underline{H}_2$)$_n$-CH$_2$), 31.91 (C$\underline{H}_2$-CH$_2$-CH$_3$), 36.57 (NHCO-C$\underline{H}_2$), 37.62 (C$\underline{H}_2$-NHCO), 51.31 (N-C$\underline{H}_2$-CH$_2$-CH$_2$-NHCO), 52.14 (N-C$\underline{H}_2$-CH$_2$-CH$_2$-C$\underline{H}_2$-N + N-C$\underline{H}_2$-CH$_2$-CH$_2$-N), 173.96 (NHC$\underline{O}$) ppm.

IR: amide N-H stretch 3296.9 cm^{-1}, sec. amide N-H stretch 3076.8 cm^{-1} ,

C-H sat. 2922.9 cm^{-1}, sec. amide C=O 1640.1 cm^{-1}, N-H bend 1549.6 cm^{-1}.

DAB-*dendr*-(lauroyl)$_{64}$ (5.17)

Lauroyl chloride was prepared according to the procedure described for undecanoyl chloride.

^{1}H-NMR ($CDCl_3$): δ 0.87 (3H, t, CH$_2$-C$\underline{H}_3$), 1.15 - 1.42 (16H, m, CH$_2$-(C$\underline{H}_2$)$_n$-CH$_2$), 1.71 (2H, m, C$\underline{H}_2$-CH$_2$-CO-Cl), 2.87 (2H, t, C$\underline{H}_2$-CO-Cl) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.11 (C$\underline{H}_3$), 22.10 (C$\underline{H}_2$-CH$_3$), 25.09 (C$\underline{H}_2$-CH$_2$-CO-Cl), 28.45 - 29.58 (CH$_2$-(C$\underline{H}_2$)$_n$-CH$_2$), 31.91 (C$\underline{H}_2$-CH$_2$-CH$_3$), 47.14 (C$\underline{H}_2$-CO-Cl) ppm.

DAB-*dendr*-(lauroyl)$_{64}$ was prepared according to the method described for **5.16**. A yellow/white solid (**5.17**) was obtained (yield 90%).

DSC: phase transition at 51.7 °C.

^{1}H-NMR ($CDCl_3$): δ 0.85 (192H, t, C$\underline{H}_3$), 1.05-1.65 (1404H, m, C$\underline{H}_2$-CH$_3$ + CH$_2$-C$\underline{H}_2$-CH$_2$), 2.05-2.50 (500H, m, NHCO-C$\underline{H}_2$ + C$\underline{H}_2$-N-(CH$_2$)$_2$), 3.20 (128H, br.s, C$\underline{H}_2$-NHCO), 7.52 (64H, br. s, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.12 (C$\underline{H}_3$), 22.69 (C$\underline{H}_2$-CH$_3$), 26.04 (NHCO-CH$_2$-C$\underline{H}_2$), 27.00 (N-CH$_2$-C$\underline{H}_2$-CH$_2$-NHCO), 29.39- 29.70 (CH$_2$-(C$\underline{H}_2$)$_n$-CH$_2$), 31.93 (C$\underline{H}_2$-CH$_2$-CH$_3$), 36.60 (NHCO-C$\underline{H}_2$), 37.60 (C$\underline{H}_2$-NHCO), 51.34 (N-C$\underline{H}_2$-CH$_2$-CH$_2$-NHCO), 52.17 (N-C$\underline{H}_2$-CH$_2$-CH$_2$-C$\underline{H}_2$-N + N-C$\underline{H}_2$-CH$_2$-CH$_2$-N), 173.95 (NHC$\underline{O}$) ppm.

IR: amide N-H stretch 3298.3 cm^{-1}, sec. amide N-H stretch 3071.6 cm^{-1} ,

C-H sat. 2920.3 cm^{-1}, sec. amide C=O 1639.8 cm^{-1}, N-H bend 1551.7 cm^{-1}.

DAB-*dendr*-(tridecanoyl)$_{64}$ (5.18)

Tridecanoyl chloride was prepared according to the procedure described for undecanoyl chloride.

^{1}H-NMR ($CDCl_3$): δ 0.87 (3H, t, CH_2-C$\underline{H}_3$), 1.15 - 1.42 (18H, m, CH_2-($C\underline{H}_2$)$_n$-CH_2), 1.71 (2H, m, C$\underline{H}_2$-CH_2-CO-Cl), 2.87 (2H, t, C$\underline{H}_2$-CO-Cl) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.03 ($\underline{C}H_3$), 22.10 ($\underline{C}H_2$-CH_3), 25.03 ($\underline{C}H_2$-CH_2-CO-Cl), 28.20 - 29.65 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.89 ($\underline{C}H_2$-CH_2-CH_3), 47.12 ($\underline{C}H_2$-CO-Cl) ppm.

DAB-*dendr*-(tridecanoyl)$_{64}$ was prepared according to the method described for **5.16**. A yellow/white solid was obtained (yield 81%).

DSC: phase transition at 56.8 °C.

^{1}H-NMR ($CDCl_3$): δ 0.82 (192H, t, C$\underline{H}_3$), 1.10-1.60 (1532H, m, C$\underline{H}_2$-CH_3 + CH_2-C$\underline{H}_2$-CH_2), 2.02-2.45 (500H, m, NHCO-C$\underline{H}_2$+ C$\underline{H}_2$-N-(CH_2)$_2$), 3.18 (128H, br. s, C$\underline{H}_2$-NHCO), 7.54 (64H, br. s, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.10 ($\underline{C}H_3$), 22.68 ($\underline{C}H_2$-CH_3), 26.03 (NHCO-CH_2-$\underline{C}H_2$), 27.30 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.37- 29.69 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.92 ($\underline{C}H_2$-CH_2-CH_3), 36.57 (NHCO-$\underline{C}H_2$), 37.64 ($\underline{C}H_2$-NHCO), 51.31 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.26 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.95 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3294.7 cm^{-1}, sec. amide N-H stretch 3083.7 cm^{-1},

C-H sat. 2919.4 cm^{-1}, sec. amide C=O 1639.8 cm^{-1}, N-H bend 1553.7 cm^{-1}.

DAB-*dendr*-(myristoyl)$_{64}$ (5.19)

Myristoyl chloride was prepared according to the procedure described for undecanoyl chloride. ^{1}H-NMR ($CDCl_3$): δ 0.88 (3H, t, CH_2-C$\underline{H}_3$), 1.18 - 1.40 (20H, t, CH_2-($C\underline{H}_2$)$_n$-CH_2), 1.72 (2H, m, C$\underline{H}_2$-CH_2-CO-Cl), 2.89 (2H, t, C$\underline{H}_2$-CO-Cl) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.09 ($\underline{C}H_3$), 21.86 ($\underline{C}H_2$-CH_3), 24.93 ($\underline{C}H_2$-CH_2-CO-Cl), 28.61 - 30.10 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.94 ($\underline{C}H_2$-CH_2-CH_3), 47.30 ($\underline{C}H_2$-CO-Cl) ppm.

DAB-*dendr*-(myristoyl)$_{64}$ was prepared according to the method described for **5.9**. Instead of an excess acid chloride, 0.85 equivalents were added. A brownish solid was obtained (yield 70%).

DSC: phase transition at 68.3 °C.

^{1}H-NMR ($CDCl_3$): δ 0.87 (192H, t, C$\underline{H}_3$), 1.05-1.70 (1660H, m, C$\underline{H}_2$-CH_3 + CH_2-C$\underline{H}_2$-CH_2), 2.13-2.48 (500H, m, NHCO-C$\underline{H}_2$ + C$\underline{H}_2$-N-(CH_2)$_2$), 3.25 (128H, br. s, C$\underline{H}_2$-NHCO), 7.50 (64H, br. s, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.11 ($\underline{C}H_3$), 22.69 ($\underline{C}H_2$-CH_3), 26.05 (NHCO-CH_2-$\underline{C}H_2$), 27.15 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.39- 29.73 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.93 ($\underline{C}H_2$-CH_2-CH_3), 36.60 (NHCO-$\underline{C}H_2$), 37.72 ($\underline{C}H_2$-NHCO), 51.29 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.22 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 173.94 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3296.5 cm^{-1}, sec. amide N-H stretch 3083.7 cm^{-1} ,

C-H sat. 2918.8 cm^{-1}, sec. amide C=O 1638.8 cm^{-1}, N-H bend 1551.3 cm^{-1}.

DAB-*dendr*-(pentadecanoyl)$_{64}$ (5.20)

Pentadecanoyl chloride was prepared according to the procedure described for undecanoyl chloride.

^{1}H-NMR ($CDCl_3$): δ 0.89 (3H, t, CH_2-$\underline{C}H_3$), 1.19 - 1.40 (24H, m, CH_2-($\underline{C}H_2$)$_n$-CH_2), 1.70 (2H, m, $\underline{C}H_2$-CH_2-CO-Cl), 2.88 (2H, t, $\underline{C}H_2$-CO-Cl) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.06 ($\underline{C}H_3$), 22.60 ($\underline{C}H_2$-CH_3), 25.02 ($\underline{C}H_2$-CH_2-CO-Cl), 28.40 - 29.60 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.98 ($\underline{C}H_2$-CH_2-CH_3), 47.08 ($\underline{C}H_2$-CO-Cl) ppm.

DAB-*dendr*-(pentadecanoyl)$_{64}$ was prepared according to the method described for **5.9**. The product was obtained as a brownish solid (yield 52%).

DSC: phase transition at 71.6 °C.

^{1}H-NMR ($CDCl_3$): δ 0.88 (192H, t, $\underline{C}H_3$), 1.10-1.70 (1788H, m, $\underline{C}H_2$-CH_3 + CH_2-$\underline{C}H_2$-CH_2), 2.11-2.52 (500H, m, NHCO-$\underline{C}H_2$+ $\underline{C}H_2$-N-(CH_2)$_2$), 3.25 (128H, br. s, $\underline{C}H_2$-NHCO), 7.63 (64H, br. s, N$\underline{H}$CO) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.11 ($\underline{C}H_3$), 22.69 ($\underline{C}H_2$-CH_3), 26.06 (NHCO-CH_2-$\underline{C}H_2$), 27.21 (N-CH_2-$\underline{C}H_2$-CH_2-NHCO), 29.39- 29.77 (CH_2-($\underline{C}H_2$)$_n$-CH_2), 31.94 ($\underline{C}H_2$-CH_2-CH_3), 36.58 (NHCO-$\underline{C}H_2$), 37.63 ($\underline{C}H_2$-NHCO), 51.31 (N-$\underline{C}H_2$-CH_2-CH_2-NHCO), 52.26 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N + N-$\underline{C}H_2$-CH_2-CH_2-N), 174.00 (NH$\underline{C}$O) ppm.

IR: amide N-H stretch 3297.7 cm^{-1}, sec. amide N-H stretch 3083.7 cm^{-1} ,

C-H sat. 2918.7 cm^{-1}, sec. amide C=O 1640.1 cm^{-1}, N-H bend 1551.7 cm^{-1}.

DAB-*dendr*-(pivaloyl)$_{64}$ (5.21)

DAB-*dendr*-(pivaloyl)$_{64}$ was prepared according to the procedure described for **5.1**. A brownish viscous oil was obtained (yield 59%).

^{1}H-NMR ($CDCl_3$): δ 1.20 (576H, s, C-(CH_3)$_3$), 1.40- 1.60 (CH_2-$\underline{C}H_2$-CH_2), 2.30-2.50 ($\underline{C}H_2$-N-(CH_2)$_2$), 3.26 ($\underline{C}H_2$-NHCO), 7.05 (N$\underline{H}$CO) ppm.

IR: amide N-H stretch 3345.8 cm^{-1}, C-H sat. 2954.6 cm^{-1}, sec. amide C=O 1638.1 cm^{-1}, N-H bend 1533.9 cm^{-1}.

DAB-*dendr*-(pivaloyl)$_{13}$ (5.22)

To a solution of 0.52 g DAB-*dendr*-$(NH_2)_{64}$ (1 eq., $6.71 \cdot 10^{-5}$ mol) in 25 ml THF 2.52 g Et_3N and 0.17 ml pivaloyl chloride (0.32 eq, 1.366 mmol) were added. After stirring for 20 hours at room temperature the solvent was evaporated. To the reaction product a solution of 1g Na_2CO_3 in 25 ml H_2O was added and the mixture was heated under reflux for 5 hours. In order to perform the same work-up procedure for all of the partially modified dendrimers, the clear solution was then dialyzed for several days in H_2O, followed by centrifugation. The one phase system was then evaporated, the obtained brownish oil was dried *in vacuo* at 40°C. 13 out of 64 end groups had reacted, according to ^{1}H-NMR.

^{1}H-NMR (D_2O): δ 1.05 (576H, s, C-($C\underline{H}_3$)$_3$), 1.45-1.78 (252H, m ,CH_2-$C\underline{H}_2$-CH_2), 2.26 - 3.15 ($C\underline{H}_2$-N-$(CH_2)_2$ + $C\underline{H}_2$-NH_2 + $C\underline{H}_2$-NHCO)) ppm.

IR: amide N-H stretch 3344.6 cm^{-1}, C-H sat. 2953.1 cm^{-1}, sec. amide C=O 1637.2 cm^{-1}, N-H bend 1533.8 cm^{-1}.

Partial modification attempt of DAB-*dendr*-$(NH_2)_{64}$ with oleyl chloride in CH_2Cl_2 (5.23)

Oleyl chloride was prepared according to the procedure described for undecanoyl chloride.

To a solution of 0.1822 g DAB-*dendr*-$(NH_2)_{64}$ (1 eq., $2.50 \cdot 10^{-5}$ mol) in 9 ml CH_2Cl_2 0.7924 g Et_3N and 0.1754 g oleyl chloride were added. After stirring for 20 hours at room temperature the solvent was evaporated. 9 ml of an aqueous Na_2CO_3 solution (2 g in 50 ml) were added and the mixture was heated under reflux for 6 hours. The obtained two-phase system was separated by centrifugation. The top layer, a viscous yellow oil, was dried *in vacuo* at 40°C. The bottom layer, a turbid aqueous phase, was dialyzed for several days. The solvent was then evaporated. The yellowish viscous oil was dried *in vacuo* at 40°C.

^{1}H-NMR: phase 1, bottom layer (D_2O): δ 1.40-1.74 (252H, m, CH_2-$C\underline{H}_2$-CH_2), 2.25 - 3.00 ($C\underline{H}_2$-N-$(CH_2)_2$ + $C\underline{H}_2$-NH_2); phase 2, top layer ($CDCl_3$): δ 0,82 ($C\underline{H}_3$), 1.00-1.60 (CH_2-$C\underline{H}_2$-CH_2 + $C\underline{H}_2$-CH_3), 2.02 ($C\underline{H}_2$-CH=CH-CH_2), 2.10-2.40 ($C\underline{H}_2$-N-$(CH_2)_2$ + NHCO-$C\underline{H}_2$), 3.30 ($C\underline{H}_2$-NHCO), 5.28 (CH_2-$C\underline{H}$=CH-CH_2) ppm.

Partial modification attempt of DAB-*dendr*-$(NH_2)_{64}$ with oleyl chloride in THF (5.24)

The same procedure was followed as described for **5.23**, but now with THF instead of CH_2Cl_2 as solvent. Again 2 phases were obtained, that were worked up as described above.

^{1}H-NMR: phase 1, bottom layer (D_2O): δ 1.45 -1.74 (252H, m, CH_2-$C\underline{H}_2$-CH_2), 2.30 - 2.93 ($C\underline{H}_2$-N-$(CH_2)_2$ + $C\underline{H}_2$-NH_2); phase 2, top layer ($CDCl_3$): δ 0,82 ($C\underline{H}_3$), 1.00-1.60 (CH_2-$C\underline{H}_2$-CH_2 + $C\underline{H}_2$-CH_3), 2.02 ($C\underline{H}_2$-CH=CH-CH_2), 2.10-2.40 ($C\underline{H}_2$-N-$(CH_2)_2$ + NHCO-$C\underline{H}_2$), 3.30 ($C\underline{H}_2$-NHCO), 5.28 (CH_2-$C\underline{H}$=CH-CH_2) ppm.

Partial modification attempt of DAB-*dendr*-$(NH_2)_{64}$ with diluted oleyl chloride in THF (5.25).
The same procedure was used as described for **5.24**, with the exception that a solution of 0.34 eq. ($3.16 \cdot 10^{-4}$ mol) of oleyl chloride in 4 ml THF was added. Again the same result was noticed. A small signal of $C\underline{H}_2$-NH_2 was observed in the top layer product, indicating that approximately 62 out of 64 end groups had reacted.
^{1}H-NMR: phase 1, bottom layer (D_2O): δ 1.45-1.70 (252H, m, CH_2-$C\underline{H}_2$-CH_2), 2.32 - 2.94 ($C\underline{H}_2$-N-$(CH_2)_2$ + $C\underline{H}_2$-NH_2); phase 2, top layer ($CDCl_3$): δ 0,87 ($C\underline{H}_3$), 1.10-1.72 (CH_2-$C\underline{H}_2$-CH_2 + $C\underline{H}_2$-CH_3), 2.01 ($C\underline{H}_2$-CH=CH-CH_2), 2.10-2.40 ($C\underline{H}_2$-N-$(CH_2)_2$ + NHCO-$C\underline{H}_2$), 3.32 ($C\underline{H}_2$-NHCO), 5.34 (CH_2-$C\underline{H}$=CH-CH_2). extra signal: 2.77 ($C\underline{H}_2$-NH_2) ppm.

Partial modification attempt of DAB-*dendr*-$(NH_2)_{64}$ with palmitoyl chloride (5.26)
The reaction was performed according to the procedure described for the reaction with oleyl chloride in CH_2Cl_2.The top layer was obtained as a white solid, the bottom layer was a yellow viscous oil.
^{1}H-NMR: phase 1, bottom layer (D_2O): δ 1.42-1.76 (252H, m, CH_2-$C\underline{H}_2$-CH_2), 2.30 - 2.96 ($C\underline{H}_2$-N-$(CH_2)_2$ + $C\underline{H}_2$-NH_2); phase 2, top layer ($CDCl_3$): δ 0,88 ($C\underline{H}_3$), 1.20-1.70 (CH_2-$C\underline{H}_2$-CH_2 + $C\underline{H}_2$-CH_3), 2.20 ($C\underline{H}_2$-N-$(CH_2)_2$), 2.35 (NHCO-$C\underline{H}_2$), 3.25 ($C\underline{H}_2$-NHCO) ppm.

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Chapter 6

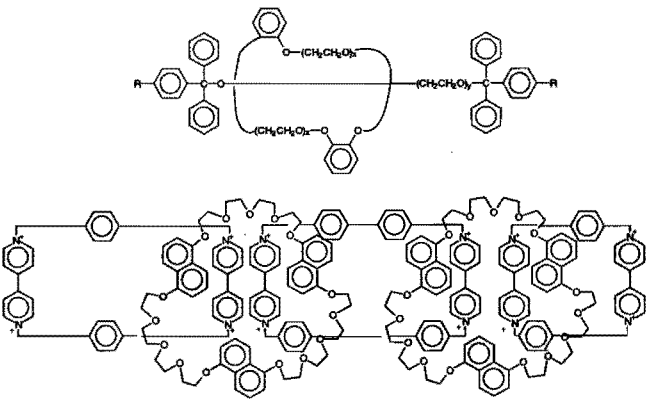
Anchoring polystyrene into the dendritic box

Summary

The concept of the dendritic box, in which guests are physically trapped by the construction of a solid shell around DAB-dendr-$(NH_2)_{64}$, has been used for a new type of mechanical coupling between polystyrene (PS) and poly(propylene imine) dendrimers. By attaching an anchoring moiety to the end of PS, we were able to lock this polymer end group inside the dendrimer, while the PS-part was sticking out. Two types of modified PS were developed. The first structure consisted of a 3,5-dimethylpyridinium anchor, separated from the PS-chain by a caprolactone-spacer. This compound was used to test whether the concept of anchoring could be realized. Indications about the formation of a complex between this compound and the dendritic box were obtained with ^{1}H-NMR, because with this technique a strong distortion of the dendritic structure was visible. In the second compound a fluorescein group was linked via a diglycine unit to PS. The use of fluorescein made it possible to extract more information from this complex than could be achieved for the former one. The load of PS-chains and the position of the head groups could be estimated with UV-VIS spectroscopy. It was found that a maximum number of 4 chains was locked in and that the head groups were shielded from the environment. For both complexes purification problems were significant. It is therefore difficult to be certain that all of the unlocked chains were removed. This new coupling method can be extended toward a broad range of other guest molecules, and can become a versatile procedure for the synthesis of mechanically locked complexes.

6.1 Introduction

Dendrimers have been employed for a broad variety of applications for which the multifunctionality of these structures is used[1], while their specific size and shape has rarely been explored. One of the exceptions are the unimolecular dendritic micelles, as described in chapter 5. In this case the combination of multifunctionality and shape determines the behavior of the dendrimers. Especially their well-defined nanoscopic size, however, makes dendrimers attractive objects to be used in supramolecular chemistry. Existing supramolecular building strategies that can be taken as example are rotaxanes and catenanes[2]. In the first case crown ethers are physically bound to polymers, in the second class of compounds rings are interlocked. Both systems make use of other than covalent bonding methods to build up nanometer-sized, well-defined molecular structures. If such a coupling mechanism could be developed for dendrimers, the size of the obtained structures would increase drastically, and it would give the opportunity to perform chemistry on a nanoscopic scale.



a

b

Figure 6.1: *a) Rotaxane, R = H, x = 8.7, y = 15.5; b) Catenane: Olympiadane*[2].

Two examples are described in literature that can be seen as a first progress toward a non-covalent coupling mechanism, based on dendrimers. Newkome et al.[3] have recently reported the use of a key-and-lock mechanism to couple two dendrimers with each other

(figure 6.2). A limitation of Newkome's system is that it is monofunctional, because at the present time a linkage can only be made between *two* dendrimers. The chemistry to expand the possibilities is regarded to be rather tedious.

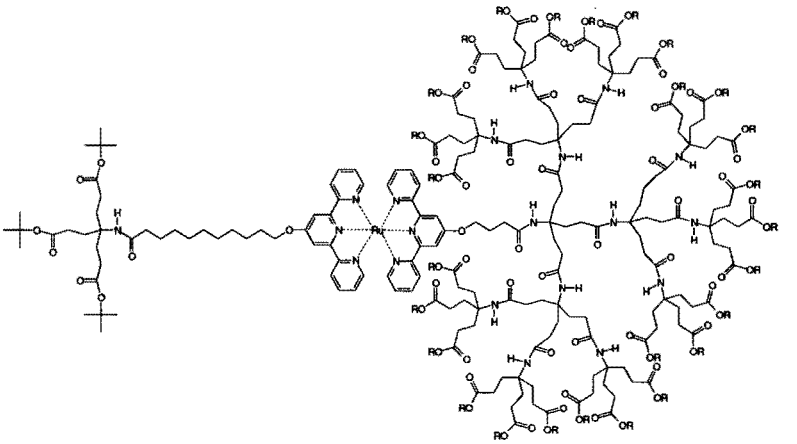


Figure 6.2: *Key-and-lock mechanism, applied for dendrimers*[3].

The second example that describes mechanical or physical locking of one molecule by the other is the dendritic box[4]. By performing an amidation reaction onto DAB-*dendr*-$(NH_2)_{64}$ with N-*t*-Boc L-phenylalanine hydroxysuccinimide ester a solid shell is built around the dendrimer, that shields the inner dendritic cavities from the environment. When this reaction is performed in the presence of guest molecules, these become physically entrapped and can only be released by (partial) removal of the shell. It is furthermore possible to lock in an integer number of guests. The drawback of this system is that the dendritic box can be seen as

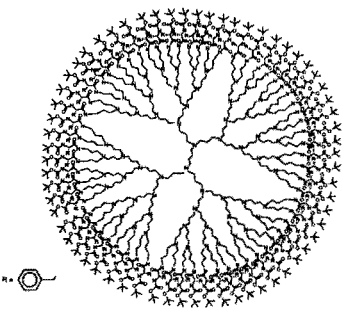
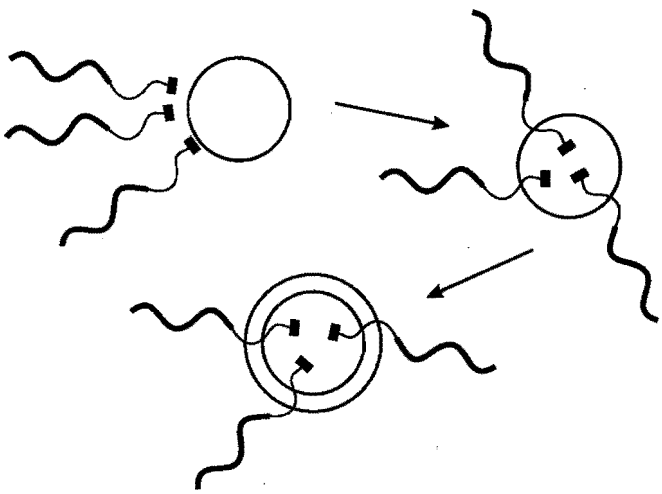


Figure 6.3: *The dendritic box*[4].

a host-guest system, comparable to crown ethers, and its guests can't have any interactions with the environment. To show resemblance with the earlier mentioned supramolecular systems, it is necessary to lock into the dendritic box larger molecules, such as polymers, that are partly sticking out, so that the architecture is determined by both components.

In this chapter the synthesis and characterization of a polystyrene-dendrimer complex is described, in which an integer number of polymers is anchored to the dendritic box. This system can be seen as the first step toward a new building concept in supramolecular chemistry. In scheme 6.1 this concept is depicted. An anchoring group is attached to polystyrene (PS). This moiety has an affinity with the interior of the dendrimer structure, and



Scheme 6.1: *Concept of anchoring polymers into a dendritic box.*

will therefore enter DAB-*dendr*-$(NH_2)_{64}$. In order to prevent PS from interference with the construction of the dendritic shell a spacer is introduced between PS and the anchor.

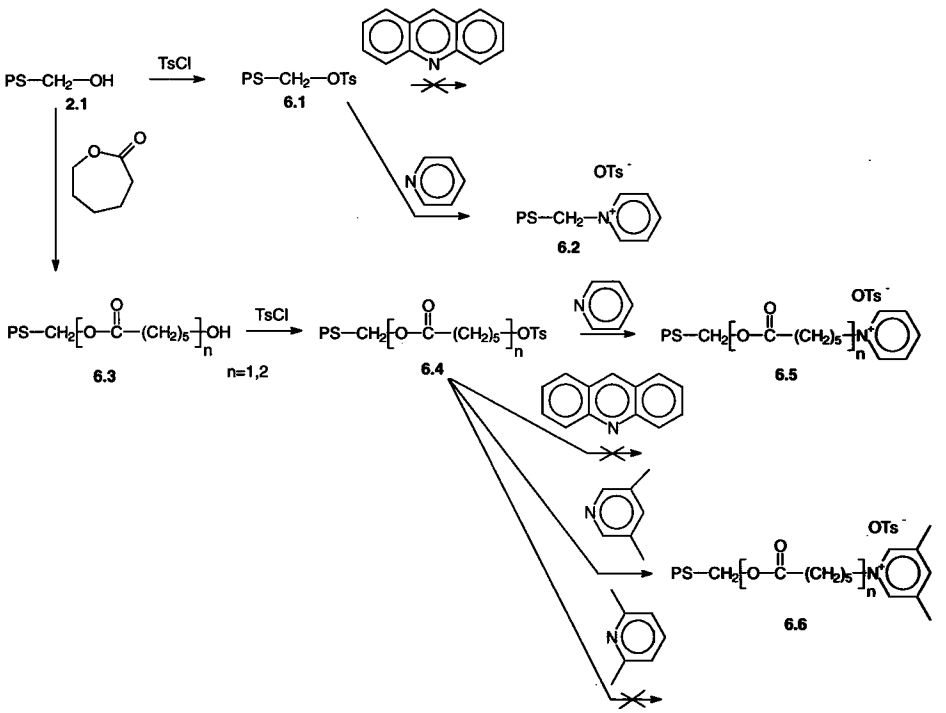
Two PS-derivatives have been developed to validate this concept. In a first approach a dimethyl-pyridinium group is linked to PS *via* a caprolactone spacer (§ 6.2), to investigate briefly the possibility of complex formation. With the second PS-structure, containing a fluorescein-group, a more detailed study can be performed after the number of PS-chains locked in a dendritic box and the position of the fluorescein head group (§ 6.3).

6.2 Encapsulation experiments with PS-pyridinium derivatives

Our first approach toward a system, in which polymer chains were physically locked into a dendritic box, was based on PS, to which a pyridinium derivative was coupled. From earlier work by Johan Jansen[5] it was shown that pyridinium derivatives were useful as guests in the dendritic box, due to their affinity with the tertiary amines in the core of the dendrimers. The choice of the caprolactone spacer was based on the ease of preparation. In §6.2.1 the synthesis of the modified PS is described, whereas the encapsulation experiments are reported in § 6.2.2.

6.2.1 Synthesis of PS-pyridinium derivatives

The synthetic approaches that were undertaken to obtain pyridinium-modified PS (**6.6**) are presented in scheme 6.2. A spacer was easily attached to PS-OH (**2.1**) by letting the



Scheme 6.2: *Synthetic approaches toward pyridinium- modified PS.*

alkoxide react with ε-caprolactone. The product (**6.3**) was obtained in 50% yield after work-up, consisting of a PS-chain to which an average of 1.6 caprolactone units was linked. The scale of reaction (1 or 10 g) didn't influence the yield of the synthesis of **6.3**. There was no pronounced effect on degree of functionalization when an excess of *n*-butyllithium was added to make the alkoxide. The average number of coupled ε-caprolactone units was determined by the ratio at the beginning of the reaction between PS and ε-caprolactone. Of both compounds **2.1** and **6.3** the tosylate was used to prepare the pyridinium-derivatives. Reaction with pyridine itself proceeded without any difficulties. However, this moiety has limited anchoring possibilities.

Therefore acridine was chosen, but unfortunately no reaction occurred at all. A second anchoring group, lutidine (dimethyl pyridine), was successfully attached, but only when 3,5-lutidine was used. The compound 2,6-lutidine didn't react. All of the synthesized products could be well characterized with spectroscopic techniques.

The yield of the spacer synthesis is rather low and doesn't exceed 60%. Because the scale of reaction hasn't got a great effect, the role of impurities in the reaction mixture can be excluded. An explanation can be that the addition of the second unit of ε-caprolactone is a faster reaction than addition of ε-caprolactone directly to the PS-chain. Steric hindrance of the polymer chain can therefore play an important role. Furthermore, it is possible that proton abstraction occurs from the ε-caprolactone unit by the alkoxide. The polymeric tosylates obtained are reactive enough for alkylation of pyridine and 3,5-lutidine. 2,6-Lutidine doesn't react, due to steric hindrance. For acridine it seems to be more complicated. In literature tosylates are reported to react smoothly with acridine[6]. In our case, the polymeric tosylate is probably less reactive, due to the shielding effect of the polymer chain, which prevents contact between acridine and the reactive polymer end group. Although acridine seems to be the moiety with the best anchoring possibilities, the obtained 3,5-lutidinium derivative (**6.6**) should also be able to be locked in by a dendritic box.

6.2.2 Encapsulation of 6.6 in a dendritic box

Two encapsulation experiments were performed with **6.6**, only differing in type of solvent used. One reaction was performed in CH_2Cl_2, the second one in DMF. A mixture consisting of a 1:1 ratio of **6.6** and DAB-*dendr*-$(NH_2)_{64}$ was stirred for 24 hours at room

temperature before the phenylalanine shell was built around the dendrimer. The work-up procedure consisted for the CH_2Cl_2 reaction of a precipitation in MeOH, followed by repeated column chromatographic purifications (eluent CH_2Cl_2/MeOH 1/1 v/v). The DMF reaction was purified without the precipitation step. On TLC two products were visible (R_f = 0.7 and 0). However, the fraction with R_f = 0 eluted first with column chromatography, probably due to partial deactivation of the silicagel by the eluent. This separation procedure proved to be reproducible, and it was found with ^{1}H-NMR that the product with R_f = 0.7 contained both PS and dendritic box. The ratio between the 2 compounds was different for the different reactions. The CH_2Cl_2-reaction showed a ratio of 16 PS-chains per dendrimer, the DMF-

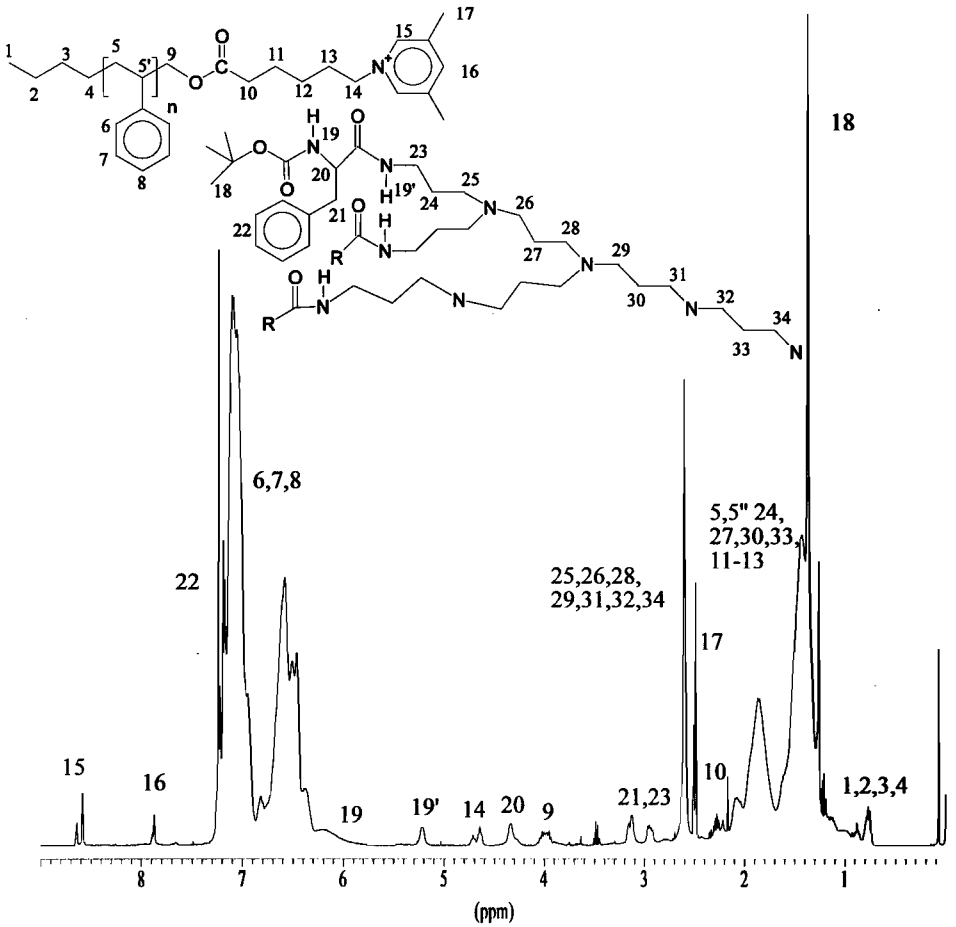


Figure 6.4: *^{1}H-NMR spectrum of the complex, prepared in CH_2Cl_2.*

product consisted of a complex with 6 chains. Both values were based on ^{1}H-NMR spectroscopy only. Evidence that we are dealing with a real PS-dendrimer complex and not a mixture, can be found in ^{1}H-NMR. The protons next to the tertiary amines show a broad singlet around 2.7-2.8 ppm. Also the amide and benzylic protons are shifted, indicating a disturbance of the dendritic shell (figure 6.4). Attempts to analyze this complex with GPC failed unfortunately.

When **6.6** is used as guest it is possible to encapsulate molecules in a dendritic box that are partly sticking out. Of utmost importance for these systems is the use of the correct work-up procedure, because in principle it is possible to have a mixture of dendritic box, **6.6** and the complex. With column chromatography purification is achieved, but it is difficult to know whether all of the unlocked chains have been removed.

There's a big difference in load when the reaction is performed in either CH_2Cl_2 or DMF. This can be explained by aggregation phenomena. Due to a larger amount of clustering of the head groups in CH_2Cl_2 than in the more polar DMF, concentration fluctuations of PS in the mixture result in a non-statistical distribution of the PS-chains over the dendrimer. By precipitation, the bulk of empty dendritic box is already removed, which also can influence the PS-load of the isolated product. The determination of the load by ^{1}H-NMR spectroscopy is only possible when the assumption is made that dendrimer and PS have approximately the same relaxation times. Because of overlap of signals, the estimated values of the PS-load are more indicative than quantitative. The disturbance of the dendritic shell is evidence for the existence of a real complex and not a mixture. The high loads and the use of ε-caprolactone as spacer account for the observed shifts. Because it is difficult to obtain additional proof of the complex by other characterization techniques, ^{1}H-NMR is the only technique on which we can rely. Therefore, this system has to be interpreted with caution and can be seen as a first positive test for the concept of locking polymers into a dendritic box.

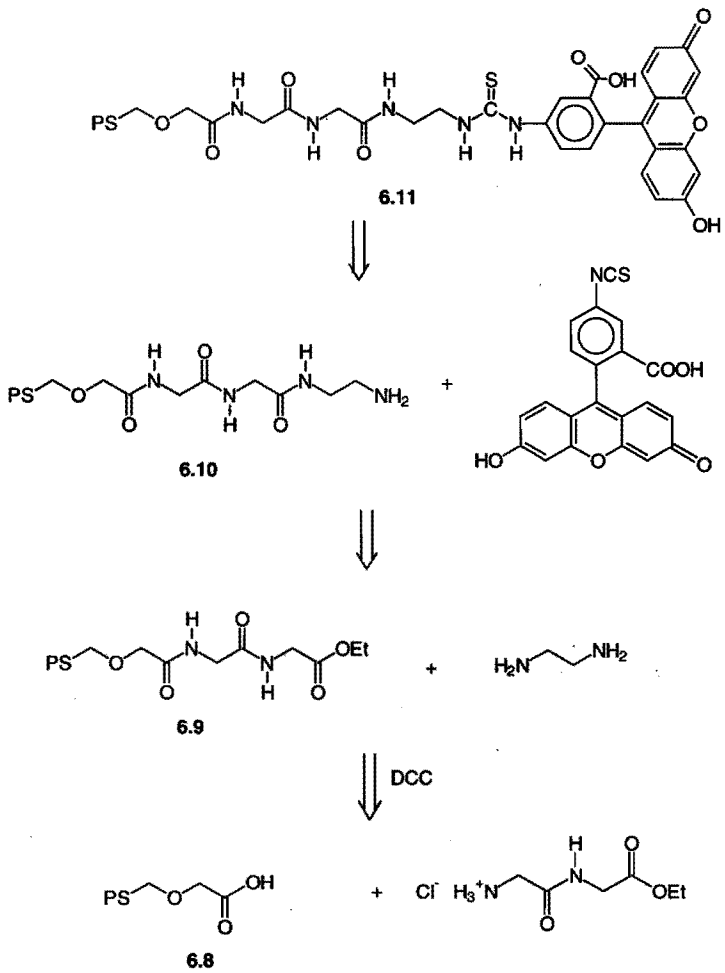
6.3 Encapsulation experiments with fluorescein-modified PS

In order to prevent characterization difficulties as mentioned in the previous paragraph, and to investigate the complex in more detail, a new type of modified PS has been designed. Fluorescein was chosen as anchoring group, because this molecule and related compounds as Bengal Rose have already been thoroughly investigated as guest in a dendritic

box[4]. Johan Jansen has performed model encapsulation studies with the reaction product of fluorescein-5-isothiocyanate and propylamine (fluorescein-5-propyl thiourea). This compound was used to determine the maximum number of fluorescein molecules inside a dendritic box. The initial ratio of fluorescein and dendrimer mixtures was varied and the load after the encapsulation reaction was determined with UV-VIS spectroscopy. The obtained calibration curve (figure 6.5, red marks) showed that an integer number of 4 molecules was built in. Furthermore, fluorescence and UV-VIS spectra showed solvent-independent behavior for the trapped molecules, contrary to free fluorescein. With this type of anchor, therefore, unambiguous proof can be obtained about the location of the fluorescein group. To improve the system even more, a diglycine unit is introduced, which shows a strong resemblance with the dendritic shell, thereby increasing the compatibility of the guests with the dendritic box. In § 6.3.1 the synthesis of this modified PS is described and in § 6.3.2 the results of the encapsulation experiments are presented.

6.3.1 Synthesis of fluorescein-modified PS (6.11)

The synthetic procedure for the preparation of PS-diglycine-fluorescein (**6.11**) is shown in a retrosynthetic approach in scheme 6.3. An acid function was introduced by the reaction of the alkoxide of PS-OH (**2.5**), made by *n*-BuLi, with potassium bromoacetate. This reaction proceeded with a yield after work-up of about 50%. The only other product obtained was the starting compound **2.5**, that could easily be separated from the desired product by column chromatography. The yield could not be increased by changing the amounts of *n*-BuLi and bromoacetate used. Coupling of the diglycine unit to acid-functionalized PS was performed according to the DCC coupling technique. Using the acid chloride of PS, a variety of by-products was formed. With DCC 2 products were obtained: the desired PS-diglycine (**6.9**) and the DCC-adduct of PS. The ratio between these products varied strongly and **6.9** was obtained in yields after work-up of 40-70%. The DCC-adduct was not reactive anymore to the diglycine-ethyl ester. Attempts to optimize this coupling procedure, by using additives as HOBT or DMAP, didn't show any improvement of the reproducibility of the yield. Compound **6.9** could be obtained in pure form by column chromatography. This technique was not possible anymore for the last 2 steps: amidation with ethylenediamine and coupling with fluorescein-5-isothiocyanate, because of the polarity of the products. Chromatography, however, was not necessary, because both reactions were performed quantitatively. The



Scheme 6.3: *Synthesis of fluorescein-modified PS in a retrosynthetic approach.*

amidation was easily executed in ethylenediamine as reactive solvent. The excess was removed by evaporation, followed by precipitation of the crude product in MeOH. A small excess of fluorescein-5-isothiocyanate was used. This excess was removed by repeated precipitation. All of the products were characterized with NMR and IR-spectroscopy. Unambiguous proof about the success of the reactions was given by MALDI-TOF analysis of the end product **6.11**.

Although the synthesis of **6.11** is rather straightforward, there are some remarks to be made about several reaction steps. The coupling of **2.5** with bromoacetate seems to be limited

to a 50% yield. It is possible that, though bromoacetate is used, freshly prepared from the reaction between *t*-BuOK and bromoacetic acid, still some acid is present that undergoes an acid-base reaction with the alkoxide. This, however, seems to be contradicted by the fact that yields are reproducible when different batches and amounts of bromoacetate are used. Another explanation that becomes more reasonable in combination with the results obtained from the coupling between ε-caprolactone and hydroxyl-functionalized PS (**6.3**), is that the alkoxide can also react with the slightly acidic protons of the acetate.

The second step, the DCC-coupling, suffers from a strong fluctuation in yield, though modification toward the DCC-adduct proceeds quantitatively. This ester is not reactive enough to be transamidated, or can't react with the amine of the diglycine unit, due to steric hindrance of the PS chain. An explanation can be that, before the active ester is made, first an ion pair has to be formed between the carboxylate of PS and the ammonium group of diglycine. When these groups are in close proximity, DCC activates the coupling. When DCC has reacted before the ion pair has formed, no driving force is left to bring the reactive groups together. The coupling with ethylenediamine proceeds quantitatively. In chapter 2, however, we have reported the formation of a diadduct for the same reaction with the acid chloride of PS. The difference between the systems is located in the polarity of the head group. The ethyl ester has less tendency to aggregate than the acid chloride. Therefore, the chance that a termolecular reaction can occur between one ethylenediamine molecule and 2 polymer head groups is further diminished.

6.3.2 Synthesis and characterization of a complex based on the dendritic box and 6.11

Four different ratios of **6.11** and DAB-*dendr*-$(NH_2)_{64}$, namely 0.6:1, 1.3:1, 5:1 and 9:1 mol PS/mol dendrimer were mixed for a night at room temperature in a CH_2Cl_2/MeOH (2/1 v/v) mixture, before the dendritic shell was constructed with L-phenylalanine. The products were purified by repeated column chromatography, using CH_2Cl_2 as eluent, in which case the brightly orange product eluted with $R_f = 0.95$. A trace of the material was left on the column, pointing in the direction of an irreversible saturation of the stationary phase with the dendritic complex, the unbound **6.11** remained at the column with $R_f = 0$. The product obtained from the 9:1 reaction mixture was also dialyzed. Characterization of the purified samples with ^{1}H-

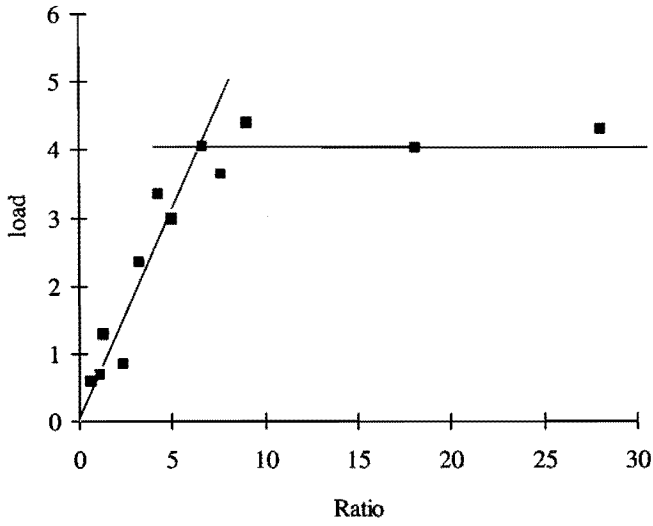


Figure 6.5: *Calibration curve of fluorescein-5-propyl thiourea (■) and* ***6. 11*** *(■) inside a dendritic box.*

NMR showed that the products consisted of both PS and dendritic box. No distortion of the shell could be observed. The loads were determined with UV-VIS spectroscopy, and it was found that the loads of all of the obtained complexes were located on the calibration curve of fluorescein in the box (figure 6.5).

A maximum number of 4 anchored PS-chains was observed. The load of the complex that resulted from the reaction mixture with a 9:1 ratio didn't change after dialysis. When a mixture of empty dendritic box and **6.11** was dialyzed for two weeks in DMF, however, also no decrease in amount of **6.11** could be detected. Proof about the position of the head group was obtained by UV-VIS (CH_2Cl_2/MeOH 2/1 v/v) and fluorescence spectroscopy (figure 6.6). Free **6.11** and a mixture of **6.11** and dendritic box showed a solvent-dependent behavior with respect to λ_{max} for UV-VIS measurements and efficiency of fluorescence. The complex showed solvent-*in*dependent behavior.

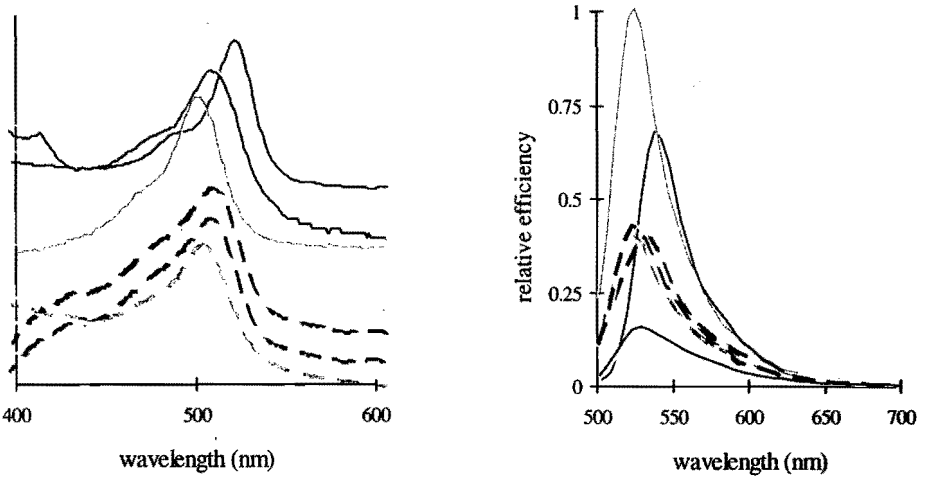


Figure 6.6: ___ *DMSO;* —— *CH_2Cl_2/MeOH 2/1 v/v;* ___ *THF.*
UV-VIS and fluorescence spectra: the dashed lines refer to the complex , the solid lines are from the measurements with free ***6.11****.*

Induced CD, a phenomenon which was earlier observed for Bengal Rose inside the box[7] could not be measured for the complex. MALDI-TOF analysis was possible for the empty dendritic box and free **6.11,** but not for the complex; only a weak signal of unattached polymer **6.11** was observed. With GPC a peak was found, corresponding to $M_n = 4 \cdot 10^3$ g/mol, tailing to lower molecular weight. TLC-behavior of the complex and a mixture of **6.11** and empty dendritic box was investigated. It was observed that in CH_2Cl_2 adsorption occurred of **6.11** onto the dendritic box, and that the polymer was dragged along during elution. This was caused by the presence of the fluorescein head group, because amine-functionalized PS or PS, equipped with spacer (**6.10**), could be easily separated on TLC from the dendritic box. The elution behavior of the mixture and the complex proved to be similar for a number of eluentia (DMSO, cyclohexane, toluene, DMSO/HOAc 3/1 v/v, MeOH/Et_3N/CH_2Cl_2 1/1/98 v/v/v, CH_2Cl_2/MeOH 95/5 v/v); with *n*-hexane/ EtOAc 6/1 v/v however, a distinct difference in elution behavior could be detected: the complex didn't elute, whereas the mixture showed an R_f = 0.5 (with tailing). When *n*-hexane/ EtOAc 9/1 v/v was used both complex and

mixture didn't elute, with *n*-hexane/ EtOAc 2/1 v/v the complex had an R_f = 0.6 and the mixture an R_f = 0.75.

The use of fluorescein instead of lutidinium as head group has its advantages. Because of the intense color, the dendritic complex is easier detectable with TLC. The strange elution behavior of this product can therefore be better understood, and a simpler column chromatographic purification procedure can be used as was performed for the complex **6.7**. The complex is apolar, but still leaves a trace on the stationary phase, as was also earlier observed with GPC and HPLC (chapter 5). This irreversible interaction seems to be quite general for these modified dendrimers, but is still hardly understood.

It is possible to determine the PS-load of the dendritic box more accurately with UV-VIS spectroscopy. Though, also in this case the assumption has to be made that the extinction coefficient of free **6.11** and encapsulated **6.11** are identical. Because the UV-VIS spectra of both compounds are quite similar in CH_2Cl_2/MeOH 2/1 v/v and the UV-values are in reasonable agreement with the NMR-data, this assumption seems valid. Because all of the measured values are on the calibration curve for free fluorescein in the box, it is justified to state that a maximum of 4 PS-chains is anchored into the dendritic box. Strong proof that the head groups are actually inside, is only obtained by UV-VIS and fluorescence spectroscopy. Unfortunately, CD doesn't give us any information about the position of the head group and MALDI-TOF only provides negative proof for the existence of a complex. With this characterization technique it is impossible to discern between a stable complex by adherence of the polymers onto or by anchoring into the box.

A big problem of the use of fluorescein as anchoring group is the fact that this moiety has interactions with the dendritic box and that it can be adsorbed onto the dendrimer surface. This makes purification a difficult task, also because of the fact that dialysis seems to be immeasurably slow, and therefore probably not suited for the removal of polystyrene. A dialysis solvent has to be chosen that is polar enough to keep the membrane pores open, and is also capable of swelling PS, which makes reptation of the polymer through the pores possible. Although DMF is very well suited for dialysis, it is a rather poor solvent for PS, which explains the dialysis problems. Alternatives for DMF are, however, hard to find.

TLC-behavior of the isolated complex and the mixture is similar for most eluentia, except for the *n*-hexane/EtOAc series. For this combination PS is precipitated at the stationary phase and in case of the mechanically locked complex, it is impossible for the

dendrimer to elute. This is not the case for the mixture, in which the dendritic box can be dissolved and therefore eluted. Purification of the crude complex with column chromatography still results in removal of non-anchored chains. This can be explained by steric hindrance induced by the anchored polymers, which make it difficult for the unattached chains to have interactions with the dendrimer surface. It is, however, not possible to exclude that still some unlocked chains are present. This can explain the MALDI-TOF results, in which a weak signal of **6.11** is detected, although this can also originate from damaging of the dendritic shell under the analysis conditions. The GPC results also can indicate the existence of some free PS-chains. Gitsov[8] has shown, however, that for an ABA triblock copolymer, in which A stands for a fourth generation Fréchet-type of dendrimer and B for a PS-chain, an M_n is detected, similar to the PS-homopolymer. From this work it becomes clear that GPC-data have to be interpreted carefully.

6.4 Conclusions

A new building concept has been developed, based on the physical encapsulation of polymer end groups inside a dendritic box. Two types of modified PS have been locked in. The first structure consists of a lutidinium anchor group, linked through a caprolactone spacer to PS. The formation of the PS-dendrimer complex is observed by ^{1}H-NMR spectroscopy. The second compound has a fluorescein group attached to PS *via* a diglycine unit. With UV-VIS spectroscopy a maximum load of 4 PS-molecules per dendrimer is found. The fluorescein groups are shielded from the environment. For both types of complexes purification is a difficult task, and it is not possible to know if all of the unlocked chains really have been removed. The concept of mechanical locking of an integer number of compounds in a dendritic box can open the way to a new field in chemistry, called modular chemistry. This sub-class of the supramolecular chemistry is concerned with the controlled construction of nanometer-sized materials out of building blocks. When instead of PS a compound is anchored with a functionality outside the box, a tetra or multivalent building block is obtained, depending on the anchor used. This building block is ideally suited for application in modular chemistry, but its versatility even extends to the use as immobilizing agent for functional structures as for example catalytic systems. The work described in this chapter can

therefore be seen as an introductory investigation of a new class of functional macro-organic compounds.

6.5 Experimental

For a general section concerning purification of solvents and spectroscopic and chromatographic techniques: see chapter 2.

MALDI-TOF measurements were performed at the Institut für Medizinische Physik und Biophysik, Westfällische Wilhelms-Universität, Münster, using a LAMMA 1000 laser microprobe, equipped with Nd-YAG laser (λ = 266 nm). As matrix dihydroxybenzoic acid was used. *UV-VIS* spectra were recorded on a Perkin Elmer UV-VIS Lambda 3B spectrometer. *Fluorescence* spectra were recorded on a Perkin Elmer luminescence LS 50 B spectrometer. *CD* measurements were performed on a Jasco J-600 CD-ORD spectrometer.

PS-OTs (6.1)

1.04 g PS-OH (**2.1**, $M_n = 3.6 \cdot 10^3$ g/mol, $2.9 \cdot 10^{-4}$ mol) in 3.5 ml of dry pyridine was added to a stirred solution of 0.23 g ($1.2 \cdot 10^{-3}$ mol) tosylchloride in 1 ml pyridine, which was cooled in an icebath. The mixture was allowed to react overnight at 4°C. Pyridinium-chloride crystals were formed. TLC (eluent CH_2Cl_2/*n*-hexane 6/4 v/v) showed quantitative formation of **6.1**. The product was precipitated in MeOH, filtrated over silica (eluent: CH_2Cl_2) and dried *in vacuo*, resulting in 0.86 g (yield 83%) of **6.1**.

^{1}H-NMR ($CDCl_3$): δ 0.73-1.22 (9H, Bu-$(CH_2$-$CHPh)_n$), 1.22 -1.71 ($(C\underline{H}_2$-$CHPh)_n$), 1.71-2.35 ($(CH_2$-$C\underline{H}Ph)_n$), 2.30-2.45 (br, s, 3H, O_2S-Ph-$C\underline{H}_3$), 2.53-2.73 (br, 1H, $C\underline{H}$Ph-CH_2-O), 3.70 -4.10 (br, m, 2H, -$C\underline{H}_2$-O-$S(O_2)$-Ph-CH_3), 6.28-7.25 ($(CH_2$-$CH\underline{Ph})_n$), 7.40-7.55 (H^3+H^5, O-$S(O_2)$-$\underline{Ph}$-CH_3) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.0 ($\underline{C}H_3$-CH_2-CH_2CH_2-$(CH_2$-$CHPh)_n$), 21.5 ($S(O_2)$-Ph-$\underline{C}H_3$), 22.5 (CH_3-$\underline{C}H_2$-CH_2-CH_2-$(CH_2$-$CHPh)_n$), 26.9 (CH_3-CH_2-$\underline{C}H_2$-CH_2-$(CH_2$-$CHPh)_n$), 31.8 (CH_3-CH_2-CH_2-$\underline{C}H_2$-$(CH_2$-$CHPh)_n$), 40.3 (br, $(CH_2$-$\underline{C}HPh)_n$), 40.0-46.5 (br, $(\underline{C}H_2$-$CHPh)_n$), 74.2 (-$\underline{C}H_2$-O-$S(O_2)$-), 124.1-127.0 (br, CH_2-$CH\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-$CH\underline{Ph}_{ortho+meta}$), 129.6 ($C^{3+5}$,O-$S(O_2)$-$\underline{Ph}$), 132.8 ($C^1$,O-$S(O_2)$-$\underline{Ph}$), 144.3 ($C^4$,O-$S(O_2)$-$\underline{Ph}$), 145.1-146.5 (br, CH_2-$CH\underline{Ph}_{ipso}$) ppm.

IR: 1176.4 cm^{-1} R-SO_2-OR'.

Reactions between 6.1 and acridine[6]

i) 0.3 g ($8 \cdot 10^{-5}$ mol) **6.1** was dissolved in 5 ml nitrobenzene. $1.65 \cdot 10^{-2}$ g ($9.2 \cdot 10^{-5}$ mol) acridine was added. The homogeneous mixture was heated at 150°C for 6 hours. No reaction could be detected.

ii) 0.1 g ($2.7 \cdot 10^{-5}$ mol) **6.1** was mixed with 0.1 g ($5.6 \cdot 10^{-4}$ mol) acridine and the mixture was heated to 120°C, beyond the m_p of acridine (107-110°C). The melt was allowed to react for 4 hours. However, no reaction occurred.

PS-pyridinium (6.2)

0.1 g ($2.7 \cdot 10^{-5}$ mol) **6.1** was dissolved in 2 ml dry pyridine. The mixture was heated at 120°C for 2 hours. TLC (eluent CH_2Cl_2/MeOH 95/5 v/v) showed quantitative reaction. **6.2** was obtained after evaporating the excess pyridine *in vacuo*.

^{1}H-NMR ($CDCl_3$): δ 0.73-1.22 (9H, Bu-$(CH_2$-CHPh$)_n$), 1.22 -1.71 ((CH_2-CHPh$)_n$), 1.71-2.35 ((CH_2-CHPh$)_n$), 2.30 (s, 3H, + $^-O_3$S-Ph-CH_3), 2.78-2.98 (br, 1H, CHPh-CH_2-Pyr), 4.42-4.70 + 4.79-5.14 (br, m, 2H, -CH_2-Pyr), 6.28-7.25 ((CH_2-CHPh$)_n$), 7.50-7.68 (2H, Pyr_{meta}), 7.75 (d, H^2+H^5, $^-O_3$S-Ph-CH_3), 8.03-8.15 (1H, Pyr_{para}), 8.23-8.55 (2H, Pyr_{ortho}) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.0 (CH_3-CH_2-CH_2CH_2-(CH_2-CHPh$)_n$), 21.3 ($^-O_3$S-Ph-CH_3), 22.5 (CH_3-CH_2-CH_2-CH_2-(CH_2-CHPh$)_n$), 26.9 (CH_3-CH_2-CH_2-CH_2-(CH_2-CHPh$)_n$), 31.8 (CH_3-CH_2-CH_2-CH_2-(CH_2-CHPh$)_n$), 40.3 (br, (CH_2-CHPh$)_n$), 40.0-46.5 (br, (CH_2-CHPh$)_n$), 124.1-127.0 (br, CH_2-$CHPh_{para}$), 126.0 (C^{2+6}, $^-O_3$S-Ph-CH_3), 127.0-129.5 (br, CH_2-$CHPh_{ortho+meta}$), 129.0 (C^{3+5}, $^-O_3$S-Ph-CH_3), 129.2 (CH_2-Pyr_{meta}), 139.0 (CH_2-Pyr_{ortho}), 143.8 (C^4, $^-O_3$S-Ph-CH_3), 144.4 (CH_2-Pyr_{para}), 145.1-146.5 (br, CH_2-$CHPh_{ipso}$),149.7 (C^1, $^-O_3$S-Ph-CH_3) ppm.

IR: 1192.6 cm^{-1} pyridine.

Reaction between 2.1 and ε-caprolactone (6.3)

2.0 g ($5.6 \cdot 10^{-4}$ mol) **2.1** was dissolved in 5 ml THF under argon atmosphere. 0.70 ml 1.6 M *n*-BuLi in *n*-hexane ($1.1 \cdot 10^{-3}$ mol, 2 eq) was added and the mixture was stirred at room temperature for 30 minutes. Next 125 µl (2 eq) ε-caprolactone was added using an Eppendorff pipette. After stirring for 2 hours TLC (eluent CH_2Cl_2/*n*-hexane 6/4 v/v) showed the formation of 2 products, with R_f = 0.45 and R_f = 0.14. Column chromatographic separation (eluent CH_2Cl_2/*n*-hexane 6/4 v/v) followed by precipitation in MeOH and drying *in vacuo*, resulted in 0.81 g **2.1** (R_f = 0.45) and 0.91 g (yield 46%) of **6.3** (R_f = 0.14), with an average coupling of 1.6 ε-caprolactone-units per PS-chain.

^{1}H-NMR ($CDCl_3$): δ 0.73-1.22 (9H, Bu-$(CH_2$-CHPh$)_n$), 1.22 -1.71 ((CH_2-CHPh$)_n$), 1.71-2.35 ((CH_2-CHPh$)_n$), 2.12-2.18 + 2.28-2.35 (br, m, -OC(O)-CH_2-), 2.35-2.55 (br, 1H, CHPh-CH_2-O), 3.53 -3.68 (br, double signal, 2H, -CH_2-OH), 3.79-4.14 (br, m, 3.3 H, CHPh-CH_2-O-C(O)- + CH_2-CH_2-O-C(O)-), (6.28-7.25 ((CH_2-CHPh$)_n$ ppm.

^{13}C-NMR ($CDCl_3$): δ 14.0 (CH_3-CH_2-CH_2CH_2-(CH_2-CHPh$)_n$), 22.5 (CH_3-CH_2-CH_2-CH_2-(CH_2-CHPh$)_n$), 24.8-26.0 (OC(O)-CH_2-CH_2-CH_2-CH_2-), 26.9 (CH_3-CH_2-CH_2-CH_2-(CH_2-CHPh$)_n$), 28.9 (-

CH_2-$\underline{C}H_2$-CH_2-OC(O)-), 31.8 (CH_3-CH_2-CH_2-$\underline{C}H_2$-(CH_2-CHPh)$_n$), 32.5 (-$\underline{C}H_2$-CH_2-OH), 34.4-34.6 (OC(O)-$\underline{C}H_2$-CH_2-), 40.3 (br, (CH_2-$\underline{C}$HPh)$_n$), 40.0-46.5 (br, ($\underline{C}H_2$-CHPh)$_n$), 63.0 (-CH_2-$\underline{C}H_2$-OH), 64.5 (-CH_2-$\underline{C}H_2$-OC(O)-), 67.4-69.3 (CH_2-CHPh-$\underline{C}H_2$-O-C(O)-), 124.1-127.0 (br, CH_2-CH$\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-CH$\underline{Ph}_{ortho+meta}$), 145.1-146.5 (br, CH_2-CH$\underline{Ph}_{ipso}$) ppm.

IR: ν_{OH} 3454.7 cm^{-1}; ν_{CO} 1734.5 cm^{-1}.

Tosylate of 6.3 (6.4)

0.47 g **6.3** ($1.2 \cdot 10^{-4}$ mol) was tosylated according to the procedure described for **6.1**. Quantitative conversion led to 0.43 g (yield 91.5%) **6.4**.

^{1}H-NMR ($CDCl_3$): δ 0.73-1.22 (9H, $\underline{Bu}$-(CH_2-CHPh)$_n$), 1.22 -1.71 (($C\underline{H}_2$-CHPh)$_n$), 1.71-2.35 ((CH_2-$C\underline{H}$Ph)$_n$), 2.19-2.35 (br, m, -OC(O)-$C\underline{H}_2$-), 2.36-2.52 (-O-S(O_2)-Ph-$C\underline{H}_3$), 2.59-2.83 (br, 1H, $C\underline{H}$Ph-CH_2-O), 3.80-4.12 (br, m, 5.3 H, CHPh-$C\underline{H}_2$-O-C(O)- + CH_2-$C\underline{H}_2$-O-C(O)- + $C\underline{H}_2$-O-S(O_2)-), (6.28-7.25 ((CH_2-$C\underline{H}$Ph)$_n$), 7.31-7.38 (H^3+H^5, O-S(O_2)-$\underline{Ph}$-CH_3), 7.75-7.82 (H^2+H^6, O-S(O_2)-$\underline{Ph}$-CH_3) ppm.

IR: ν_{CO} 1734.1 cm^{-1}; R-SO_2-R' 1176.6 cm^{-1}; 1097.8 cm^{-1}.

Pyridinium adduct of 6.4 (6.5)

0.26 g ($8 \cdot 10^{-5}$ mol) **6.4** was dissolved in 5 ml dry pyridine and heated under reflux for 2 hours. The excess pyridine was removed by evaporation, followed by stripping with toluene. NMR and TLC (eluent CH_2Cl_2/MeOH 95/5 v/v) showed quantitative formation of the pyridinium adduct **6.5** (0.26 g).

^{1}H-NMR ($CDCl_3$): δ 0.73-1.22 (9H, $\underline{Bu}$-(CH_2-CHPh)$_n$), 1.22 -1.71 (($C\underline{H}_2$-CHPh)$_n$), 1.71-2.35 ((CH_2-$C\underline{H}$Ph)$_n$), 2.18-2.32 (br, m, -OC(O)-$C\underline{H}_2$-), 2.33 (s, $^-O_3$S-Ph-$C\underline{H}_3$), 2.35-2.55 (br, 1H, $C\underline{H}$Ph-CH_2-O), 3.79-4.14 (br, m, 5.3 H, CHPh-$C\underline{H}_2$-O-C(O)- + CH_2-$C\underline{H}_2$-O-C(O)-), 4.63-4.88 (br, double signal, $C\underline{H}_2$-Pyr), 6.28-7.25 ((CH_2-$C\underline{H}$Ph)$_n$), 7.68-7.83 (d, 2H, H^2+H^6, $^-O_3$S-$\underline{Ph}$-CH_3), 7.85-8.13 (CH_2-$\underline{Pyr}_{meta}$), 8.22-8.38 (CH_2-$\underline{Pyr}_{para}$), 8.90-9.25 (br, double signal, CH_2-$\underline{Pyr}_{ortho}$) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.0 ($\underline{C}H_3$-CH_2-CH_2CH_2-(CH_2-CHPh)$_n$), 21.2 ($^-O_3$S-Ph-$\underline{C}H_3$), 22.5 (CH_3-$\underline{C}H_2$-CH_2-CH_2-(CH_2-CHPh)$_n$), 23.9-26.9 (OC(O)-CH_2-$\underline{C}H_2$-$\underline{C}H_2$-CH_2-CH_2-OC(O)- + OC(O)-CH_2-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-CH_2-Pyr), 26.9 (CH_3-CH_2-$\underline{C}H_2$-CH_2-(CH_2-CHPh)$_n$), 28.2 (-CH_2-$\underline{C}H_2$-CH_2-OC(O)-), 31.3 (OC(O)-CH_2-CH_2-$\underline{C}H_2$-CH_2-CH_2-Pyr), 31.8 (CH_3-CH_2-CH_2-$\underline{C}H_2$-(CH_2-CHPh)$_n$), 33.5+34.0 (OC(O)-$\underline{C}H_2$-CH_2-), 40.3 (br, (CH_2-$\underline{C}$HPh)$_n$), 40.0-46.5 (br, ($\underline{C}H_2$-CHPh)$_n$), 61.7 ($\underline{C}H_2$-Pyr), 64.0 (-CH_2-$\underline{C}H_2$-OC(O)-), 67.4-68.4 (double signal, CH_2-CHPh-$\underline{C}H_2$-O-C(O)-), 124.1-127.0 (br, CH_2-CH$\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-CH$\underline{Ph}_{ortho+meta}$), 127.3 ($C^{2+6}$, $^-O_3$S-$\underline{Ph}$-CH_3), 128.6 (C^{3+5}, $^-O_3$S-$\underline{Ph}$-CH_3), 128.9 (CH_2-$\underline{Pyr}_{meta}$), 139.2 (CH_2-$\underline{Pyr}_{ortho+para}$), 143.6 ($C^4$, $^-O_3$S-$\underline{Ph}$-CH_3), 145.1-146.5 (br, CH_2-CH$\underline{Ph}_{ipso}$), 172.4-173.9 (-CH_2-CH_2-O$\underline{C}$(O)-) ppm.

IR: ν_{CO} 1734.1 cm^{-1}; pyridine 1181.4 cm^{-1}; 1121.2 cm^{-1}.

3,5-lutidinium adduct of 6.4 (6.6).

1.9 g ($5 \cdot 10^{-4}$ mol) **6.4** was dissolved in 10 ml 3,5-lutidine. The mixture was heated at 150°C for 2 hours. The excess 3,5-lutidine was distilled off. The crude product was purified by column chromatography (eluent CH_2Cl_2/MeOH 95/5 v/v), resulting in 1.5 g (yield 79%) **6.6**.

^{1}H-NMR ($CDCl_3$): δ 0.73-1.22 (9H, Bu-$(CH_2\text{-}CHPh)_n$), 1.22 -1.71 ($(CH_2\text{-}CHPh)_n$), 1.71-2.35 ($(CH_2\text{-}CHPh)_n$), 2.18-2.32 (br, m, -OC(O)-CH_2-), 2.31 (s, ^-O_3S-Ph-CH_3), 2.35-2.55 (br, 1H, CHPh-CH_2-O), 2.42-2.54 (CH_2-Pyr(CH_3)$_2$), 3.79-4.14 (br, m, 5.3 H, CHPh-CH_2-O-C(O)- + CH_2-CH_2-O-C(O)-), 4.58-4.82 (br, double signal, CH_2-Pyr(CH_3)$_2$), 6.28-7.25 ($(CH_2\text{-}CHPh)_n$), 7.68-7.83 (d, 2H, H^2+H^6, ^-O_3S-Ph-CH_3), 7.79-7.89 (CH_2-Pyr$_{para}$), 8.74-8.88 (br, CH_2-Pyr$_{ortho}$) ppm.

^{13}C-NMR ($CDCl_3$): δ 14.0 (CH_3-CH_2-CH_2CH_2-$(CH_2\text{-}CHPh)_n$), 18.4 (CH_2-Pyr(CH_3)$_2$), 21.2 (^-O_3S-Ph-CH_3), 22.5 (CH_3-CH_2-CH_2-CH_2-$(CH_2\text{-}CHPh)_n$), 23.9-26.9 (OC(O)-CH_2-CH_2-CH_2-CH_2-CH_2-OC(O)- + OC(O)-CH_2-CH_2-CH_2-CH_2-CH_2-Pyr), 26.9 (CH_3-CH_2-CH_2-CH_2-$(CH_2\text{-}CHPh)_n$), 28.5 (-CH_2-CH_2-CH_2-OC(O)-), 31.3 (OC(O)-CH_2-CH_2-CH_2-CH_2-CH_2-Pyr), 31.8 (CH_3-CH_2-CH_2-CH_2-$(CH_2\text{-}CHPh)_n$), 33.3+33.5 (OC(O)-CH_2-CH_2-), 40.3 (br, $(CH_2\text{-}CHPh)_n$), 40.0-46.5 (br, $(CH_2\text{-}CHPh)_n$), 61.2 (CH_2-Pyr), 64.1 (-CH_2-CH_2-OC(O)-), 67.4-68.4 (double signal, CH_2-CHPh-CH_2-O-C(O)-), 124.1-127.0 (br, CH_2-CHPh$_{para}$), 127.0-129.5 (br, CH_2-CHPh$_{ortho+meta}$), 127.3 (C^{2+6}, ^-O_3S-Ph-CH_3), 128.4 (C^{3+5}, ^-O_3S-Ph-CH_3), 138.8 (C^{2+6}, CH_2-Pyr$_{meta}$), 139.0 (C^{3+5}, CH_2-Pyr), 141.9 (C^4, CH_2-Pyr), 143.6 (C^4, ^-O_3S-Ph-CH_3), 145.1-146.5 (br, CH_2-CHPh$_{ipso}$), 173.1-173.4 (-CH_2-CH_2-OC(O)-) ppm.

IR: ν_{CO} 1731.8 cm^{-1}; lutidine 1197.5 cm^{-1}; 1120.5 cm^{-1}; 1031.0 cm^{-1}.

Coupling attempts between 6.4 and acridine and 2,6-lutidine

0.03 g ($7.9 \cdot 10^{-6}$ mol) **6.4** and 0.01 g ($5.6 \cdot 10^{-5}$ mol) acridine were dissolved in 1 ml nitrobenzene. This mixture was heated at 130°C for 3 hours. After evaporation of the solvent and separation of the reaction mixture with column chromatography (eluent CH_2Cl_2/MeOH 99/1 v/v) NMR analysis showed that no product was formed.

0.11 g ($2.9 \cdot 10^{-5}$ mol) **6.4** was dissolved in 5 ml 2,6-lutidine. The mixture was heated to 140°C for 1 hour. NMR analysis showed no formation of desired product.

Entrapment of 6.6 in a dendritic box (6.7)

638 mg ($8.9 \cdot 10^{-5}$ mol) DAB-*dendr*-$(NH_2)_{64}$ was dissolved in 10 ml CH_2Cl_2. 330 mg ($8.7 \cdot 10^{-5}$ mol) **6.6** was added and the mixture was stirred overnight. 1.9849 g ($5.5 \cdot 10^{-3}$ mol, 62 eq.) N-*t*-Boc-L-phenylalanine hydroxysuccinimide ester was added next. The reaction mixture was stirred for one day and was then precipitated in MeOH. 0.23 g of the crude product was purified by column chromatography (eluent CH_2Cl_2/MeOH 1/1 v/v). A fraction (0.12 g) containing both dendritic box and **6.6** was obtained in a ratio of 16 PS-chains per dendrimer. In ^{1}H-NMR, a shift of the proton resonances

next to the tertiary amines and amides was clearly visible, the benzylic proton signals were shifted and splitted. A second column chromatographic purification of this fraction, using the same eluent, resulted in a product with an unaltered PS-dendrimer ratio. This complex could not be analyzed with GPC, only a very small signal ascribed to **6.6** could be detected. The same procedure was performed using DMF as solvent. Column chromatographic purification of 0.27 g crude product resulted in 0.012 g complex, with a load of 6 PS-chains per dendrimer. Again the earlier observed ^{1}H-NMR shifts were visible.

^{1}H-NMR ($CDCl_3$): δ 0.73-1.22 (Bu-$(CH_2$-$CHPh)_n$), 1.32 (*t*-Boc_{dendr}), 1.22 -1.71 ($(CH_2$-$CHPh)_n$), 1.71-2.35 ($(CH_2$-$CHPh)_n$), 2.18-2.32 (br, m, -OC(O)-CH_2-), 2.35-2.55 (br, 1H, $CHPh$-CH_2-O), 2.42-2.54 (CH_2-$Pyr(CH_3)_2$), 2.68-2.81 (s, br, -CH_2-$N(CH_2$-$)_{2dendr}$), 2.89-3.37 (m, double signal, CH_2-Ph_{dendr}), 3.79-4.14 (br, m, CHPh-CH_2-O-C(O)- + CH_2-CH_2-O-C(O)-), 4.19-4.55 (C(O)-$CH(CH_2)$-NH-), 4.58-4.82 (br, double signal, CH_2-$Pyr(CH_3)_2$), 5.06-5.28 + 5.3-6.1 (C(O)NH-), 6.28-7.25 ($(CH_2$-$CHPh)_n$ + Ph_{dendr}), 7.79-7.89 (CH_2-Pyr_{para}), 8.51-8.68 (br, CH_2-Pyr_{ortho}) ppm.

^{13}C-NMR ($CDCl_3$): dendrimer part δ 24.4, 25.5, 28.3, 38.0, 55.2, 79.4, 126.5, 129.5, 137.1, 155.5, 174.0–176.0 ppm. polystyrene part δ 14.0, 18.4, 22.4, 23.7-26.9, 31.8, 33.5, 61.6, 64.1, 67.8-68.6, 138.7, 141.7, 173.1-173.4 ppm.

Coupling of PS-OH (2.5) with bromoacetate (6.8)

0.53 g (M_n= $4\cdot10^3$ g/mol, $1.33\cdot10^{-4}$ mol) **2.5** was dissolved in 5 ml THF. 0.10 ml 1.6 M ($1.6\cdot10^{-4}$ mol) *n*-BuLi in *n*-hexane was added at room temperature under argon atmosphere. After 1 hour 45 mg ($2.5\cdot10^{-4}$ mol) $BrCH_2COOK$, prepared by equimolar reaction between bromoacetic acid and *t*-BuOK, was added. The solution became slightly yellow. The reaction was followed with TLC (eluent CH_2Cl_2/*n*-hexane 6/4 v/v). Two spots were visible (R_f = 0.9 and R_f = 0.05), of which the ratio didn't change anymore after 2 hours reaction time. Separation of both products was possible with column chromatography (eluent CH_2Cl_2/MeOH 99/1 v/v to remove the first product, eluent CH_2Cl_2/MeOH 95/5 v/v was used to isolate the second product).The first product was **2.5** (0.21 g), the second product proved to be **6.8** (0.29 g, yield 55%).

^{1}H-NMR ($CDCl_3$): δ 0.54-0.78 (br, 6H, CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 0.78-2.44 (CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 3.18-3.53 (br, 2H, $(CH_2$-$CHPh)_n$-CH_2-O-CH_2-COOH), 3.61-3.90 (br, 2H, $(CH_2$-$CHPh)_n$-CH_2-O-CH_2-COOH), 6.25-7.32 (CH_2-$CHPh$) ppm.

^{13}C-NMR ($CDCl_3$): δ 11.0-11.4 (m, CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 18.5-19.8 (m, CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 28.7-30.4 (m, CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 31.5 (CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 40.8 (CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 40.3-46.7 (br, CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 68.6 ($(CH_2$-$CHPh)_n$-CH_2-O-), 75.6 ($(CH_2$-$CHPh)_n$-CH_2-O-CH_2-COOH), (124.1-127.0 (br, CH_2-$CHPh_{para}$), 127.0-129.5 (br, CH_2-$CHPh_{ortho+meta}$), 145.1-146.5 (br, CH_2-$CHPh_{ipso}$), 168.8-173.8 (br, $(CH_2$-$CHPh)_n$-CH_2-O-CH_2-COOH) ppm.

IR: $\nu_{C=O}$ 1653.8 cm^{-1}, CH_2-O-CH_2 stretch 1135.2 cm^{-1}.

Coupling of 6.8 with diglycine-ethyl ester (6.9)

1.08 g ($2.7 \cdot 10^{-4}$ mol) **6.8** was dissolved in 10 ml DMF under argon atmosphere. 160 mg diglycine ethyl ester ($8.13 \cdot 10^{-4}$ mol) was added, followed by 200 mg dicyclohexyl carbodiimide (DCC ($9.7 \cdot 10^{-4}$ mol)).The mixture was stirred for 6 days and heated in an oil bath of 80°C. The reaction was followed with TLC (eluent CH_2Cl_2/MeOH 99/1 v/v). After one day more than 50% of **6.8** was converted, based on TLC. An additional 0.93 g DCC was then added. The reaction was terminated by precipitation in MeOH. Column chromatographic separation (eluent first: CH_2Cl_2/MeOH 99/1 v/v, followed by CH_2Cl_2/MeOH 95/5 v/v) resulted in 0.77 g (yield 71%) **6.9**.

^{1}H-NMR ($CDCl_3$): δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-$CH(C\underline{H}_3)$-$(CH_2$-$CHPh)_n$), 1.2-1.3 (t, 3H, -CONH-$CH_2C(O)O$-CH_2-$C\underline{H}_3$), 0.78-2.44 (CH_3-$C\underline{H}_2$-$C\underline{H}(CH_3)$-$(C\underline{H}_2$-$C\underline{H}Ph)_n$), 3.18-3.58 (br, 2H, $(CH_2$-$CHPh)_n$-$C\underline{H}_2$-O-CH_2-CONH-), 3.61-3.90 (br, $(CH_2$-$CHPh)_n$-CH_2-O-$C\underline{H}_2$-CONH- + CONH-CH_2-CONH-$C\underline{H}_2C(O)O$-CH_2-CH_3), 3.9-4.02 (br, s, 2H, CONH-$C\underline{H}_2$-CONH-$CH_2C(O)O$-CH_2-CH_3), 4.12-4.23 (q, 2H, -CONH-$CH_2C(O)O$-$C\underline{H}_2$-CH_3), 6.25-7.32 (CH_2-$CH\underline{Ph}$) ppm.

^{13}C-NMR ($CDCl_3$): δ 11.0-11.4 (m, $\underline{C}H_3$-CH_2-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 14.1 (-CONH-$CH_2C(O)O$-CH_2-$\underline{C}H_3$), 18.5-19.8 (m, CH_3-CH_2-$CH(\underline{C}H_3)$-$(CH_2$-$CHPh)_n$), 28.7-30.4 (m, CH_3-$\underline{C}H_2$-$CH(CH_3)$-$(CH_2$-$CHPh)_n$), 31.5 (CH_3-CH_2-$\underline{C}H(CH_3)$-$(CH_2$-$CHPh)_n$), 40.8 (CH_3-CH_2-$CH(CH_3)$-$(CH_2$-$\underline{C}HPh)_n$), 40.3-46.7 (br, CH_3-CH_2-$CH(CH_3)$-$(\underline{C}H_2$-$CHPh)_n$), 61.5 (-CONH-$CH_2C(O)O$-$\underline{C}H_2$-CH_3), 69.9 ($(CH_2$-$CHPh)_n$-$\underline{C}H_2$-O-), 76.6 ($(CH_2$-$CHPh)_n$-CH_2-O-$\underline{C}H_2$-CONH), (124.1-127.0 (br, CH_2-$CH\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-$CH\underline{Ph}_{ortho+meta}$), 145.1-146.5 (br, CH_2-$CH\underline{Ph}_{ipso}$), 168.5 (-$\underline{C}$ONH-$CH_2C(O)O$-CH_2-CH_3), 169.4 (-CONH-$CH_2\underline{C}(O)O$-CH_2-CH_3), 170.7 ($(CH_2$-$CHPh)_n$-CH_2-O-CH_2-$\underline{C}$ONH) ppm.

IR: ν_{amide} 1526.2, 1670.0 cm^{-1}, ν_{ester} 1748.1 cm^{-1}.

Amidation of 6.9 with ethylenediamine (6.10)

0.5 g **6.9** ($1.2 \cdot 10^{-4}$ mol) was dissolved in 2 ml DMF and 4.5 ml ethylenediamine. The mixture was heated at 80°C. TLC after one hour (eluent CH_2Cl_2/MeOH 95/5 v/v) showed quantitative conversion. The mixture was precipitated in MeOH after 1.5 hours reaction time, and dried *in vacuo* at 40°C. 0.43 (yield 86%) of **6.10** was obtained.

^{1}H-NMR ($CDCl_3$): δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-$CH(C\underline{H}_3)$-$(CH_2$-$CHPh)_n$), 1.2-1.3 (t, 3H, -CONH-$CH_2C(O)O$-CH_2-$C\underline{H}_3$), 0.78-2.44 (CH_3-$C\underline{H}_2$-$C\underline{H}(CH_3)$-$(C\underline{H}_2$-$C\underline{H}Ph)_n$), 2.69-2.78 (br, -CH_2CONH-CH_2-$C\underline{H}_2$-NH_2), 3.15-3.27 (br, -CH_2CONH-$C\underline{H}_2$-CH_2-NH_2), 3.28-3.92 (br, $(CH_2$-$CHPh)_n$-$C\underline{H}_2$-O-$C\underline{H}_2$-CONH-), 3.47-3.60 (br, s, CONH-CH_2-CONH-$C\underline{H}_2$CONH-), 3.80-3.86 (br, s, CONH-$C\underline{H}_2$-CONH-CH_2CONH-), 6.25-7.32 (CH_2-$CH\underline{Ph}$) ppm.

^{13}C-NMR ($CDCl_3$): δ 11.0-11.4 (m, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 18.5-19.8 (m, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 28.7-30.4 (m, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 31.5 (CH_3-CH_2-$\underline{C}$H(CH_3)-(CH_2-CHPh)$_n$), 40.8 (CH_3-CH_2-CH(CH_3)-(CH_2-$\underline{C}$HPh)$_n$), 40.3-46.7 (br, CH_3-CH_2-CH(CH_3)-($\underline{C}H_2$-CHPh)$_n$), 69.9 ((CH_2-CHPh)$_n$-$\underline{C}H_2$-O-), 76.6 ((CH_2-CHPh)$_n$-CH_2-O-$\underline{C}H_2$-CONH), (124.1-127.0 (br, CH_2-CH$\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-CH$\underline{Ph}_{ortho+meta}$), 145.1-146.5 (br, CH_2-CH$\underline{Ph}_{ipso}$), 168.8+168.9 (-$\underline{C}$ONH-$CH_2\underline{C}$ONH-CH_2-), 171.2 ((CH_2-CHPh)$_n$-CH_2-O-CH_2-$\underline{C}$ONH) ppm.

IR: ν_{NH} 3370.9, 3316.0 cm^{-1}; ν_{CO} 1664.1 cm^{-1}; 1265.5 cm^{-1}.

Coupling of fluorescein-5-isothiocyanate and 6.10 (6.11)

0.4 g ($9.5\cdot10^{-5}$ mol) **6.10** was dissolved in 3 ml DMF. 51 mg fluorescein-5-isothiocyanate ($1.31\cdot10^{-4}$ mol, 1.3 eq.) was added under argon atmosphere. A clear orange solution was obtained. The mixture was stirred at room temperature for 4 hours. Then the mixture was precipitated in MeOH/H_2O 3/1 v/v. The product was filtrated and the residue washed with water until no coloration of the filtrate occurred anymore. 0.37 g (yield 86%) of **6.11** was obtained.

MALDI-TOF: A distribution of 20 styrene-oligomers was observed with the top at 41 styrene-units. Molecular weight of 46 units: 5470 g/mol experimentally, 5475 g/mol calculated.

^{1}H-NMR (d_6-DMSO/$CDCl_3$): δ 0.54-0.78 (br, 6H, $C\underline{H}_3$-CH_2-CH($C\underline{H}_3$)-(CH_2-CHPh)$_n$), 1.2-1.3 (t, 3H, -CONH-CH_2C(O)O-CH_2-$C\underline{H}_3$), 0.78-2.44 (CH_3-$C\underline{H}_2$-$C\underline{H}$(CH_3)-($C\underline{H}_2$-$C\underline{H}$Ph)$_n$), 3.58-3.84 (br, (CH_2-CHPh)$_n$-$C\underline{H}_2$-O-$C\underline{H}_2$-CONH-, + CONH-CH_2-CONH-$C\underline{H}_2$CONH- + CONH-$C\underline{H}_2$-CONH-CH_2CONH-), 6.25-7.32 (CH_2-CH$\underline{Ph}$), 8.0-8.1 ($\underline{H}^6$) ppm.

^{13}C-NMR ($CDCl_3$): δ 11.0-11.4 (m, $\underline{C}H_3$-CH_2-CH(CH_3)-(CH_2-CHPh)$_n$), 18.5-19.8 (m, CH_3-CH_2-CH($\underline{C}H_3$)-(CH_2-CHPh)$_n$), 28.7-30.4 (m, CH_3-$\underline{C}H_2$-CH(CH_3)-(CH_2-CHPh)$_n$), 31.5 (CH_3-CH_2-$\underline{C}$H(CH_3)-(CH_2-CHPh)$_n$), 40.8 (CH_3-CH_2-CH(CH_3)-(CH_2-$\underline{C}$HPh)$_n$), 40.3-46.7 (br, CH_3-CH_2-CH(CH_3)-($\underline{C}H_2$-CHPh)$_n$), 70.6 ((CH_2-CHPh)$_n$-$\underline{C}H_2$-O-), 76.6 ((CH_2-CHPh)$_n$-CH_2-O-$\underline{C}H_2$-CONH), 103.3 ($\underline{C}^{11}$), 112.4 ($\underline{C}^9$), 118.9 ($\underline{C}^6$), 121.6 ($\underline{C}^3$), (124.1-127.0 (br, CH_2-CH$\underline{Ph}_{para}$), 127.0-129.5 (br, CH_2-CH$\underline{Ph}_{ortho+meta}$), 130.6 ($\underline{C}^{10}$), 141.1 ($\underline{C}^2$) 145.1-146.5 (br, CH_2-CH$\underline{Ph}_{ipso}$), 155.8 ($\underline{C}^{8+13}$), 169.3 + 169.9 + 170.4 (-$\underline{C}$ONH-$CH_2\underline{C}$ONH-CH_2 + (CH_2-CHPh)$_n$-CH_2-O-CH_2-$\underline{C}$ONH +$\underline{C}^7$), 181.1 (-NH-$\underline{C}$(S)-NH-) ppm.

IR: 3380-3269, 1750.5, 1668, 1330.3, 1261.2 cm^{-1}.

Entrapment of 6.11 in a dendritic box (6.12)

A mixture of 247.4 mg **6.11** ($53.8\cdot10^{-6}$ mol, 9 eq.) and 43.2 mg ($6.03\cdot10^{-6}$ mol) DAB-*dendr*-$(NH_2)_{64}$, dissolved in 6 ml CH_2Cl_2/MeOH 2/1 v/v, was stirred for a night at room temperature. Next the dendritic shell was built by adding 168.3 mg ($464\cdot10^{-6}$ mol, 1.2 eq.) N-*t*-Boc-L-phenylalanine hydroxysuccinimide ester. After stirring for an additional 24 hours, the solvent was evaporated. The crude product was purified by repeated column chromatography (eluent CH_2Cl_2). This purification

was followed by dialysis in DMF. The reaction was also carried out with initial ratios of **6.11** to dendrimer of 0.5, 1.3 and 5.0. These products were not dialyzed. Yields after work-up amounted to 50 to 60%.

^{1}H-NMR ($CDCl_3$): PS-part: δ 0.48-0.73 ($C\underline{H}_3$-CH_2-$CH(C\underline{H}_3)$-$(CH_2$-$CHPh)_n$), 0.85-2.05 (CH_3-$C\underline{H}_2$-$C\underline{H}(CH_3)$-$(C\underline{H}_2$-$C\underline{H}Ph)_n$),; 6.20-7.40 (CH_2-$C\underline{H}Ph$) ppm. Dendrimer part: δ 1.18-1.38 ($(C\underline{H}_3)_3$-C); 2.05-3.5 (-$C\underline{H}_2$-$N(C\underline{H}_2$-$)_{2dendr}$ + -$C\underline{H}_2$-Ph_{dendr}), 4.1-4.9 (C(O)-$C\underline{H}(CH_2)$-NH-), 5.6-6.0 (C(O)N$\underline{H}$-), 6.0-7.1 ($\underline{Ph}_{dendr}$), 7.5-8.12 (C(O)N$\underline{H}$-) ppm.

GPC: $M_n = 3.8 \cdot 10^3$ g/mol, $M_w/M_n = 1.11$.

Loads of **6.11** per dendrimer were determined with UV-VIS spectroscopy, with CH_2Cl_2/MeOH 2/1 as solvent. Solvent dependence of fluorescence and λ_{max} was studied with DMSO, THF and CH_2Cl_2/MeOH 2/1. CD-measurements were performed in $CHCl_3$. MALDI-TOF measurements showed only a weak absorption of free **6.11**.

TLC of **6.12** (load = 3) and a mixture of 2.5 eq. of **6.11** and dendritic box: *n*-hexane/EtOAc 9/1 v/v, cyclohexane: $R_f = 0$, for both products; *n*-hexane/EtOAc 6/1 v/v: $R_f = 0$, for **6.12**, R_f = 0-0.5, for the mixture; DMSO: R_f = 0.27-0.9, for both products; DMSO/HOAc 3/1 v/v: R_f = 0.27-0.7, for both products; *n*-hexane/EtOAc 2/1 v/v: R_f = 0-0.6, for **6.12**, R_f = 0-0.74, for the mixture; toluene, CH_2Cl_2/HOAc 9/1 v/v, *n*-hexane/EtOAc 2/1 v/v + 10 vol% Et_3N, CH_2Cl_2/MeOH 95/5 v/v, CH_2Cl_2/MeOH/ Et_3N 98/1/1 v/v/v: $R_f = 0.95$ for both products.

6.6 References and Notes

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Summary

In this thesis the synthesis of new molecular architectures, based on poly(propylene imine) dendrimers is described. Dendrimers are well-defined, highly branched globular macromolecules that emanate from a central core. In chapter 1 a literature overview is given of dendrimer research. The attention is focused on supramolecular chemistry and dendrimers, the combination of dendrimers and linear polymers, and on dendrimers with amphiphilic behavior. At the end of this chapter the scope of this thesis is explained.

Chapters 2 to 4 deal with the synthesis of a new class of amphiphilic molecules, the polystyrene (PS) - poly(propylene imine) dendrimer diblock copolymers. In chapter 2 the preparation of the PS-part is described. In order to build up a poly(propylene imine) dendrimer onto PS, a primary amine end group had to be introduced. With the use of the anionic polymerization technique well-defined, functionalized PS could be obtained. Direct amination was not possible. The introduction of a carboxylic acid function could be performed quantitatively with CO_2. An indirect amination route was developed, consisting of reduction of the acid to an alcohol-function, followed by cyanoethylation with acrylonitrile and subsequent hydrogenation to the corresponding amine.

Chapter 3 deals with the divergent poly(propylene imine) dendrimer synthesis onto the amine-functionalized PS. In a 10-step process 5 different dendrimer generations, from PS-*dendr*-$(NH_2)_2$ to PS-*dendr*-$(NH_2)_{32}$ were prepared in yields of 70 to 90%. The molecular structure was analyzed in detail. Generation-dependent amphiphilic behavior at an air/water and a water/toluene interface was observed with monolayer and conductivity measurements, respectively. Dynamic light scattering and transmission electron microscopy showed that in aqueous phases PS-*dendr*-$(NH_2)_{32}$ forms spherical micelles, PS-*dendr*-$(NH_2)_{16}$ micellar rods and PS-*dendr*-$(NH_2)_8$ vesicular structures. The lower generations show inverted micellar behavior in toluene. This observed effect of amphiphile geometry on aggregation is in qualitative agreement with the theory of Israelachvili. These amphiphiles are similar in shape but different in size as compared with surfactants, while similar in size, but different in shape as compared with traditional amphiphilic block copolymers.

In chapter 4 two modification reactions of the PS-poly(propylene imine) block copolymers are described. Acid hydrolysis of the nitrile-functionalized intermediates PS-

dendr-$(CN)_2$ to PS-*dendr*-$(CN)_{32}$ resulted in high yields in acid-functionalized dendrimers PS-*dendr*-$(COOH)_n$. Quaternization with MeI of the primary as well as the tertiary amines was performed on PS-*dendr*-$(NH_2)_n$ with n = 1 to 16. The acid-functionalized structures showed pH-dependent amphiphilic behavior, when studied with conductivity measurements. For both modified structures an increase in polarity and head group size, compared to the amine derivatives was noticed. The PS-poly(propylene imine) dendrimers represent a new, versatile class of amphiphiles, because their amphiphilic behavior is generation-dependent and can be tuned by modifications of the dendritic head group.

In chapter 5 the formation of unimolecular inverted dendritic micelles of different generations and with different alkyl chain lengths is studied by reaction of alkylacid chlorides with poly(propylene imines). An extreme auto-acceleration effect was observed during the reaction of alkylacid chlorides with an excess of dendrimers. Only 2 products were formed: fully modified and totally unreacted dendrimers. The development of dendritic character, going from low to higher generations, was clearly observed with ^{1}H-NMR and DSC by the shielding of the amide bond. With these inverted dendritic micelles it was possible to physically encapsulate Rose Bengal and improve the compatibility of this dye with apolar materials.

In the last chapter a new molecular building concept is investigated, based on the dendritic box. Guest molecules were linked *via* a spacer to a PS-chain. Encapsulation of the guests in a dendritic box resulted in anchoring of the PS-chain onto the box, and a physically locked complex was obtained. The first indication that this concept worked was obtained with a 3,5-dimethylpyridinium moiety, connected to a PS-chain *via* a caprolactone spacer. More detailed information could be obtained with the second modified PS-chain, to which *via* a diglycine unit fluorescein was coupled. With UV-VIS spectroscopy the number of fluorescein molecules and their position inside the box could be detected. One major problem proved to be the purification of the complexes formed. When instead of PS functional groups are locked to the dendritic box, a multivalent building block is obtained, which can play an important role in modular chemistry.

Samenvatting

In dit proefschrift wordt de synthese van nieuwe moleculaire architecturen, gebaseerd op dendrimeren, beschreven. Dendrimeren zijn goed gedefinieerde, sterk vertakte bolvormige macromolekulen, die vanuit een kern opgebouwd zijn. Het eerste hoofdstuk geeft een literatuuroverzicht van onderzoek aan dendrimeren. De aandacht is daarbij gericht op supramoleculaire chemie en dendrimeren, de combinatie van dendrimeren en lineaire polymeren, en dendrimeren en amfifiel gedrag. Tenslotte wordt het doel van het onderzoek beschreven.

In hoofdstuk 2 tot en met 4 wordt de synthese van een nieuwe klasse van amfifielen, de polystyreen (PS) - poly(propyleen imine) dendrimeer diblokcopolymeren behandeld. In hoofdstuk 2 wordt de bereiding van het PS-gedeelte beschreven. Om een poly(propyleen imine) dendrimeer op te kunnen bouwen aan PS moest een primair amine als eindgroep ingevoerd worden. Met behulp van de anionische polymerisatie-techniek werd goed gedefinieerd, functioneel PS verkregen. Directe aminering bleek niet mogelijk. Een carbonzuur-functie kon wel kwantitatief geïntroduceerd worden met CO_2. Een indirecte amineringsroute werd ontwikkeld, bestaande uit reductie van de zuurfunctie naar een alcohol, gevolgd door cyanoethylering met acrylonitril, en hydrogenering van de nitril tot het overeenkomstige amine.

Hoofdstuk 3 behandelt de divergente dendrimeersynthese aan het amine-gefunctionaliseerde PS. In een 10-staps proces werden 5 verschillende dendrimeer-generaties, van PS-*dendr*-$(NH_2)_2$ tot PS-*dendr*-$(NH_2)_{32}$ bereid in rendementen van 70 tot 90%. De moleculaire structuur werd tot in detail gekarakteriseerd. Generatie-afhankelijk amfifiel gedrag aan een water/lucht en een water/tolueen grensvlak werd vastgesteld met respectievelijk monolaag- en geleidbaarheidsmetingen. Dynamische lichtverstrooiing en transmissie electronen microscopie toonden aan dat in een waterige omgeving PS-*dendr*-$(NH_2)_{32}$ sferische micellen vormt, PS-*dendr*-$(NH_2)_{16}$ staafvormige aggregaten en PS-*dendr*-$(NH_2)_8$ vesiculaire structuren. De lagere generaties vertoonden geïnverteerd micellair gedrag in tolueen. Dit waargenomen effect van de geometrie van het amfifiel op aggregatie is in kwalitatieve overeenstemming met de theorie van Israelachvili. Deze amfifielen zijn vergelijkbaar wat betreft vorm met surfactants, maar verschillen van deze qua grootte, terwijl ze wat betreft grootte overeenkomen met traditionele amfifiele blokcopolymeren, maar met deze niet te vergelijken zijn qua vorm.

In hoofdstuk 4 worden twee modificatiereacties van de PS-poly(propyleen imine) blokcopolymeren beschreven. Zure hydrolyse van de nitril-getermineerde tussenprodukten PS-*dendr*-$(CN)_2$ tot PS-*dendr*-$(CN)_{32}$ resulteerde in hoge opbrengst in zuur-gefunctionaliseerde dendrimeren PS-*dendr*-$(COOH)_n$. Quaternisering met MeI van zowel de primaire als tertiaire amines werd uitgevoerd op PS-*dendr*-$(NH_2)_n$ met n = 1 tot 16. Met behulp van geleidbaarheidsmetingen werd vastgesteld dat de zuur-gefunctionaliseerde structuren pH-afhankelijk gedrag vertoonden. Vergeleken met PS-*dendr*-$(NH_2)_n$ werd voor beide gemodificeerde structuren een toename in polariteit en kopgroepgrootte waargenomen. De PS-poly(propyleen imines) vormen een nieuwe, veelzijdige klasse van amfifielen, omdat hun amfifiel gedrag generatie-afhankelijk is en wordt beïnvloed door kopgroep-modificaties.

In hoofdstuk 5 wordt de bereiding van unimoleculaire, geïnverteerde dendritische micellen van verschillende generaties en met verschillende alkyllengtes bestudeerd door middel van de reactie tussen alkylzuurchlorides met poly(propyleen imines). Een extreem autoacceleratie-effect werd waargenomen voor de reactie van een ondermaat aan alkylzuurchlorides met dendrimeren. Slechts 2 produkten werden gevormd: volledig omgezet en totaal ongereageerd dendrimeer. Gaande van lage naar hoge generaties werd een ontwikkeling in dendritisch karakter vastgesteld met behulp van ^{1}H-NMR en DSC, door afscherming van de amide-band. Met deze geïnverteerde micellen was het mogelijk om Bengaal Rose fysisch in te sluiten en de compatibiliteit van deze kleurstof met apolaire materialen te verbeteren.

In het laatste hoofdstuk is een nieuw bouwprincipe onderzocht, gebaseerd op het dendrimere doosje. Gastmolekulen werden verbonden via een spacer aan een PS-keten. Insluiting van deze gasten in een dendrimere doosje resulteerde in verankering van de PS-ketens aan het dendrimeer, en een fysisch gebonden complex was gevormd. Een eerste indicatie dat dit concept werkte werd gevonden met een 3,5-dimethylpyridinium eenheid, die verbonden was aan een PS-keten via een caprolacton-spacer. Gedetailleerdere informatie werd verkregen met een tweede gemodificeerd PS-molekuul, waaraan via een diglycine-eenheid fluoresceine gekoppeld was. Met UV-VIS spectroscopie kon het aantal en de positie van deze fluoresceine-molekulen vastgesteld worden. Een belangrijk probleem bleek de opzuivering van de gevormde complexen. Wanneer in plaats van PS functionele groepen worden verankerd aan het dendrimere doosje, wordt een multivalente bouwsteen verkregen, die een belangrijke rol kan spelen in de modulaire chemie.

Curriculum Vitae

Jan van Hest werd op 27 september 1968 te Tilburg geboren. Na het behalen van het gymnasium-β diploma in 1986 aan het Theresialyceum in Tilburg, studeerde hij Scheikundige Technologie aan de Technische Universiteit Eindhoven. Tijdens zijn afstuderen verrichtte hij onderzoek naar de synthese van polystyreen-2,4-ionene blokcopolymeren en de toepassing van deze systemen in de katalytische oxidatie van thiolen. Dit onderzoek werd uitgevoerd bij de vakgroep Polymeerchemie en Technologie onder begeleiding van prof. dr. ir. A.L. German. In december 1991 studeerde hij cum laude af, waarna hij per 1 januari 1992 begon als AIO-4 in de vakgroep Organische Chemie van de Technische Universiteit Eindhoven, onder begeleiding van prof. dr. E.W. Meijer. Het verrichte onderzoek in de periode van januari 1992 tot januari 1996 ligt ten grondslag aan dit proefschrift. In mei 1995 werd dit werk bekroond met de toekenning van de eerste prijs voor Nederland van de DSM-prijs voor Chemie en Technologie. Vanaf half april 1996 zal hij voor 1 jaar werkzaam zijn als post-doc in de groep van prof. dr. D.A. Tirrell aan de universiteit van Massachusetts (USA) op het gebied van polypeptide engineering en materiaalwetenschappen.

Publicatielijst

M.H.P. van Genderen, M.W.P.L. Baars, J.C.M. van Hest, E.M.M. de Brabander-van den Berg, E.W. Meijer "Observing individual generations in poly(propylene imine) dendrimers with natural abundance ^{15}N-NMR spectroscopy" *Receuil* **113/12**, 573 (1994).

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S. Stevelmans, J.C. M. van Hest, J.F.G.A. Jansen, E.W. Meijer, D. van Boxtel, E.M.M. de Brabander-van den Berg "Auto-accelerated synthesis, characterization and guest-host properties of inverted unimolecular dendritic micelles" *J. Am. Chem. Soc.*, in press.

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Bij Fellenoord en de zaalvoetbalclub Anomientje kon ik altijd de frustraties van het onderzoek wegsporten. Het is al die jaren tijdens clubavonden, competities en zeilweekenden erg gezellig geweest.

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STELLINGEN

behorende bij het proefschrift

New Molecular Architectures Based on Dendrimers

van

Jan Cornelis Maria van Hest

1. Dendrimeren kunnen beschouwd worden als de bucky-ballen van de jaren 90.

2. Het gebruik van superkritisch CO_2 als medium voor de bereiding van poly(para-fenyleenoxide) is niet aan te raden, omdat het voordeel van een gemakkelijk te verwijderen solvent teniet gedaan wordt door de noodzaak van het toevoegen van een zeer moeilijk te verwijderen polymere stabilisator. (K.K. Kapellen, C.D. Mistele, J.M. DeSimone, *Macromolecules* **29**, 495 (1996).)

3. Door gebruik te maken van een systematische afkorting bij de naamgeving van dendrimeren verkrijgt men meer inzicht in de structuur dan wanneer men de volledige naam vermeldt. (G.R. Newkome, G.R, Baker, J.K. Young, J.G. Traynham, *J. Polym. Sci. A* **31**, 641 (1993). S. Mattei, P. Seiler, F. Diederich, V. Gramlich, *Helv. Chim. Acta* **78**, 1904 (1995).)

4. De bewering van Luisi et al. dat het micellaire systeem natriumoctanoaat/octanol in staat is tot zelf-replicatie, gaat voorbij aan het feit dat na reactie de cosurfactant octanol volledig verdwenen is, en er in principe een ander micellair systeem overblijft. De voor zelf-replicatie noodzakelijke specificiteit is verder niet aangetoond en ook niet te verwachten. (P.A. Bachmann, P. Walde, P.L.Luisi, J. Lang, *J. Am. Chem. Soc.* **113**, 8204 (1991).)

5. Het vaak onbegrepen gedrag van aggregatie van geladen polymeren kan verklaard worden door een vergelijking te maken met interacties binnen een NaCl kristal. Hieruit blijkt dat een eenvoudige oplossing vaak over het hoofd gezien wordt. (zie hoofdstuk 4, S.A. Buckingham, C.J. Garvey, G.G. Warr, *J. Phys. Chem* **97**, 10236 (1993). M. Sedlák, *Macromolecules* **26**, 1158 (1993). N. Ise, *Angew. Chem.* **98**, 323 (1986).)

6. Dendrimeren zijn ideaal om de grenzen van de huidige analysetechnieken te verkennen.

7. Basiskennis, zoals de definitie van pKa, blijkt bij ervaren onderzoekers wel eens te verwateren. (D.L. Holmes, D.A. Lightner, *Tetrahedron* **51(6)**, 1607 (1995).)

8. Het siert wetenschappers hun eigen werk net zo kritisch te bekijken als dat van hun collega's. (M. Morgan Conn, E.A. Wintner, J. Rebek jr., *J. Am. Chem. Soc.* **116**, 8823 (1994). F.M. Menger, A.V. Eliseev, N.A. Khanjin, M.J. Sherrod, *J. Org. Chem.* **60**, 2870 (1995).)

9. Een populaire naamgeving begint in het chemisch onderzoek steeds belangrijker te worden. (D.B. Amabilino, P.R. Ashton, C.L. Brown, E. Córdova, L.A. Godínez, T.T. Goodnow, A.E. Kaifer, S.P. Newton, M. Pietraszkiewicz, D. Philp, F.M. Rayno, A.S. Reder, M.T. Rutland, A.M.Z. Slawin, N. Spencer, J.F. Stoddart, D.J. Williams, *J. Am.Chem. Soc.* **117**, 1271 (1995) :Olympiadaan. D.A. Tomalia, H. Baker, J.R. Dewald, M. Hall, G. Kallos, S. Martin, J. Roeck, J. Ryder, P. Smith, *Polym. J.* **17**, 117 (1985). G.R. Newkome, Z.-q. Yao, G.R. Baker, V.K. Gupta, *J. Org. Chem.* **50**, 2003 (1985) : dendrimeer vs arborol.)

10. Het stijgend niveau van het Nederlandse proftennis staat in schril contrast met het vaak amateuristische Nederlandse tenniscommentaar.

11. Het begrip 'camp' doorbreekt het taboe van de slechte smaak.

12 Voor het creëren van een optimale werksfeer is het van groot belang dat elke promovendus de juiste balans vindt tussen zijn/haar individueel gerichte onderzoek en zijn/haar sociale inspanningen voor de werkgroep.

13. De slogan 'Let's make things better' is inderdaad voor verbetering vatbaar.

14. Een verenigd Europa munt niet uit in creativiteit (Euro).

14 maart 1996