Dendritic macromolecules : host-guest chemistry and self-assembly by design

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PROEFSCHRIFT

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When one door is shut, another opens…

– Miguel de Cervantes

Success is getting what you want
Happiness is liking what you get…

– H. Jackson Brown

Aan mijn ouders en zus

Voor Annemarie

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Host–Guest Chemistry of Dendritic Molecules

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Abstract: *In this chapter the contribution of dendritic macromolecules to the field of supramolecular host–guest chemistry is discussed. Ever since the first publications on dendrimers more than two decades ago, their properties as molecular recognition compounds have been discussed many times. A brief introduction to the common host–guest interactions using traditional supramolecular systems is accompanied by a short overview on specific properties of the highly branched, three-dimensional dendritic macromolecules. Attention will be paid to the existence of internal voids in the dendritic interior. Subsequently, a selected overview will be given of the reported dendritic host–guest systems. The host–guest systems discussed are arranged by type of interactions from physical entrapment to electrostatic, hydrophobic or hydrogen-bonding interactions. This overview will emphasize various selected contributions in which the pre-organized three-dimensional dendritic structure and the high local concentration of sites might display cooperative effects and is interesting towards future applications. Such a rationalization of the typical dendrimer characteristics, like their functionalization, characterization and application, is the scope of the subsequent chapters.*

For a complete overview of 'Host–Guest Chemistry of Dendritic Molecules', you are referred to: Baars, M. W. P. L.; Meijer, E. W. *Top. Curr. Chem.* **2000**, in press.

1.1 Introduction

Based upon the first reports on cascade molecules,[1] Maciejewski[2] presented a theoretical discussion of highly branched molecules as ideal molecular containers, showing the challenges in host–guest interactions of dendritic molecules. Experimentally, dendrimers were introduced by Newkome[3] and Tomalia[4, 5] and their initial publications suggested a plethora of applications including those related to controlled release of pharmaceuticals.[6] Now, almost 20 years later, the field of host–guest properties of dendritic molecules has grown to a special brand of supramolecular chemistry.[6–9] The latter is generally described as the chemistry beyond the covalent bond and takes into account specific molecular interactions and the relationship between geometrical structure and binding sites.

With a combination of theoretical and experimental studies, we discuss these new type of dendritic macromolecules and try to increase the understanding of their conformational behavior; an issue of vital importance in supramolecular host–guest chemistry. Of particular interest is the discovery of specific functions and properties that are a direct consequence of the dendritic architecture. A specific property for dendrimers is that their structure can produce localized micro-environments or internal voids (cavities), analogous to those found in the active sites of enzymes. With this in mind, the concept of physical entrapment of guests is introduced, which refers to the binding of guests in internal and confined cavities of a host system.[2] In addition, dendrimers contain three topologically different regions (core, branches and surface), each of which can exhibit functional properties modulated by the dendrimer as a whole.[10] Moreover, this first chapter will show the main contributions of these structures in the field of host–guest chemistry. The examples presented indicate that dendrimers can mimic some of the functions of natural proteins.

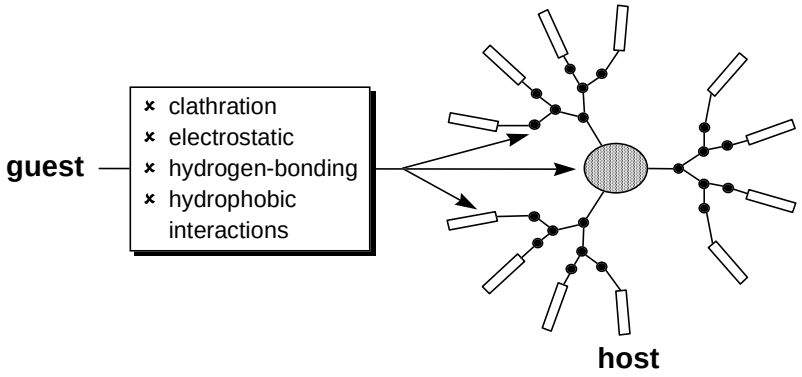

Figure 1.1: *Classification of dendritic host–guest systems according to type and site of interaction.*

The dendritic host–guest systems discussed are classified according to the type of host–guest interactions, for instance electrostatic, hydrogen bonding or hydrophobic interactions. But these results are also subdivided according to the site of molecular recognition, either in the core, at the branching points or at the periphery of dendrimers (Fig. 1.1). With all the examples of dendritic host–guest systems presented and with an increased understanding of molecular recognition in dendrimers, further optimization of future host–guest systems towards applications is an obvious next step.

1. 2 Supramolecular Host–guest Chemistry

Host–guest chemistry involves the binding of a substrate molecule (guest) with a receptor molecule (host). The design and construction of hosts that are capable of selectively binding guest molecules requires precise control over geometrical features and interactional complementarity. This can be achieved by using versatile building blocks that allow the introduction of binding sites with directional binding interactions at well-defined positions. Several types of interactions can be involved, like electrostatic, hydrophobic and hydrogen-bond interactions. A combination thereof will enhance selectivity and strength of binding and will be the determining factor in the development of more efficient host–guest systems. Several highlights in the supramolecular field will be briefly addressed first.

A translation of the constraints and rules of the traditional supramolecular field to dendritic host–guest systems will help in the understanding and characterization of these systems and will give the possibility to highlight systems with clear-cut cooperative and / or dendritic effects.

1.2.1 Molecular Recognition

Complexation of Cations. The discovery of crown ethers (Fig. 1.2a) by Pedersen[11, 12] approximately 30 years ago, has started a new era in the chemistry of complexes with neutral ligands.[13] This has led to the construction of families of crown compounds,[14] coronands (hetero-crowns),[15] cryptands,[16] podands[17] and spherands[14] by Cram, Lehn and others. These cyclic ligands are capable of chelating metal or ammonium ions in a selective way, based on geometrical features, like chirality. Therefore, precise control is warranted over supramolecular systems with interesting properties in for instance transport technology.[7]

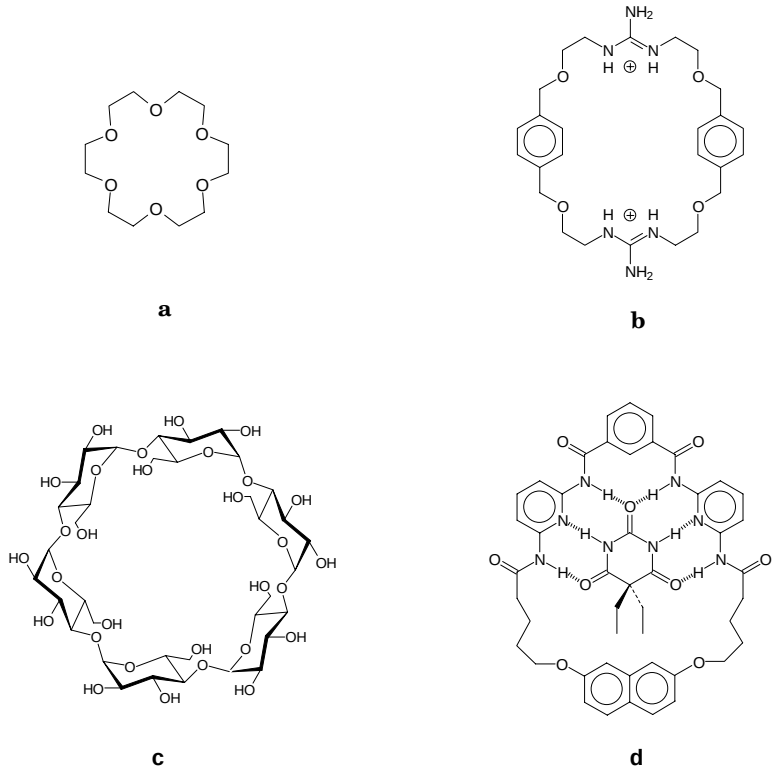

Figure 1.2: *Four different examples of molecular recognition: crown-ethers (***a***), a guanidium-containing macrocycle (***b***), β-cyclodextrin (***c***) and Hamilton receptor (***d***).*

Organic Acids and Anions. Despite the role of anions in biological systems, for example amino acids, peptides and nucleotides, the coordination chemistry of anions has only recently received attention,[18–21] in sharp contrast to the more advanced development of binding cations. The first attempts to develop receptor models for anionic guests containing carboxylate groups, concentrated on protonated macrocylic oligoamines.[22, 23] These compounds effectively bind their anionic guests via electrostatic interactions. Binding constants become higher as the number of protonated host nitrogen atoms increases. A major limitation of oligoamine receptors is the use of strongly acidic media to achieve their full protonation, a problem which can be avoided by the use of more basic groups, like guanidines (Fig. 1.2b).[24] Examples in which biorelevant species like zwitterionic amino acid residues or the structurally diverse nucleotides can be complexed, have also been published.[23] However, due to the complex nature of these species, a simultaneous recognition of several sites is often required for effective molecular recognition.

Hydrophobic Interactions. The tendency of relatively apolar molecules to assemble in aqueous solutions is explained by hydrophobic interactions.[25] These interactions play a vital role in surfactant aggregation, the assembly of lipids in biomembranes, and

enzyme-substrate interactions. Although the role of hydrophobic interactions in host–guest chemistry and molecular recognition is still ambiguous, it is generally accepted that complexation of neutral apolar molecules with macrocyclic hosts is governed by hydrophobic interactions.[26, 27] Among the building blocks frequently used are the cyclophanes[28] and cyclodextrins (Fig. 1.2c).[29] Hydrophobic guests like arenes or steroids can be complexed, dependent on the size of the cyclophane ring. Cyclodextrin is capable of complexing hydrophobic guest molecules within the cavity in aqueous media; the principal binding interactions are most likely a summation of van der Waals interactions, hydrophobic interactions and the release of 'high energy water' from the cavity. The contribution from each effect depends on the type of cyclodextrin, solvent, and guest. For instance, β-cyclodextrin can host bulky benzene derivatives, naphthalene, ferrocenyl- or adamantyl-derivatives.[30] In general, the guest molecule prefers the apolar cavity of the host, where it is to some extent shielded from the solvent.

Hydrogen-Bonding Interactions. The highly selective and directional nature of the hydrogen bond makes it an ideal building block for its use in the construction and stabilization of large non-covalently linked molecular and supramolecular architectures.[31] As a consequence hydrogen-bonding interactions can be used to complex guest molecules. The Jorgensen model[32] has shown that cooperativity of the hydrogen bonds, for instance by using an array of hydrogen bonds, increases strength, specificity and directionality of the interaction. Illustrative is the synthesis of an artificial receptor developed by Hamilton *et al.*,[33] in which a combination of complementarity, directionality and geometry generates an efficient host–guest complex (Fig. 1.2d).

1.2.2 Clathrate Inclusion Compounds

In the previous discussion many examples of inclusion are discussed. A cavity-containing host component incorporates, on a molecular level, one or several guest components, without any covalent bonding. The term clathrate[34] is usually introduced when guest molecules are incorporated into existing extramolecular cavities, like for instance in a crystal lattice. Most clathrates have been discovered purely by chance, *e.g.* by recrystallizing a compound for example.[35] This type of reversible physical entrapment of guests even without directional forces makes clathrates interesting for applications in (chiral) separation processes, organic conductors or to perform reactions in a geometrical confined surrounding.[7]

1.2.3 A First Step Towards Dendritic (Host) Molecules

The practical exploitation of the non-covalent interactions described in Section 1.2, through a precise programming of the molecular recognition process, yielded significant progress in the development of nanoscopic assemblies. In quest for large, substrate-selective ligands, many efforts have been focused on the synthesis of "octopus" [36–38] and "tentacle" [39] molecules. In 1978, it was stated by Vögtle *et al.*[1] that for the construction of such ligands with large molecular cavities, it would be advantageous to devise synthetic pathways with an iterative reaction-sequence. Experimentally, the hypothesis was tested by the design of a series of cascade molecules (Fig. 1.3). Although the synthetic scheme used was still elaborate and troublesome, the construction of a new type of (oxygen-free) hexaaza-cryptands, capable of host–guest interactions, could be realized.

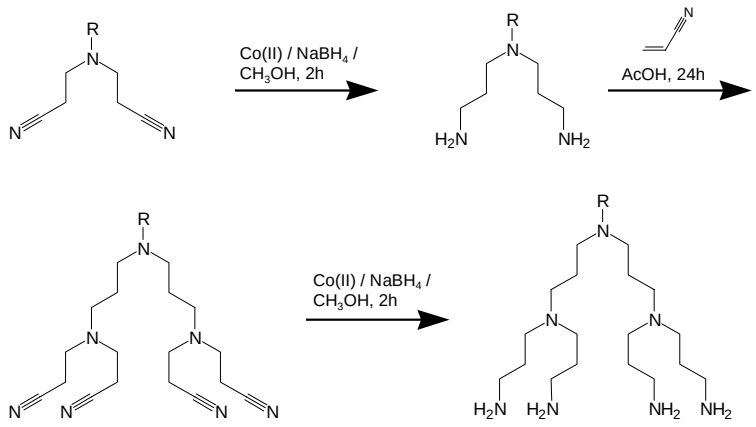

Figure 1.3: *First example of an iterative reaction sequence, as developed by Vögtle.*

1.3 Dendrimers: a New Type of Supramolecular Hosts

1.3.1 Dendritic Macromolecules

Tomalia[4, 5] and Newkome[3] established their names in the field of highly branched macromolecules as early pioneers with the synthesis of polyamidoamine dendrimers and arborols, respectively. Newkome and Vögtle[40] published an excellent monograph on historical accounts,[41] synthetic methodologies and terminology of the dendrimer field. Ideally, these structures are perfect monodisperse macromolecules with a regular and highly branched three-dimensional structure and are produced in an iterative sequence of reaction steps and each additional iteration leads to a higher generation material. These structures are established as a new class of well-defined macromolecules, with

dimensions and molecular weights in between the traditional synthetic molecules and classical polymers. Two methodologies have been developed to construct dendrimers, *i.e.* either the divergent 'from-core-to-periphery' route[4, 42, 43] or the convergent 'from-periphery-to-core' strategy.[44–48] The latter approach was first targeted by Fréchet *et al.*[44] Four well-known dendrimer families are depicted in Figure 1.4.

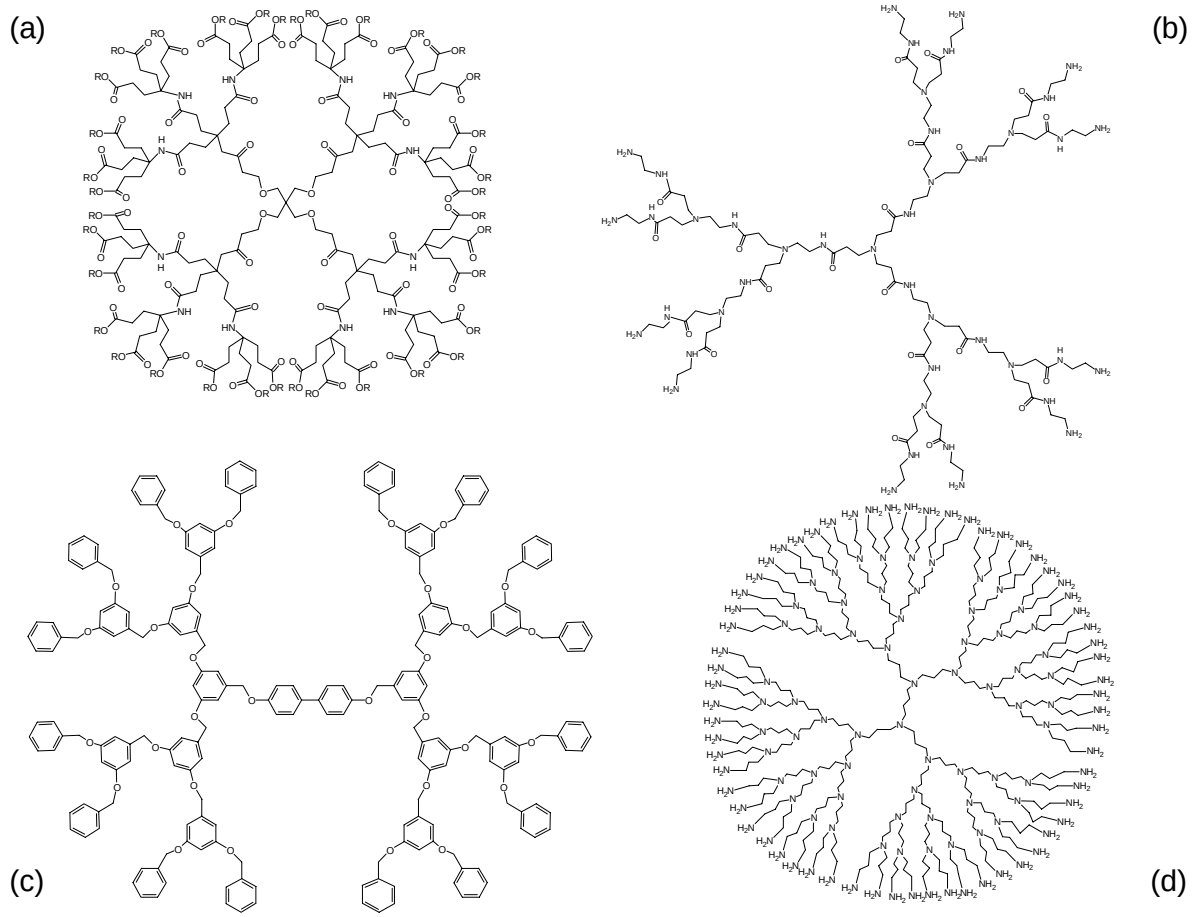

Figure 1.4: *Structure of Newkome's arborols (a), Tomalia's poly(amidoamine) dendrimers (PAMAMs) (b), Fréchet's polyether dendrimers (c) and the poly(propylene imine) dendrimers (d).*

Currently, only the divergent approach is attractive for the production of kilogram quantities and only two classes of dendrimers are commercially available, poly(amidoamine) dendrimers[4–6] and poly(propylene imine) dendrimers.[42, 49] The synthesis of the latter can even be scaled up to multikilogram quantities and the reaction scheme starts with a double Michael-addition with acrylonitrile to 1,4-diaminobutane and is followed by a Raney/Co catalyzed hydrogenation of the nitrile endgroups to the corresponding amines. This method, independently developed by de Brabander/Meijer[42] and Mülhaupt *et al.*[43] is an adaptation of the cascade synthesis developed by Vögtle.[1] Furthermore, the use of cheap and readily accessible starting

materials in combination with a reaction route that can be scaled up, allow a commercially attractive process.

The unique branched architecture, as well as the multifunctional number of endgroups that become available with these dendritic structures, can be used as a tool to display desired functions, such as well-defined shape, internal voids or a variable surface functionalization. Many of the intriguing properties of dendrimers – from design and synthesis towards applications – are reviewed by various experts in the field.[6, 50–63] Moreover, many applications have been claimed in the field of host–guest chemistry and pharmaceutics, like their use as molecular carriers, enzyme mimics[64] or potential drug–delivery vehicles.[65–68] Before showing the dendritic host–guest systems (Section 1.4), the physical properties of dendrimers have to be understood in detail, and many intriguing questions can be raised. What is the shape of dendrimers? Do dendrimers contain cavities? Is there a change in physical properties as a function of generation and the molecular dimensions? How special are the dendritic properties in comparison with linear analogues? In other words: what is the conformational behavior of dendrimers? Finally, are we able to understand these properties in a general way, even with many different sets of dendrimers available today, and is it possible to tailor the properties of dendritic host–guest systems towards nanoscopic devices or selective drug-delivery vehicles?

1.3.2 Conformational Characteristics

One of the most interesting topological aspects of dendrimers is the exponential increase of endgroups as a function of generation, while the sphere that is conformationally available only increases with the cube of generation. The increase in branch density is believed to have striking effects on the conformational shape of dendrimers. The localization of the endgroups or the presence of internal cavities is still an issue of current debate. With an overview of the theoretical calculations and experimental studies, it is attempted to clarify this issue.

Theoretical Calculations. So far, many theoretical studies discussed the shape of dendrimers, their density distribution as a function of the radius and their dependence as a function of solvent polarity and ionic strength. The resulting properties might depend strongly on the type of dendrimer that is used in the calculation, *i.e.* an ideal theoretical structures with a branched geometry or existing dendritic compounds. This complicates a general conclusion on some of the intriguing questions. Whereas, de Gennes and Hervet,[69] presented a model with growth up to a certain – predictable – limiting generation and a low density region at the core, and suggested the presence of

cavities, the model of Lescanec and Muthukumar[70] predicts a monotonic decrease in density on going from the center of the dendrimer to its periphery. Mansfield and Klushin[71] have obtained similar results with Monte Carlo simulations, except that in the latter the results correspond to an equilibrium situation. Other studies in this field are from Murat and Grest,[72] who show an increase of backfolding with generation and the strong effect of solvent polarity on the mean radius of generation, and from Boris and Rubinstein,[73] who also predict that density decreases monotonically from the center using a self-consistent mean field model. So far these studies deal with non-existing model molecules. Studies on specific dendrimers have been reported by Naylor *et al*.[74] who discussed poly(amidoamine) dendrimers and Scherrenberg *et al*.[75] on poly(propylene imine) dendrimers. In the latter case, the conformational changes as a function of solvent quality (Fig. 1.5) were nicely demonstrated and a relatively homogeneous radial density distribution is observed, Welch and Muthukumar[76] demonstrated the dramatic change in dendrimer conformation depending on the ionic strength of the solvent. Since the polyelectrolytes examined are topological analogues of the poly(propylene imine) dendrimers and also to some extent of the PAMAM-dendrimers, the two main (commercially) available dendrimers are covered.

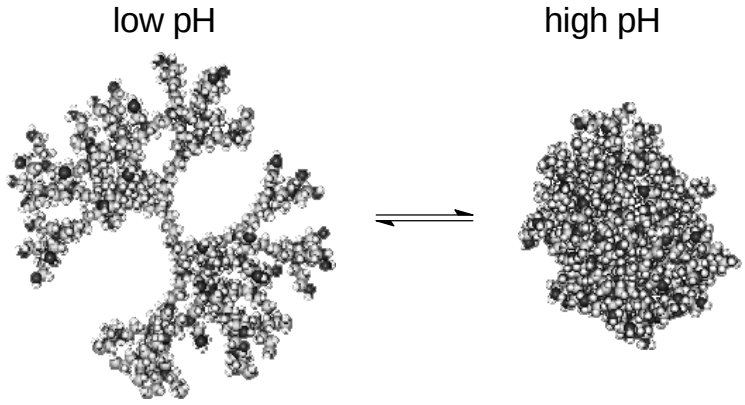

Figure 1.5: *Dense shell and dense core conformations of the amine-functionalized poly(propylene imine) dendrimers at different ionic strength (picture kindly provided by B. Coussens, DSM Research, The Netherlands).*

Goddard *et al*.[77] and Cavallo and Fraternali[78] discussed the properties of the dendritic box, a fifth generation poly(propylene imine) dendrimer functionalized with bulky amino acid residues. This is one of the few publications in which an existing dendritic system is studied at a molecular level, in contrast to the many simulations on ideal theoretical molecules discussed above. The investigations showed a low-density region inside the higher generation dendrimers and an increasing inter-endgroup interaction when going from first to the fifth generation. These data showed that the molecular conformation is strongly influenced by the type of endgroups and specific non-

covalent interactions that can take place between the endgroups. None of the theoretical studies presented so far discriminates between dendrimers with or without specific secondary interactions within the structure. Therefore, even though detailed computer modeling studies and theoretical calculations on dendrimers have been performed and a great deal of insight can be obtained from these studies, the results must be interpreted with care.

Experimental Studies. Polyether dendrimers synthesized by Fréchet *et al.*[44] have been studied with many techniques to understand their conformational properties. Size exclusion measurements performed by Mourey *et al.*,[79] rotational-echo double resonance (REDOR) NMR studies by Wooley *et al.*[80] and spin lattice relaxation measurements by Gorman *et al.*[81] reveal that backfolding takes place and the endgroups can be found throughout the molecule. The observed trends are in qualitative agreement with the model of Lescanec and Muthukumar.[70] Scherrenberg *et al.*[75] studied poly(propylene imine) dendrimers using viscosimetry and SANS-measurements and observed a linear relationship between the radius of gyration of the dendrimer and its generation number. These results agree well with the molecular dynamics studies of Murat and Grest.[72] From another SANS study it was concluded that the same type of dendrimers tend to stretch upon protonation.[82] All these data are indicative of the flexibility of poly(propylene imine) dendrimers when no specific interactions between the endgroups have to be taken into account.

However, it is evident from many studies[83–88] that upon endgroup modification of the dendrimer, phase segregation between the dendritic core and the endgroups can take place. Reviewing the cited reports, the chemical structure of the dendrimer in question determines the conformational behavior of the macromolecule. This is in sharp contrast to the flexible nature[89] of most known (unmodified) dendrimers for which a homogeneous density distribution is encountered; thus, the voids inside the dendrimer are filled up to a certain extent by the peripheral endgroups. The presence of secondary interactions, such as π–π interactions, electrostatic interactions, hydrophobic effects or hydrogen-bonding interactions, makes it possible to assemble the endgroups at the periphery of the dendrimer. Backfolding is thereby precluded, yielding an inhomogeneous density distribution over the dendritic macromolecule and a decrease in flexibility.

1.3.3 Do Cavities exist in Dendrimers?

The issue of internal cavities in dendritic molecules is still under debate. Many of the theoretical discussions lack the influence of solvents and suggest the presence of

voids. The three-dimensional motif of dendrimers imparts them with unique structural features, unlike linear polymers which possess random coil structures with a high degree of conformational freedom. On the other hand, pre-organized supramolecular receptor molecules might contain internal cavities, but they lack the presence of a distinct micro-environment suitable for complexation of multiple molecules. The concept of trapping guest molecule(s), *i.e.* topological trapping, by a (dendritic) host molecule with a spherical structure has been suggested for the first time by Maciejewski in 1982.[2] Compared to the relatively open structures of lower generation dendrimers, the higher generations tend to adopt an extended conformation with a spherical surface containing pockets of spaces in the interior, which are capable of guest inclusion. In a more collapsed state, due to an increase in backfolding, the size of these voids might be significantly diminished.

The conformational behavior of PAMAM-dendrimers has been examined with various techniques[90, 91] based on SEC in combination with intrinsic viscosimetry measurements. The authors conclude that these dendrimers have a hollow core and a densely packed outer layer, in agreement with the de Gennes model. However, these inhomogeneous distributions are in contrast to findings for most known, unmodified, dendrimers. The hydrogen-bonding interactions at the branching segments might account for these findings. Jansen and Meijer[92] reacted a fifth generation amine-functionalized poly(propylene imine) dendrimer with a (*t*-BOC)-protected L-phenylalanine residue resulting in a dendrimer with a flexible core–rigid shell structure, coined "dendritic box", with a molecular weight of almost 23 kD (Fig. 1.6). The dendritic structure was characterized with a variety of techniques, like IR, UV, ^{1}H and ^{13}C NMR spectroscopy and all data are in full agreement with the structure assigned. However, a significant line broadening of the resonances in the ^{13}C NMR spectra for the higher generations prompted measurements of spin-lattice (T_1) and spin-spin (T_2) relaxation time. The observed increase of T_1 relaxation times after the third generation is indicative of a decrease in molecular motion for the higher generations; an almost solid-phase behavior of the shell in solution is proposed. Further evidence for this close packing of the shell is obtained from chiroptical studies.[93] Presumably, intramolecular hydrogen bonding between several L-Phe residues in the shell is contributing to this solid-phase character. The dimensions of the amino-acid-derivative proved critical for the construction of a dense shell structure. According to NMR and modeling studies, the modification with L-Phe residues provided ideal dense shell characteristics in contrast to the more bulkier L-Trp, in which incomplete reaction took place, or L-Ala, which is too small to yield a dense shell packing.

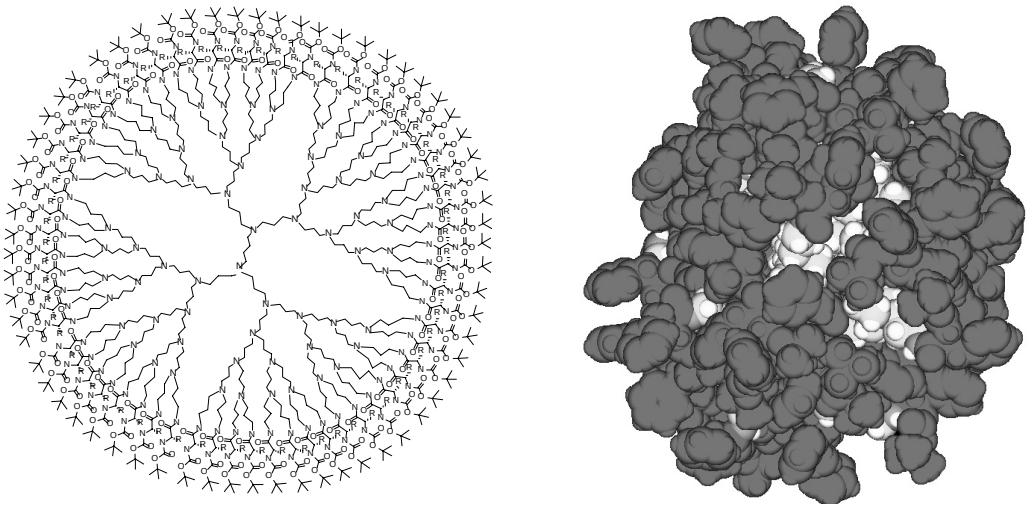

Figure 1.6: *Chemical structure and molecular modeling structure of the dendritic box.*

CHARMm molecular mechanics calculations of the dendritic box were performed to get insight into the three-dimensional structure. The interior is (almost) completely shielded by the bulky endgroups and a globular architecture is found with an estimated radius of 2.3 ± 0.3 nm, similar to dimensions obtained from dynamic light scattering studies and SAXS measurements.[94] From these characteristics, it is suggested that the dendritic structure possesses a flexible core and a dense shell, that will have internal cavities available for guest molecules.

In conclusion, shallow cavities or voids in the dendritic interior depend strongly on the actual dendritic structure. Especially secondary interactions between endgroups in combination with a critical endgroup modification seem to be very important to create a soft core-dense shell motif. In all cases dependent on the conditions used, the cavities can be filled up by endgroups, solvents or guests.

1.4 Dendritic Host–Guest Systems

1.4.1 Solvent Encapsulation

Solvent molecules are the simplest examples of guests one can imagine. Seebach *et al*.[95] observed the formation of very stable clathrates with several chiral dendrimers. Physical encapsulation of carbon tetrachloride, 1,4-dioxane, ethyl acetate or water was observed and removal of solvents proved to be elaborate. Although the term “clathrate” might be questionable (see Section 1.2.2), these observations clearly indicate that dendritic structures can host solvent molecules. It has been commonly observed that it

becomes more difficult to remove solvents with increasing generation. The flexible dendritic molecules try to retain their conformation as much as possible by a physical inclusion of solvent molecules. Once solvents have been removed, the conformation of the dendrimers is likely to change to a collapsed state as it usually requires a long time to redissolve dried dendrimer samples.

1.4.2 Physical Entrapment: The Dendritic Box[96]

Encapsulation of Guest Molecules. The experimental and modeling results of the dendritic box, as shown by Jansen and Meijer[92–94] suggested a solid shell-flexible core structure with internal cavities available for guest molecules. As the shell is constructed in the last step, it is possible to perform this coupling reaction in the presence of guest molecules. In fact, guest molecules with some affinity for tertiary amines can be encapsulated within the dendritic box. Excess of guests and/or traces of guests adhering to the surface are removed by extensive washing and/or dialysis (Fig. 1.7).

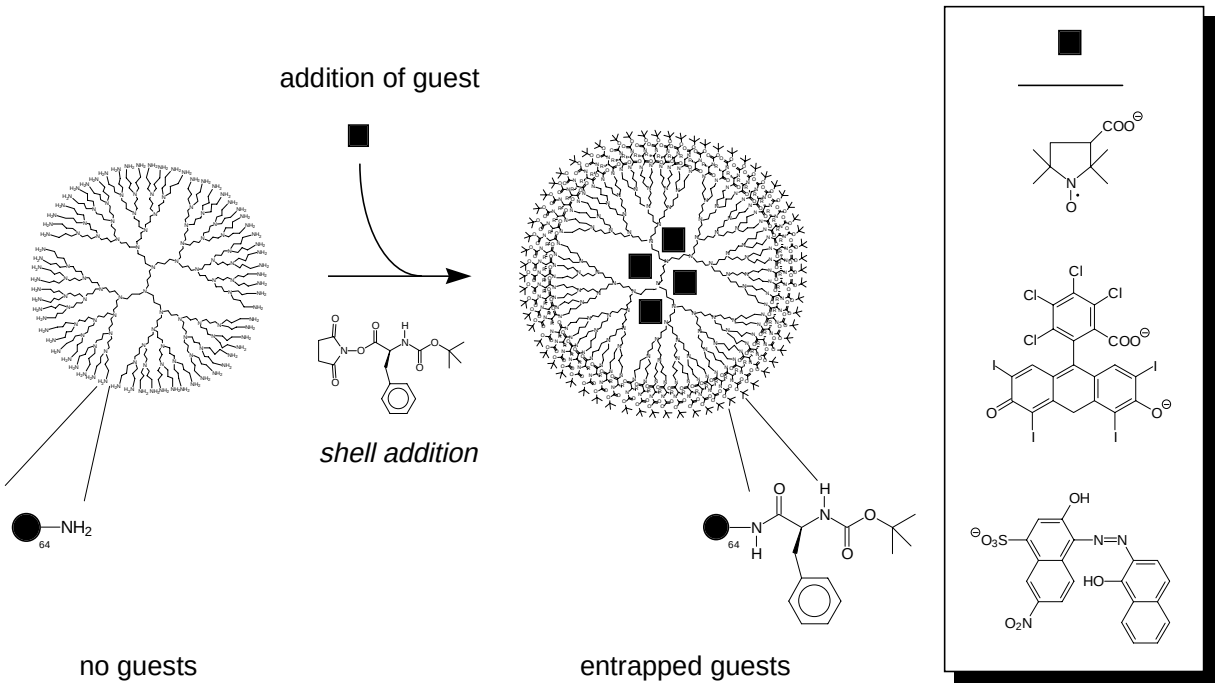

Figure 1.7: *Topological entrapment of guests in the dendritic box.*

Successful encapsulation when using a dendrimer of lower generation proved impossible since the shell is not dense enough to capture the guests and removal by extraction is possible A large variety of guest molecules have been encapsulated and this opens a plethora of interesting chemical and biochemical applications. Typical

guests that are encapsulated are 3-carboxy-PROXYL, Rose Bengal and Eriochrome Black as their encapsulation can be demonstrated with ESR, UV-spectroscopy, CD-spectroscopy. Even after prolonged heating, dialysis or sonification, no diffusion of the dye out of the box could be observed. By comparing the encapsulation results of a large variety of dye molecules, it became apparent that many coplanar dye molecules with an anionic functionality can be encapsulated into the dendritic box, and the affinity seems to be related to acid–base interactions between guest and dendritic host.

Shape-Selective Release of Encapsulated Guests. The rigid, densely packed shell of the dendritic box limits the diffusion out of the box of almost all guest molecules studied. However, the size of the amino-acid residues can be used as a tool to tune the permeability of the dendritic shell. For instance, a semi-permeable box can be obtained, when the dendrimer is functionalized with *t*-BOC protected glycine units[86, 97] or by using L-Phe derivatives without the protective *t*-BOC group. The latter compound is used to allow a shape-selective liberation of guests.[98] After encapsulation of Rose Bengal and *p*-nitrobenzoic acid in the dendritic box, a selective release of the *p*-nitrobenzoic acid can be achieved by hydrolysis of the *t*-BOC groups; however all molecules of Rose Bengal remain entrapped and can be released only after a complete hydrolysis of the dendritic shell using strong acidic conditions. This two-step hydrolysis procedure could be applied to a variety of (mixtures of) guest molecules, indicating that this shape-selective liberation is a general principle. Moreover, by changing the amino acids in the shell and the protecting group of the amino acid, a fine-tuning of the liberation principle was possible.[97]

1.4.3 Dendrimers as Unimolecular Amphiphiles

Newkome *et al*.[99] showed in pioneering studies that water-soluble hydrophobic dendrimers, *i.e.* Micellanoic™ acids (Fig. 1.8), act analogously to micelles and that these dendrimers, with a unimolecular micellar structure, can encapsulate hydrophobic guests within their branches. These dendrimers are monomeric in aqueous media over a broad range of concentrations as is indicated by dynamic light scattering studies.

The specific host–guest characteristics of these poly(ammonium carboxylate)s were demonstrated by UV/vis analysis of guest molecules, such as pinacyanol chloride (PC), phenol blue (PB) and naphthalene, and fluorescence lifetime decay experiments employing diphenylhexatriene as a molecular probe. Additional evidence for inclusion (solubilization) was provided by using naphthalene as a probe, which changes in absorption intensity upon solubilization in the Micellanoate. All probe molecules are solubilized in the dendrimer interior. Using PC as a probe, and comparing these results

with micellar systems like sodium dodecylsulfate (SDS), it could be proven that if there is any critical micelle concentration present, it must be smaller than 0.39 μM.

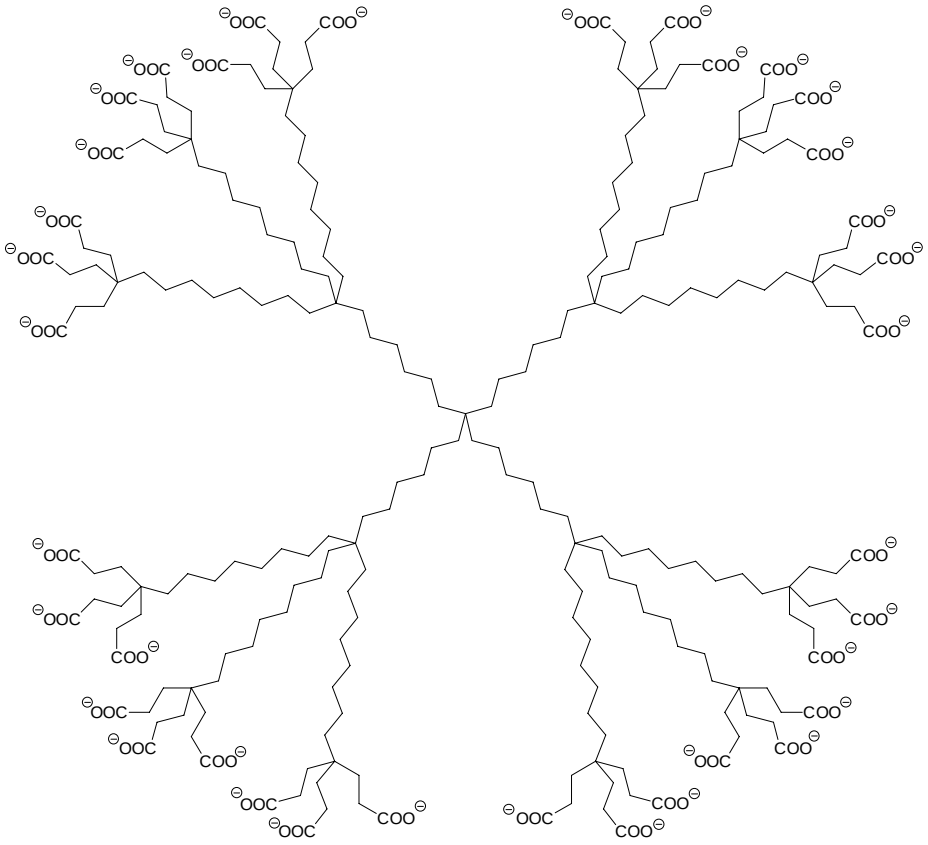

Figure 1. 8: *Unimolecular all-hydrocarbon micelle, coined Micellanoic™ acid.*

The Micellanoate dendrimers have been examined as micellar substitutes for the separation of a homologous series of alkyl parabens via electrokinetic capillary chromatography[100] employing aqueous mobile phase conditions in order to eliminate or effectively reduce the effect of micellar concentration, solvent strength, pH and temperature. Addition of the dendritic micellar substitutes to the analysis buffer separated the parabens as a function of their affinity for the hydrophobic micro-environment of the dendrimer. Separations using dendrimers yield excellent efficiency and resolution. Higher generation dendrimers demonstrate enhanced affinity for the parabens relative to lower generation dendrimers. The observed results are superior to reports of polymerized surfactant aggregates in which the presence of a critical aggregation concentration and the use of organic cosolvents in the mobile phase decreases the efficiency of micellar inclusion.

1.4.4 Recognition based on Hydrophobic Interactions

Diederich *et al.*[101] developed water-soluble dendritic cyclophanes (dendrophanes) as models for globular proteins. These dendrimers contain well-defined cyclophane recognition sites as initiator cores for the complexation of small aromatic guests, like steroids[26, 102–104] or arenes, using π–π stacking and C–H···π interactions. As a consequence dendritic cyclophanes (Fig. 1.9) mimic apolar binding sites buried within globular protein superstructures. Enlargement of the cyclophane core is used as a tool to complex larger steroid molecules.[26, 103]

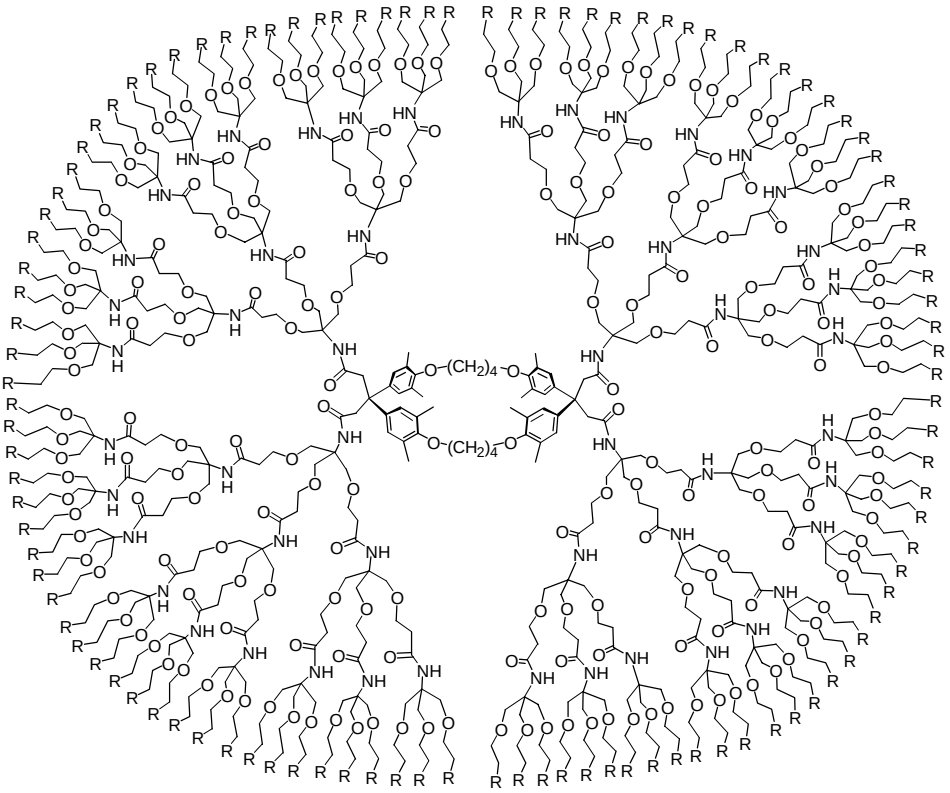

Figure 1.9: *Dendritic cyclophanes as a receptor of hydrophobic compounds (picture kindly provided by prof. F. Diederich (ETH, Switzerland).*

The substrates are located exclusively in the cyclophane cavities and nonspecific incorporation into voids in the dendritic shell is negligible. ^{1}H-NMR binding titrations and fluorescence relaxation measurements in basic aqueous buffer solutions indicated fast host–guest kinetics. The dendrimers form inclusion complexes with association constants of 10^3 M^{-1}, which is of similar stability to those of the initiator core cyclophanes. This suggests a relatively open structure of the dendrimer for all generations. Fluorescent probes like 6-(*p*-toluidino)naphthalene-2-sulfonate (TNS) demonstrated that the micropolarity around the binding cavity was significantly reduced with increasing dendritic size and comparable with ethanol for the higher

generations. This suggests that these water-soluble dendrophanes are attractive targets for catalytically active mimics of globular enzymes, since the exchange rate and the polarity around the binding cavity are only slightly reduced for the higher generation dendrimers in comparison with non-dendritic cyclophanes.

Recently, Diederich *et al.*[105] described the threading of dendritic cyclophanes on molecular rods functionalized with steroid termini. The threading of the dendrophanes onto the testosterone termini is hydrophobically driven (apolar interactions, hydrophobic desolvation) and yields well-defined structures with molecular weights exceeding 14 kD. Ion-pair interactions are also likely to play a role, due to the anionic nature of the dendritic endgroups and the cationic nature of rods. Information about optimal threading, like K_a and ΔH_b, has been obtained from NMR and fluorescence spectroscopy techniques. The threading is highly dependent on the generation number of the dendrophanes and the dimensions of the bifunctional steroid rod. For larger dendrophanes a larger distance between the testosterone termini is required to obtain a 2:1 complex, whereas a 1:1 complex formed for smaller rods. The procedure of hydrophobic threading promises to provide a rapid, efficient way to construct higher molecular architectures based on dendritic modules.[106–108]

1.4.5 Recognition based on Hydrogen-Bonding Interactions

The effect of dendrimer generation on hydrogen-bonding complexation has been nicely investigated by Zimmerman and Moore[109] who reported the suitability of dendrimers to site-specifically complex molecules within their interiors (Fig. 1.10). Two classes of dendritic hosts have been synthesized with naphthyridine units at the focal points capable of hydrogen bonding two types of benzamidinium derivatives. Different (dendritic) guests have been used as a probe of the dendrimer's internal accessibility and polarity.

Two hosts, differing only in the polarity, have been studied and their association constants have been determined by ^{1}H-NMR in $CD_3CN/CDCl_3$ mixtures. An accurate determination of the (larger) association constants in pure $CDCl_3$ proved impossible. The observed results suggest that the environment at the naphthyridine core of both hosts is either apolar or controlled by the solvent, indicating that no distinct dendritic environment is obtained even when using the highest generation. These data are in contrast to the observations by Hawker and Fréchet[110] who reported a change in the local polarizability parameter at the core as a function of the dendrimer generation. In the case of Zimmerman and Moore a negligible influence of the dendrimer is observed, and the hosts are highly porous for small complementary guests even for the highest

generation. Only for the bulkier dendritic guests the binding weakens with increasing generation, reflecting the increased steric constraints for complexation.

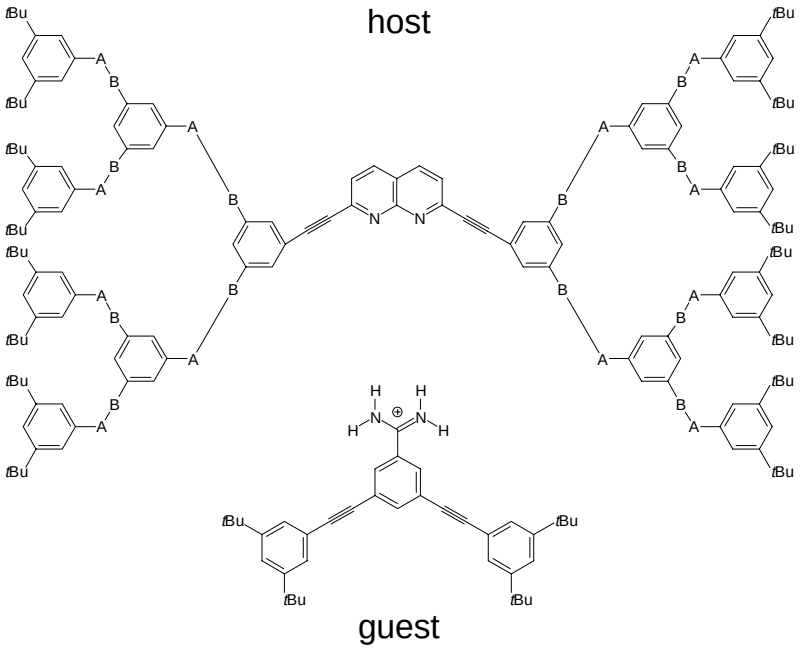

Figure 1.10: *Dendritic wedges functionalized with anthypyridine-units at the focal point (A–B = CH_2–O or C≡C) and a study of the hydrogen-bond interactions with benzamidinium guests.*

Similarly, Zimmerman *et al.*[111] have studied the complexation of anthypyridine-based dendrimers (AAA-motif) via hydrogen-bond interactions with benzamidinium and pentamidine derivatives (DD-motif). The association constants, as determined in $CD_3CN/CDCl_3$ with ^{1}H-NMR gives values of *ca.* 3×10^4 M^{-1} for a benzamidinium guest. Using the bifunctional pentamidine derivative, it was possible to construct a didendron with molecular weight larger than 10 kD from smaller, accessible sub-units. Unfortunately, complexation of the dendritic host with a fully complementary DDD-motif using 2,6-diamino-1,4-dihydropyridine proved impossible due to instability of the latter compound.

1.4.6 Electrostatic Interactions: Recognition of Anions

Inorganic anions. Astruc *et al.* designed neutral[112] and cationic[113] polyamido-ferrocene dendrimers. In the case of the neutral dendrimer (Fig. 1.12), ^{1}H-NMR and Cyclic Voltammetry are used to study interactions between dendrimer and small inorganic anions, like $H_2PO_4^-$, HSO_4^-, Cl^- and NO_3^-.

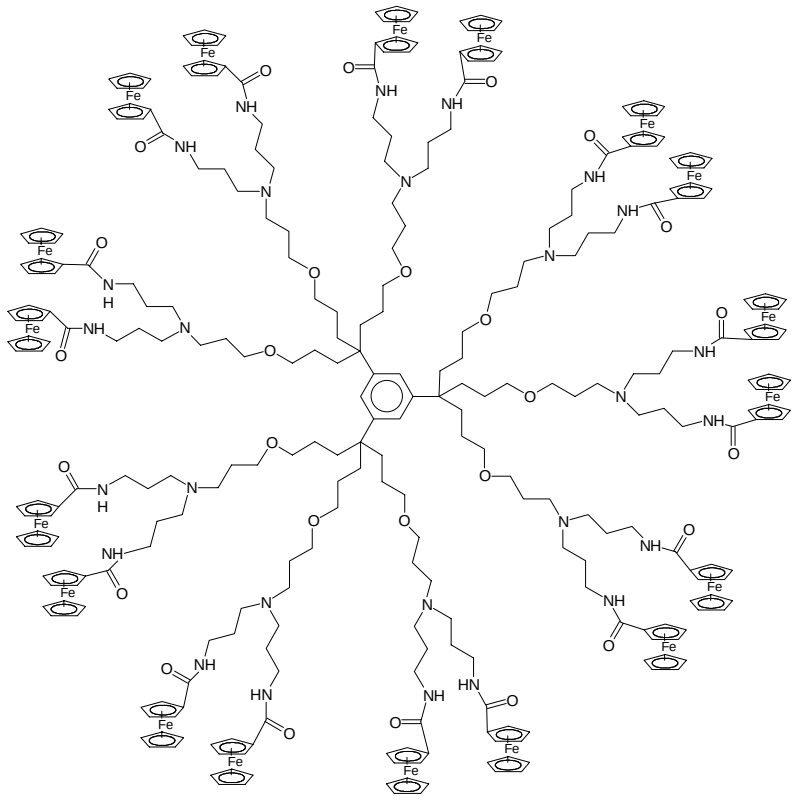

Figure 1.11: *Ferrocenyl-functionalized dendrimers.*

It was found that all redox centers behave independently and that strong interactions are observed in case of the higher generation dendrimers. These interactions can be rationalized by an electrostatic interaction (involving ferricinium cation and anion) and hydrogen-bonding of the amide H atom with the anion. In case of hydrogen-bonding alone, the interaction is usually weak. The sensing of anions (especially $H_2PO_4^-$ and HSO_4^-) by cyclic voltammetry increases with generation (3 → 9 → 18 endgroups). The authors explain this by a shape selectivity originating from the dendrimer. For the polyamidoferrocene dendrimers presented above, recognition in the neutral state is by far weaker (and only present for $H_2PO_4^-$) than in the cationic state, since the neutral diamagnetic 18-electron form does not usually interact efficiently with anions.

A polycationic ferrocene-functionalized dendrimer[113] was synthesized in an attempt to create recognition of anions with ferrocene in its 18-electron form, without the need of cyclic voltammetry. These dendrimers show a large dendritic effect, *i.e.* better association with increasing generation, for the recognition of Cl^- and Br^-. Chelating anions like $H_2PO_4^-$ are not recognized, in contrast to the neutral species, probably due a difference in molecular structure. Whereas the neutral species contains amide-linkages, the cationic dendrimers contain secondary amines that preferentially interact with

single-atom halogens anions, like Cl^- and Br^-. Synergistic effects between the single X^-···H–N hydrogen bond, the electrostatic attraction, and the shape selectivity of the dendritic structure (peripheral cavities, dendrimer branches) account for the recognition of the halogens Cl^- and Br^-.

Organic Acids. Tomalia *et al.*[74] reported the random complexation of host molecules in dendritic structures by monitoring the change in guest ^{13}C spin-lattice relaxation times (T_1). PAMAM dendrimers with methyl ester termini were used as the dendritic host with aspirin and 2,4-dichlorophenoxyacetic acid as guest molecule (Fig. 1.12). T_1–values of the guests in $CDCl_3$ change in the presence of dendrimer and a distinct dependence of the generation is observed. The values for T_1 decreased, as the generation number increased from 0.5 to 3.5, but remained constant for higher generations. The maximum concentration of the guests is roughly 3:1 based on a molar comparison of the carboxylic guest and the interior tertiary amines, suggesting an acid–base interaction between host and guest.

Similar results have been obtained by Twyman and Mitchell,[114] who developed a convenient route to highly water-soluble dendrimers starting from PAMAM-dendrimers. These dendrimers are capable of binding and solubilizing small acidic, water insoluble, hydrophobic molecules, like benzoic acid, salicylic acid and 2,6-dibromonitrophenol. However, tioconazole and other small non-ionic molecules could not be retained within the dendrimer. Again an interaction between the acidic functionality of the guests and the basic tertiary nitrogens of the dendritic hosts is suggested. In case of a second generation dendrimer up to 46 benzoic acids can be dissolved, *i.e.* an average of 3 guests per tertiary amine site, in good agreement with the results of Tomalia *et al.*[74] Unfortunately, the exact mode and mechanism of binding is not yet elucidated.

Recently, Crooks *et al.*[115] reported the transfer of amine-functionalized poly(amidoamine) dendrimers into toluene containing dodecanoic acid. The method is based on the formation of ion pairs between the fatty acids and the terminal amine-endgroups. The amount of dendrimer that can be dissolved corresponds roughly to a stoichiometry of 1 fatty acid per amine-endgroup as evidenced by Transmission FT-IR spectroscopy. In the presence of large excess of dodecanoic acid, proton transfer extends to the tertiary amine groups within the dendrimer interior. Finally, the dendrimer-fatty acid complexes can be used as a phase transfer vehicle for the transport of Methyl Orange, an anionic dye molecule, into the organic medium.

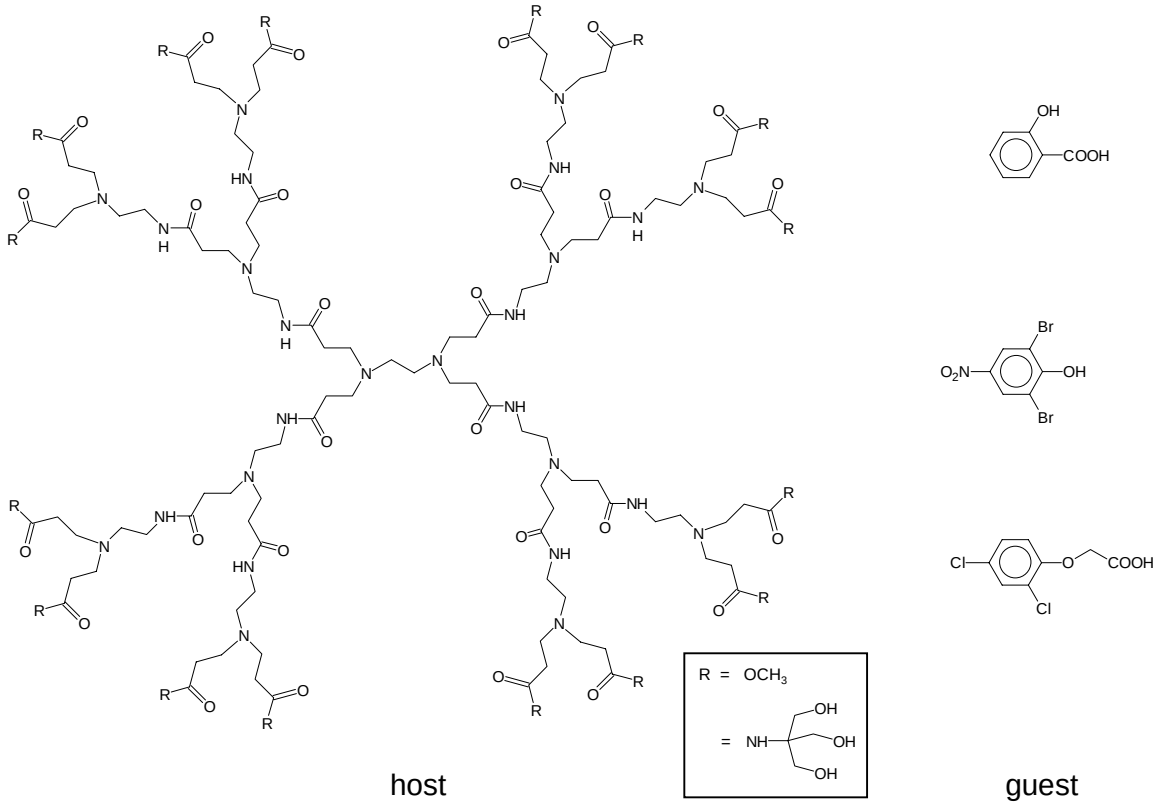

Figure 1.12: *Interaction of organic acids, like salicylic acid, 2,6-dibromophenol or 2,4-dichlorophenoxyacetic acid (from top to bottom) with poly(amidoamine) dendrimers.*

Stevelmans *et al.*[116] have reported on the modification of the amine-terminated poly(propylene imine) dendrimers with fatty acids, like palmitic acid. The functionalized dendrimers consist of an polar interior and an apolar periphery and resemble a unimolecular inverted micelle (Fig. 1.13). These dendritic molecules are soluble in organic media, but insoluble in aqueous media and it was shown that the compatibility of Bengal Rose and an apolar solvent such as hexane or toluene could be strongly improved by addition of the functionalized dendrimer. It proved impossible to release the guest by washing with water. Later, Balzani, de Cola and Vögtle[117] reported the first attempts to develop a host–guest system of which the interactions could be tuned by an external stimulus, for instance light. The interaction of a fourth generation azobenzene-functionalized poly(propylene imine) dendrimer with Eosin Y was studied in DMF. It was also shown that light absorbed by Eosin is effective to promote the photoisomerization of azobenzene moieties from the E-form to Z-form. Fluorescence quenching experiments show that Eosin is hosted inside the dendrimer and suggest that the Z-forms of the dendrimers are better hosts than the E-form.

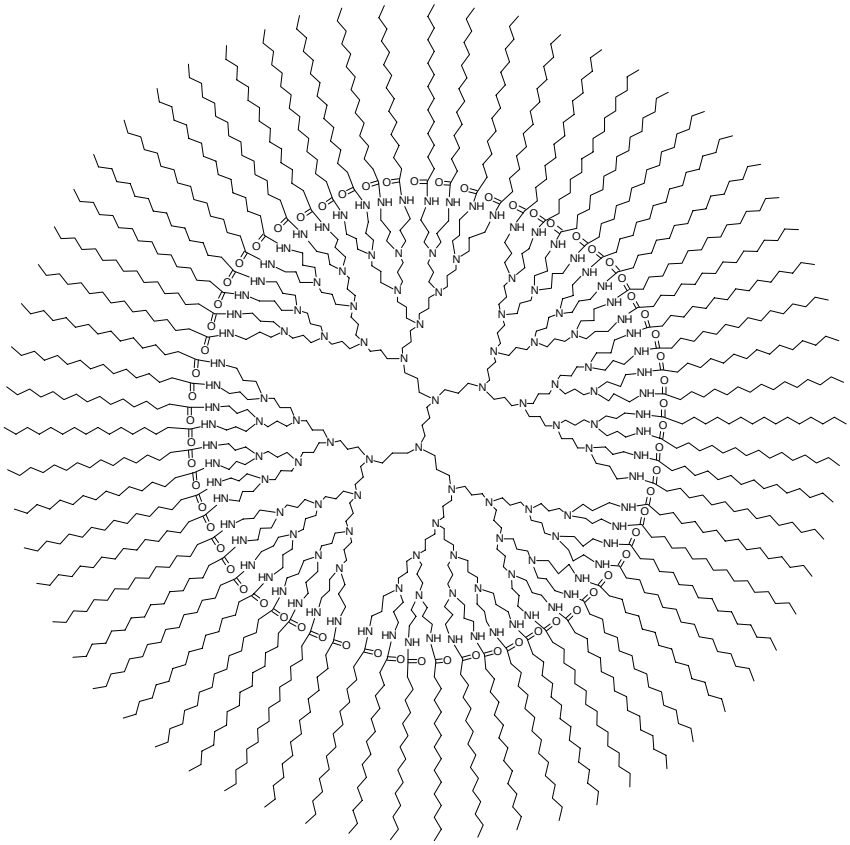

Figure 1.13: *Palmitoyl-functionalized poly(propylene imine) dendrimers as unimolecular inverted micelles.*

1.4.7 Electrostatic Interactions: Recognition of Cations

Many examples are known in the field of metal complexation. The dendrimer serves as an ideal polyfunctional ligand, *i.e.* host, for the complexation of metals, either at the periphery or with complexation at the interior. This has been of interest in the field of catalysis.[118, 119] Challenging possibilities for ultrafiltration are foreseen. Recently, a highly sensitive sensor was based on dendrimer-based ligands.[120] In this section, the main contributions in the field of dendrimers and metal complexation are discussed. Dendrimers that use metal ions as a building block will not be discussed, since these topics have only a slight interaction with the framework of host–guest complexation, but one is referred to more extensive reviews on metal-containing dendrimers.[57, 121, 122]

Dendrimers with Peripheral Ligands. Bosman *et al.*[123] reported the use of amine-terminated poly(propylene imine) dendrimers as polyvalent ligands (Fig. 1.14) for various transition metals, like Cu(II), Zn(II) or Ni(II).

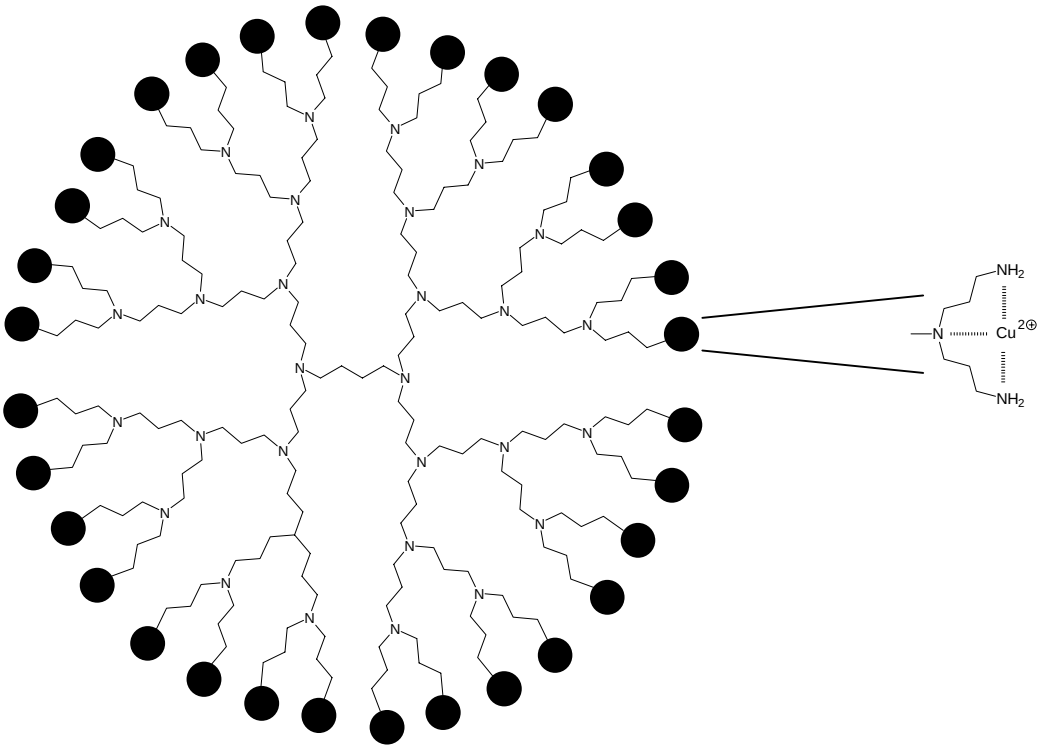

Figure 1.14: *Amine-terminated poly(propylene imine) dendrimers as tridentate ligands for the complexation of Cu(II).*

The bis(propylamine)amine pincer, already present at the periphery of the parent poly(propylene amine) dendrimers, acts as a tridentate ligand for these metals as evidenced by UV/vis, EPR and NMR measurements. The amine-functionalized poly(propylene imine) dendrimers represent one of the few examples of dendritic polyfunctional ligands, without the need for modification.[52, 124] Many of the systems known today require an additional modification step to link the coordination site to the dendrimer.[125–134]

1.5 Aim and Scope of the Thesis

After the initial reports of Tomalia and Newkome, the field of dendrimers has emerged as a new field in macromolecular chemistry. The combination of discrete number of functionalities, high local densities of functions in one molecule together with the nanometer dimensions have explained the broad interest. Due to the large body of research that has been performed on the synthesis of these structures, in principle almost all properties can be tailored. Many methodologies are established to give the chemist an ideal control over architecture, functionality and micro-environment. Moreover, the incorporation of special functions, at the core, in their branches or at the periphery, should enable the supramolecular dendrimer chemists to construct the 'ideal

host–guest system'. It needs to be emphasized, however, that this requires a detailed understanding of the dendritic scaffold used. Fortunately, the poly(propylene imine) dendrimers used in this study are commercially available, which facilitates a thorough investigation on the one hand, but on the other hand stresses the importance of studies on this type of dendrimers. The aim of this thesis is to apply the dendritic scaffold in technologies where dendrimers have an additional value. This requires a functionalization of the dendritic skeleton and an exploration of the ideal modification route. Furthermore, the typical characteristics of (functionalized) poly(propylene imine) dendrimers, like their secondary interactions, need to be addressed. A thorough rationalization of the dendritic skeleton is necessary to apply these structures into new technologies, such as extraction processes or liquid crystalline devices.

In Chapter 2, dendrimers are used as a multifunctional scaffold for endgroup-modification. Three different routes with a high efficiency for endgroup-modification are discussed, and the reaction of dendrimers with activated esters is investigated in more detail to address the modification of the primary amine-endgroups with respect to the secondary amine defects. The typical interactions of the synthesized dendrimers, like protonation behavior and hydrogen-bonding interactions are characterized in Chapter 3. The poly(propylene imine) dendrimers consist of tertiary amines in the dendritic interior that interact with inorganic acids and their protonation behavior is discussed for different types of endgroups. The hydrogen-bonding interactions of dendrimers containing amide- and urea-linkages, that are formed upon endgroup-modification with acidic or isocyanate derivatives, are studied in solution (IR and NMR-spectroscopy) and in the solid state (DSC). Both type of endgroup and linkage can be used to tune the flexibility of the dendritic skeleton.

In Chapter 4, dendrimers with alkyl endgroups are used as a new type of tertiary amine extractants for the extraction of anionic dye molecules from water into organic media. Typical characteristics of the dendritic scaffold like the high local concentration of tertiary amine sites and the presence of a local micro-environment make these dendrimers to ideal hosts, that are superior to their low-molecular weight analogues. Subsequently, dendritic extractants are applied in a water-purification technology to remove anionic compounds from aqueous waste streams. Similarly, perfluoroalkyl dendrimers are prepared to perform extraction into an environmentally green solvent, *i.e.* supercritical carbon-dioxide and their behavior is compared with alkyl dendrimers in organic media.

In Chapter 5, a water-soluble oligoethyleneoxy-functionalized dendrimer is synthesized, towards the development of controlled release system. The dendrimers used shows strong interactions with Bengal Rose, an anionic guest, as indicated by

UV/vis spectroscopy and X-ray measurements. The latter technique indicated the preferential location of these guests in the dendritic interior.

In Chapter 6 the liquid crystalline properties of alkoxycyanobiphenyl dendrimers are discussed, to answer the question: is a dendrimer in conflict between spherical shape and mesogen order? It is evidenced from a combination of Optical Microscopy, DSC measurements and X-ray diffraction that the poly(propylene imine) scaffold adapts to the (spatial) requirements of the mesogenic endgroups and adopts a flat conformation. Subsequently, Chapter 7 describes the use of these alkoxy-cyanobiphenyl dendrimers and alkyl dendrimers as additives to a nematic liquid crystal. These blends are used in the development of a (promising) electro-optical switch based on light scattering. Especially, alkyl-substituted derivatives show a fast and reversible switching even when compared with a 'state of the art' PDLC.

Finally, in Chapter 8 the use of dendrimers as a nanometer-sized module is described. Whereas such studies failed several years ago, based on encapsulation procedures with the 'dendritic box', a new supramolecular methodology applied to dendrimers is disclosed. From the knowledge gathered in Chapter 1 and 3, guest molecules are designed that 'click' into specific binding sites of the functionalized dendrimers skeleton via acid–base and hydrogen-bonding interactions.

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Functionalization of Poly(Propylene Imine) Dendrimers

2

Abstract: *The amine-terminated poly(propylene imine) dendrimers allow reaction with a large variety of reagents yielding functionalities to be incorporated at the periphery of the dendrimers. The modification with acid- and isocyanate-functionalized derivatives or with Michael-reagents and the purification of the products is discussed. The modification with pyridine-endgroups is used to discuss the purity of modified poly(propylene imine) dendrimers. The modification reaction can be performed with an efficiency of 99.6% and is selective with respect to the type of endgroup. Primary amine endgroups react smoothly in contrast to secondary amine defects that are present in the defects of the parent dendrimers.*

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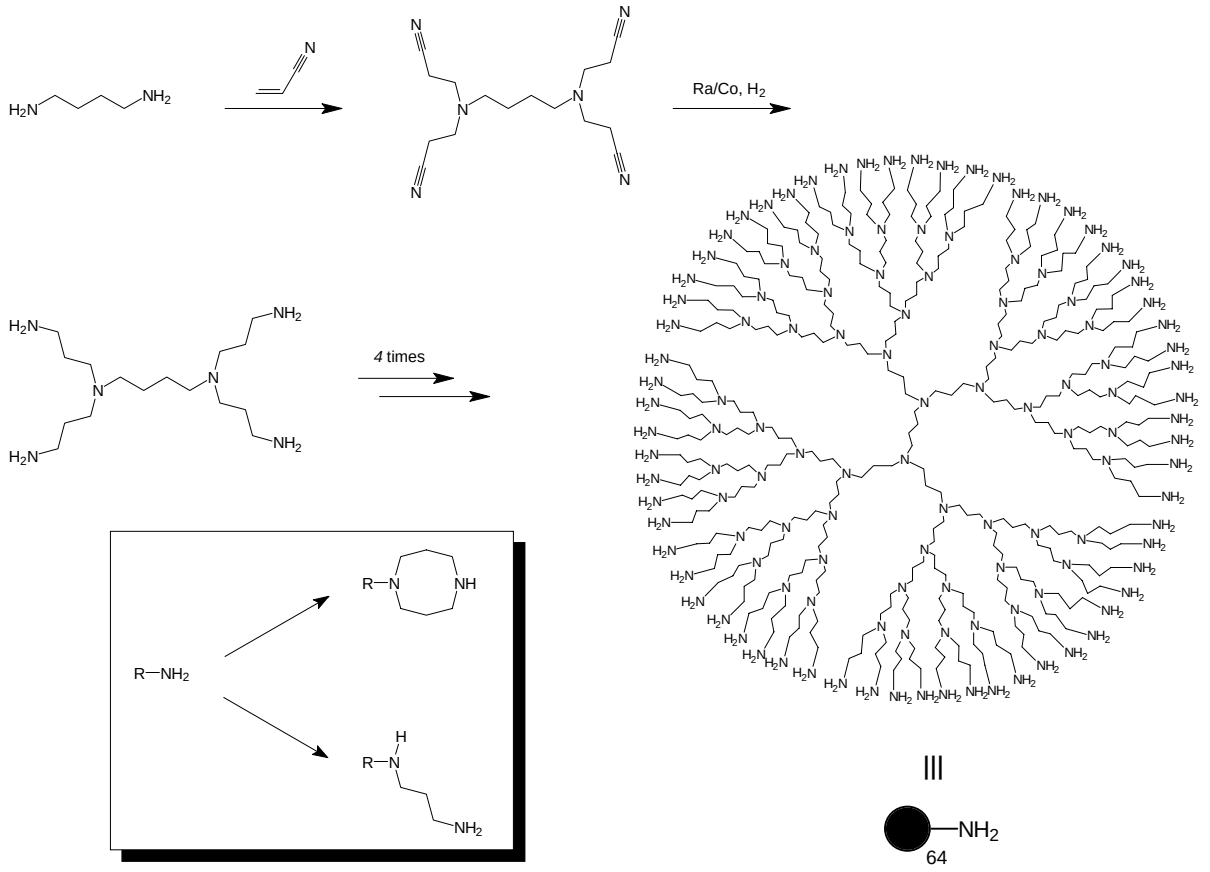
2.1 Introduction

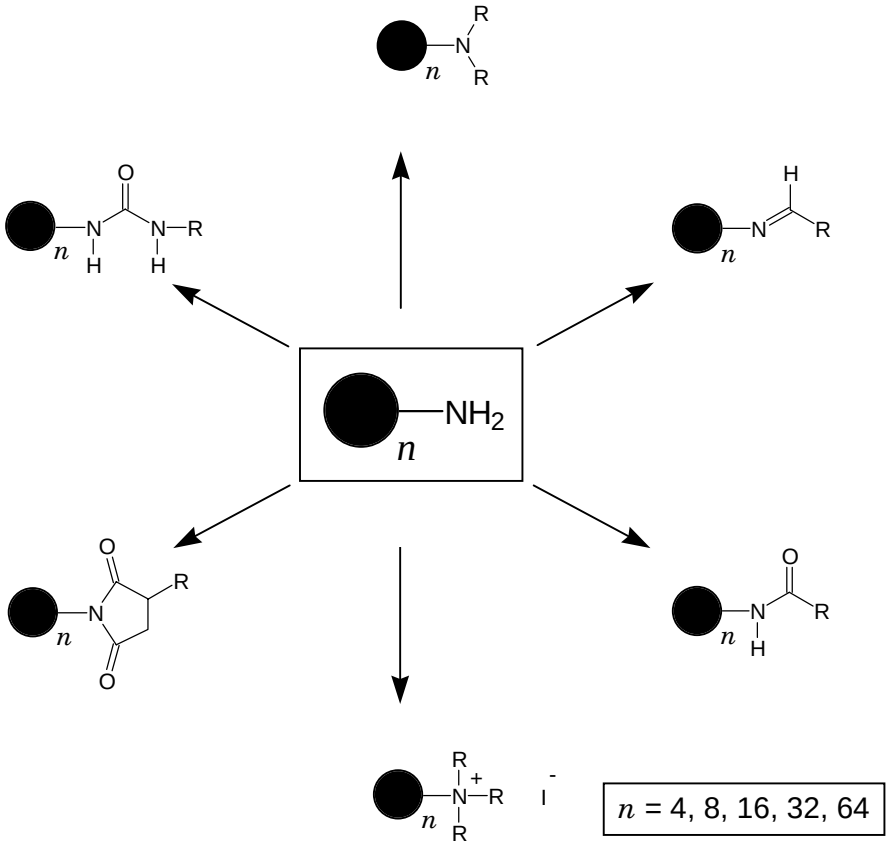
Tomalia[1, 2] and Newkome[3] established their names in the field of highly branched macromolecules as early pioneers with the divergent synthesis of polyamidoamine dendrimers and arborols, respectively. The convergent approach was introduced by Fréchet *et al*.[4] Newkome and Vögtle[5] published an excellent monograph on historical accounts, synthetic methodologies and terminology of the dendrimer field. Later, it was realized that the unique branched architecture, as well as the multifunctional number of endgroups that become available with these dendritic structures, can be used as a tool to display desired functions, such as well-defined shapes or internal voids.[6, 7] During the last five years attention has been focussed on the application of dendrimers through modification of the dendritic scaffold.[8, 9] This has led to many examples of dendrimers that are decorated with various endgroups,[10–13] emphasizing the need to use dendritic scaffolds that are easily accessible, well-defined and can be easily modified.

Currently, the divergent 'from-core-to-periphery' route[14–16] is the only attractive route for the production of kilogram quantities of dendrimers and only two classes are commercially available, poly(amidoamine) dendrimers[14] and poly(propylene imine) dendrimers.[42, 17] Ideally, these structures are perfect monodisperse macromolecules with a regular and highly branched three-dimensional structure, which are produced in an iterative sequence of reaction steps where each additional iteration leads to a higher generation material. However, the divergent methodology has synthetic limitations and the perfection of the final dendritic product is related to the synthetic approach used. The synthetic scheme of the poly(propylene imine) dendrimers and the possible side reactions are depicted in Scheme 2.1. Since the dendrimer is grown in a stepwise manner from a central core, and numerous reactions have to be performed on a single molecule without a possibility of purification, every reaction has to be highly selective to ensure the integrity of the final product. The best method for structural analysis of dendrimers is mass spectrometry.[18–22] The sensitivity of this technique gives a more realistic picture of the purity of a given dendrimer than possible with any other technique. In case of the poly(propylene imine) dendrimers, all generations with amine- or nitrile end groups have been fully analyzed with ESI-MS to determine the amount of various side reactions.[22] The history of the dendrimer synthesis is fully mapped and every defect in the dendritic structure could be addressed. In case of a fifth generation amine-terminated poly(propylene imine) dendrimer the dendritic purity, *i.e.* the percentage of dendritic material that is defect free, amounts to *ca.* 23%, corresponding to an average selectivity of 99.4% in 248 reaction steps. The reality of statistical defect structures is also recognized in the iterative synthesis of polypeptides or polynucleotides on a solid support, known as the Merrifield synthesis.[23]



Scheme 2.1: *The synthesis of poly(propylene imine) dendrimers and undesired defect structures. Cartoon representation of a fifth generation poly(propylene imine) dendrimer is also depicted.*

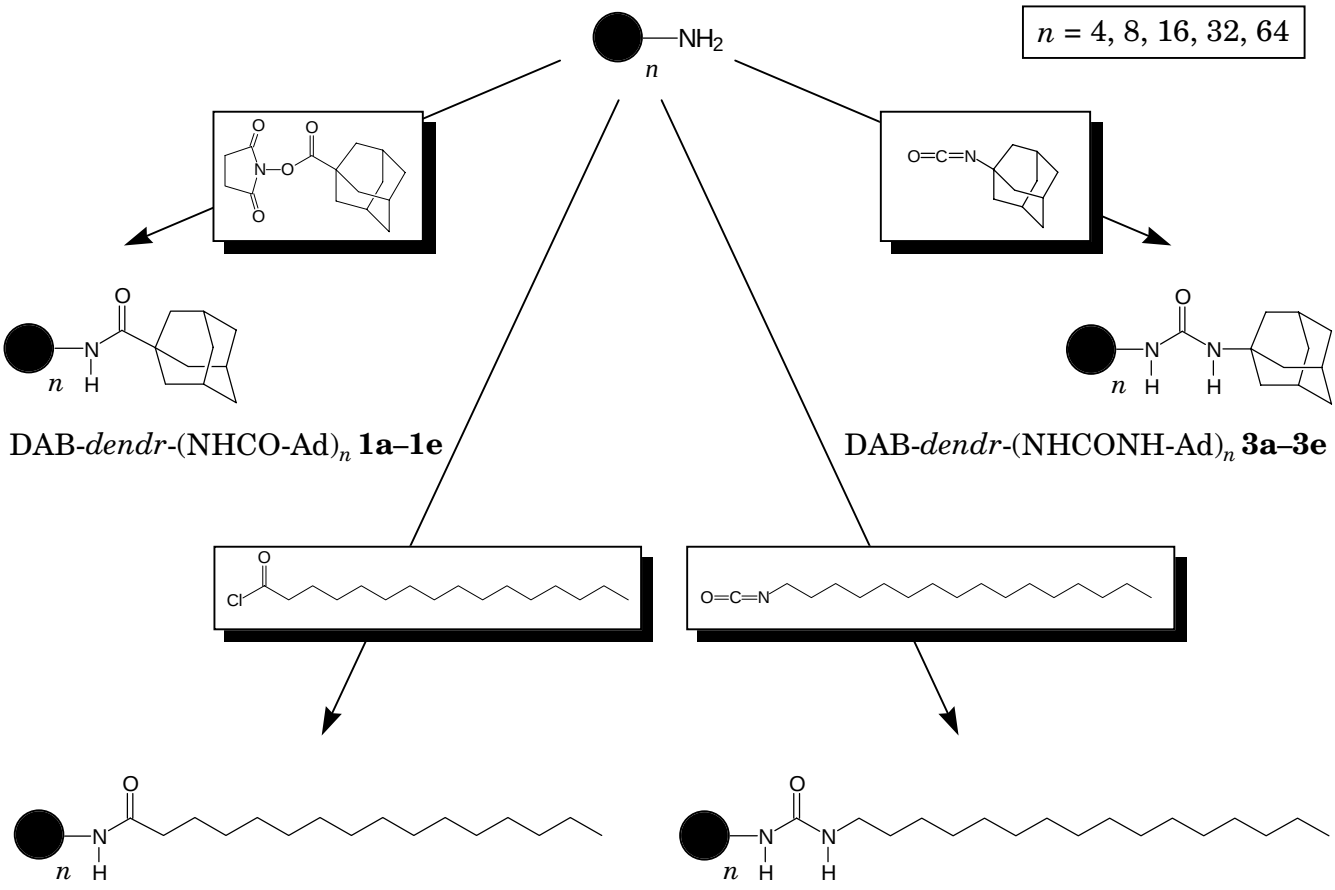
This chapter addresses the high synthetic value of amine-terminated poly(propylene imine) dendrimers for a large variety of modification reactions, as illustrated in Scheme 2.2[24] Three examples are discussed, *i.e.* modification with acid[25] and isocyanate-functionalized apolar endgroups (Section 2.2) or reaction with Michael-type reagents (Section 2.3). The importance of a high efficiency modification is further addressed by discussion of the modification and a full structural characterization of pyridine-functionalized poly(propylene imine) dendrimers (Section 2.4).[26] The latter modification can be performed in a very high efficiency (*ca.* 99.6% per endgroup) and characterization with ESI-MS gives insight into the selective modification of the primary amine endgroups compared to the secondary amine defects that are present in the dendritic structure.



Scheme 2.2: *An overview of various endgroup modifications of poly(propylene imine) dendrimers.*

2.2 Functionalization with Apolar Endgroups[27]

The coupling of apolar endgroups to a polar dendritic scaffold generates a new type of unimolecular (inverted) micelles and it is expected that these structures have interesting amphiphilic properties in solution, at interfaces or in bulk.[28–30] Two different types of apolar substituents were chosen: (i) a rigid, bulky adamantyl-unit[31] as an attempt to mimic the 'dendritic box',[32] yet with an all hydrocarbon periphery, and (ii) a flexible, linear alkyl chain. Two synthetic routes were chosen to connect these endgroups to the dendritic scaffold, either via a carboxylic acid-functionality or via isocyanates.[33] The amine-terminated poly(propylene imine) dendrimers, denoted as DAB-*dendr*-$(NH_2)_n$,[34] with n = 4, 8, 16, 32 and 64, are reacted with palmitoyl chloride (hexadecanoylchloride), hexadecyl isocyanate, 1-adamantyl isocyanate and succinimidyl 1-adamantane carboxylate. This resulted in four series of dendrimers, *i.e.* DAB-*dendr*-$(NHCO\text{-}Ad)_n$, DAB-*dendr*-$(NHCO\text{-}C_{15}H_{31})_n$, DAB-*dendr*-$(NHCONH\text{-}Ad)_n$ and DAB-*dendr*-$(NHCONH\text{-}C_{16}H_{33})_n$ with n = 4, 8, 16, 32, 64 (Scheme 2.3).



Scheme 2.3: *Synthetic scheme for the modification of poly(propylene imine) dendrimers with apolar endgroups.*

2.2.1 Synthesis of Adamantyl Dendrimers

Adamantyl-carboxylic acid was first activated with N-hydroxysuccinimide in 1,2-dimethoxyethane in the presence of 1,3-dicyclohexylcarbodiimide to yield the corresponding succinimidoyl ester in 71%. The reaction of all amine-terminated dendrimers proceeded nicely in CH_2Cl_2 at room temperature during 16 h when a small excess of the activated ester (1.1 eq per NH_2) was used. The resulting adamantyl-dendrimers **1a**-**1e** connected *via* an amide-linkage, have molecular weights up to 18 kD for the fifth generation and were extensively purified from excess activated ester and N-hydroxysuccinimide using extraction with 1 M Na_2CO_3 and column chromatography. Although the interior of the poly(propylene imine) dendrimer is very basic and interacts with the silica column, these interactions can be severely reduced through modification with bulky adamantyl-endgroups. This suggests the formation of an apolar cover around the basic interior, similar to the 'dendritic box'.[32] The modified dendrimers were highly soluble in $CHCl_3$ and CH_2Cl_2, but insoluble in solvents like acetone and alcohols.

The coupling of 1-adamantyl isocyanate with the amine-terminated dendrimers in $CHCl_3$ proceeds nicely at room temperature under argon atmosphere. Pure products **3a**-**3e** could be obtained by precipitation of the reaction mixture in diethyl ether, which is a good solvent for isocyanates, but a non-solvent for the urea-functionalized dendrimers.

2.2.2 Synthesis of Alkyl-Chain Modified Dendrimers[35]

All amine-terminated dendrimers were reacted with palmitoyl chloride (1.05 eq per NH_2) in THF during 16 h using K_2CO_3 as a base. Purification of the dendrimers was obtained by filtration of the precipitate and refluxing the insoluble material in 1 M NaOH solution for 3 h, yielding nice solids **2a**-**2e** in good yields (74 %). The products obtained are soluble (concentration used *ca.* 1 mg/ml) at room temperature in a wide range of organic solvents, like dichloromethane or chloroform, toluene and THF; however, maximum solubility (up to 10 mg/ml) increases significantly with temperature.

The modification of hexadecyl isocyanate with the amine-terminated poly(propylene imine) dendrimers was conducted in $CHCl_3$ at room temperature under argon atmosphere during 16 h. Work-up was achieved by precipitating the viscous reaction mixture in diethyl ether. Again a selective precipiation of the dendritic product is observed. However, a small amount of dimeric compound ($C_{16}H_{33}$-NHCONH-$C_{16}H_{33}$) is formed due to partial hydrolysis (1%) of the hexadecyl isocyanate during reaction and this side-product could not be removed by precipitation in diethyl ether. However, since the solubility of the side-product in $CHCl_3$ at room temperature was substantially higher than that of the dendritic products, purification could be achieved by repeated filtration of a concentrated solution with overall yields of *ca.* 80%. Pure alkyl-modified poly(propylene imine) dendrimers with urea linkages, **4a**-**4e**, showed limited solubility in organic solvents, like $CHCl_3$ and CH_2Cl_2 at room temperature, but could be nicely dissolved at 333 K. The formation of urea-linkages is known to have significant effects on the solubility[36] of (dendritic) products.

2.2.3 Discussion and Characterization

The modification of an amine-terminated dendrimer can be monitored by ^{1}H-NMR spectroscopy from a disappearance of the CH_2NH$_2$-resonance at 2.8 ppm and a shift to 3.1–3.3 ppm, dependent on the type of linkage that is formed. In all cases with a combination of ^{1}H-NMR, ^{13}C-NMR and IR-spectroscopy and TLC the purity of the modified dendrimers can be warranted.

In case of modification of succinimidyl 1-adamantane carboxylate, purity is confirmed by the absence of N-hydroxysuccinimide and activated ester according to ^{1}H-NMR spectroscopy, IR and TLC. Also no indication was found for the presence of 1-

adamantane carboxylic acid, due to hydrolysis of the ester. The purity of the adamantyl-functionalized dendrimers was further confirmed with FAB-MS. All dendrimers measured (n = 4, 8, 16) gave peaks at the expected mass and no indication for uncomplete modification was observed. Thus, the modification of amine-terminated endgroups with succinimidyl-esters provides a mild and highly efficient method, even though MALDI-TOF-MS of the higher generations (n = 32, 64) was not attempted.
Characterisation of the alkyl-amide dendrimers with ^{1}H-NMR, ^{13}C-NMR, IR indicates full conversion. Similarly, FAB-MS of the lower generation (n = 4, 8, 16) proves the identity of the dendrimers. Small deviations between the calculated and observed mass can be explained by the accuracy of the measurement, typically 0.05%. Especially, for the higher generations this can already account for the deviations observed.[37] However, even when small deviations are observed, mass spectrometry can be used to determine the selectivity of the modification step, since the mass differences due to one endgroup missing are much larger than the experimental deviations.

Although the coupling of acid chlorides with dendrimers yields a fast method for modification of the dendrimer, there are also some drawbacks: (i) Upon coupling of the acid chloride with the amine-terminated poly(propylene imine) dendrimers, hydrochloric acid is released. The tertiary amine interior of the dendrimer is protonated even when substantial amounts of a homogeneous base like triethylamine or a heterogeneous base, like anhydrous potassium carbonate are used. Furthermore, the coupling of (bulky) apolar endgroups hinders the deprotonation step of the dendritic interior by a base, because an apolar cover is formed around the dendritic scaffold. Deprotonation requires harsh conditions, *i.e.* either extraction of a CH_2Cl_2 solution of a dendrimer with a 1 M NaOH solution, at high temperatures, or heating of the dendritic product in 1 M NaOH under reflux conditions. (ii) Moreover, the excess acid which is formed after quenching of the excess chloride, can interact with the tertiary amines in the dendritic interior. When using the activated ester route, purification can be achieved by techniques that separate on differences in molecular weigth, like precipitation, centrifugation or biobeads chromatography, whereas such techniques are not effective when an acid chloride coupling is used. Therefore, a coupling with activated esters is preferred over acid chlorides, especially in the case of unstable endgroups. Important to note is that ^{1}H-NMR spectroscopy can distinguish between a functionalized dendrimer in a protonated state and a deprotonated state. Upon protonation of the tertiary amines by hydrochloric acid or excess acid, the resonances of the methylene protons adjacent to the nitrogen sites shift downfield from 2.3–2.4 to *ca.* 2.8 ppm.

The modification of poly(propylene imine) dendrimers with isocyanate endgroups represents a mild strategy with the use of precipitation as an easy and effective work-up

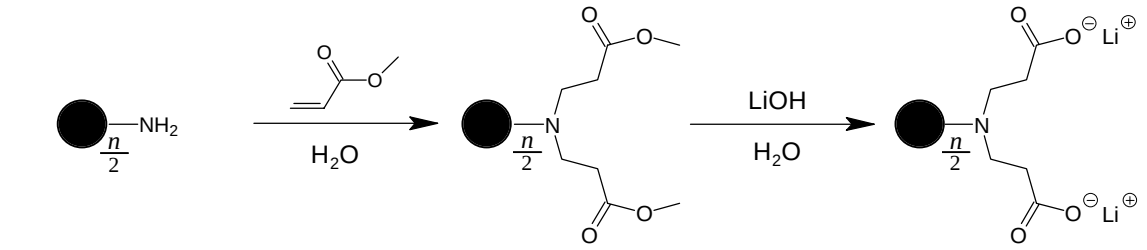
procedure and without problems concerning protonation of the dendrimer. Moreover, almost any aliphatic amine-terminated substituent, can be converted into an isocyanate using 'di-*tert*-butyl tricarbonate' chemisty.[24] FAB-MS of the lower generations (n = 4, 8 and 16) and MALDI-TOF MS of a fourth generation dendrimers with a urea linkage, DAB-*dendr*-(NHCONH-Ad)$_{32}$ and DAB-*dendr*-(NHCONH-$C_{16}H_{33}$)$_{32}$ yielding masses of 9174.0 D (calcd. 9185.7 D) and 12072.2 D (calcd. 12072.4 D), respectively, indicate the purity of the functionalized dendrimers. These results indicate that amine-terminated poly(propylene imine) dendrimers can be completely reacted with (various) isocyanate derivatives in a high selectivity. Functionalized dendrimers of the fifth generation could not be measured under identical experimental conditions, due to the instability of the compounds. In several cases fragmentation of the dendritic compound was observed resulting from formation of pyrolidinium or azetidinium based fragments.[38] Finally, the most important remark on the modification of poly(propylene imine) dendrimers is the fact that the purity of the amine-terminated dendrimer determines the final purity of the dendritic product, as long as the issue of steric constraints of the endgroup does not play a role[39] and the reactivity of the endgroup is high.

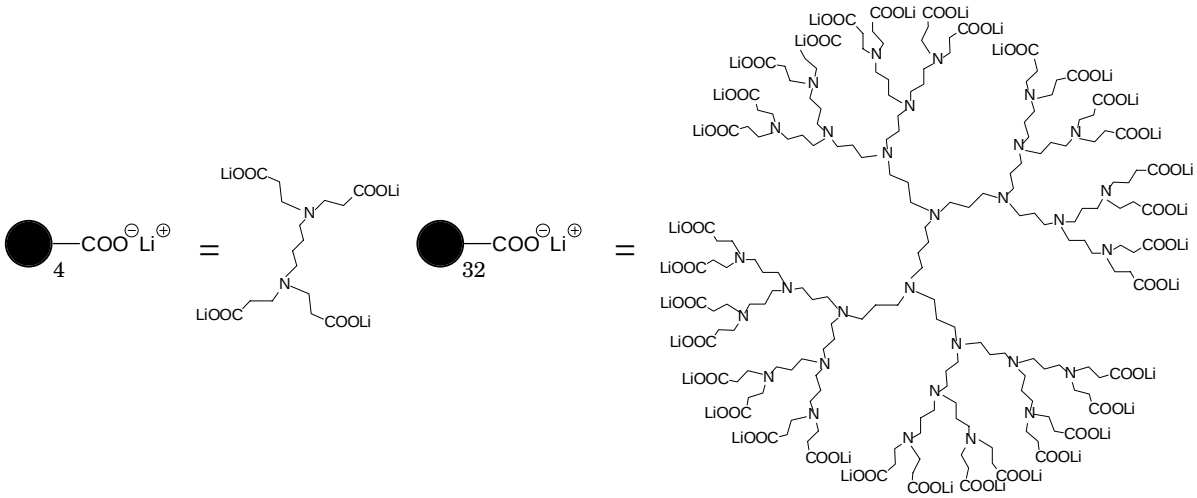
2.3 Synthesis of Carboxylate-Functionalized Dendrimers

Acid-functionalized poly(propylene imine) dendrimers have been used in Electrokinetic Chromatography[40] and constitute of a new series of acid-functionalized dendrimers with a polar interior of tertiary amines in contrast to the acid-functionalized unimolecular micelles with an apolar interior.[29, 41–43] Two routes can be used to obtain poly(propylene imine) dendrimers with carboxylic endgroups. One of these routes involved acidic hydrolysis of the nitrile-functionalized poly(propylene imine) dendrimers, and uses intermediates that are directly available from the dendrimer synthesis.[42] However, the synthesis of acid-functionalized dendrimers requires harsh conditions and the dendritic compounds contain a high concentration of salts (*ca.* 30 wt%), are very hygroscopic and have a brownish color, especially for the higher generations.

In order to bypass these difficulties a new route[44] towards acid-functionalized poly(propylene imine) dendrimers, *i.e.* DAB-*dendr*-(COO^-Li^+)$_n$, was developed and the synthesis thereof is outlined in Scheme 2.4. The number of terminal carboxylate functionalities (4, 8, 16, 32 and 64, for generation 1 to 5, respectively) is represented by n, thus $n/2$ is the number of amine-functionalities. The synthesis starts from the commercially available amine-terminated poly(propylene imine) dendrimers,[6] *i.e.* DAB-

dendr-$(NH_2)_{n/2}$ {n = 4, 8, 16, 32, 64}. Michael addition of two equivalents of methyl acrylate to the amines of the dendrimer yields methyl ester-functionalized poly(propylene imine) dendrimers, *i.e.* DAB-*dendr*-$(COOMe)_n$ with n = 4–64. The Michael-addition with methyl acrylate is commonly used for the synthesis of the polyamidoamine dendrimers[1, 2] and the addition can be performed with a high selectivity, similar to that of the reaction of amine-terminated poly(propylene imine) dendrimers with acrylonitrile.[42] Excess methyl acrylate can be removed by evaporation of the reaction mixture *in vacuo*. The selectivity of this reaction can be estimated from ^{1}H-NMR and ^{13}C-NMR spectroscopy. Extra peaks can be observed in case of uncomplete Michael-addition.





Scheme 2.4: *Synthetic scheme towards carboxylate-functionalized poly(propylene imine) dendrimers* ***5a****-****5e****, with a detailed chemical structure of* ***5a*** *and* ***5d****.*

Subsequently, basic hydrolysis of the methyl ester-functionalized poly(propylene imine) dendrimers, using LiOH in a water/methanol mixture, yields carboxylate-functionalized dendrimers as white powders, denoted with DAB-*dendr*-$(COO^-Li^+)_n$ with n = 4 : **5a**; n = 8 : **5b**; n = 16 : **5c**; n = 32 : **5d**; n = 64 : **5e**. ^{1}H-NMR, ^{13}C-NMR and IR-spectra prove the chemical structure of **5a**–**5e** by the absence of methyl resonances in

NMR and a shift of the C=O vibration in IR. Strong evidency on the purity of these dendrimers is obtained from Electrospray Analysis. ESI-MS spectra of dendrimers **5a–5d** are presented in Figure 2.1. Parent peaks can be assigned to the correct products. Up to the fifth generation almost no defect structures are observed, indicative of the (high) purity of the compounds.

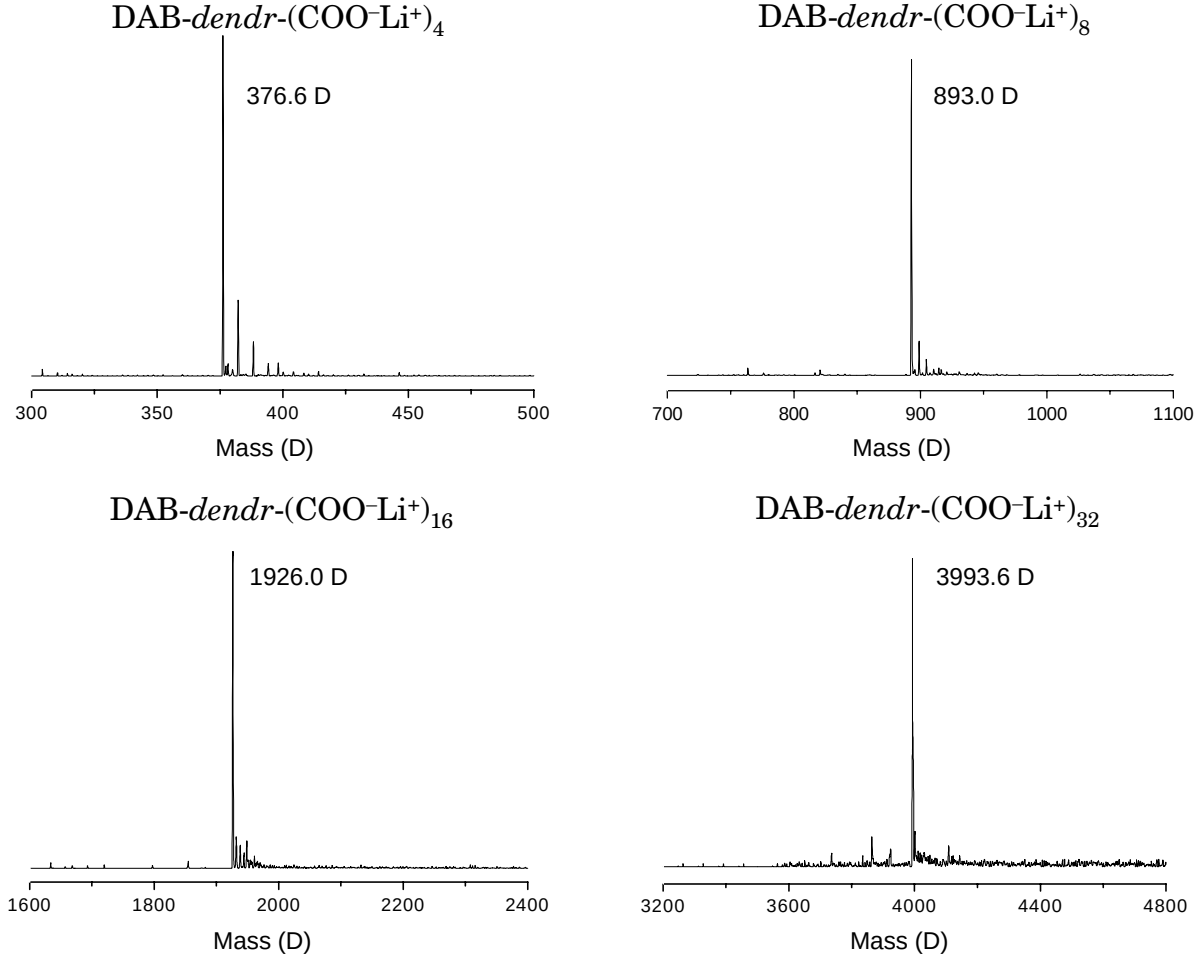


Figure 2.1: *ESI-MS spectra of carboxylate dendrimers **5a-5d,** in positive ion mode. Mass units are depicted in D.*

Unfortunately, ESI-MS analysis of the fifth generation proved unsuccessful under the conditions used; however, this is not due to an ill-defined structure as can be derived from other characterization techniques (^{1}H-NMR, ^{13}C-NMR, IR). In all cases, the parent peaks can be assigned to the theoretically predicted mass. The small peaks at higher mass can be attributed to (multiple) Li^{+}-ions, that coordinate to the carboxylate moiety and originate from the synthetic procedure. This suggests the use of these carboxylate moieties as coordinating agents (see Chapter 3). The purity of the carboxylate-dendrimers, as shown by ESI-MS is a direct proof of the high efficiency of

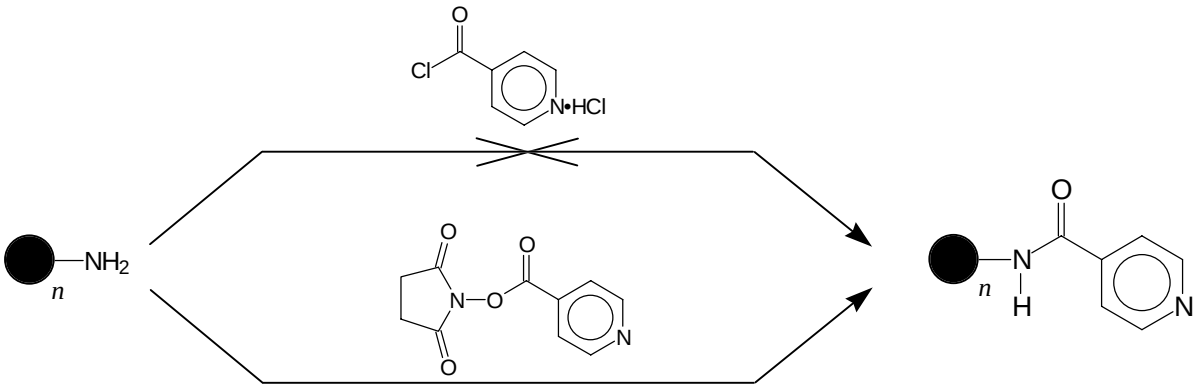
both Michael-addition and hydrolysis reaction. In conclusion, the Michael-reaction is an easy route to introduce branching and to double the amount of endgroup functionalities in the final step.

2.4 Modification of dendrimers with pyridine units

Pyridine-functionalized derivatives are commonly used in the formation of hydrogen-bonded supramolecular structures.[45–48] The hydrogen-bonding interactions can be easily tuned, for instance by changing temperature or medium. In this section, the modification of a poly(propylene imine) dendrimer with succinimidyl 4-pyridine carboxylate is not used to study such supramolecular interactions,[49] but to determine the average selectivity of the modification step, to characterize the reactivity of the activated ester with respect to the defects in the dendrimers and to study the effect of modification and work-up procedures on the purity of the functionalized poly(propylene imine) dendrimers.

2.4.1 Synthesis

The modification with 4-pyridine carboxylic acid derivatives is depicted in Scheme 2.5. The coupling of pyridine carboxylic acid derivatives with amine-terminated derivatives, failed in the case of the acid chloride route. It was impossible to obtain pure dendrimers, even though the reaction was performed in different solvents, with different additives (bases), and at different temperatures. Presumably, the presence of the basic pyridine moiety at the periphery interferes with an efficient coupling. Therefore, the synthesis of the corresponding succinimidoyl ester was performed and the coupling to the amine-terminated poly(propylene imine) dendrimers investigated. The activated ester is synthesized using DCC, N-hydroxysuccinimide and 4-pyridine carboxylic acid in DMF at moderate temperatures, due to the low solubility of 4-pyridine carboxylic acid. This reaction resulted in a black reaction mixture, but crystallization from 2-propanol afforded the pure ester. Since the ester nicely dissolves in organic media, like dichloromethane or chloroform, the reaction with the amine-terminated poly(propylene imine) dendrimers was conducted in chloroform. However, upon addition of the ester to the dendrimer-containing solution a direct precipitation of the product occurred.



n = 4, 8, 16, 32, 64

DAB-*dendr*-(NHCO-4py)$_n$ **6a–6e**

Scheme 2.5: *Modification with 4-pyridine carboxylic acid derivatives.*

Surprisingly, as indicated by ^{1}H-NMR from a disappearance of the C*H*$_2$NH$_2$ resonance at 2.8 ppm, modification was complete in less than one minute. Upon extraction of the organic phase with water, the excess activated ester stays behind whereas the pyridine-functionalized dendrimer prefers the aqueous phase. Separation of aqueous phase and subsequent addition of base, yields a precipitation of the dendrimer as a pure glassy solid. Analysis of the dendrimers with ^{1}H-NMR and ^{13}C-NMR spectroscopy indicated that the correct products were formed. No indication was found for incomplete modification, even though a direct precipitation of the dendritic product occurred. In the next section the structure of the modified poly(propylene imine) dendrimer is discussed in more detail.

2.4.2 Detailed Characterization with ESI-MS

The purity of the poly(propylene imine) dendrimers has already been fully mapped with ESI-MS spectroscopy.[22] DAB-*dendr*-(NH$_2$)$_4$ and DAB-*dendr*-(NH$_2$)$_8$ are characterized as pure organic molecules without (detectable amounts of) defects. DAB-*dendr*-(NH$_2$)$_{16}$ and DAB-*dendr*-(NH$_2$)$_{32}$ contain defects lacking one or more branches or having cyclized endgroups (Scheme 2.1). DAB-*dendr*-(NH$_2$)$_{64}$ is characterized as a well-defined macromolecule with a dendritic purity of 23% and an overall polydispersity of 1.002. Modification of the poly(propylene imine) dendrimers with pyridine yields water-soluble dendrimers and use of the same analysis technique would allow a detailed discussion on the degree of modification and the purity of dendrimer after modification. Analysis of the first and second generation pyridine-dendrimer yields monodisperse

products with peaks at 737.3 and 1614.8 amu, respectively, corresponding to the correct mass. The characterization of DAB-*dendr*-(NHCO-4py)$_{16}$ (Table 2.1) and DAB-*dendr*-(NHCO-4py)$_{32}$ (Table 2.2) is discussed in detail and their ESI-MS spectra are shown in Figure 2.2. Unfortunately, DAB-*dendr*-(NHCO-4py)$_{64}$ could not be analyzed with ESI-MS, nor with MALDI-TOF-MS. Using the latter, formation of pyrolidinium or azetidinium based fragments at approximately half of the expected mass were observed, but a detailed analysis failed due to low resolution.

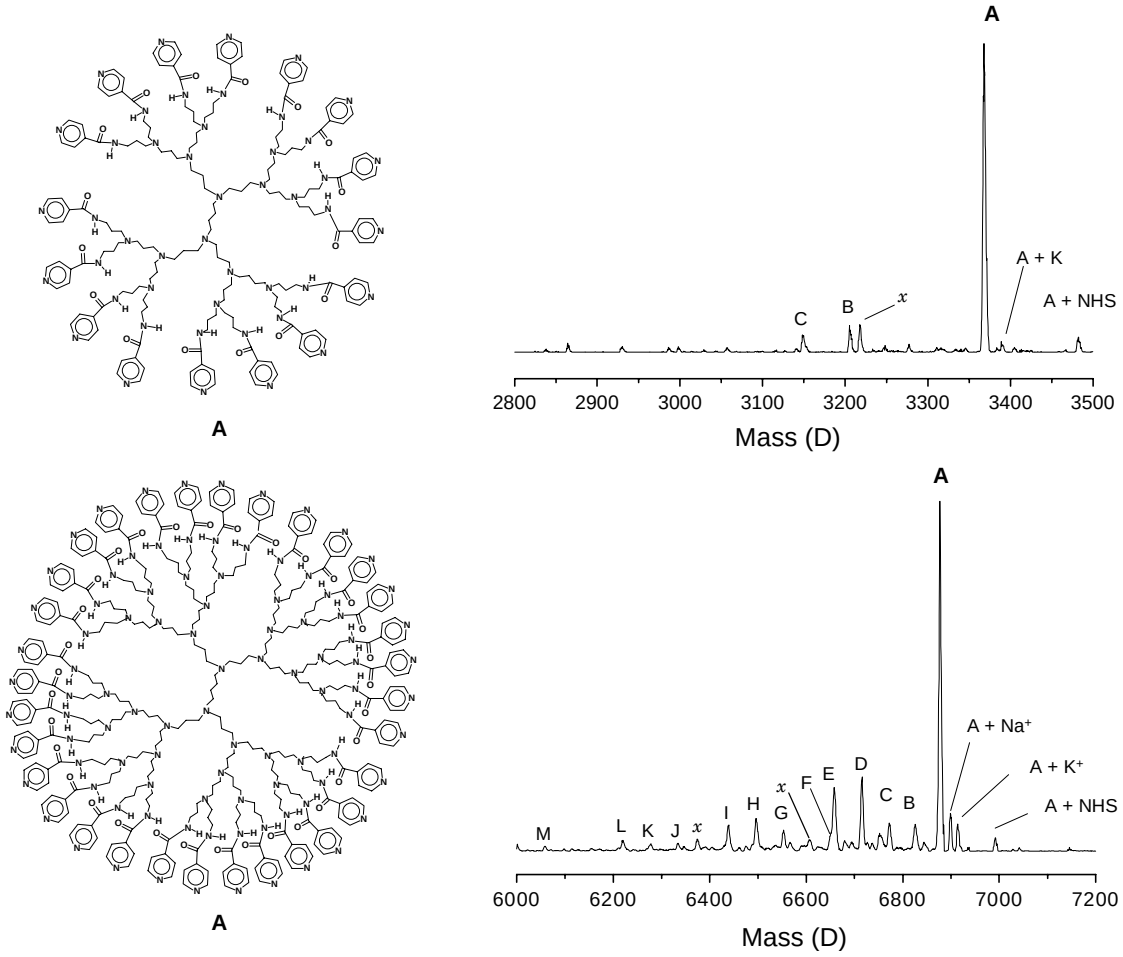


Figure 2.2: *ESI-MS spectra of a third (top) and fourth generation (bottom) pyridine dendrimer.*

The interpretation of the third generation pyridine-functionalized dendrimer reveals several features. The pure dendrimer is present as the main product and proves the high efficiency of modification. Moreover, the number of defects (B and C) is limited and can be explained from defects already present in the parent dendrimer, and no peaks are observed due to incomplete modification of the dendrimer.

Table 2.1: *Interpretation of the structure of DAB-dendr-(NHCO-4py)$_{16}$*

Observed mass (D)	Relative intensity (–)	Notation	Mass-difference (D)	Defect history
3595.8	4	A + 2 * NHS [(a)]	+ 227	pure dendrimer H-bonding with 2 molecule of NHS
3481.8	20	A + NHS	+ 113	pure dendrimer H-bonding with 1 molecule of NHS
3405.6	13	A + K^+	+ 37	pure dendrimer + K^+
3368.8	**100**	**A**	**[–]**	**pure dendrimer**
3217.8	9	*x*	– 151	not explained [(b)]
3206.6	8	B	– 162	missing one branch modification of primary amine only
3149.2	8	C	– 220	missing two branches on 1 pincer with modification

(a) NHS: N-hydroxysuccininimde. (b) Peak could not be explained from defect structures, an unknown fragmentation reaction is likely.

Furthermore, two peaks at higher mass are observed with mass differences 113 and 227 with the correct dendrimer, and are explained by interaction (hydrogen-bonding) of N-hydroxysuccinimide (NHS) with the dendrimer. Surprisingly, defect dendrimers with a cyclic structure or with three defects are not detected by ESI-MS, despite their presence in the starting dendrimer, DAB-*dendr*-$(NH_2)_{16}$. This suggests a purification due to the work-up procedure used, *i.e.* a precipitation in an aqueous medium.

Similarly, the mass spectrum of a DAB-*dendr*-$(NH_2)_{32}$ could be resolved (Table 2.2). Structural explanation of the observed peaks is shown in Figure 2.3. Since the starting dendrimer, *i.e.* DAB-*dendr*-$(NH_2)_{32}$, contains more defect structures it is even a better probe for the characterization of a modification reaction. The mass spectrum can be resolved with 15 peaks that can be assigned on the basis of defects already present in the dendritic structure and the pure dendrimer as the most abundant peak. Peaks E, I and L, which have a relatively large mass difference with the ideal dendrimers, can be explained from defect structures that were already present in the lower generations. Two peaks with a small intensity, indicated by *x*, could not be assigned, but are presumably due to an unknown fragmentation pattern. Only one peak (C) can be attributed to incomplete modification: $\Delta m = -105$ amu with a relative intensity of 10. A modification efficiency can be calculated of 99.6% $(= 100*\{1-0.1\})^{1/32}$ per amine-endgroup,

assuming that at least 90% of the dendrimer-endgroups are properly modified. The observed efficiency is even higher than an efficiency of the overall dendrimer synthesis of 99.4%. Similar to DAB-*dendr*-(NHCO-4py)$_{16}$, small peaks at higher mass are observed that are proposed to be due to interaction of N-hydroxysuccinimide with the dendritic scaffold.

Table 2.2: *Interpretation of the structure of DAB-dendr-(NHCO-4py)$_{32}$*

Observed mass (D)	**Relative intensity (–)**	**Notation**	**Mass-difference (D)**	**Defect history**
6991	4	A + NHS [(a)]	+ 114	pure dendrimer H-bonding with 1 NHS-molecule
6914	16	A + K^+	+37	pure dendrimer + K^+
6900	7	A + Na^+	+ 23	pure dendrimer + Na^+
6877	**100**	**A**	**[–]**	**pure dendrimer**
6826	11	B	– 51	missing one branch; modification of primary and secondary amine
6772	10	C	– 105	missing modification
6715	29	D	– 162	missing one branch modification of primary amine only
6658	26	E	– 219	missing two branches on 1 pincer with modification
6652	7	F	– 225	cyclic structure no modification
6623	3	*x*	– 254	not explained [(b)]
6553	7	G	– 324	2 times D [(c)]
6496	13	H	– 381	1 time D + E [(c)]
6439	10	I	– 438	2 times E
6376	4	*x*	– 501	not explained [(b)]
6334	3	J	– 543	2 times D and 1 time E
6277	2	K	– 600	1 time D and 2 times E
6220	4	L	– 657	3 times E
6058	4	M	– 819	1 time D and 3 times E

(a) NHS: N-hydroxysuccinimide. (b) Peak could not be explained from defect structures; an unknown fragmentation reaction is likely. (c) Abbreviation is used to explain multiple defect structures. A reference is made to peaks D and E and their defect history.

Peak B is the only evidence for reaction of the activated ester with a secondary amine-defect. On the contrary, peaks D, F, H, I, L, M and O can be explained by a modification of the primary amine only, while no reaction with the secondary amine takes place. This indicates that the N-hydroxysuccinimide ester is rather selective to

modification of the primary amines and that, in theory, the secondary amine defects can be used as a reactive handle for a subsequent modification reaction.

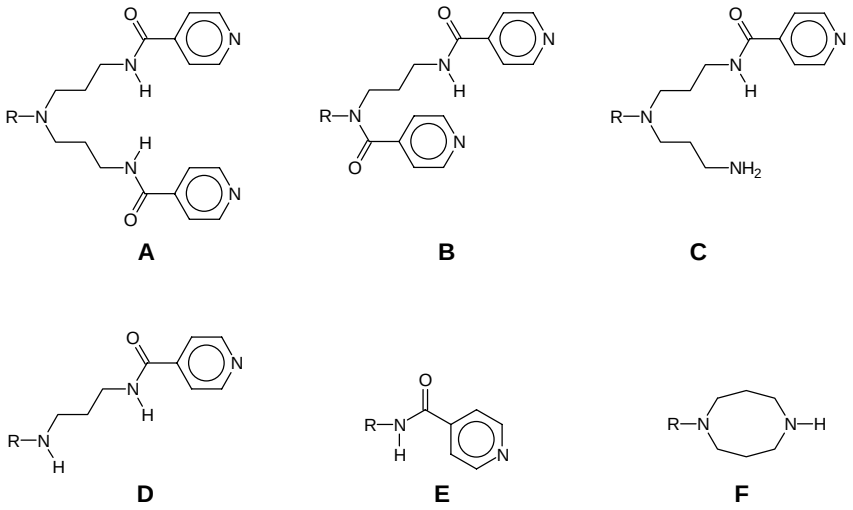


Figure 2.3: *Explanation of the defect structures for DAB-dendr-(NHCO-4py)$_{32}$. Notation is adopted from Table 2.2.*

2.5 Overall Conclusions

The commercially available amine-terminated poly(propylene imine) dendrimers are an ideal synthetic handle for modification reactions. Coupling reactions with acidic or isocyanate functionalities or with Michael-type reagents proceed in high selectivity. The modification steps that are used in principle allow coupling of almost every type of endgroup to the dendritic scaffold. Important to note is that in all cases, the type and polarity of the endgroup determines the work-up procedure that can or must be used (see also Experimental Section in Chapter 5 and 6). Modification with the succinimidyl ester of 4-pyridinecarboxylic acid, is used as an example to illustrate the efficiency of the modification reaction, which proceeds in efficiencies even higher than that of the dendrimer synthesis. Furthermore it has been proven that the coupling reagent is rather selective to the type of amine that is functionalized. Whereas all primary amines can be modified, the secondary amines are still available for further modification-steps.

2.6 Experimental Section

General Methods and Materials

The amine-terminated poly(propylene imine) dendrimers, DAB-*dendr*-$(NH_2)_n$ (n = 4, 8, 16, 32, 64), were kindly provided by DSM Research (Geleen, The Netherlands) and used as received. All solvents used, dimethoxyethane, dimethylformamide (DMF), 2-propanol, dichloromethane, chloroform, tetrahydrofuran (THF), diethyl ether, methanol and toluene were of p.a. quality. THF was distilled over Na/K/benzophenone under an argon atmosphere, prior to use. Water was de-ionized before use. Triethylamine (Fluka, p.a) was

stored on KOH-pellets. LiCl (98 %, Merck), $LiOH{\cdot}H_2O$ (99 %, Acros Chimica), methyl acrylate (99 %, Merck), hydrochloric acid (37+ %, Vel), palmitoylchloride (Aldrich, 98%), 1-adamantane carboxylic acid (Acros, 99%), N-hydroxysuccinimide (Acros, 98+%), 1,3-dicyclohexylcarbodiimide (DCC) (Aldrich, 99%), 1-adamantyl isocyanate (Aldrich, 98%), hexadecyl isocyanate (Aldrich, 97%).LiCl (98 %, Merck), potassium carbonate (Acros, p.a.) and 4-pyridinecarboxylic acid (Acros, 99%) were used as received. FAB MS and MALDI-TOF MS measurements were performed at the University of Copenhagen, and the University of Berkeley, respectively.

^{1}H-NMR and ^{13}C-NMR Spectroscopy

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-400 spectrometer at 400.13 MHz and 100.62 MHz respectively. Chemical shifts are given in ppm (δ) relative to TMS. All spectra were recorded at 298 K with unless noted otherwise. COSY spectra using standard software were recorded to elucidate structure of urea-functionalized dendrimers **3a**-**3e** and **4a**-**4e**.

IR Spectroscopy

Infrared spectra were recorded at 298 K on a Perkin Elmer 1605 IR spectrophotometer operating between 4400 and 450 cm^{-1} using KBr pellets.

Electrospray Ionisation Mass Spectrometry

Electrospray mass spectra were recorded on a API 300 MS/MS mass spectrometer (PE-Sciex, Foster City, USA). Preparation and measurement of the samples were performed analogous to the ones in previous publications.[22] The mass spectrometer was used in positive ion mode. Electrospray data were deconvoluted to yield the resulting ESI-MS spectra.

Elemental Analysis

All measurements were run on a Perkin Elmer 2400 Series CHNS/O analyzer.

Melting Points

Melting points were determined on a Büchi Schmelzpunktbestimmungsapparat (nach Dr. Tottoli).

Synthesis of succinimidyl 1-adamantanecarboxylate[50]

To a solution of adamantane-carboxylic acid (9.0 g, 0.050 mol) in dimethoxyethane (50 ml) is added 5.81 g N-hydroxysuccinimide (0.051 mol, 1.01 eq). After cooling the solution in an ice-bath to 5°C, 11.3 g of 1,3-dicyclocarbodiimide (0.055 mol, 1.10 eq) is added and the reaction mixture is stirred for 16 h. The precipitate (DHU) is filtered off and the filtrate evaporated *in vacuo*, yielding the crude ester. Crystallisation in 2-propanol yielded pure succinimidyl 1-adamantane carboxylate as a white solid (9.88 g, 71%). ^{1}H-NMR ($CDCl_3$): δ = 1.76 (6H, *H*-4), 2.09 (s, 9H, *H*-3 {3H} + *H*-2 {6H}), 2.82 (s, 4H, (CH_2)$_2$); ^{13}C-NMR ($CDCl_3$): δ = 25.6 (2C, (CH_2)$_2$), 27.6 (3C, *C*–3), 36.1 / 38.4 (6C, *C*–2 {3C} + *C*–4 {3C}], 40.4 (1C, *C*–1), 169.2 (2C, *C*O), 172.2 (1C, *C*OO); IR (KBr): ν (cm^{-1}) = 2905 (C–H sat), 1778 (C=O), 1741 (C=O ester).

Typical Procedure for Adamantyl Dendrimers with an Amide-Linkage: DAB-*dendr*-(NHCO-Ad)$_{16}$, 1c

To a solution of DAB-*dendr*-(NH_2)$_{16}$ (200 mg, 0.12 mmol) in CH_2Cl_2 (15 mL) is added 1-succinimidoyl adamantane carboxylate (653 mg, 2.372 mmol). After stirring the reaction mixture for 24 h an equal volume of a NaOH solution (1 M) is added. After vigorous stirring of the two phase system for 16 h, the organic phase is extracted and the solvent is evaporated in vacuo to yield the crude product as a white foam. The product is taken up in a CH_2Cl_2 / MeOH mixture (99:1 v/v) and filtrated over silica to remove residual salts, yielding **1c** (350 mg, 69%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.54 (m, 24H, $NCH_2CH_2CH_2N$), 1.62 (q, 32H, $NCH_2CH_2CH_2NHCO$) 1.67/1.70/1.73/1.76 (96H, *H*-4), 1.85 (96H, *H*-2), 2.03 (48H, *H*-3), 2.38-2.43 (m, 84H, $NCH_2CH_2CH_2CH_2N$ {4H} + $NCH_2CH_2CH_2N$ {48H} + $NCH_2CH_2CH_2NHCO$ {32H}), 3.29 (q, 32H, $NCH_2CH_2CH_2NHCO$), 6.67 (t, 16H, N*H*CO); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.7 (12C, $NCH_2CH_2CH_2N$), 25.1 (2C, $NCH_2CH_2CH_2CH_2N$), 26.8 (16C, $NCH_2CH_2CH_2NHCO$), 28.2 (48C, *C-3*), 36.6 / 39.4 (96C, *C*-2 {48C} + *C*-4 {48C}), 38.3 (16C, $NCH_2CH_2CH_2NHCO$), 40.5 (16C, *C*-1), 52.0 (16C, $NCH_2CH_2CH_2NHCO$), 52.1 (8C, $NCH_2CH_2CH_2N$), 52.3 / 52.5 (8C, $NCH_2CH_2CH_2N$), 52.6 (8C, $NCH_2CH_2CH_2N$), 54.4 (2C, $NCH_2CH_2CH_2CH_2N$), 178.1 (16C, NH*C*O); IR (KBr): ν (cm^{-1}) = 3299.0 (N–H stretch), 2903.6 (C–H sat), 1636.4 (C=O); FAB-MS: Calcd. for $C_{264}H_{432}N_{30}O_{16}$: 4285.5. Found 4281.8.

DAB-*dendr*-(NHCO-Ad)$_4$, 1a

^{1}H-NMR ($CDCl_3$): δ = 1.41 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.61 (q, 8H, $NCH_2CH_2CH_2NHCO$), 1.67/1.70/1.73/1.76 (24H, *H*-4), 1.85 (24H, *H*-2), 2.03 (12H, *H*-3), 2.38 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 2.43 (t, 8H, $NCH_2CH_2CH_2NHCO$), 3.29 (dt, 8H, $NHCH_2CH_2CH_2NHCO$), 6.40 (t, 4H, NHCO); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.9 (2C, $NCH_2CH_2CH_2CH_2N$), 26.8 (4C, $NCH_2CH_2CH_2N$), 28.1 (12C, *C*-3), 36.6 (12C, *C*-2), 38.3 (4C, *C*-1), 39.3 (12C, *C*-4), 40.5 (4C, $NCH_2CH_2CH_2NHCO$), 52.0 (4C, $NCH_2CH_2CH_2NHCO$), 54.1 (2C, $NCH_2CH_2CH_2CH_2N$), 178.0 (4C, NHCO); IR (KBr): ν (cm^{-1}) = 3354.4 (N–H stretch), 2904.0 (C–H sat.), 1636.4 (C=O); FAB-MS: Calcd. for $C_{60}H_{96}N_6O_4$: 965.46. Found 965.44 $[M+H]^+$.

DAB-*dendr*-(NHCO-Ad)$_8$, 1b

^{1}H-NMR ($CDCl_3$): δ = 1.36 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.54 (m, 8H, $NCH_2CH_2CH_2N$), 1.61 (q, 16H, $NCH_2CH_2CH_2NHCO$) 1.67/1.70/1.73/1.76 (48H, *H*-4), 1.85 (48H, *H*-2), 2.03 (24H, *H*-3), 2.37 (m, 20H, $NCH_2CH_2CH_2CH_2N$ {4H} + $NCH_2CH_2CH_2N$ {16H}), 2.42 (t, 16H, $NCH_2CH_2CH_2NHCO$), 3.29 (q, 16H, $NCH_2CH_2CH_2NHCO$), 6.56 (t, 8H, NHCO); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 24.7 (4C, $NCH_2CH_2CH_2N$), 25.1 (2C, $NCH_2CH_2CH_2CH_2N$), 26.8 (8C, $NCH_2CH_2CH_2NHCO$), 28.2 (24C, *C*-3), 36.6 / 39.4 (48C, *C*-2 {24C} + *C*-4 {24C}), 38.3 (8C, $NCH_2CH_2CH_2NHCO$), 40.5 (8C, *C*-1), 52.1 (12C, $NCH_2CH_2CH_2N$ {4C} + $NCH_2CH_2CH_2NHCO$ {8C}), 52.6 ($NCH_2CH_2CH_2N$), 54.2 (2C, $NCH_2CH_2CH_2CH_2N$), 178.1 (8C, NHCO); IR (KBr): ν (cm^{-1}) = 3355.9 (N–H stretch), 2903.6 (C–H sat.), 1636.4 (C=O); FAB-MS: Calcd. for $C_{128}H_{208}N_{14}O_8$: 2071.1. Found 2071.87 $[M+H]^+$.

DAB-*dendr*-(NHCO-Ad)$_{32}$, 1d

^{1}H-NMR ($CDCl_3$): δ = 1.38 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.50-1.65 (m, 120H, $NCH_2CH_2CH_2N$ {56H} + $NCH_2CH_2CH_2NHCO$ {64H}), 1.67/1.70/1.72/1.75 (192H, *H*-4), 1.86 (192H, *H*-2), 2.02 (96H, *H*-3), 2.38-2.43 (m, 180H, $NCH_2CH_2CH_2CH_2N$ {4H} + $NCH_2CH_2CH_2N$ {112H} + $NCH_2CH_2CH_2NHCO$ {64H}), 3.29 (q, 64H, $NCH_2CH_2CH_2NHCO$), 6.81 (t, 32H, NHCO); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.3 (12C, $NCH_2CH_2CH_2N$), 24.5 (16C, $NCH_2CH_2CH_2N$), 24.9 (2C, $NCH_2CH_2CH_2CH_2N$), 26.8 (32C, $NCH_2CH_2CH_2NHCO$), 28.1 (96C, *C*-3), 36.6 / 39.4 (192C, *C*-2 {96H} + *C*-4 {96C}), 38.1 (32C, $NCH_2CH_2CH_2NHCO$), 40.5 (32C, *C*-1), 51.9 (32C, $NCH_2CH_2CH_2NHCO$), 52.0 / 52.5 (56C, $NCH_2CH_2CH_2N$), 54.4 (2C, $NCH_2CH_2CH_2CH_2N$), 178.0 (32C, NHCO); IR (KBr): ν (cm^{-1}) = 3357.9 (N–H stretch), 2904.0 (C–H sat.), 1636.0 (C=O).

DAB-*dendr*-(NHCO-Ad)$_{64}$, 1e

^{1}H-NMR ($CDCl_3$): δ 1.38 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.50-1.65 (m, 368H, $NCH_2CH_2CH_2N$ {120H} + $NCH_2CH_2CH_2NHCO$ {128H}), 1.66/1.69/1.72/1.75 (384H, *H*-4), 1.86 (384H, *H*-2), 2.02 (192H, *H*-3), 2.30-2.55 (m, 372H, $NCH_2CH_2CH_2CH_2N$ {4H} + $NCH_2CH_2CH_2N$ {240H} + $NCH_2CH_2CH_2NHCO$ {128H}), 3.28 (br., 128H, $NCH_2CH_2CH_2NHCO$), 6.95 (t, 64H, NHCO); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.4 (28C, $NCH_2CH_2CH_2N$ {16C+8C+4C}), 24.7 (32C, $NCH_2CH_2CH_2N$), 25.0 (2C, $NCH_2CH_2CH_2CH_2N$), 26.9 (64C, $NCH_2CH_2CH_2NHCO$), 28.2 (192C, *C*-3), 36.6 / 39.3 (192C, *C*-2 {96C} + *C*-4 {96C}), 38.2 (64C, $NCH_2CH_2CH_2NHCO$), 40.5 (64C, *C*-1), 51.9 (64C, $NCH_2CH_2CH_2NHCO$), 52.0-52.5 (120C, $NCH_2CH_2CH_2N$), 54.4 (2C, $NCH_2CH_2CH_2CH_2N$), 178.1 (64C, NHCO); IR (KBr): ν (cm^{-1}) = 3354.4 (N–H stretch), 2904.0 (C–H sat.), 1636.4 (C=O).

Typical Procedure for Alkyl-Chain Modified Dendrimers with an Amide-Linkage: DAB-*dendr*-(NHCO-$C_{15}H_{31}$)$_{16}$, 2c

Triethylamine (41.8 g, 0.41 mol) was added to a solution of DAB-*dendr*-$(NH_2)_{16}$ (6.23 g, 3.69 mmol) in THF (300 mL). Palmitoylchloride (22.8 g, 0.083 mol) was slowly added over a period of 10 minutes. After stirring for 43 h, the turbid solution was evaporated *in vacuo*. The residue was refluxed with a NaOH solution (1 M, 300 ml) during 2.5 h. The solution was precipitated into a NaOH solution (1 M, 2.5 l). The precipitate was washed with a NaOH solution (1 M, 300 mL) and consequently with demineralized water, yielding the crude product. Refluxing the product in diethyl ether and centrifugation was necessary to remove salts. After decanting of the solution, the residue was mixed with diethyl ether and centrifuged again. The combined organic phases were evaporated *in vacuo*, yielding **2c** (15.0 g, 73.9 %) as a yellowish product. This product was pure according to ^{1}H-NMR, ^{13}C-NMR and IR. An analytically pure sample for Elemental Analysis was obtained by dissolving the sample in chloroform and subsequent precipitation in acetone. ^{1}H-NMR ($CDCl_3$): δ = 0.88 (t, 48H, $CH_3(CH_2)_{14}CONH$), 1.18-1.75 (m, 476H, $CH_3(CH_2)_{13}CH_2CONH$ {416H} + $NCH_2CH_2CH_2CH_2N$ {4H} + $NCH_2CH_2CH_2N$ {24H} + $NCH_2CH_2CH_2NHCO$ {32H}), 2.16 (t, 32H, $CH_3(CH_2)_{13}CH_2CONH$), 2.31-2.45 (m, 84H, $NCH_2CH_2CH_2CH_2N$ {4H} + $NCH_2CH_2CH_2N$ {48H} +

$NC\mathit{H}_2CH_2CH_2NHCO$ {32H}), 3.25 (q, 32H, $NCH_2CH_2C\mathit{H}_2NHCO$), 7.26 (t, 16H, $N\mathit{H}CO$); ^{13}C-NMR (MHz, $CDCl_3$): δ = 14.1 (16C, $\mathit{C}H_3(CH_2)_{14}CONH$), 22.7 (16C, $CH_3\mathit{C}H_2(CH_2)_{13}CONH$), 24.9 (14C, $NCH_2\mathit{C}H_2\mathit{C}H_2CH_2N$ {2C} + $NCH_2\mathit{C}H_2CH_2N$ {12C}), 26.0 (16C, $CH_3(CH_2)_{12}\mathit{C}H_2CH_2CONH$), 27.1 (16C, $NCH_2\mathit{C}H_2CH_2NHCO$), 29.3-29.7 (160 C, $CH_3CH_2(\mathit{C}H_2)_{10}CH_2CH_2CONH$), 31.9 (16C, $CH_3CH_2\mathit{C}H_2(CH_2)_{12}CONH$), 36.7 (16C, $CH_3(CH_2)_{12}CH_2\mathit{C}H_2CONH$), 37.8 (16C, $NCH_2CH_2\mathit{C}H_2NHCO$), 51.4 (16C, $N\mathit{C}H_2CH_2CH_2NHCO$), 52.2 (24C, $N\mathit{C}H_2CH_2\mathit{C}H_2N$), 54.5 (2C, $N\mathit{C}H_2CH_2CH_2\mathit{C}H_2N$), 173.8 (16C, $NH\mathit{C}O$); IR (KBr): ν (cm^{-1}) = 3299.0 (N–H stretch), 2918.1 (C–H sat.); 1639.9 (C=O); Anal. Calcd. for $C_{344}H_{688}N_{30}O_{16}$: C 75.10, H 12.60, N 7.64. Found: C 74.86 H 12.59 N 7.72; FAB-MS: Calcd. for $C_{344}H_{688}N_{30}O_{16}$: 5501.49. Found 5500.1.

DAB-*dendr*-(NHCO-$C_{15}H_{31}$)$_4$, 2a

^{1}H-NMR ($CDCl_3$): δ = 0.88 (t, 12H, $C\mathit{H}_3(CH_2)_{14}CONH$), 1.18-1.62 (m, 116H, $CH_3(C\mathit{H}_2)_{13}CH_2CONH$ {104H} + $NCH_2C\mathit{H}_2C\mathit{H}_2CH_2N$ {4H} + $NCH_2C\mathit{H}_2CH_2NHCO$ {8H}), 2.15 (t, 8H, $CH_3(CH_2)_{13}C\mathit{H}_2CONH$), 2.31-2.45 (m, 12H, $NC\mathit{H}_2CH_2CH_2C\mathit{H}_2N$ {4H} + $NC\mathit{H}_2CH_2CH_2NHCO$ {8H}), 3.28 (q, 8H, $NCH_2CH_2C\mathit{H}_2NHCO$), 6.51 (t, 4H, $N\mathit{H}CO$); ^{13}C-NMR ($CDCl_3$): δ = 14.1 (4C, $\mathit{C}H_3(CH_2)_{14}CONH$), 22.7 (4C, $CH_3\mathit{C}H_2(CH_2)_{13}CONH$), 25.1 (2C, $NCH_2\mathit{C}H_2\mathit{C}H_2CH_2N$), 25.9 (4C, $CH_3(CH_2)_{12}\mathit{C}H_2CH_2CONH$), 27.1 (4C, $NCH_2\mathit{C}H_2CH_2NHCO$), 29.5-29.7 (40 C, $CH_3CH_2(\mathit{C}H_2)_{10}CH_2CH_2CONH$), 31.9 (4C, $CH_3CH_2\mathit{C}H_2(CH_2)_{12}CONH$), 36.9 (4C, $CH_3(CH_2)_{12}CH_2\mathit{C}H_2CONH$), 38.2 (4C, $NCH_2CH_2\mathit{C}H_2NHCO$), 52.0 (4C, $N\mathit{C}H_2CH_2CH_2NHCO$), 53.9 (2C, $N\mathit{C}H_2CH_2CH_2\mathit{C}H_2N$), 173.4 (4C, $NH\mathit{C}O$); IR (KBr): ν (cm^{-1}) = 3319.2 (N–H stretch), 2918.2 (C–H sat.), 1638.4 (C=O); Anal. Calcd. for $C_{80}H_{160}N_6O_4$: C 75.65, H 12.70, N 6.62. Found: C 75.79 H 12.77 N 6.59; FAB-MS: Calcd. for $C_{344}H_{688}N_{30}O_{16}$: 1270.2. Found 1270.0 $(M+H)^+$.

DAB-*dendr*-(NHCO-$C_{15}H_{31}$)$_8$, 2b

^{1}H-NMR ($CDCl_3$): δ = 0.90 (t, 24H, $C\mathit{H}_3(CH_2)_{14}CONH$), 1.18-1.75 (m, 236H, $CH_3(C\mathit{H}_2)_{13}CH_2CONH$ {208H} + $NCH_2C\mathit{H}_2C\mathit{H}_2CH_2N$ {4H} + $NCH_2C\mathit{H}_2CH_2N$ {8H} + $NCH_2C\mathit{H}_2CH_2NHCO$ {16H}), 2.17 (t, 16H, $CH_3(CH_2)_{13}C\mathit{H}_2CONH$), 2.31-2.45 (m, 36H, $NC\mathit{H}_2CH_2CH_2C\mathit{H}_2N$ {4H} + $NC\mathit{H}_2CH_2C\mathit{H}_2N$ {16H} + $NC\mathit{H}_2CH_2CH_2NHCO$ {16H}), 3.28 (q, 16H, $NCH_2CH_2C\mathit{H}_2NHCO$), 6.95 (t, 8H, $N\mathit{H}CO$); ^{13}C-NMR ($CDCl_3$): δ = 14.1 (8C, $\mathit{C}H_3(CH_2)_{14}CONH$), 22.7 (8C, $CH_3\mathit{C}H_2(CH_2)_{13}CONH$), 24.9 (6C, $NCH_2\mathit{C}H_2\mathit{C}H_2CH_2N$ {2C} + $NCH_2\mathit{C}H_2CH_2N$ {4C}), 26.0 (8C, $CH_3(CH_2)_{12}\mathit{C}H_2CH_2CONH$), 27.1 (8C, $NCH_2\mathit{C}H_2CH_2NHCO$), 29.4-29.7 (80 C, $CH_3CH_2(\mathit{C}H_2)_{10}CH_2CH_2CONH$), 31.9 (8C, $CH_3CH_2\mathit{C}H_2(CH_2)_{12}CONH$), 36.8 (8C, $CH_3(CH_2)_{12}CH_2\mathit{C}H_2CONH$), 37.9 (8C, $NCH_2CH_2\mathit{C}H_2NHCO$), 51.6 (8C, $N\mathit{C}H_2CH_2CH_2NHCO$), 52.2 (8C, $N\mathit{C}H_2CH_2\mathit{C}H_2N$), 54.5 (2C, $N\mathit{C}H_2CH_2CH_2\mathit{C}H_2N$), 173.6 (8C, $NH\mathit{C}O$); IR (KBr): ν (cm^{-1}) = 3319.2 (N–H stretch), 2918.2 (C–H sat.); 1638.4 (C=O); Anal. Calcd. for $C_{168}H_{336}N_{14}O_8$: C 75.65, H 12.70, N 6.62. Found: C 75.79 H 12.77 N 6.59; FAB-MS: Calcd. for $C_{168}H_{336}N_{14}O_8$: 2680.61. Found 2680.59 $(M+H)^+$.

DAB-*dendr*-(NHCO-$C_{15}H_{31}$)$_{32}$, 2d

^{1}H-NMR ($CDCl_3$): δ = 0.88 (t, 96H, $C\mathit{H}_3(CH_2)_{14}CONH$), 1.20-1.70 (m, 956H, $CH_3(C\mathit{H}_2)_{13}CH_2CONH$ {832H} + $NCH_2C\mathit{H}_2C\mathit{H}_2CH_2N$ {4H} + $NCH_2C\mathit{H}_2CH_2N$ {56H} + $NCH_2C\mathit{H}_2CH_2NHCO$ {64H}), 2.16 (t, 64H, $CH_3(CH_2)_{13}C\mathit{H}_2CONH$), 2.31-2.45 (m, 180H, $NC\mathit{H}_2CH_2CH_2C\mathit{H}_2N$ {4H} + $NC\mathit{H}_2CH_2C\mathit{H}_2N$ {112H} + $NC\mathit{H}_2CH_2CH_2NHCO$ {64H}), 3.25 (q, 64H, $NCH_2CH_2C\mathit{H}_2NHCO$), 7.42 (t, 32H, $N\mathit{H}CO$); ^{13}C-NMR ($CDCl_3$): δ = 14.1 (32C, $\mathit{C}H_3(CH_2)_{14}CONH$), 22.7 (32C, $CH_3\mathit{C}H_2(CH_2)_{13}CONH$), 26.0 (32C, $CH_3(CH_2)_{12}\mathit{C}H_2CH_2CONH$), 27.1 (32C, $NCH_2\mathit{C}H_2CH_2NHCO$), 29.4-29.8 (320C, $CH_3CH_2(\mathit{C}H_2)_{10}CH_2CH_2CONH$), 31.9 (32C, $CH_3CH_2\mathit{C}H_2(CH_2)_{12}CONH$), 36.6 (32C, $CH_3(CH_2)_{12}CH_2\mathit{C}H_2CONH$), 37.7 (32C, $NCH_2CH_2\mathit{C}H_2NHCO$), 51.4 (32C, $N\mathit{C}H_2CH_2CH_2NHCO$), 52.3 (56C, $N\mathit{C}H_2CH_2\mathit{C}H_2N$), 173.9 (32H, $NH\mathit{C}O$); IR (KBr): ν (cm^{-1}) = 3300.4 (N–H stretch), 2918.0 (C–H sat.); 1637.0 (C=O).

DAB-*dendr*-(NHCO-$C_{15}H_{31}$)$_{64}$, 2e

^{1}H-NMR ($CDCl_3$): δ = 0.89 (t, 192H, $C\mathit{H}_3(CH_2)_{14}CONH$), 1.20-1.75 (m, 1916H, $CH_3(C\mathit{H}_2)_{13}CH_2CONH$ {1664H} + $NCH_2C\mathit{H}_2C\mathit{H}_2CH_2N$ {4H} + $NCH_2C\mathit{H}_2CH_2N$ {120H} + $NCH_2C\mathit{H}_2CH_2NHCO$ {128H}), 2.19 (br. t, 128H, $CH_3(CH_2)_{13}C\mathit{H}_2CONH$), 2.31-2.45 (m, 372H, $NC\mathit{H}_2CH_2CH_2C\mathit{H}_2N$ {4H} + $NC\mathit{H}_2CH_2C\mathit{H}_2N$ {240H} + $NC\mathit{H}_2CH_2CH_2NHCO$ {128H}), 3.25 (br. t, 128H, $NCH_2CH_2C\mathit{H}_2NHCO$), 7.64 (s, 64H, $N\mathit{H}CO$); ^{13}C-NMR ($CDCl_3$): δ = 14.1 (64C, $\mathit{C}H_3(CH_2)_{14}CONH$), 22.7 (64C, $CH_3\mathit{C}H_2(CH_2)_{13}CONH$), 26.1 (64C, $CH_3(CH_2)_{12}\mathit{C}H_2CH_2CONH$), 27.2 (64C, $NCH_2\mathit{C}H_2CH_2NHCO$), 29.4-29.8 (640C, $CH_3CH_2(\mathit{C}H_2)_{10}CH_2CH_2CONH$), 31.9 (64C, $CH_3CH_2\mathit{C}H_2(CH_2)_{12}CONH$), 36.6 (64C, $CH_3(CH_2)_{12}CH_2\mathit{C}H_2CONH$), 37.6 (64C, $NCH_2CH_2\mathit{C}H_2NHCO$), 51.3 (64C, $N\mathit{C}H_2CH_2CH_2NHCO$), 52.2 (120C, $N\mathit{C}H_2CH_2\mathit{C}H_2N$), 174.0 (64C, $NH\mathit{C}O$); IR (KBr): ν (cm^{-1}) = 3299.8 (N-H stretch), 2917.0 (C-H sat.); 1640.6 (C=O), Anal. Calcd. for $C_{1400}H_{2800}N_{126}O_{64}$ (22426.34): C 74.98, H 12.58, N 7.87. Found: C 74.51, H 12.57 N 7.83.

Typical Procedure for Adamantyl Dendrimers with an Urea-Linkage: DAB-*dendr*-(NHCONH-Ad)$_{16}$, 3c

To a solution of DAB-*dendr*-$(NH_2)_{16}$ (0.50 g, 0.30 mmol) in chloroform (10 ml) is added 1-adamantyl isocyanate (0.88 g, 4.98 mmol, 1.1 eq. per NH_2). After stirring for 2 h the homogeneous solution is precipitated in diethyl ether to remove excess isocyanate. The precipitate is filtered off and dried *in vacuo*, yielding pure **3c** (1.11 g, 83%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ = 1.41 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.58 (m, 56H, $NCH_2CH_2CH_2NHCONH$ {32H} + $NCH_2CH_2CH_2N$ (24H}) 1.65 (s, 96H, *H*-2), 1.98 (s, 96H, *H*-4), 2.05 (s, 48H, *H*-3), 2.40 (m, 84H, $NCH_2CH_2CH_2NHCONH$ {32H} + $NCH_2CH_2CH_2N$ {48H} + $NCH_2CH_2CH_2CH_2N$ {4H}, 3.13 (s, 32H, $NCH_2CH_2CH_2NHCONH$), 5.41 (s, 16H, $CH_2NHCONH$), 6.15 (s, 16H, $CH_2NHCONH$); ^{13}C-NMR: δ = 25.0 (12C, $NCH_2CH_2CH_2N$), 26.3 (2C, $NCH_2CH_2CH_2CH_2N$), 28.3 (16C, $NCH_2CH_2CH_2NHCONH$), 29.8 (48C, *C*-2), 36.7 (48C, *C*-3), 38.4 (16C, $NCH_2CH_2CH_2NHCONH$), 42.9 (48C, *C*–4), 50.7 (16C, *C*-1), 52.0 (16C, $NCH_2CH_2CH_2NHCONH$), 52.6 (24C, $NCH_2CH_2CH_2N$), 54.5 (2C, $NCH_2CH_2CH_2CH_2N$), 158.7 (16C, NHCONH); IR (KBr): ν (cm)$^{-1}$ = 3362.0 (N–H stretch), 2906.0, (C–H sat), 1640.6 (C=O); FAB-MS: Calcd. for $C_{264}H_{448}N_{36}O_{16}$: 4522.7. Found 4522.9.

DAB-*dendr*-(NHCONH-Ad)$_4$, 3a

^{1}H-NMR ($CDCl_3$): δ = 1.41 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.62 (q, 8H, $NCH_2CH_2CH_2NHCONH$), 1.65 (s, 24H, *H*-2), 1.93 (s, 24H, *H*-4), 2.03(s, 12H, *H*-3), 2.35 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 2.40 (t, 8H, $NCH_2CH_2CH_2NHCONH$), 3.17 (q, 8H, $NCH_2CH_2CH_2NHCONH$), 5.07 (s, 4H, $CH_2NHCONH$), 5.76 (t, 4H, $CH_2NHCONH$); ^{13}C-NMR ($CDCl_3$) : δ = 24.6 (2C, $NCH_2CH_2CH_2CH_2N$), 27.9 (4C, $NCH_2CH_2CH_2NHCONH$), 29.6 (12C, *C*-3), 36.5 (12C, *C*-2), 38.3 (4C, $NCH_2CH_2CH_2NHCONH$), 42.6 (12C, *C*-4), 50.5 (4C, *C*-1), 51.8 (4C, $NCH_2CH_2CH_2NHCONH$), 53.6 (2C, $NCH_2CH_2CH_2CH_2N$), 158.5 (4C, NHCONH); IR (KBr): ν (cm)$^{-1}$ = 3357.9 (N–H stretch), 2915.0, (C–H sat), 1645.0 (C=O); FAB-MS: Calcd. for $C_{60}H_{100}N_{10}O_4$: 1025.5. Found 1025.9.

DAB-*dendr*-(NHCONH-Ad)$_8$, 3b

^{1}H-NMR ($CDCl_3$): δ = 1.41 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.54 (s, 8H, $NCH_2CH_2CH_2N$), 1.60 (q, 16H, $NCH_2CH_2CH_2NHCONH$), 1.65 (s, 48H, *H*-2), 2.00 (s, 48H, *H*-4), 2.05 (s, 24H, *H*-3), 2.35 (m, 36H, $NCH_2CH_2CH_2NHCONH$ {16H} + $NCH_2CH_2CH_2N$ {16H} + 16H $NCH_2CH_2CH_2CH_2N$ {4H}, 3.14 (q, 16H, $NCH_2CH_2CH_2NHCONH$), 5.25 (s, 8H, $CH_2NHCONH$), 5.95 (s, 8H, $CH_2NHCONH$); ^{13}C-NMR : δ = 24.5 (6C, $NCH_2CH_2CH_2N$ {4C} + $NCH_2CH_2CH_2CH_2N$ {2C}), 27.9 (8C, $NCH_2CH_2CH_2NHCONH$), 29.6 (24C, *C*-2), 36.5 (24C, *C*-3), 38.2 (8C, $NCH_2CH_2CH_2NHCONH$), 42.6 (48C, *C*-4), 50.4 (8C, *C*-1), 51.6 (8C, $NCH_2CH_2CH_2NHCONH$), 52.1 (8C, $NCH_2CH_2CH_2N$), 53.9 (2C, $NCH_2CH_2CH_2CH_2N$), 158.6 (8C, NHCONH); IR (KBr): ν (cm)$^{-1}$ = 3365.1 (N–H stretch), 2912.7, (C–H sat), 1639.1 (C=O); FAB-MS: Calcd. for $C_{128}H_{216}N_{22}O_8$: 2191.3. Found 2191.4.

DAB-*dendr*-(NHCONH-Ad)$_{32}$, 3d

^{1}H-NMR ($CDCl_3$): δ = 1.40 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.58 (m, 120H, $NCH_2CH_2CH_2NHCONH$ {64H} + $NCH_2CH_2CH_2N$ {56H}), 1.65 (s, 192H, *H*-2), 1.98 (s, 192H, *H*-4), 2.05 (s, 96H, *H*-3), 2.40 (m, 4H, $NCH_2CH_2CH_2NHCONH$ {64H}) + $NCH_2CH_2CH_2N$ {112H} + $NCH_2CH_2CH_2CH_2N$ {4H}, 3.12 (s, 64H, $NCH_2CH_2CH_2NHCONH$), 5.41 (s, 32H, $CH_2NHCONH$), 6.19 (s, 32H, $CH_2NHCONH$); ^{13}C-NMR: δ = 25.2 (28C, $NCH_2CH_2CH_2N$), 28.4 (32C, $NCH_2CH_2CH_2NHCONH$), 29.9 (96C, *C*-2), 36.8 (96C, *C*-3), 38.4 (32C, $NCH_2CH_2CH_2NHCONH$), 42.9 (96C, *C*-4), 50.7 (32C, *C*-1), 52.0 (32C, $NCH_2CH_2CH_2NHCONH$), 52.6-52.9 (56C, $NCH_2CH_2CH_2N$), 158.8 (32C, NHCONH); IR (KBr): ν (cm)$^{-1}$ = 3364.1 (N–H stretch), 2906.0, (C–H sat), 1640.06 (C=O); MALDI-TOF-MS: Calcd. for $C_{536}H_{912}N_{94}O_{32}$: 9185.7 Found 9174.0 $[M + H]^+$.

DAB-*dendr*-(NHCONH-Ad)$_{64}$, 3e

^{1}H-NMR ($CDCl_3$): δ = 1.40 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.58 (m, 248H, $NCH_2CH_2CH_2NHCO$ {128H} + $NCH_2CH_2CH_2N$ {120H}), 1.65 (s, 384H, *H*-2), 1.96 (s, 384H, *H*-4), 2.03 (s, 192H, *H*-3), 2.25-2.50 (m, 372H, $NCH_2CH_2CH_2NHCO$ {128H} + $NCH_2CH_2CH_2N$ {240H} $NCH_2CH_2CH_2CH_2N$ {4H}), 3.10 (br., 128H, $NCH_2CH_2CH_2NHCO$), 5.46 (s, 64H, $CH_2NHCONH$), 6.19 (s, 64H, $CH_2NHCONH$); ^{13}C-NMR : δ = 24.6 (60C, $NCH_2CH_2CH_2N$), 28.0 (64C, $NCH_2CH_2CH_2NHCO$), 29.6 (192C, *C*-3), 36.5 (192C, *C*-2), 38.0 (64C, $NCH_2CH_2CH_2NHCO$), 42.6 (192C, *C*-4), 50.4 (64C, *C*-1), 51.4-52.1 (184C, $NCH_2CH_2CH_2NHCO$ {64C} + $NCH_2CH_2CH_2N$ {120C}, 158.7 (64C, NHCONH); IR (KBr): ν (cm)$^{-1}$ = 3365.4 (N–H stretch), 2905.5, (C–H sat), 1639.7 (C=O).

Typical Procedure for Alkyl-Chain Modified Dendrimers with an Urea-Linkage: DAB-*dendr*-(NHCONH-$C_{16}H_{33}$)$_{16}$, 4c

To a solution of DAB-*dendr*-(NH_2)$_{16}$ (0.25 g, 0.15 mmol) in chloroform (10 ml) is added hexadecyl isocyanate (0.70 g, 2.62 mmol, 1.1 eq per NH_2), yielding a turbid solution of higher viscosity. After stirring overnight under an argon atmosphere, the reaction mixture is precipitated in diethyl ether to remove excess hexadecyl isocyanate. However a small amount of impurity could be detected that corresponded to the coupling product of hexadecyl isocyanate with hexadecyl amine. Pure **4c** (0.69 g, 78%) could be obtained by heating a concentrated solution of the crude product in chloroform under reflux, allow the mixture to cool down, and filtration of the precipate. ^{1}H-NMR ($CDCl_3$, 333K): δ = 0.88 (t, 48H, C*H*$_3$(CH$_2$)$_{15}$NHCONH), 1.20-1.37 (m, 416H, CH$_3$(C*H*$_2$)$_{13}$CH$_2$CH$_2$NHCONH), 1.37-1.70 (br, 92H, CH$_3$(CH$_2$)$_{13}$C*H*$_2$CH$_2$NHCONH {32H} + NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N {4H} + NCH$_2$C*H*$_2$CH$_2$N {24H} + NCH$_2$C*H*$_2$CH$_2$NHCONH {32H}), 2.25-2.48 (br, 84H, NC*H*$_2$CH$_2$CH$_2$NHCONH {32H} + NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N {4H} + NC*H*$_2$CH$_2$C*H*$_2$N {48H}), 3.13 (q, 32H, CH$_3$(CH$_2$)$_{14}$C*H*$_2$NHCONH), 3.18 (t, 32H, NCH$_2$CH$_2$C*H*$_2$NHCONH), 5.75 (t, 16H, CH$_3$(CH$_2$)$_{15}$N*H*CONH), 6.13 (s, 16H, NCH$_2$CH$_2$CH$_2$N*H*CONH); ^{13}C-NMR ($CDCl_3$, 333K): δ = 14.0 (16C, *C*H$_3$(CH$_2$)$_{15}$NHCONH), 22.7 (16C, CH$_3$(CH$_2$)$_{13}$*C*H$_2$CH$_2$NHCONH), 25.0 (br., 14C, NCH$_2$*C*H$_2$CH$_2$N {12C} + NCH$_2$*C*H$_2$*C*H$_2$CH$_2$N {2C}), 28.1 (16C, NCH$_2$*C*H$_2$CH$_2$NHCONH), 27.2 / 29.4 / 29.6 / 29.7 / 29.8 / 30.6 / 32.0 (208C, CH$_3$(*C*H$_2$)$_{13}$CH$_2$CH$_2$NHCONH), 38.2 (16C, NCH$_2$CH$_2$*C*H$_2$NHCONH), 40.5 (16C, CH$_3$(CH$_2$)$_{14}$*C*H$_2$NHCONH), 51.3 (16C, N*C*H$_2$CH$_2$CH$_2$NHCONH), 51.9 / 52.5 (24C, N*C*H$_2$CH$_2$*C*H$_2$N), 54.1 (2C, N*C*H$_2$CH$_2$CH$_2$*C*H$_2$N), 159.8 (16C, NH*C*ONH); IR (KBr): ν (cm)$^{-1}$ = 3334.4 (N–H stretch), 2919.1 (C–H sat), 1624.0 (C=O).

DAB-*dendr*-(NHCONH-$C_{16}H_{33}$)$_4$, 4a

^{1}H-NMR ($CDCl_3$, 333K): δ = 0.88 (t, 12H, C*H*$_3$(CH$_2$)$_{15}$NHCONH), 1.20-1.35 (m, 104H, CH$_3$(C*H*$_2$)$_{13}$CH$_2$CH$_2$NHCONH), 1.35-1.52 (m, 12H, CH$_3$(CH$_2$)$_{13}$C*H*$_2$CH$_2$NHCONH {8H} + NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N {4H}), 1.61 (q$_5$, 8H, NCH$_2$C*H*$_2$CH$_2$NHCONH), 2.33 (s, 4H, NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N), 2.40 (t, 8H, NC*H*$_2$CH$_2$CH$_2$NHCONH), 3.13 (q, 8H, CH$_3$(CH$_2$)$_{14}$C*H*$_2$NHCONH), 3.21 (t, 8H, NCH$_2$CH$_2$C*H*$_2$NHCONH), 5.03 (t, 4H, CH$_3$(CH$_2$)$_{15}$N*H*CONH), 5.47 (s, 4H, NCH$_2$CH$_2$CH$_2$N*H*CONH); ^{13}C-NMR ($CDCl_3$, 333K): δ = 14.0 (4C, *C*H$_3$(CH$_2$)$_{15}$NHCONH), 22.7 (4C, CH$_3$(CH$_2$)$_{13}$*C*H$_2$CH$_2$NHCONH), 25.0 (2C, NCH$_2$*C*H$_2$*C*H$_2$CH$_2$N), 27.8 (4C, NCH$_2$*C*H$_2$CH$_2$NHCONH), 27.1 / 29.4 / 29.5 / 29.7 / 30.6/ 32.0 (52C, CH$_3$(*C*H$_2$)$_{13}$CH$_2$CH$_2$NHCONH), 39.2 (4C, NCH$_2$CH$_2$*C*H$_2$NHCONH), 40.6 (4C, CH$_3$(CH$_2$)$_{14}$*C*H$_2$NHCONH), 52.3 (4C, N*C*H$_2$CH$_2$CH$_2$NHCONH), 54.1 (2C, N*C*H$_2$CH$_2$CH$_2$*C*H$_2$N), 159.2 (4C, NH*C*ONH); IR (KBr): ν (cm)$^{-1}$ = 3324.4 (N–H stretch), 2919.0, (C–H sat), 1620.3 (C=O); FAB-MS: Calcd. for $C_{84}H_{172}N_{10}O_4$: 1386.4. Found 1385.8.

DAB-*dendr*-(NHCONH-$C_{16}H_{33}$)$_8$, 4b

^{1}H-NMR ($CDCl_3$, 333K): δ = 0.88 (t, 24H, C*H*$_3$(CH$_2$)$_{15}$NHCONH), 1.20-1.37 (m, 208H, CH$_3$(C*H*$_2$)$_{13}$CH$_2$CH$_2$NHCONH), 1.37-1.70 (br, 44H, CH$_3$(CH$_2$)$_{13}$C*H*$_2$CH$_2$NHCONH {16H} + NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N {4H} + NCH$_2$C*H*$_2$CH$_2$N {8H} + NCH$_2$C*H*$_2$CH$_2$NHCONH {16H}), 2.30-2.47 (m, 36H, NC*H*$_2$CH$_2$CH$_2$NHCONH {16H} + NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N {4H} + NC*H*$_2$CH$_2$C*H*$_2$N {16H}), 3.12 (q, 16H, CH$_3$(CH$_2$)$_{14}$C*H*$_2$NHCONH), 3.18 (t, 16H, NCH$_2$CH$_2$C*H*$_2$NHCONH), 5.51 (t, 8H, CH$_3$(CH$_2$)$_{15}$N*H*CONH), 5.88 (s, 8H, NCH$_2$CH$_2$CH$_2$N*H*CONH); ^{13}C-NMR ($CDCl_3$, 333K) : δ 14.0 (8C, *C*H$_3$(CH$_2$)$_{15}$NHCONH), 22.7 (8C, CH$_3$(CH$_2$)$_{13}$*C*H$_2$CH$_2$NHCONH), 24.7 (6C, NCH$_2$*C*H$_2$CH$_2$N {4C} + NCH$_2$*C*H$_2$*C*H$_2$CH$_2$N {2C}), 28.1 (8C, NCH$_2$*C*H$_2$CH$_2$NHCONH), 27.2 / 29.4 / 29.5 / 29.7 / 30.6 / 32.0 (104C, CH$_3$(*C*H$_2$)$_{13}$CH$_2$CH$_2$NHCONH), 38.4 (4C, NCH$_2$CH$_2$*C*H$_2$NHCONH), 40.5 (8C, CH$_3$(CH$_2$)$_{14}$*C*H$_2$NHCONH), 52.0 (8C, N*C*H$_2$CH$_2$CH$_2$NHCONH) 52.5 (8C, N*C*H$_2$CH$_2$*C*H$_2$N), 54.1 (2C, N*C*H$_2$CH$_2$CH$_2$*C*H$_2$N), 159.7 (8C, NH*C*ONH); IR (KBr): ν (cm)$^{-1}$ = 3334.2 (N–H stretch), 2919.1 (C–H sat), 1622.7 (C=O); FAB-MS: Calcd. for $C_{176}H_{360}N_{22}O_8$: 2912.9. Found 2913.4.

DAB-*dendr*-(NHCONH-$C_{16}H_{33}$)$_{32}$, 4d

^{1}H-NMR ($CDCl_3$, 333K): δ 0.88 (t, 96H, C*H*$_3$(CH$_2$)$_{15}$NHCONH), 1.20-1.37 (m, 832H, CH$_3$(C*H*$_2$)$_{13}$CH$_2$CH$_2$NHCONH), 1.37-1.70 (br, 188H, CH$_3$(CH$_2$)$_{13}$C*H*$_2$CH$_2$NHCONH {64H} + NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N {4H} + NCH$_2$C*H*$_2$CH$_2$N {56H} + NCH$_2$C*H*$_2$CH$_2$NHCONH {64H}), 2.25-2.50 (br, 180H, NC*H*$_2$CH$_2$CH$_2$NHCONH {64H} + NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N {4H} + NC*H*$_2$CH$_2$C*H*$_2$N {112H}), 3.12 (q, 64H, CH$_3$(CH$_2$)$_{14}$C*H*$_2$NHCONH), 3.17 (t, 64H, NCH$_2$CH$_2$C*H*$_2$NHCONH), 5.84 (t, 32H, CH$_3$(CH$_2$)$_{15}$N*H*CONH), 6.20 (s, 32H, NCH$_2$CH$_2$CH$_2$N*H*CONH); IR (KBr): ν (cm)$^{-1}$ = 3336.2 (N–H stretch), 2919.2 (C–H sat), 1624.1 (C=O); MALDI-TOF-MS: Calcd. for $C_{728}H_{1488}N_{94}O_{32}$: 12072.4 Found 12072.2 [M + H].$^+$

DAB-*dendr*-(NHCONH-$C_{16}H_{33})_{64}$, 4e

^{1}H-NMR ($CDCl_3$, 333K): δ 0.88 (t, 192H, C*H*$_3$(CH$_2$)$_{15}$NHCONH), 1.20-1.37 (m, 1664H, CH$_3$(C*H*$_2$)$_{13}$CH$_2$CH$_2$NHCONH), 1.37-1.70 (br, 380H, CH$_3$(CH$_2$)$_{13}$C*H*$_2$CH$_2$NHCONH {128H} + NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N {4H} + NCH$_2$C*H*$_2$CH$_2$N {120H} + NCH$_2$C*H*$_2$CH$_2$NHCONH {128H}), 2.25-2.50 (br, 372H, NC*H*$_2$CH$_2$CH$_2$NHCONH {128H} + NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N {4H} + NC*H*$_2$CH$_2$C*H*$_2$N {240H}), 3.12 (q, 128H, CH$_3$(CH$_2$)$_{14}$C*H*$_2$NHCONH), 3.17 (t, 128H, NCH$_2$CH$_2$C*H*$_2$NHCONH), 5.84 (s, 64H, CH$_3$(CH$_2$)$_{15}$N*H*CONH), 6.20 (s, 64H, NCH$_2$CH$_2$CH$_2$N*H*CONH); IR (KBr): ν (cm)$^{-1}$ = 3337.3 (N–H stretch), 2919.0 (C–H sat), 1629.4 (C=O).

Typical Procedure for Synthesis of Carboxylate-Dendrimers:

DAB-*dendr*-($COO^-Li^+)_{32}$, 5d

Methyl acrylate (4.95 g, 57.48 mmol) was added to a stirred and cooled (ice/water) solution of DAB-*dendr*-$(NH_2)_{16}$ (2.02 g, 1.19 mmol) and LiCl (12 mg) in methanol (14 ml) in a drop wise fashion during 10 minutes. After removing the ice/water bath, the reaction mixture was stirred overnight at room temperature and the solvent was evaporated *in vacuo*. The residue was stripped with dichloromethane in order to remove excess methanol and methyl acrylate, yielding the intermediate methyl ester-functionalized dendrimer, DAB-*dendr*-$(COOMe)_{32}$, (5.21 g, 98 %) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 3.65 (s, 96H, COOC*H*$_3$), 2.75 (t, *J* = 7.2 Hz, 64H, NC*H*$_2$CH$_2$COOCH$_3$), 2.43 (t, *J* = 7.1 Hz, 64H, NCH$_2$C*H*$_2$COOCH$_3$), 2.40 (m, 116H, NC*H*$_2$CH$_2$C*H*$_2$N {112H} + NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N {4H}), 1.56 {m, 56H, NCH$_2$C*H*$_2$CH$_2$N}, 1.39 (m, 4H, NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N). LiOH·H$_2$O (0.931 g, 22.2 mmol) was added to a stirred and cooled (ice/water bath) solution of DAB-*dendr*-$(COOMe)_{32}$ (3.08 g, 0.69 mmol) in methanol (10 ml) and water (6 ml). After removing the ice/water bath, the reaction mixture was stirred overnight and the solvent was evaporated *in vacuo*. The remaining oil was redissolved in methanol and again evaporated *in vacuo*. Drying under vacuum resulted in 2.84 g (98 %) of a white powder **5d**, denoted as DAB-*dendr*-$(COO^-Li^+)_{32}$. ^{13}C-NMR (D_2O): δ = 184.2 (32C, *C*OOH), 56.2 (2C, N*C*H$_2$CH$_2$CH$_2$*C*H$_2$N), 54.3 (4C, N*C*H$_2$CH$_2$CH$_2$N), 53.6/53.4 (52C, NCH$_2$CH$_2$*C*H$_2$N {4C} + N*C*H$_2$CH$_2$*C*H$_2$N {16C} + N*C*H$_2$CH$_2$*C*H$_2$N {32C}, 52.1 (32C, N*C*H$_2$CH$_2$COOH), 36.7 (32C, NCH$_2$*C*H$_2$COOH), 26.3 (2C, NCH$_2$*C*H$_2$*C*H$_2$CH$_2$N), 25.0 (24C, NCH$_2$*C*H$_2$CH$_2$N), 24.6 (4C, NCH$_2$*C*H$_2$CH$_2$N); IR (KBr): ν (cm^{-1}) = 1572 (C=O, a), 1413 (C=O, s); ESI-MS: Calcd. for $C_{184}H_{464}N_{30}O_{64}$: 3992.82. Found 3993.6 [M + H$^+$].

DAB-*dendr*-($COO^-Li^+)_4$, 5a

^{13}C-NMR (D_2O): δ = 184.4 (4C, *C*OOH), 55.0 (2C, N*C*H$_2$CH$_2$CH$_2$*C*H$_2$N), 52.1 (4C, N*C*H$_2$CH$_2$COOH), 36.7 (4C, NCH$_2$*C*H$_2$COOH), 26.4 (2C, NCH$_2$*C*H$_2$*C*H$_2$CH$_2$N); ESI-MS: Calcd. for $C_{16}H_{28}N_2O_8$: 376.40. Found 376.6 [M + H$^+$].

DAB-*dendr*-($COO^-Li^+)_8$, 5b

^{13}C-NMR (D_2O): δ = 184.3 (8C, *C*OOH), 55.7 (2C, N*C*H$_2$CH$_2$CH$_2$*C*H$_2$N), 53.7 (4C, N*C*H$_2$CH$_2$CH$_2$N), 53.3 (4C, NCH$_2$CH$_2$*C*H$_2$N), 52.1 (8C, N*C*H$_2$CH$_2$COOH), 36.7 (8C, NCH$_2$*C*H$_2$COOH), 26.2 (2C, NCH$_2$*C*H$_2$*C*H$_2$CH$_2$N), 24.9 (4C, NCH$_2$*C*H$_2$CH$_2$N); ESI-MS: Calcd. for $C_{40}H_{72}N_6O_{16}$ 893.03. Found 893.0 [M + H$^+$].

DAB-*dendr*-($COO^-Li^+)_{16}$, 5c

^{13}C-NMR (D_2O): δ = 184.2 (16C, *C*OOH), 55.9 (2C, N*C*H$_2$CH$_2$CH$_2$*C*H$_2$N), 53.9 (4C, N*C*H$_2$CH$_2$CH$_2$N), 53.6 (12C, N*C*H$_2$CH$_2$CH$_2$N {8C} + NCH$_2$CH$_2$*C*H$_2$N {4C}), 53.3 (8C, NCH$_2$CH$_2$*C*H$_2$N), 52.0 (16C, N*C*H$_2$CH$_2$COOH), 36.6 (16C, NCH$_2$*C*H$_2$COOH), 26.2 (2C, NCH$_2$*C*H$_2$*C*H$_2$CH$_2$N), 24.8 (8C, NCH$_2$*C*H$_2$CH$_2$N), 24.5 (4C, NCH$_2$*C*H$_2$CH$_2$N); IR (KBr): ν (cm^{-1}) = 1579 (C=O, a), 1413 (C=O, s); ESI-MS: Calcd. for $C_{88}H_{160}N_{14}O_{32}$: 1926.30. Found 1926.6 [M + H$^+$].

DAB-*dendr*-($COO^-Li^+)_{64}$, 5e

^{13}C-NMR (D_2O): δ = 184.2 (64C, *C*OOH), 56.2 (2C, N*C*H$_2$CH$_2$CH$_2$*C*H$_2$N), 55.1/54.7/53.6/53.3 (120C, N*C*H$_2$CH$_2$*C*H$_2$N), 52.1 (64C, N*C*H$_2$CH$_2$COOH), 36.7 (64C, NCH$_2$*C*H$_2$COOH), 26.3 (2C, NCH$_2$*C*H$_2$*C*H$_2$CH$_2$N), 25.1/24.7 (60C, NCH$_2$*C*H$_2$CH$_2$N); IR (KBr): ν (cm^{-1}) = 1572 (C=O, a), 1413 (C=O, s).

Synthesis of succinimidyl 4-pyridine carboxylate

4-Pyridine carboxylic acid (10.0 g, 0.081 mol) and N-hydroxysuccinimide (9.43 g, 0.082, 1.01 eq) are dissolved in dry DMF at 80 °C. Under an argon atmosphere, 1,3-dicyclohexylcarbodiimide (18.44 g, 0.089, 1.10 eq) is added and the mixture is allowed to cool down and stirred overnight. The colored reaction mixture is filtrated twice to remove DHU and the filtrate is evaporated in vacuo. The crude product is recystallized twice from 2-

propanol, yielding white plates that are characterized as pure succinimidyl 4-pyridine carboxylate (11.44 g, 64%). ^{1}H-NMR ($CDCl_3$): δ 2.95 (s, 4H, (CH_2)$_2$), 7.92 (d, *J* = 4.5 Hz, 2H, py-*H*2), 8.88 (d, J = 4.5 Hz, py-*H*3).

Typical Procedure for Pyridine-Functionalized Dendrimers: DAB-*dendr*-(NHCO-4py)$_{16}$, 6c

To a solution of DAB-*dendr*-(NH_2)$_{16}$ (0.50 g, 0.30 mmol) in 10 ml dichloromethane is added 1.10 g (4.98 mmol, 1.04 eq. per NH_2) of N-succinimidyl-4-pyridine carboxylate. Upon addition of the activated ester, the temperature of the reaction mixture increases and a precipitate is formed. After stirring the reaction mixture for 16 h, an equal volume of water is added. The aqeous layer is extracted to remove residual succinimidyl ester. The pH of the aqueous phase is adjusted to pH = 12 through addition of 10% w/w NaOH until precipitation of the dendrimer takes place. Drying of the sample *in vacuo* yields a pure glassy solid **6c** (0.79 g, 80 %). ^{1}H-NMR (CD_3OD): δ 1.41 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.58 (s, 24H, $NCH_2CH_2CH_2N$), 1.79 (q, 32H, $NCH_2CH_2CH_2NHCO$), 2.41 (m, 52H, $NCH_2CH_2CH_2N$ {48H} + $NCH_2CH_2CH_2CH_2N$ {4H}, 2.51 (t, 32H, $NCH_2CH_2CH_2NHCO$), 3.43 (t, 32H, CH_2NHCO), 7.74 (d, *J* = 4.5 Hz, 32H, py-H2), 8.64 (d, *J* = 4.5 Hz, 32H, py-H3); ^{13}C-NMR (CD_3OD) : δ 24.6 (4C, $NCH_2CH_2CH_2$); 24.9 (8C, $NCH_2CH_2CH_2$); 25.7 (2C, $NCH_2CH_2CH_2CH_2N$) ; 26.1 (16C, CH_2CH_2NHCO); 39.7 (16C, CH_2NHCO); 52.7 (16C, $NCH_2CH_2CH_2NHCO$); 53.0 / 53.1 (24C, $NCH_2CH_2CH_2N$); 55.1 (2C, $NCH_2CH_2CH_2CH_2N$); 122.8 (32C, py-C2); 143.8 (16C, py-C1); 151.0 (32C, py-C3); 167.3 (16C, NH*C*O); ESI-MS: Calcd. For $C_{184}H_{256}N_{46}O_{16}$: 3368.4. Found 3368.8 [M + H$^+$].

DAB-*dendr*-(NHCO-4-py)$_4$, 6a

^{1}H-NMR ($CDCl_3$): δ 1.65 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.93 (q, 8H, m, CH_2CH_2NHCO), 2.84 (4H, $NCH_2CH_2CH_2CH_2N$), 2.94 (8H, $NCH_2CH_2CH_2NHCO$), 3.52 (8H, q, *J* = Hz, CH_2NHCO), 7.75 (8H, d, *J* = 5.7 Hz, py-*H*2), 8.10 (4H, t, *J* = 5.6 Hz, N*H*CO), 8.69 (8H, d, *J* = 6.0 Hz, py-*H*3); ^{13}C-NMR ($CDCl_3$) : δ 25.0 (2C, $NCH_2CH_2CH_2CH_2N$); 26.5 (4C, $NCH_2CH_2CH_2NHCO$); 39.2 (4C, CH_2NHCO); 52.2 (4C, $NCH_2CH_2CH_2NHCO$); 53.8 (2C, $NCH_2CH_2CH_2CH_2N$); 130.9 (8C, py-*C*2); 141.7 (4C, py-*C*1); 150.4 (8C, py-*C*3); 167.3 (4C, NH*C*O); ESI-MS: Calcd. for $C_{40}H_{52}N_{10}O_4$: 736.9. Found 737.2 [M + H$^+$].

DAB-*dendr*-(NHCO-4-py)$_8$, 6b

^{1}H-NMR (CD_3OD): δ 1.37 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.58 (s, 8H, $NCH_2CH_2CH_2N$), 1.77 (q, 16H, CH_2CH_2NHCO), 2.38-2.44 (m, 20H, $NCH_2CH_2CH_2N$ {16H} + $NCH_2CH_2CH_2CH_2N$ {4H}), 2.52 (t, 16H, *J* = 6.8 Hz, $NCH_2CH_2CH_2NHCO$), 3.42 (t, 16H, *J* = 6.9 Hz, CH_2NHCO), 7.74 (d, 16H, *J* = 5.7 Hz, py-H2), 8.64 (d, 16H, *J* = 6.0 Hz, py-H3); ^{13}C-NMR ($CDCl_3$): δ 25.0 (2C, $NCH_2CH_2CH_2CH_2$); 26.5 (4C, $NCH_2CH_2CH_2N$); 27.6 (8C, $NCH_2CH_2CH_2NHCO$); 39.2 (8C, CH_2NHCO); 52.2 (4C, $NCH_2CH_2CH_2NHCO$); 53.8 (2C, $NCH_2CH_2CH_2CH_2N$); 130.9 (16C, py-*C*2); 141.7 (8C, py-*C*1); 150.4 (16C, py-*C*3); 167.3 (8C, NH*C*O); ESI-MS: Calcd. for $C_{88}H_{120}N_{22}O_8$: 1614.1. Found 1614.8 [M + H$^+$].

DAB-*dendr*-(NHCO-4-py)$_{32}$, 6d

^{1}H-NMR (CD_3OD): δ 1.39 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.46 (s, 56H, $NCH_2CH_2CH_2N$), 1.75 (q, 64H, CH_2CH_2NHCO), 2.38 (m, 116H, $NCH_2CH_2CH_2N$ {112H} + $NCH_2CH_2CH_2CH_2N$ {4H}), 2.49 (t, 64H, *J* = 6.8 Hz, $NCH_2CH_2CH_2NHCO$), 3.39 (t, 64H, *J* = 6.9 Hz, CH_2NHCO), 7.74 (d, 64H, *J* = 5.7 Hz, py-H2), 8.64 (d, 64H, *J* = 6.0 Hz, py-H3); ^{13}C-NMR ($CDCl_3$): • 24.7 / 24.9 (28C, $NCH_2CH_2CH_2N$), 25.8 (2C, $NCH_2CH_2CH_2CH_2N$), 27.6 (32C, $NCH_2CH_2CH_2NHCO$), 39.7 (32C, CH_2NHCO), 52.2 (32C, $NCH_2CH_2CH_2NHCO$), 52.6 / 53.0 / 53.2 / 53.3 (56C, $NCH_2CH_2CH_2N$), 55.4 (2C, $NCH_2CH_2CH_2CH_2N$), 123.0 (64C, py-C2), 143.7(32C, py-C1), 151.0 (64C, py-C3), 167.3 (32C, NH*C*O); ESI-MS: Calcd. for $C_{376}H_{528}N_{940}O_{32}$: 6876.9. Found 6877.0 [M + H$^+$].

DAB-*dendr*-(NHCO-4-py)$_{64}$, 6e

^{1}H-NMR (CD_3OD): δ 1.38 (s, 4H, $NCH_2CH_2CH_2CH_2N$), 1.52 (s, 120H, $NCH_2CH_2CH_2N$), 1.74 (q, 128H, $NCH_2CH_2CH_2NHCO$), 2.32 (m, 244H, $NCH_2CH_2CH_2N$ {240H} + $NCH_2CH_2CH_2CH_2N$ {4H}), 2.45 (t, 64H, *J* = 6.8 Hz, $NCH_2CH_2CH_2NHCO$), 3.39 (t, 128H, *J* = 6.9 Hz, CH_2NHCO), 7.75 (d, 128H, *J* = 5.7 Hz, py-H2), 8.65 (d, 128H, *J* = 6.0 Hz, py-H3); ^{13}C-NMR ($CDCl_3$): δ 24.6 / 24.7 / 24.9 (28C, $NCH_2CH_2CH_2N$), 25.8 (2C, $NCH_2CH_2CH_2CH_2N$), 27.6 (64C, $NCH_2CH_2CH_2NHCO$), 39.7 (64C, CH_2NHCO), 52.2 (64C, $NCH_2CH_2CH_2NHCO$), 52.6 / 53.0 / 53.2 / 53.3 (120C, $NCH_2CH_2CH_2N$), 55.4 (2C, $NCH_2CH_2CH_2CH_2N$), 123.0 (128C, py-C2), 143.7(64C, py-C1), 151.0 (128C, py-C3), 167.3 (64C, NH*C*O).

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Poly(Propylene Imine) Dendrimers: Characteristic Interactions

3

Abstract: *The intramolecular and intermolecular interactions of (functionalized) poly(propylene imine) dendrimers are addressed. The protonation of amine- and acid-functionalized poly(propylene imine) dendrimers with inorganic acids has been investigated with ^{15}N-NMR spectroscopy and potentiometric titrations. These measurements yield a quantitative description of the titration curves of the individual shells, that can be understood if Coulombic repulsions are taken into account. Subsequently, the hydrogen-bonding interactions of four series of functionalized poly(propylene imine) dendrimers are studied as a function of the endgroup and endgroup linkage used. ^{1}H-NMR and IR spectroscopy reveal stronger hydrogen bonding interactions in solution of urea-linkages compared to amides and of linear alkyl-endgroups compared to bulky adamantyl-substituents. Similarly, thermal properties of the four series in the solid state are investigated with DSC and suggest a decrease in flexibility (shape persistency) of the dendrimers with urea-linkages in stead of amides and adamantyl-units compared to linear alkyl endgroups. The characteristic secondary interactions that play a key role in functionalized poly(propylene imine) dendrimers, i.e. electrostatic and hydrogen-bonding interactions have been mapped, and this understanding allows the construction of a new supramolecular dendritic host–guest motif which is described in Chapter 8.*

Part of this work has been published: Van Genderen, M. H. P.; Baars, M. W. P. L.; van Hest, J. C. M.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 573-574. Koper, G. J. M.; van Genderen, M. H. P.; Elissen-Román, C.; Baars, M. W. P. L.; Meijer, E. W.; Borkovec, M. *J. Am. Chem. Soc.* **1997**, *119*, 6513-6521. Van Duijvenbode, R. C.; Rajanayagam, A.; Koper, G. J. M.; Baars, M. W. P. L.; De Waal, B. F. M.; Meijer, E. W.; Borkovec, M. *Macromolecules* **1999**, in press.

3.1 Introduction

Already from the first reports on dendrimers[1] it has been suggested that these branched molecules with a three-dimensional skeleton can be used in a number of applications including those related to controlled release of pharmaceuticals.[2, 3] To understand the role of dendrimers in the supramolecular field[4] one has to understand the specific molecular interactions that play a role in the dendritic molecules used. Not only the dendritic architecture, *i.e.* dynamics,[5] conformation,[6, 7] or assembly[8] is important for understanding the role of dendritic molecules, but every type of dendrimer has its unique chemical properties and many of these properties emanate from the type of building blocks and groups used at the periphery.

As already discussed in Chapter 1,[9] four principal supramolecular rules can be translated to dendritic host-guest systems. With a combination of clathration, electrostatic interactions, hydrogen-bonding and hydrophobic interactions the specific properties of each type of dendrimer can be understood. In principle, with the attachment of a functional endgroup to a dendritic skeleton any property can be tailored. However the dendritic skeleton also provides for certain intrinsic properties and it is of vital importance to address the inter- and intramolecular interactions. The three-dimensional structure of dendritic macromolecules makes them particularly useful to encapsulate (or dissolve) solvent molecules. With the combination of an apolar interior core and a polar periphery one obtains unimolecular micelles in aqueous media,[10–13] with the possibility to harvest hydrophobic molecules. Unimolecular inverted micelles with a polar interior and an apolar periphery dissolve hydrophilic compounds in organic media.[14, 15] Depending on the polarity of the dendrimer interior either hydrophobic interactions[16] or a combination of electrostatic[17–19] and hydrogen bonding[20] interactions will play predominant role. Both poly(amidoamine) dendrimers[21–25] and poly(propylene imine) dendrimers[26, 27] are a special brand of dendrimers, due to their commercial availability, of which the (supramolecular) interactions are well-established. Electrostatic interactions of these types of dendrimers have been thoroughly investigated.

In case of the poly(propylene imine) dendrimers, the synthetic methodology used yields molecules with tertiary amines at the branching point. Since these dendrimers consist of branch points that are also the sites that can be protonated, properties like conformation, dimension or intermolecular interactions of these dendrimers vary as a function of pH.[28–32] Here, the protonation of amine-functionalized poly(propylene imine) dendrimers with inorganic acids is thoroughly studied using ^{15}N-NMR spectroscopy (Section 3.2.2) preceded by a short introduction of this technique (Section 3.2.1). Similarly, the protonation of carboxylate-functionalized poly(propylene imine)

dendrimers is investigated with potentiometric titrations (Section 3.2.3). The data obtained result in a quantitative description of the protonation in each shell, and provide detailed information on the degree of protonation of every site. [33]

Moreover, the amine- or nitrile- functionalized intermediates that become available with the syntheses open the possibility for a large variety of endgroup modifications as has already been discussed in Chapter 2. For instance, modification with acid or isocyanate-functionalized endgroups yields dendrimers with amide and urea-linkages, respectively. It is expected that the three-dimensional scaffold imposes strong influence on the organization[34, 35] and dynamics of these linkages.[36–38] Moreover, both the type and shape of endgroups and the type of linkage, either an amide or a urea unit, will have significant effects on certain physical properties, like for instance conformational freedom, solubility or transition temperature of the dendritic compounds. Therefore, hydrogen-bonding interactions of these units have been investigated in solution and in solid state (Section 3.3). The type of linkage and the shape of the endgroups have a strong effect on the hydrogen-bonding and the phase transition temperature of the dendritic material. Bulky endgroups disturb the packing and therefore yield weaker interactions.

3.2 Protonation of Poly(Propylene Imine) Dendrimers

3.2.1 An Introduction to ^{15}N-NMR Spectroscopy

A technique that might be useful to characterize poly(propylene imine) dendrimers is ^{15}N-NMR spectroscopy, since nitrogen is a substantial component and is present in a unique chemical environment in each new generation. The natural abundance ^{15}N-NMR spectra for nitrile-terminated poly(propylene imine) dendrimers, DAB-*dendr*-$(CN)_n$ in $CDCl_3$ with n = 4, 8, 16 and 32 is given in Figure 3.1 for the tertiary amines that are observed at ~240 ppm. The CN resonances are recorded at ~ 240 ppm for all generations and not shown. The spectra show a limited number of resonances compared to the number of nitrogen nuclei in the molecule because all nuclei that, due to the symmetry, are indistinguishable contribute to the same resonance and up to n = 32 all layers are observed. Moreover the integral ratios confirm the exponential increase of the number of nitrogens in each layer. For n = 64 it is no longer possible to observe all peaks within a reasonable acquisition period. Moreover, the integral ratios are systematically lower for the interior nitrogens, which suggests that the core dynamics changes with generation. The chemical shift of the tertiary nitrogens is a good indicator of their position relative to the exterior of the dendrimer. Stronger deshielding occurs in

the interior, and apparently the distance from the nitrile group determines the chemical shift and can not be due to solvent effects only.[39] In case of the amine-functionalized poly(propylene imine) dendrimers small differences in the chemical shift of the different shells are observed.[40]

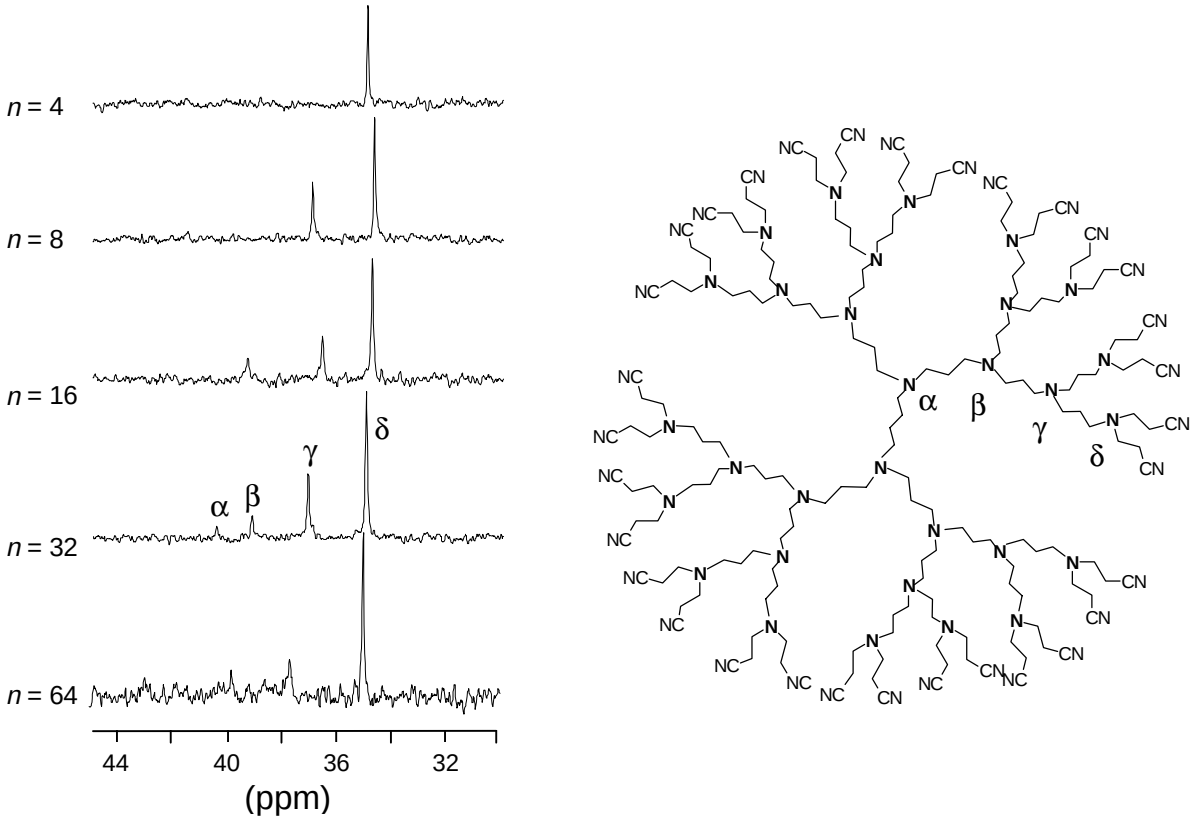
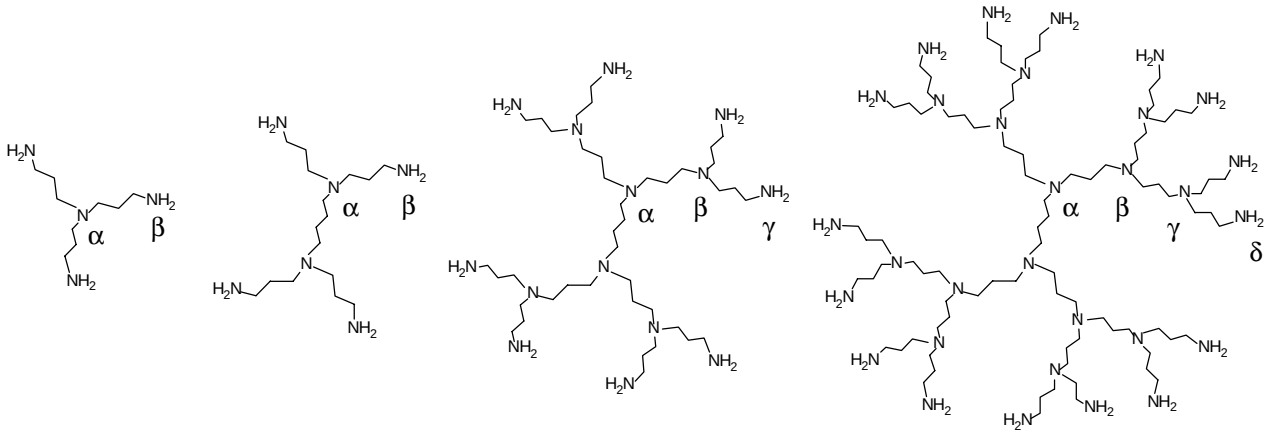


Figure 3.1: *Tertiary amine region of the inverse-gated ^{15}N-NMR spectra of DAB-dendr-(CN)$_n$ measured in CDCl$_3$. Nitrogens α-δ are indicated in spectra and explained for DAB-dendr-(CN)$_{32}$.*

3.2.2 ^{15}N-NMR Spectroscopy of Amine-Terminated Dendrimers

The results for the nitrile-terminated dendrimers suggest that natural abundance ^{15}N-NMR spectroscopy with inverse gated decoupling[41] provides for a unique method to follow the protonation[42] of the individual shells in the dendritic structure. Other nuclei, such as ^{1}H and ^{13}C, have also been proposed,[43, 44] for instance in the case of (low-molecular) linear polyamines.[45] However, because the dissociable protons are directly attached to nitrogen nuclei, the ^{15}N chemical shifts are more sensitive to protonation and also the similarity of the dendritic shells make it almost impossible to distinguish between the different shells and elucidate protonation effects of the different shells using ^{1}H-NMR and ^{13}C-NMR spectroscopy.



Scheme 3.1: *Structure of the amine-functionalized dendrimers studied; (from left to right) NH_3-dendr-$(NH_2)_3$, DAB-dendr-$(NH_2)_4$, DAB-dendr-$(NH_2)_8$, DAB-dendr-$(NH_2)_{16}$.*

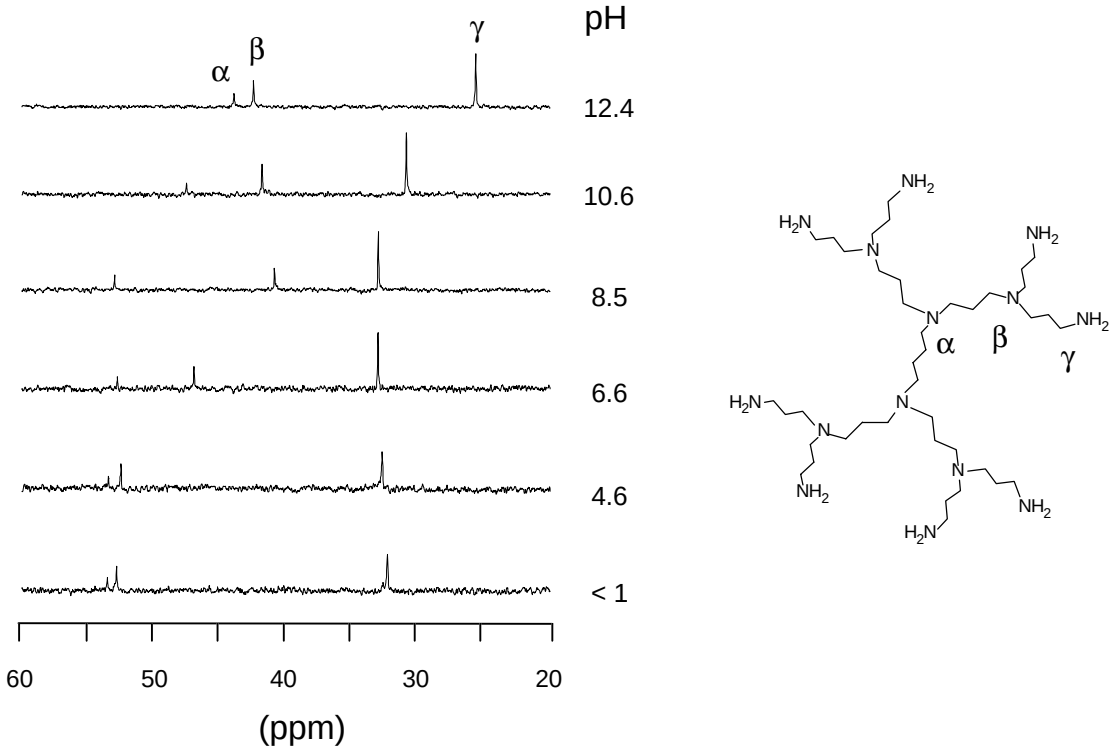


Figure 3.2: *Natural abundance ^{15}N-NMR spectra of DAB-dendr-$(NH_2)_8$ for different pH-values. Symbols α, β and γ indicate nitrogen nuclei in the different shells.*

Scheme 3.1 represents the chemical structure of the dendrimers that have been characterized with ^{15}N-NMR spectroscopy at different pH-values. The different sites are indicated with symbol α–δ. Characteristic spectra in the titration of DAB-*dendr*-$(NH_2)_8$ with hydrochloric acid are depicted in Figure 3.2. The ^{15}N-NMR spectra show a limited number of resonances compared to the number of nitrogen nuclei in the molecule because all nuclei that, due to the symmetry, are indistinguishable contribute to the same resonance. In the case of DAB-*dendr*-$(NH_2)_{16}$ four different resonances can be observed. In addition, the resonances could be assigned unequivocally using the fact

that the integrals of the resonances are proportional to the number of contributing nuclei. The presence of only one resonance for multiple nitrogen nuclei, even when the molecule is partially protonated, indicates that all motions and proton exchange processes are fast with respect to the NMR time scale. The observed chemical shifts have been plotted as a function of pH for all four compounds with the different sites indicated (Fig. 3.3), and it is assumed that this variation in the chemical shift corresponds only to the degree of protonation of the nitrogen nuclei themselves, *i.e.* to the shell protonation according to Webb *et al*.[42] Since the chemical shift differences between the tertiary amine nitrogen nuclei in shells α and β, for instance in the case of DAB-*dendr*-$(NH_2)_4$, are virtually identical at both ends of the titration curve, it is evidenced that the chemical shift of a specific nitrogen nucleus is not influenced by other nitrogen nuclei,[46] but solely determined by its protonation.

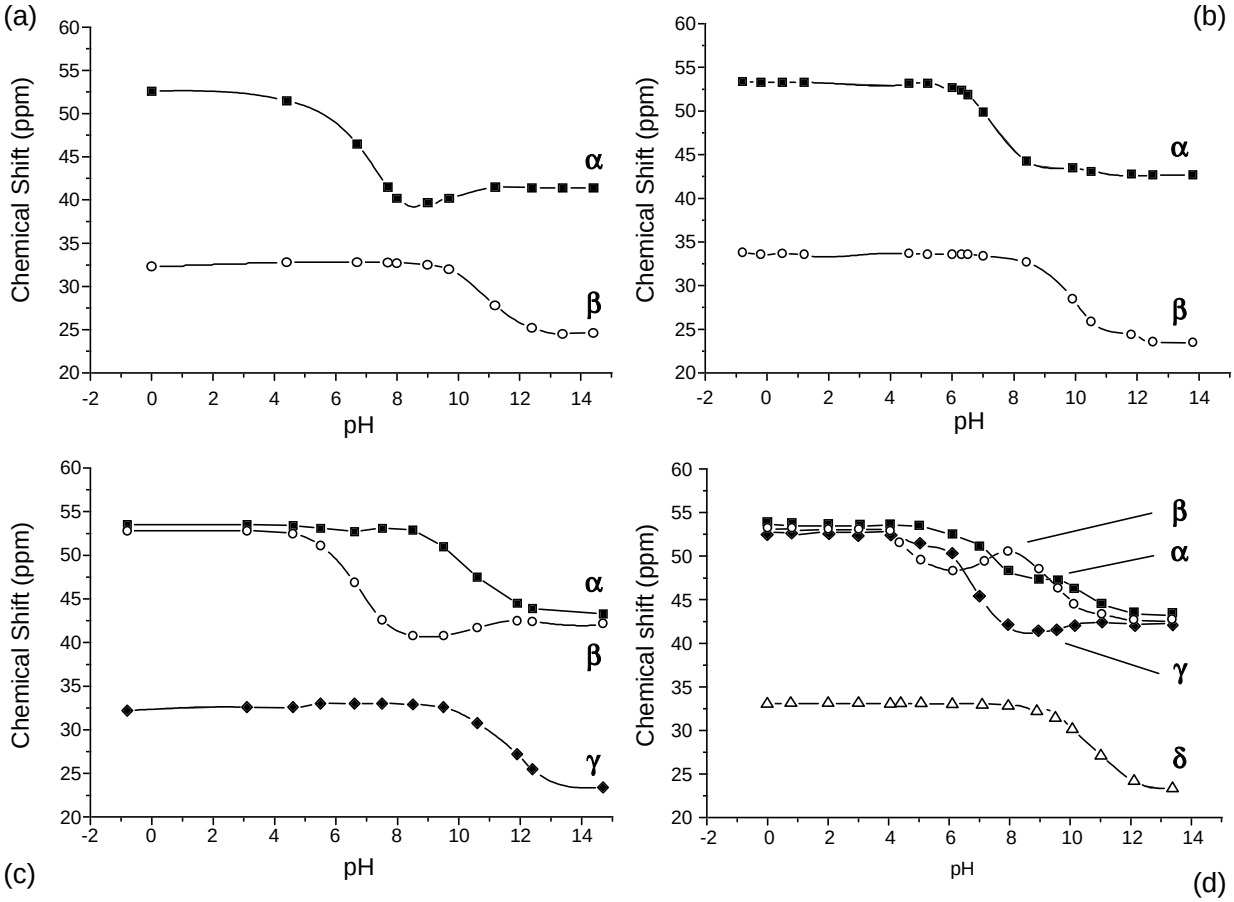


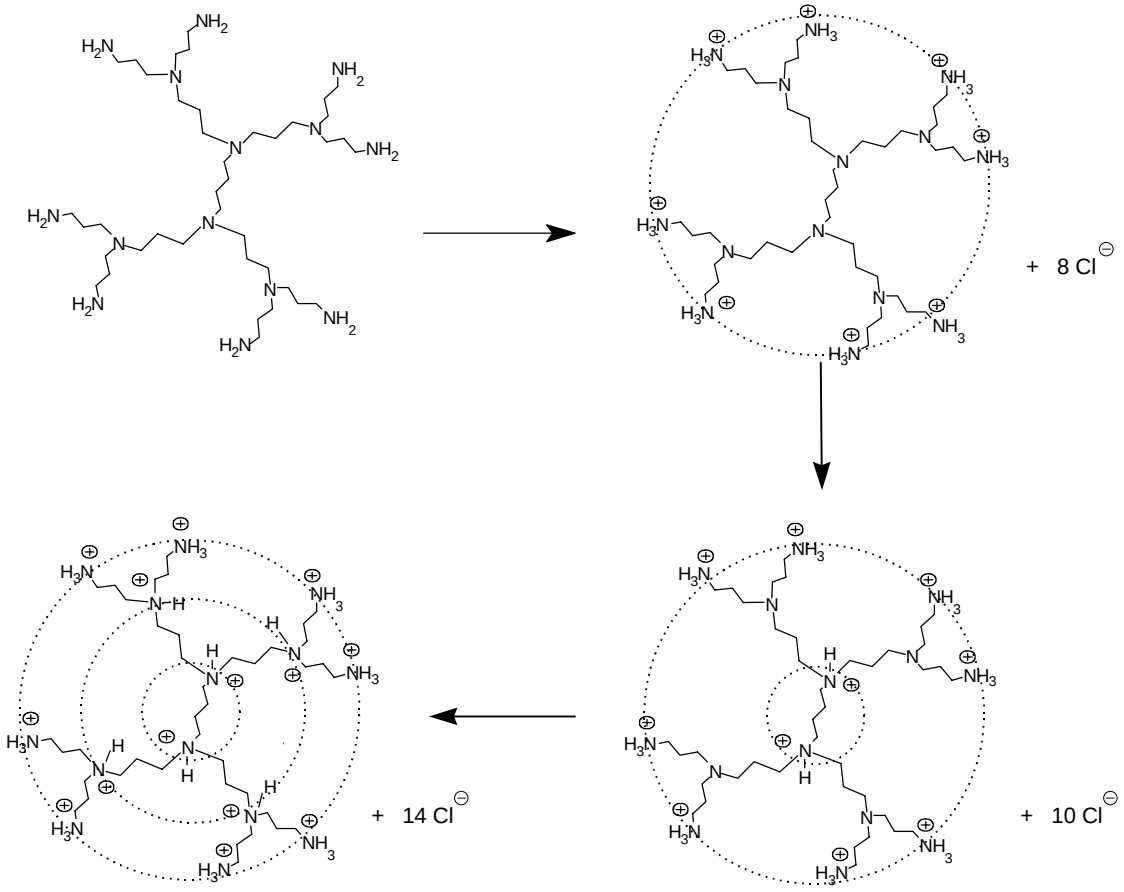
Figure 3.3: *Chemical shifts for the different tertiary amine sites (α, β, γ, δ) obtained from the pH-titration of NH_3-dendr-$(NH_2)_3$ (a), DAB-dendr-$(NH_2)_4$ (b), DAB-dendr-$(NH_2)_8$ (c) and DAB-dendr-$(NH_2)_{16}$ (d).*

The titration behavior can be described as follows: because the proton affinity of the primary amines is higher than that of the tertiary amines, the terminal sites protonate first at low proton concentrations (high pH). The complex behavior, like the presence of

relative maxima and/or minima can be explained by Coulombic repulsions between the different protonated nitrogens in the dendritic structure. For instance in the case of DAB-*dendr*-$(NH_2)_8$, first the outer γ-shell and the most inner α-shell protonate with increasing proton concentrations. The middle β-shell follows at lower pH because of its higher formation free energy, due to the additional energy of neighboring pairs. The local maximum around pH = 11 for the degree of protonation of the β-shell is due to the fact that initially, at low proton concentrations, this shell can protonate simultaneously with the surrounding shells without having neighboring sites protonated. At higher proton concentrations the inner and outer shell are too much protonated to avoid protonated pairs. Around pH = 7 an interesting local minimum in the degree of protonation of the α-shell is observed, most easily explained by a state with one proton in the α-shell and two in the β-shell. The formation free energy of this state is comparable to a situation with two protons in the α-shell and only one in the β-shell. Further increase in the proton concentration results in full protonation of the inner shell and this explains the dip in the degree of protonation. The overall protonation sequence for DAB-*dendr*-$(NH_2)_8$ is depicted in Scheme 3.2, with γ- and α- nitrogens that protonate first, followed by the β-shell. The largest dendrimer investigated with ^{15}N-NMR spectroscopy is DAB-*dendr*-$(NH_2)_{16}$, although the chemical shifts in some cases are barely detectable. With increasing protonation concentration, protonation of the α, γ and δ-shell takes place. Around pH = 9.5 the β-shell catches up because it can accommodate more protons while not forming pairs with neighboring sites and can have a local maximum in order to avoid Coulombic repulsions. At pH = 8 both δ and β-shell are the preferred protonation sites. At higher proton concentrations the γ-shell starts to protonate, with a small drop in protonation degree of the β-shell to avoid to many neighboring protonated sites. This also favors full protonation of the α-shell. At very low pH all shells fully protonate.

The protonation behavior of the poly(propylene imine) dendrimers up to generation 3 is rationalized with a combination of the presented ^{15}N-NMR data and the so-called Ising model.[47, 48] This model requires a limited set of parameters, site protonation constants and pair interaction free energies, that can subsequently be used for a rationalization of the microscopic and macroscopic equilibrium constants for all the measured molecules. The results obtained from ^{15}N-NMR spectroscopy and potentiometric titrations in combination with the Ising model can be translated in pK-values for the dendritic structures. No large differences were found between pK_b-values of primary amines (*ca*. 3.3) and pK_b-values of tertiary amines between 3.5 and 4.2 for the different generations. Thus, the sequence of protonation can be understood by taking into account a minimization of Coulombic repulsions.

Similarly, potentiometric titrations have been performed on the amine-functionalized poly(propylene imine) dendrimers (up to the fifth generation).[28, 49] These titration experiments could be used in combination with the Ising model to understand the protonation behaviour especially of the higher generations. The titration curves feature two distinct steps around pH = 6 and 10 with an intermediate plateau at 2/3 of the total ionizable sites. This pattern reflects short-range repulsive interactions between ionizable sites and can be analyzed quantitatively with an Ising model[47] that uses nearest neighbor pair interactions. The intermediate plateau results from the stability of an onion-like structure where all odd shells of the dendrimer are protonated, while the even ones remain deprotonated.



Scheme 3.2: *Sequence of protonation for DAB-dendr-(NH2)8.*

3.2.3 Acid-Functionalized Poly(Propylene Imine) Dendrimers

In Chapter 2.3 an alternative and highly efficient synthesis route for carboxylate-functionalized poly(propylene imine) dendrimers, *i.e.* DAB-*dendr*-$(COO^{-}Li^{+})_n$ with n = 4, 8, 16, 32, 64, has been developed that does not have the drawbacks (structural

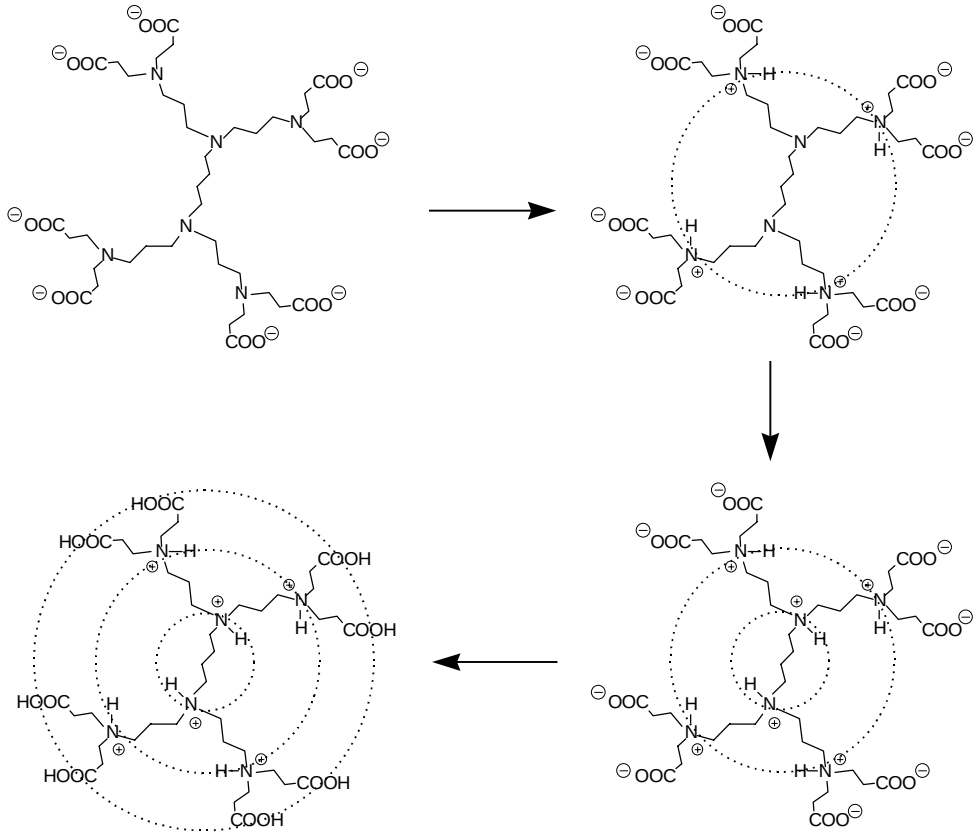
defects, hygroscopic, high salt concentration) of other routes.[50] The first generation, *i.e.* DAB-*dendr*-(COO^-Li^+)$_4$, with two tertiary amines and four carboxylate groups, closely resembles EDTA, which is well known for its complexing power.[51] All generations of the carboxylate-functionalized poly(propylene imine) dendrimers consist of similar structural elements, but contain considerably more coordination sites than EDTA. Because of the high local concentration of functional groups, these tree-like molecules possess a very high charge density. The charge density and the functional interior make them potential complexing agents,[52] which would appropriately be called polydentate ligands.

The protonation behavior of these potential complexing agents is studied with potentiometric titrations in 0.1 M and 1.0 M KCl solutions and rationalized with the Ising model.[47] For the first generation the rather pronounced difference in dissociation constant between carboxylic groups and amines yields two distinct steps in their titration curves. This results in low buffer capacity after protonation of the two inner amines, one-third of all sites. Only below pH 4 the carboxylic groups are involved in protonation. With the similarity of the outer shell for all dendrimer generations, the endgroups experience the same interactions with the interior amines, and the last part of the titration is similar. The protonation sequence is illustrated in Scheme 3.2 for DAB-*dendr*-(COO^-Li^+)$_8$. The outermost shell of tertiary amines protonates first, since these amines appear to have a higher p*K* value due to the neighboring carboxyl groups. Subsequently, the two interior tertiary amines are protonated before protonation of the carboxylate groups takes place. The pair-wise interactions between neighboring groups lead to onion-like shell protonation behavior (odd-even shell protonation), such as already observed for the amine-functionalized poly(propylene imine) dendrimers[28] (see Section 3.2.2).

The opposite type of charges on these dendrimeric structures makes it possible to create a negatively charged surface and a core with a high positive charge density. All generations exhibit amines and carboxylate groups in a (n-2) : n ratio, where n is the number of carboxylate endgroups (n = 4, 8, 16, 32, 64). The tertiary amine groups will be protonated at higher pH than the carboxylate groups. The so-called zero point of charge or iso-electric point is around p*H* 4.5 at 0.1 M, and 4.7 at 1.0 M for the higher generations.

The Ising model was used to rationalize the complete set of titration data simultaneously for five generations with only one microscopic pK value for each additional shell and a set of three nearest neighbor pair interaction parameters. Nearly all parameters were kept at the same value for all generations of dendrimers, except for the first generation. A pK_b value for the carboxylate endgroups of 9.9 and for the inner

tertiary amines of 4.4 has been found. The pK value found for the inner amines of the two higher generations is similar to the pK value obtained earlier for the amine-functionalized poly(propylene imine) dendrimers. Moreover, the interior of the dendrimer does not seem to be affected by the presence of the carboxylic endgroups. This indicates that the carboxylate endgroups are not folding back, as that would have its effect on the interior.



Scheme 3.3: *Sequence of protonation for DAB-dendr-(COO⁻Li⁺)₈. The counter-ions are omitted for the sake of clarity.*

3.3 Hydrogen-Bonding Interactions

Dendrimers obtained by modification with acidic or isocyanate functionalities yield amide and urea linkages respectively. Four different series, DAB-*dendr*-(NHCO-Ad)$_n$, DAB-*dendr*-(NHCONH-Ad)$_n$, DAB-*dendr*-(NHCO-$C_{15}H_{31}$)$_n$ and DAB-*dendr*-(NHCONH-$C_{16}H_{33}$)$_n$ with 4, 8, 16, 32, 64) have been synthesized and characterized before (Section 2.2). For this purpose model compounds have been synthesized based on propylamine (n = 1) and diaminobutane (n = 2). The difference in linkage yields interesting structural differences with respect to hydrogen-bonding properties. While amides contain one N-H

proton, two N–H protons are present for urea-linkages. The structural differences are investigated with ^{1}H-NMR, IR-spectroscopy and DSC.

3.3.1 In Solution[53, 54]

^{1}H-NMR Spectroscopy. The hydrogen-bonding interactions of DAB-*dendr*-(NHCO-Ad)$_n$, DAB-*dendr*-(NHCONH-Ad)$_n$, DAB-*dendr*-(NHCO-$C_{15}H_{31}$)$_n$ and DAB-*dendr*-(NHCONH-$C_{16}H_{33}$)$_n$ with n = 1, 2, 4, 8, 16, 32, 64) have been studied in detail with ^{1}H-NMR spectroscopy. All measurements have been conducted in $CDCl_3$ with a constant concentration of the endgroups of 25 mM. For all generations the NH-resonances are monitored and a down-field shift is observed with generation indicative of (an increase in) hydrogen-bonding interactions (Fig. 3.4). The observed increase originates from a closer proximity of the endgroups, since the local density of the endgroup linkages increases with generation.[1, 8, 55] The increase of δ_{NH} for both amide-series, even at the highest generation, suggests that the maximum in hydrogen-bonding interactions is still not achieved and that both H-bonded and non-H-bonded states are present. However, for the urea-dendrimers with adamantyl or alkyl-endgroups a constant value is reached at the third generation (n = 16). This suggests that in this case all endgroups are hydrogen-bonded at the third generation, although the local density of the endgroup-linkages still increases with generation. The observation of two resonances for the urea protons in both series shows that they are non-equivalent except for the propylamine-model of the alkyl-urea series. This is obvious in case of the adamantyl-dendrimers were the bulky endgroups disturb efficient hydrogen-bonding interactions of the outer NH, resulting in a distinct difference between both resonances in ^{1}H-NMR. Also in the case of the alkyl-dendrimers, two separate resonances are observed, though the difference is smaller. In this case the density-effect plays an important role, since the NH closest to the periphery has more space available yielding a larger probability for hydrogen-bonding and thus a more downfield shift.

Concentration-dependence measurements of the lower generations are indicative of concurrent intermolecular hydrogen-bonding interactions; however, these interactions are absent for the higher generations. For the higher generations, a three-dimensional structure and the location of (bulky) apolar endgroups at the periphery prevent intermolecular hydrogen-bonding interactions to take place, whereas the more open structure for the lower generations[8] is capable of intermolecular interactions.

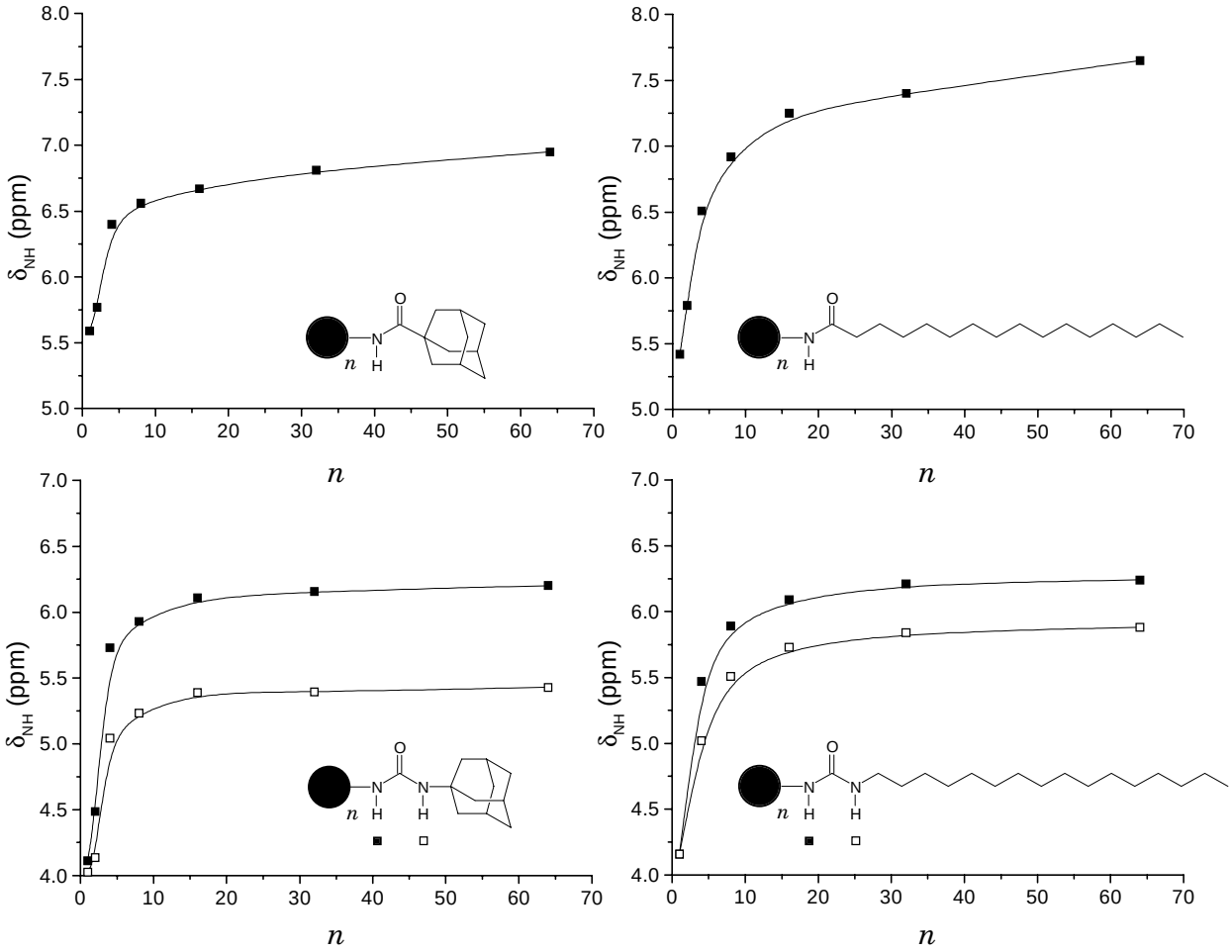


Figure 3.4: *NH-shift (ppm) as a function of the number of endgroups n in the dendrimer. Top-left: adamantyl-amide; top-right: alkyl-amide; Bottom-left: adamantyl-urea; Bottom-right: alkyl-urea In case of the urea-functionalized dendrimers,* ■ *and* □ *are used as markers to distinguish N–H protons.*

Due to the fast exchange of H-bonding with respect to the NMR-time scale, it is not possible to separate H-bonding and non H-bonding states and thus it is impossible to determine the amount of hydrogen-bonding directly from ^{1}H-NMR spectroscopy. Molecular dynamics calculations on poly(propylene imine) dendrimers functionalized with amino-acid residues describe an increase in hydrogen-bonding with generation and also calculate the amount of hydrogen-bonding.[56] Similarly, the amount of hydrogen-bonding has been determined for glycine-functionalized poly(propylene imine) dendrimers using IR-measurements, since the latter technique can distinguish between hydrogen-bonding and non-hydrogen bonding states.[57]

IR-spectroscopy. Infrared measurements (Fig. 3.5) have been performed in CH_2Cl_2 at 298 K with a constant concentration of the endgroups of 25 mM), and reveal qualitative information on the hydrogen-bonding interactions between the endgroup linkages in the dendrimer. In all four series, the propylamine-derivative exhibits a

single resonance corresponding to the non-hydrogen bonded species. For the dendrimers, however, an extra (broad) resonance at lower wavenumber comes up, the intensity of which increases with generation, indicative of a hydrogen-bonding state of the endgroups. Moreover, the observed wavenumber is a rough indication of the hydrogen-bonding strength between the different endgroups.[58–60] In case of the alkyl-amide series, the hydrogen-bonds become stronger with generation as is suggested by a shift to lower wavenumber. Furthermore, the lower wavenumber of the alkyl-series, compared to the adamantyl-series suggests stronger hydrogen bonds. For the highest generations, with amide linkages, non-hydrogen bonding states are still present.

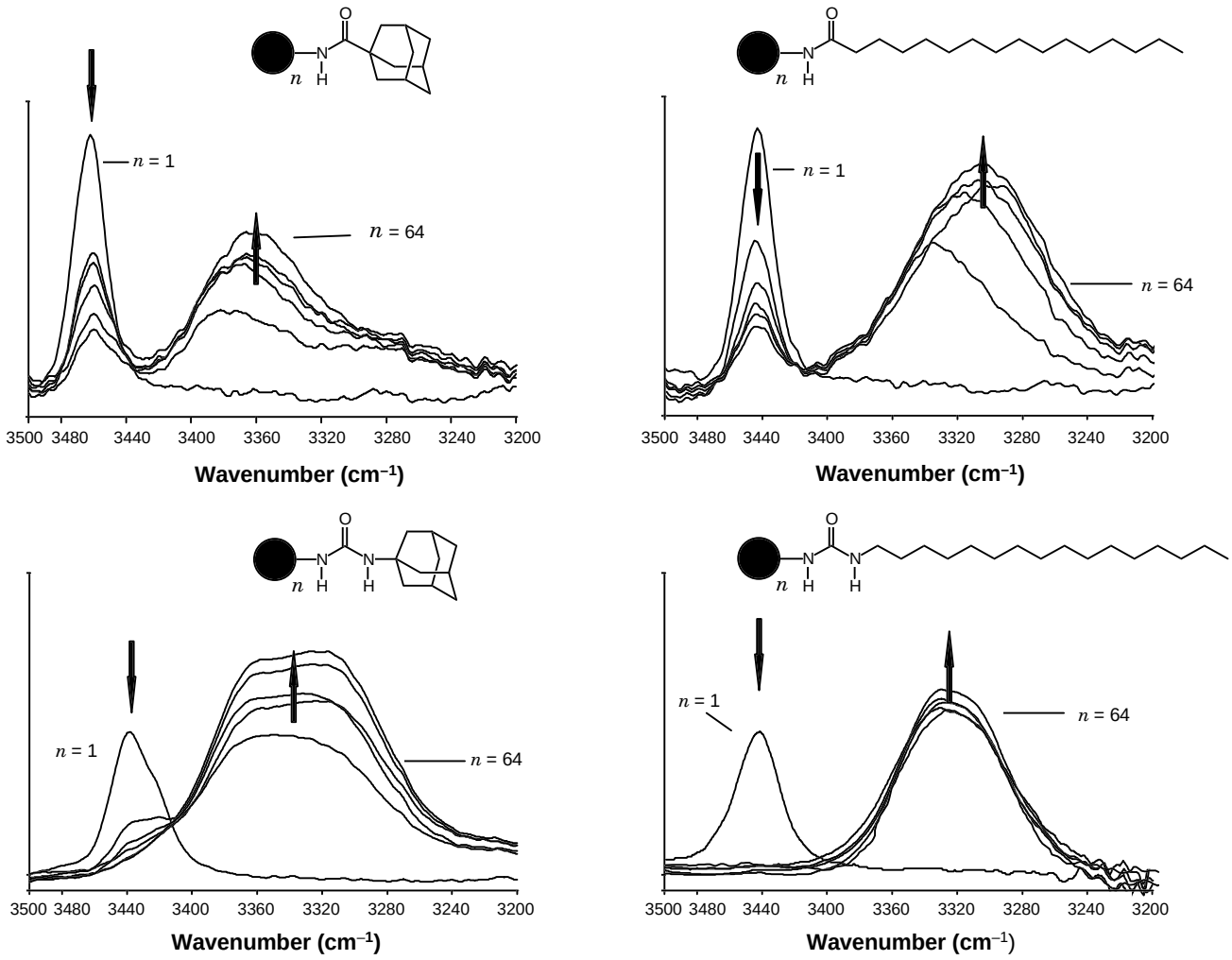


Figure 3.5: *IR-spectra for the different series as a function of the number of endgroups in the dendrimer. Top-left: adamantyl-amide; top-right: alkyl-amide; Bottom-left: adamantyl-urea; Bottom-right: alkyl-urea.*

In case of the urea-dendrimers, the non-hydrogen bonding state decreases strongly compared to similar generations amide-dendrimers. For a fifth generation adamantyl-

urea dendrimer, the non hydrogen-bonding state is completely absent. Surprisingly, for the alkyl-urea dendrimers the non-hydrogen bonded state is also absent for the lower generations, which indicates that very strong intramolecular hydrogen-bonding can take place. In case of the adamantyl-ureas, two resonances at different wavenumber can be distinguished, as can be observed from the spectra that show two (overlapping) maxima; the resonance at higher wavenumber originates from the NH close to the adamantyl-unit which is less favored for hydrogen bonding. In case of the alkyl-ureas the hydrogen bonding strength for both bonds are (almost) similar, yielding only one resonance of which the value compares quite nicely to the strongest hydrogen bonds of the adamantyl-series.

Discussion. It is not trivial to explain the relative chemical shift of the NH-resonance, since electronic effects can influence the absolute shift,[61] however all endgroups are hydrocarbon-residues. A difference can be observed between the adamantyl-dendrimers and the alkyl-dendrimers when comparing the δ_{NH} values for the amide-series. The shift is larger for the linear alkyl-derivatives than for the bulky adamantyl derivatives. In the latter case efficient hydrogen bonding interactions are less likely due to steric reasons. Similar results can be obtained from IR-spectroscopy where the wavenumber of the hydrogen-bonding resonance and the (relative) amount of the hydrogen-bonding state give a direct indication on the (strength of) hydrogen-bonding.

3.3.2. In Solid State

Differential Scanning Calorimetry (DSC). The thermal behavior of the functionalized poly(propylene imine) dendrimers is studied with Differential Scanning Calorimetry and the results are depicted in Table 3.1.

The amine- and nitrile-functionalized dendrimers show glass transitions (T_g) at low temperatures, in between –90° and –65° or –60° to –45°C,[26] respectively and are independent of generation from generation three onwards. It is assumed that a glass transition temperature is linked to the mobility of the segments within a single dendritic molecule, and thus low values are indicative of a large degree of conformational freedom.[62] The thermal transitions depend strongly on the type of endgroups,[53, 63, 64] as is shown in Table 1 for the different series of functionalized dendrimers. Compared to the amine-functionalized dendrimers a huge increase in transition temperature is observed of almost 200 °C.

Table 3.1: *Phase-transition temperatures and thermodynamic data of substituted poly(propylene imine) dendrimers.*

Compound	T_g (°C)	Δc_p (J/g·K)	T_m (°C)	ΔH (J/g)
DAB-*dendr*-(NHCO-Ad)$_n$				
n = 4	65	0.428		
n = 8	62	0.403		
n = 16	51	0.305		
n = 32	45	0.252		
n = 64	45	0.153		
DAB-*dendr*-(NHCO-$C_{15}H_{31}$)$_n$				
n = 4			116	(n.d.)
n = 8			74	(n.d.)
n = 16			75	(n.d.)
n = 32			76	(n.d.)
n = 64			72	(n.d.)
DAB-*dendr*-(NHCONH-Ad)$_n$				
n = 4	113	0.500		
n = 8	131	0.353		
n = 16	128	0.215		
n = 32	136	0.204		
n = 64	99	0.176		
DAB-*dendr*-(NHCONH-$C_{16}H_{33}$)$_n$				
n = 4			98–126	(n.d.)
n = 8			94	66
n = 16			93	56
n = 32			92	47
n = 64			88	40

(n.d.) = not determined

The structural elements, 1-adamantanecarboxylic acid or 1-adamantamine show transitions at 174 and 206 °C, respectively. Similarly hexadecanoic acid or hexadecyl amine show transitions at 63 and 47 °C, respectively. Adamantyl-functionalized dendrimers show T_g-values between 50–60 °C and 100–130 °C for the amide- and urea-series, respectively. The glass transition can be explained as follows: dendrimers with rigid and bulky adamantyl endgroups yield amorphous solids and it is suggested that the dendritic structure adopts a persistent globular conformation, similar to the dendritic box;[36] due to the three-dimensional dendritic scaffold, the endgroups can not organize into a closely packed array. Incorporating stronger hydrogen-bonding units in the dendritic units, *i.e.* urea-linkages in stead of amides, further reduces the conformational freedom of the dendrimers and thus the molecular flexibility, yielding an increase in the glass transition temperature with *ca.* 50 °C.[65, 66]

In case of poly(propylene imine) dendrimers functionalized with linear flexible chains[54] a clear melting behavior is observed, with T_m-values determined at ca. 75 °C and 90-100 °C for the amide- and urea-series respectively, except for the first generation which shows higher phase transition temperatures of ca. 116 °C for both series. The different behavior of first generation poly(propylene imine) dendrimers is commonly observed, since the flat geometry yields intermolecular hydrogen-bonding interactions between the different dendrimer molecules. Consequently, phase transition temperatures are considerably higher than for the other generations in which the hydrogen bonds are shielded by the periphery and the main interactions are governed by the endgroups.[67] The observed melting transition suggests that the endgroups are tightly packed into a (semi)crystalline arrangement and suggests that the poly(propylene imine) scaffold is highly flexible. Furthermore, it has been proven with other techniques, like TEM, X-Ray-spectroscopy[68] and SANS-measurements[69] that the alkyl-modified poly(propylene imine) dendrimers phase-separate in bulk and adopt a lamellar organization,[35b] indicative of the high flexibility of the dendritic scaffold and the possibility to adapt to the constraints of the endgroups. This issue is further addressed in Chapter 6. In case of the alkyl-dendrimers with urea-linkages, the transition temperatures are increased by 30 °C due to stronger hydrogen-bonding interactions.

The decrease of Δc_p (Table 3.1) with generation in the case of both series of adamantyl-functionalized dendrimers is a common effect for functionalized dendrimers with a glass-transition temperature.[35] The enthalpy changes for the alkyl-functionalized poly(propylene imine) dendrimers also decrease with generation and suggest a decrease in organization for the larger generation dendrimers, at least in case of urea-linkages. Mobility decreases due to increased hydrogen-bonding interactions in the 'urea-shell' of the dendrimer, and hinders a proper organization of the dendritic scaffold.

3.4 Overall Conclusions

The synthesis and modification of poly(propylene imine) dendrimers yields dendrimers with intrinsic physical properties. The electrostatic interactions of amine- and acid-functionalized dendrimers in aqueous media and the hydrogen bonding interactions of functionalized dendrimers in organic media and in the solid state have been studied. The availability of tertiary amines in the dendritic interior shows the possibility of electrostatic (acid-base) interactions with acid-functionalized compounds, like inorganic acids used and suggests the exploration of dendrimers as a new type of host-molecules (see also Chapter 4). The two most effective routes for modification of

the amine-functionalized dendrimers, by reaction with acids or isocyanates, yield endgroups that are linked to the dendritic skeleton via hydrogen-bonding units. These interactions affect the dendritic structure as evidenced from solution and bulk studies. Both the structure (shape) of the endgroups, *i.e.* 'linear and flexible' or 'rigid and bulky', as well as the type of linkage can be used to tailor properties of the dendritic structure, like rigidity, phase transition temperature and overall shape.

Two key interactions, *e.g.* electrostatic and hydrogen-bonding interactions, that are well-known in supramolecular chemistry have been translated to functionalized poly(propylene imine) dendrimers, Recently, a combination thereof has been used to 'click' guest molecules in the dendritic host via secondary interactions and will be discussed in Chapter 8.[70]

3.5 Experimental Section

General Methods and Materials

Chloroform, dichloromethane, toluene and hydrochloric acid were of p.a. quality and used as received, except for dichloromethane which was distilled prior to use. Water was demineralized before use. The synthesis of NH_3-*dendr*-$(NH_2)_3$ is described below. The synthesis of carboxylate-functionalized dendrimers, DAB-*dendr*-$(COO^-Li^+)_n$ (n = 4, 8, 16, 32, 64) is described in Chapter 2. The synthesis and characterization of poly(propylene imine) dendrimers with an apolar periphery, DAB-*dendr*-(NHCO-Ad)$_n$, DAB-*dendr*-(NHCO-$C_{15}H_{31}$)$_n$, DAB-*dendr*-(NHCONH-Ad)$_n$ and DAB-*dendr*-(NHCONH-$C_{16}H_{33}$)$_n$ with n = 4, 8, 16, 32, 64 is described in Chapter 2.

Synthesis of NH_3-*dendr*-$(NH_2)_3$ [*N,N,N*-tris(3-aminopropyl)amine]

N, N, N-tris(2-cyanoethyl)amine[71] (20 g, 0.113 mol) was dissolved in 150 ml of toluene and transferred to a Parr reaction vessel. Three grams of Raney-Cobalt catalyst suspension in water was decanted, rinsed with methanol (3 times) and toluene (once), and added to the Parr reactor. The solution was purged three times with hydrogen, and 4.4 g ammonia was added. The system was stirred mechanically at 80 bar hydrogen pressure. The temperature was increased stepwise from 30 °C (1 h), 55 °C (1 h), 75 °C (1 h), to 105 °C (24 h). After cooling and releasing the pressure, the catalyst was removed by filtration over diatomaceous earth on a glass filter. Removal of the solvent and the distillation afforded pure product as a colorless liquid (9.5 g, bp 99-102 ° at 0.02 mbar). Characterization data (IR, ^{1}H and ^{13}C-NMR) agree with data reported in ref 72.

^{15}N-NMR Measurements of Amine-Functionalized Dendrimers

Solutions for NMR were made in demineralized water, with concentrations of approximately 5 g of dendrimer or oligomer in 5 g of H_2O. However, due to the exponential increase in the number of nitrogen nuclei, the concentration of basic sites remain fairly constant. Samples were prepared and kept under argon. pH measurements were performed with a Schott CG840 instrument using a combination glass electrode (Schott N 37A), and the pH was adjusted by stepwise addition of concentrated HCl (16 mol/kg) or concentrated NaOH (between 5 mol/kg and 15 mol/kg). The pH-values below 2 and over 11 are readings of the pH-meter only and are not reliable. The data points at these extreme pH-values ate added to demonstrate the behavior of the investigated molecule under these conditions. Since the pH-electrode was calibrated in standard buffer solutions, the high ionic strength (over 1 mol/kg) and the high concentrations of the molecules under investigation will lead to an additional potential difference which will influence the pH-values. Therefore in the range between 2 and 11, the pH-values should be read as having an error of ± 0.5 or larger on an absolute scale.

Spectra were obtained on a Bruker AM-400 spectrometer at 40.55 MHz with a switchable pretuned four nucleus probehead in 5 mm NMR-tubes. The diameter of the insert was 2 mm. A 20 kHz spectral width was

used with 64 K datapoints. A 90° pulse of 7 μs and a delay of 60 s were used for the inverse-gated proton-decoupled experiments. This delay is much larger than the T_1-relaxation times of the nitrogens; the spectra are recorded under 'fully relaxed' conditions. Generally, more than 100 scans were needed for one spectrum due to the low ^{15}N abundance (0.36 %) resulting in rather long measurement times: 2 h for each 100 scans. The field-frequency lock on the spectrometer was obtained with an internal capillary tube containing CD_3NO_2. Chemical shifts are determined with an external reference of CD_3NO_2 (δ = 380.23 ppm)[73] and, for convenience, expressed in terms of the, often used, fictitious scale with liquid NH_3 at 25°C as reference (δ = 0 ppm).

Potentiometric Titration Experiments of Acid-Functionalized Dendrimers

Potentiometric titrations were carried out at (22±1) °C, with a VIT90 Video Titrator and a combined electrode (Radiometer, Copenhagen). Electrode calibration was based on buffer solutions p*H* 7 and 10 (Titrisol, Merck). The titrations were performed with HCl and KOH (Titrisol, Merck) in 0.1 M and 1.0 M KCl (p.a., Merck). The condition of constant ionic strength throughout the measurement was fulfilled using acid and base in the same concentrations as the supporting electrolyte. The contribution of the dendrimer concentration to the ionic strength was negligible (< 10^{-2} M sites). More detailed information about both the method and the analysis is given in a previous publication.[15] For all titrations the degree of protonation could be reproduced within an error of ± 1% within the p*H*-range of 2.5-11.
The nitrogen content, necessary to calculate the degree of protonation, was determined with a TN 3000 nitrogen analyzer (Euroglas, Delft, the Netherlands).

^{1}H-NMR and ^{13}C-NMR Spectroscopy

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-400 spectrometer at 400.13 MHz and 100.62 MHz respectively. Chemical shifts are given in ppm (δ) relative to TMS. All spectra were recorded at 298 K with unless noted otherwise.

IR Spectroscopy

Infrared spectra were recorded at 298 K on a Perkin Elmer 1605 IR spectrophotometer operating between 4400 and 450 cm^{-1} using a 1 mm cell with NaCl windows. All spectra were obtained after substraction of a solvent-spectrum. Dichloromethane was used as the solvent and typical concentrations of the endgroups were 5 mM.

Differential Scanning Calorimetry

Transition temperatures and thermodynamic data of the poly(propylene imine) dendrimers functionalized with apolar endgroups were determined on a Perkin-Elmer Pyris 1 under a nitrogen atmosphere with heating and cooling rates of 20 $K \cdot min^{-1}$.

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Dendritic Extractants:

Properties and Applications

4

Abstract: *A new family of tertiary amine extractants is obtained by modification of the poly(propylene imine) dendrimers with apolar endgroups, like palmitoyl or adamantyl units. The dendritic extractants are very effective and selective in the transfer of anionic solutes from an aqueous medium into an organic phase, typically dichloromethane or toluene. The interaction between the solute and the dendrimer depends on the acidity of the solute and depends strongly on the pH of the aqueous medium. The dendrimer generation determines the number of tertiary amine sites, and as a consequence determines the amount of solute molecules that can be extracted per dendrimer. The endgroups determine the solubility characteristics of the dendritic molecule, but have no major effect on the extraction characteristics. Palmitoyl-functionalized dendrimers are applied in a commercial MPPE-technology™, a purification technology of aqueous (waste)streams and extend the range of solutes that can be removed. Modification of a fifth generation poly(propylene imine) dendrimer with perfluoro-octanoyl chains enables the extraction of water-soluble solutes into supercritical-carbon dioxide with maximum loadings that agree well with that of palmitoyl-dendrimers in organic media using comparable conditions.*

Part of the work described in this Chapter has been published: Baars, M.W.P.L.; Froehling, P.E.; Meijer, E.W., *Chem. Commun.* **1997**, 1959-1960.

4.1 Introduction

Liquid-liquid extraction is a well-known technique in the field of (preparative) organic, inorganic and analytical chemistry and is an efficient, economical and environmentally friendly method for the separation of products.[1, 2] The technique is based on the transfer of a substance (solute) from one liquid (*e.g.* aqueous phase) to a second liquid (e.g. organic phase), the latter being reasonably immiscible with the first one. Extractants are used to influence the distribution of the solute molecules between the two phases[3] and are, therefore, of vital importance in commercial purification processes of waste[4] and process streams, including fermentation processes.[3, 5–9]

Acidic extractants, like alkylphosphoric acids and alkylcarboxylic acids can extract positively charged (metal) ions,[1] while basic extractants, like amine extractants, are capable of extracting acids from water to the organic phase. The latter extractants, however, are also capable of complexing metal-containing species. Primary, secondary and tertiary amines are interesting extractants because of their organophilic nature (high solubility in organic solvents) and their basicity.[10–12] Well-known amine extractants are tri-*n*-octylamine (TOA), trilaurylamine (TLA), diisododecylamine (DIDA), Aliquat 336, Alamine 336 and Amberlite LA-2. For instance, the extraction of anionic species, *e.g.* citric acid or lauric acid are based on acid-base interactions.[13]

Eyal *et al.*[10] showed that the extraction of acids by amine-based extractants is determined by four major effects: a combination of ion-pair formation, H-bonding interactions, solvation and anion exchange interactions. Ion-pair formation takes place when the amines are basic enough to bind a proton to form the ammonium-cation. This cation further binds to an anion to maintain neutrality. If the amine is not basic enough to dissociate the extracted acid, it can form an H-bond with the acid. Furthermore, ion-pairs formed on extraction by strong amines are in many cases basic enough to interact with additional acid molecules through H-bonds. The term solvation is used for extraction that is due to replacement of water molecules by solutes without any specific interaction. Anion-exchange may take place on equilibrating an aqueous solution of an acid or its salt with an extractant comprising of an amine salt, *i.e.* protonated or alkylated. Ion-exchange depends on hydrophilicity and pK_a of the acids that are present. Except for extreme cases (very strong or very weak acid) extraction is in many cases determined by more than one mechanism and in most cases an intermediate between ion-pair and H-bond. Furthermore, these acid-base interactions are extremely sensitive to the type and polarity of the eluent (organic medium),[10, 12, 14] concentration of the acid used,[12] pH of the aqueous phase[3] and temperature of the extraction process.[15–17] Extraction properties can also be influenced by the use of 'modifiers'[3] or 'additives'.[18] As a consequence, temperature and

pH can be used as a tool to regulate the amount of extraction, or to regenerate the desired anionic compounds.

In the previous chapter it has been shown that the tertiary amines in the dendritic interior of the poly(propylene imine) dendrimers can be protonated with inorganic acids. Previously, it has been shown by Stevelmans *et al.*[19] that palmitoyl-functionalized[20] poly(propylene imine) dendrimers are used to increase the compatibility of anionic dyes, like Rose Bengal in organic media. Later, deSimone *et al.*, [21a] Tomalia *et al.*,[21e] and recently Crooks *et al.* [21b] and Vögtle[21c] showed that amine-based dendrimers can be used in liquid-liquid extractions.

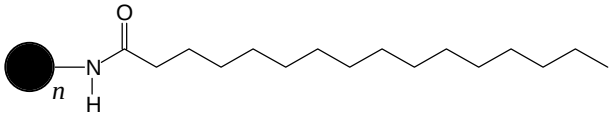
This chapter addresses the extractant properties of poly(propylene imine) dendrimers with an apolar periphery as a function of pH, temperature and eluent used. Also the effect of generation and type of endgroups is discussed. Because of the high amount of tertiary amines availabe in the dendritic interior[22] and the presence of a polar micro-environment, the dendritic extractants prove to be a new family of macromolecular extractants with a high reversibility, effectivity and selectivity. The dendritic extractants are also compared with tertiary amine extractants like TOA. Subsequently, the extractant–solute complexes are characterized with UV/vis spectroscopy and small angle X-ray scattering (Section 4.3). Moreover, these dendritic extractants have been applied in a commercial MPPE-technology[23] and the preliminary results are discussed in Section 4.4. With the use of dendritic extractants, the range of products that can be separated is significantly broadened, without major changes to the developed commercial process. The possibilities of dendritic extractants are extended by a functionalization of the dendrimers with perfluoroalkyl units (Section 4.5)[24] and enables the extraction of anionic solutes in environmentally friendly solvents, using supercritical carbon dioxide, and allows for a comparision with the extractant behavior in organic media.

4.2 Liquid-Liquid Extraction

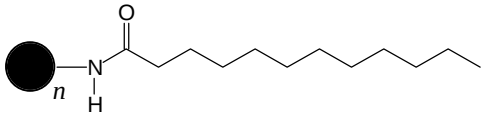
4.2.1 Setup and Characteristics

Dendritic Extractants. The dendritic extractants (Scheme 4.1) have been obtained by modification of the amine-functionalized poly(propylene imine) dendrimers with alkyl derivatives (**A**-**C**), a tBOC-protected amino acid residue (**D**) or perfluoroalkyl derivatives (**E**). Dendrimers **A**-**D** are discussed in section 4.2, 4.3 and 4.5, while perfluoroalkyl dendrimer (**E3-E5**) are discussed in Section 4.4.Synthesis of **A1-A5** and

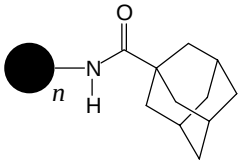
C5 is already discussed in Chapter 2, the synthesis of **E5** is discussed in this chapter, whereas synthesis of **B3**, **B5**[19] and **D5**[25, 26] is described in literature. Different types of anionic solutes have been used (Scheme 4.2), for instance xanthene dyes like Fluorescein (**I**) or Rose Bengal (**IV**) and azobenzene dyes, like Methyl Orange (**VIII**) or New Coccine (**IX**). These solutes allowed characterization of the extraction process with UV/vis spectroscopy.



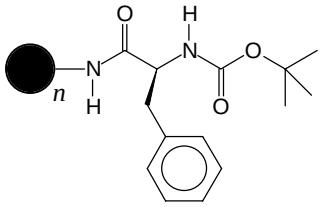
n = 4 : **A1**
n = 8 : **A2**
n = 16 : **A3**
n = 32 : **A4**
n = 64 : **A5**



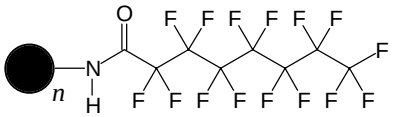
n = 16 : **B3**
n = 64 : **B5**



n = 64 : **C5**



n = 64 : **D5**

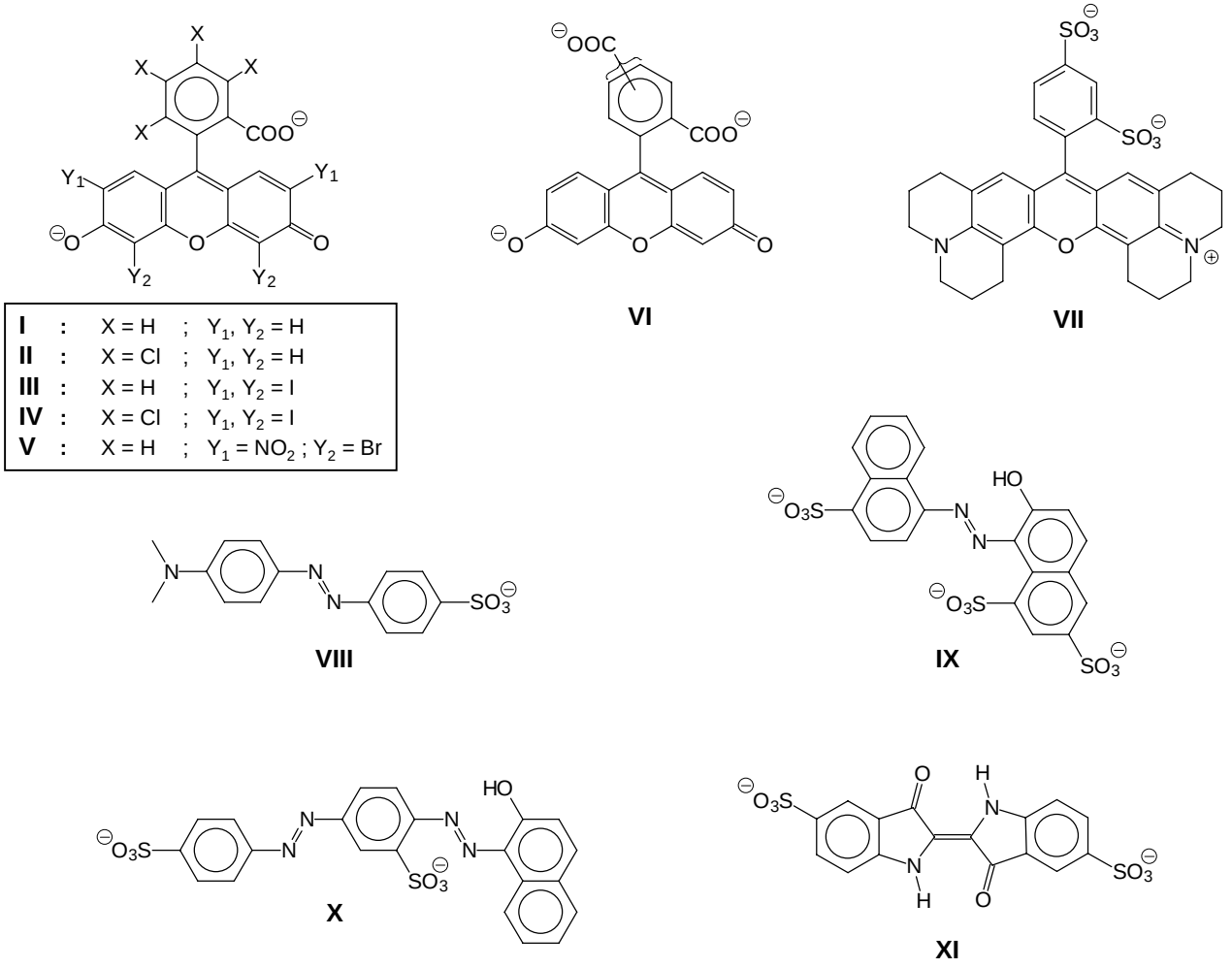


n = 64 : **E5**

Scheme 4.1: *Dendritic extractants that were used in the extraction experiments: palmitoyl-dendrimers (**A1**-**A5**), lauroyl-functionalized dendrimers (**B3** and **B5**), adamantyl-functionalized dendrimers (**C5**), t-BOC-L-Phe dendrimers (**D5**). Marker **A**-**D** indicates series, 1-5 indicates generation number and n represents number of endgroups.*

The functionalized poly(propylene imine) dendrimers are soluble in organic media and in a liquid-liquid extraction experiment, no distribution into the aqueous phase is observed.[27] This property is one of the main prerequisites for an effective extractant molecule.

Type of solutes. The anionic solutes show good solubilities in aqueous media and in a two phase system (aqueous / organic phase, pH > 2) the transfer of the solutes into the organic medium is negligible, if no additives are used.



Scheme 4.2: *Solute molecules: Fluorescein (**I**); 4,5,6,7-Tetrachlorofluorescein (**II**); Erythrosin B, (**III**); Rose Bengal (**IV**); Eosin (**V**); Carboxyfluorescein (**VI**); Sulforhodamine (**VII**)[28]; Methyl Orange (**VIII**); New Coccine (**IX**); Biebrich Scarlet (**X**); Indigocarmine (**XI**). All solutes are depicted in the anion-form.*

Conditions used. The transfer of anionic solutes is studied from an aqueous medium, of a certain pH, into the organic phase. Hereto, the two phase system is vigorously stirred for 5 minutes to reach equilibrium conditions. In all cases the aqueous media ($2 < pH < 12$) are buffered . These buffers (type: Hydrion, Aldrich) are necessary to ensure a constant pH during the extraction experiment. Test experiments further showed that the inorganic solutes present in these buffers, have no significant effect on the extraction process. Dichloromethane is used as solvent for extraction. Extraction is performed at room temperature. Dendritic extractant **A5** is used unless otherwise noted and equal volumes are used for both phases. Unless otherwise noted, extractant-solute ratios of 1:1 are used in the setup, with typical concentrations of dendritic extractants of *ca.* $2.5 \cdot 10^{-5}$ M to allow easy UV-detection of the solute.

Definition of Extraction Yield and Extractant Value. *The extraction yield* is defined as the percentage of solute that is transferred from the aqueous phase into the organic medium. In all cases the extraction yield determined is specified for a (typical) extractant-solute ratio. The extraction yield is determined by measuring the decrease and increase in absorption of the aqueous phase and organic layer, respectively. In all cases a decrease in absorption of the aqueous layer yields a complementary increase in absorption of the organic layer. The absorption is determined at λ_{max} in both solvents for all dyes, where a small solvatochromic shift in λ_{max} in organic solvents is observed. The characteristics of the dendrimer-solute complexes in organic media are discussed in Section 4.3.

Furthermore *an extractant value* is defined as the pH at which 50% of the solute is transferred to the organic phase and used only in the case of dendrimer/dye ratios of 1:1. This value is used to compare the extraction of different solutes and it is even attempted to correlate these to the pK-values of the solute.

4.2.2 pH-Dependence

The extraction yield of **II** with **A5** was determined as a function of pH. Figure 4.1 shows a complete transfer of the solute at low pH up to pH = 7.4 (solid line). At higher pH a sharp decrease of the extraction yield is observed. The dashed line shows the back-extraction of **II** as a function of pH, using an organic phase prepared by extraction at pH = 7. The dendrimer-solute interactions are reversible and depend strongly on pH, resulting in an extraction efficiency which is strongly modulated by the pH of the aqueous medium.

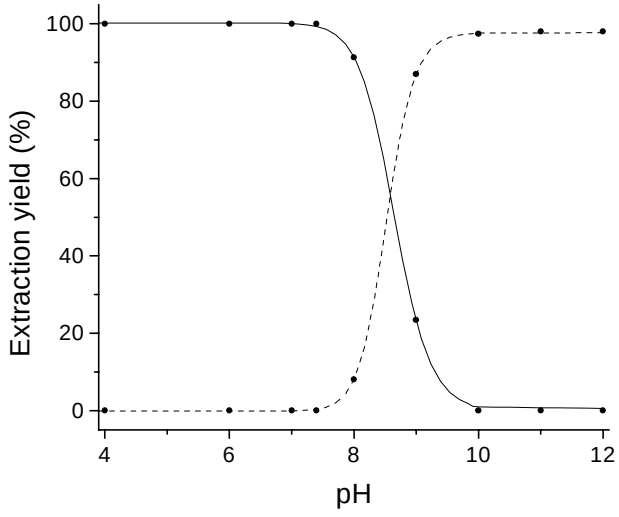


Figure 4.1: *Extraction yield of **A5** as a function of **pH** for solute **II**. (——) Extraction of **II** from aqueous phase to organic phase; (– – –) Back-extraction of **II** from organic phase to aqueous phase.*

The pH-dependent properties of the extraction efficiency can be related to the protonation degree of the dendritic extractant. At lower pH all tertiary amines can be fully protonated.[29] [30] The interaction of the extractant with the anionic solutes becomes stronger with increasing proton concentration. Previously, macrocylic oligo-amines have been reported for which the binding constants with anions becomes higher as the number of protonated host nitrogen atoms increases.[31, 32] Moreover, when model compounds are used based on propylamine but without tertiary amines, no extraction takes place. The reversible host-guest interactions of the extractant-solute complex contrast to 'the dendritic box', in which a restricted number of guests could be encapsulated[33–36] and released after chemical modification of the shell only.[37] Figure 4.2 represents the extraction yield of a series of xanthene dyes, **I**-**IV**. The range over which complete extraction is possible, is strongly dependent on the structure of the xanthene dye. The larger the number of halogen substitution, the stronger is the extraction. This effect can be rationalized by an increase in acidity when going from **I** to **IV**. Also the higher hydrophobicity of **III** and **IV**, due to the incorporation of iodine-atoms in the skeleton,[38] are likely to improve extraction characteristics.

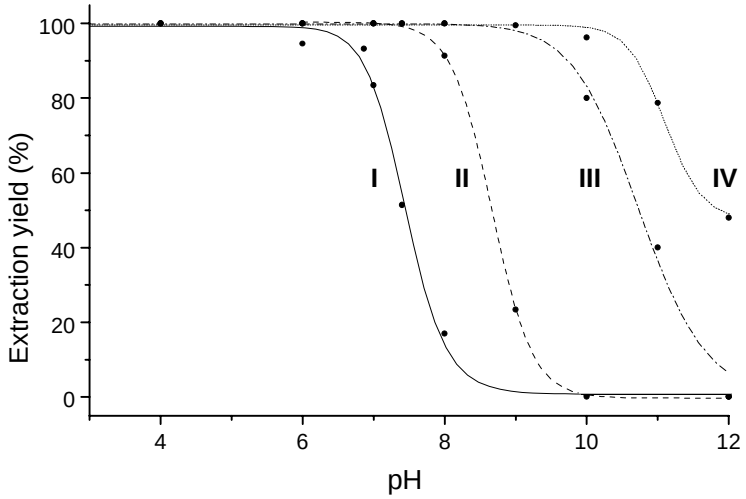


Figure 4.2: *Extraction yield of **A5** for xanthene dyes **I**-**IV** as a function of pH.*

Indicative of the strength of extraction is the so-called extractant-value, *i.e.* the pH at which 50% of the solute is extracted, listed in Table 4.1 for solutes **I**-**XI**. A large difference in the extractant value enables a selective extraction of *one* solute out of mixture of solute molecules. For instance, if we perform an extraction experiment of a mix of Fluorescein (**I**) and Rose Bengal (**IV**) (1:1 mol/mol) with **A5** at pH = 10, a selective extraction of Rose Bengal into dichloromethane takes place, whereas all Fluorescein is retained in the aqueous medium. Even in the case of Fluorescein/Rose Bengal ratios of 10000:1, complete extraction of the latter compound takes place, indicating that the dendritic extractants show high selectivity, comparable to complexation of alkali-metals by crown-ethers

derivatives.[39] Finally, dendritic extractants can be used as a shuttle for the selective transport of solutes from one aqueous phase (with a low pH) to another aqueous medium with a higher pH, via an organic phase[40] similar to liquid membrane systems used by Stang *et al.*[41] and others.[42]

Table 4.1: *pK_a and extractant values of solutes **I-XI** using extractant **A5**.*

Solute	pK_a (–)	Extractant value (–)
I	6.99 (ref. 43)	7.5
II	(–)	8.7
III	4.18	10.7
IV	3.72	11.9
V	(–)	10.4
VI	7.45	6.8
VII	(–)	(n.d.)
VIII	3.40 (ref.44)	10.0
IX	(–)	8.8
X	(–)	11.0
XI	(–)	8.4

(-) = not reported in literature. (n.d.) = not determined

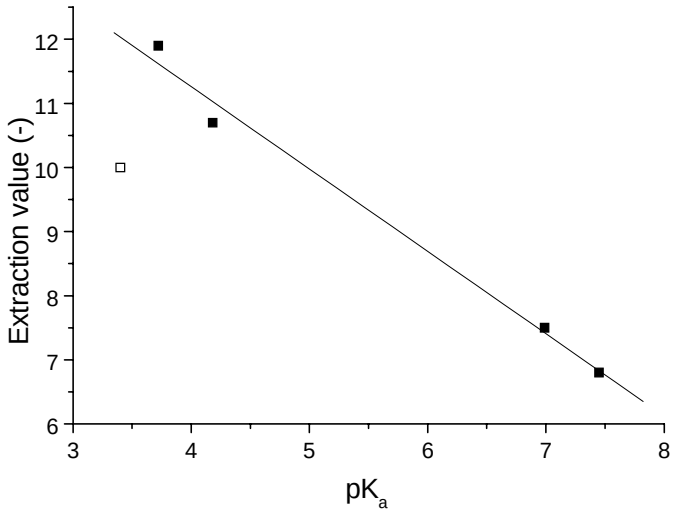


Figure 4.3: *Correlation between pK_a and extraction value for the anionic solute molecules:* ■ *xanthene dyes,* □ *azobenzene dye.*

Although, it was difficult to obtain pK_a-values from literature data for most of the solute molecules, in case of the xanthene dyes **I**, **III** and **IV** a nice trend can be observed: the extractant value increases for more acidic solutes. This is a general trend for all solute-molecules and agrees well with the results of Eyal *et al.*[10]: the stronger the

acid, the stronger the (electrostatic) extractant-solute interactions and as a result the larger the amount of solutes that is extracted at a certain pH. However, the difference in chemical nature for solutes **I-XI** makes it almost impossible to correlate pK_a-values with the corresponding extractant values as can be concluded from the deviation of Methyl Orange, an azobenzene dye (□), compared to the xanthene series (■) (Fig. 4.3). Apparently, not only pK_a-values play an important role in the extraction process, but also the nature (polarity) of the solute.[10]

In case of Rose Bengal (**IV**), which displayed the strongest extractions of solutes **I-XI**, the extraction yield at different pH-values is studied as a function of the dendrimer/solute ratio (Fig. 4.4). At pH = 14 and 11, the solute is distributed over the two phases and upon increasing the concentration of dendrimer (larger dendrimer/solute ratio), more solute can be extracted into the organic medium. However, at pH = 7, the extraction is much stronger and even at very low dendrimer-to-dye ratios, extraction is complete. Figure 4.4 (right) indicates that a fifth generation palmitoyl-dendrimer with 62 tertiary amines extracts *ca.* 50 dye-molecules. Ideally, this suggests that, with strong dendrimer-solute interactions and every tertiary amine available for protonation, a 1:1 complexation between solute and tertiary amine should be possible. In comparison, for Fluorescein (**I**), the complexation is weaker and the fifth generation dendrimer complexes one dye molecule, on the average.

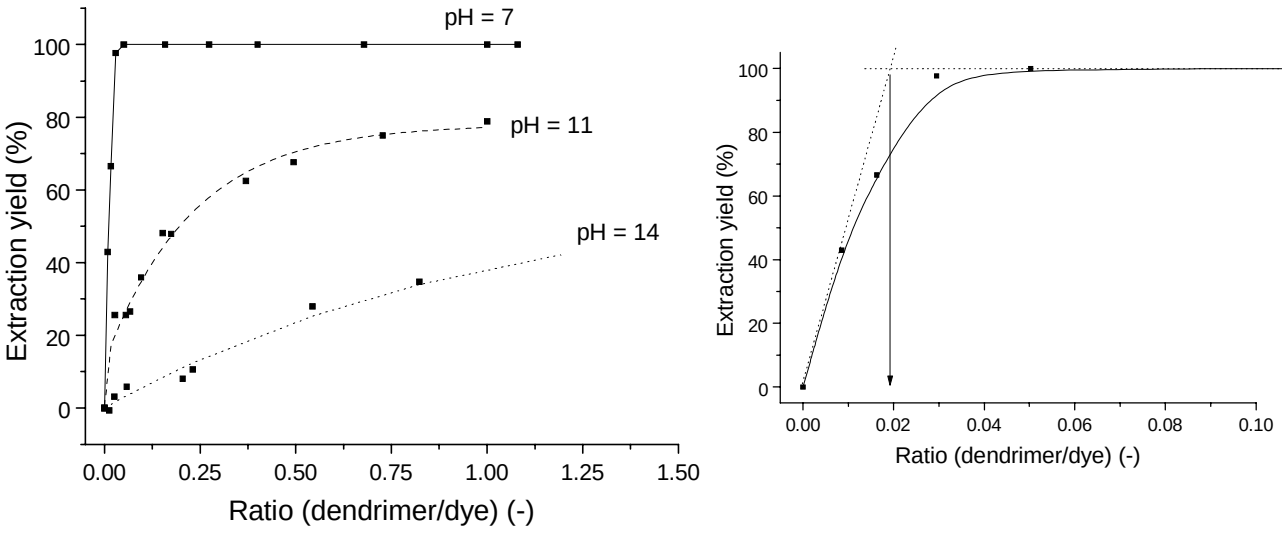


Figure 4.4: *(left) Extraction of Rose Bengal (**IV**) as a function of the dendrimer-to-dye ratio for three different pH-values, using **A5** as the extractant. (right) Enlarged curve for extraction at pH = 7; a cut-off is observed at a ratio of ≅ 0.020, i.e. initially 50 molecules of **IV** are extracted per dendrimer **A5**.*

4.2.3 Solvent dependence

The extraction of anionic solutes by tertiary amine extractants is based on ion-pair formation. The organic medium has a tremendous effect on the stability of these ion-pairs, and usually a large solvent dependence is observed for extraction in solvents of different polarity.[12, 14] In this section the solvent-dependence for (a family of) dendritic extractants is discussed. All experiments were conducted with the same number (concentration) of tertiary amine sites. The solute chosen for these experiments was Fluorescein (**I**), which shows relative weak interactions with the dendritic extractants as has been shown in Figure 4.2 and as a consequence is more sensitive for the effect of generation.

The extraction of **I** using **A1** as the extractant is dependent on the polarity of the solvent (Fig. 4.5, left). When the polarity of the solvent decreases, the observed extraction value decreases by one pH-unit indicative of a stronger extraction. This is in agreement with results for low molecular weight extractants,[10, 12, 14] but contrasts with the results for **A5** (Fig. 4.5, right) in which the influence of solvent is almost negligible. Presumably, the branched dendritic structure yields a strong basic micro-environment for the higher generations in which the dendrimer-solute interactions will be shielded from the organic medium, thereby favoring the extraction compared to the lower generations in which the extractant-solute interactions are sensitive towards solvent used. As a consequence, even with the same amount of tertiary amines used, a higher generation dendrimer shows a better extraction performance.

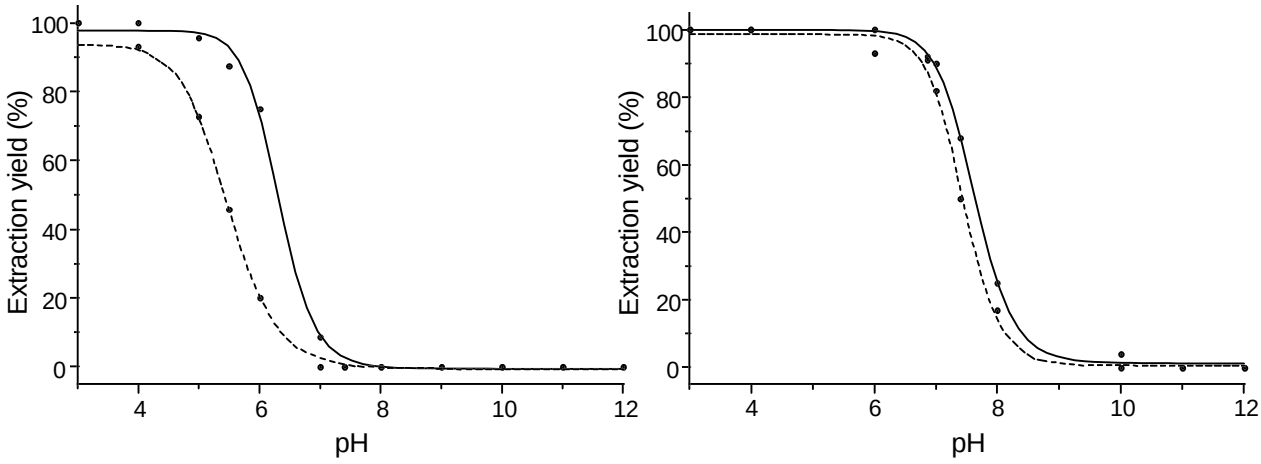


Figure 4.5: *(left) Extraction of **I** with **A1** in dichloromethane (——) and toluene (– – –); (right) Extraction of **I** with **A5** in dichloromethane (——) and toluene (– – –).*

4.2.4 Effect of Generation / Molecular Weight

When using higher generation dendrimers, the number of tertiary amine sites increases. This should be reflected in a (maximum) capacity of anionic solutes molecules extracted per dendrimer; a value that is generation-dependent.

When comparing the palmitoyl-functionalized poly(propylene imine) dendrimers **A1**–**A5**, we can conclude that the load of solute molecules is directly related to the number of tertiary amines in the dendritic interior, in case of solutes with a strong interaction with the dendrimer, like Rose Bengal (Fig. 4.6). Furthermore, the extraction of Fluorescein (**I**) is investigated in dichloromethane for different dendrimer generations (**A1** and **A5**) and compared with tri-*n*-octylamine, using similar concentrations of tertiary amines. Tri-*n*-octylamine (TOA) is not capable of extracting Fluorescein (**I**), dendritic extractants **A1** and **A5** show efficient extraction with extractant values of 6.4 and 7.7, respectively. The difference between dendritic extractants and TOA can not be explained by a difference in the tertiary amine sites. However, with increasing molecular weight of the dendrimer, more tertiary amine sites are located in close proximity and the polarity will increase due to a dendritic micro-environment exists. In In the case of solutes with weak dendrimer-dye interaction, like **I**, a strong difference in extraction is displayed as a function of generation: (i). The number of complexed dyes can be smaller and (ii) the relative amount of dye that is complexed per tertiary amine changes with generation.

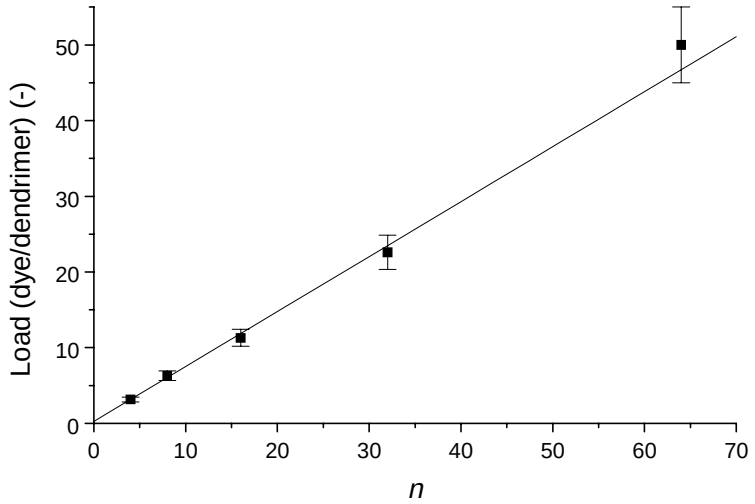


Figure 4.6: *Maximum load of Rose Bengal (IV) per dendrimer as a function of the number of endgroups n in dendrimers **A1**-**A5**, as extracted at pH = 7. The loadings for **A1**-**A5** are determined from titration experiments as depicted in Figure 4.4.*

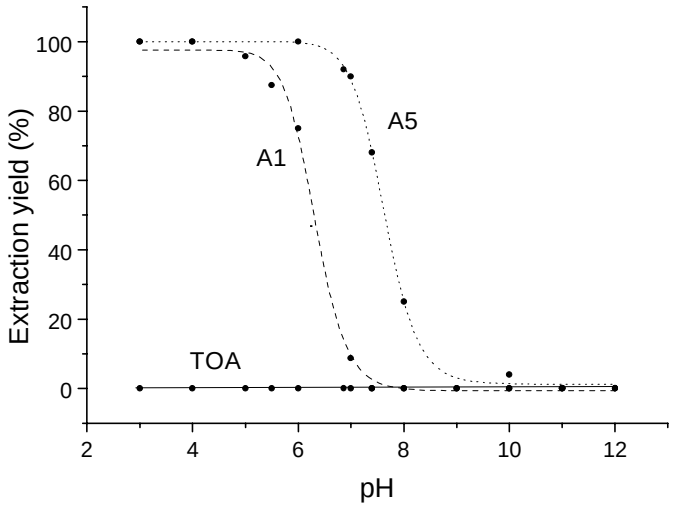


Figure 4.7: *Extraction of **I** with TOA, **A1** and **A5** using dichloromethane as eluent.*

4.2.5 Effect of Endgroups

The poly(propylene imine) dendrimers have been modified with different endgroups, like palmitoyl, lauroyl, adamantyl and *t*-BOC-*L*-phenylalanine, to yield series **A**-**D**, respectively. In all cases, these dendrimers show good solubilities in both dichloromethane and toluene, except for the adamantyl-functionalized dendrimers which are not soluble in toluene. In this section, the effect of endgroups is discussed by studying the extraction of Rose Bengal (**IV**) for **A5**, **C5** and **D5** as a function of pH (Fig. 4.8), since one might expect a limiting load for different extractants.

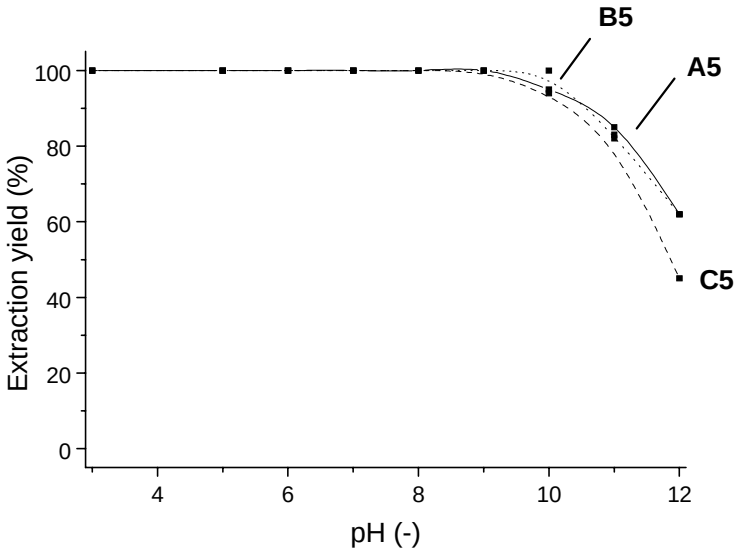


Figure 4.8: *Extraction of **IV** with **A5**, **C5** and **D5** in dichloromethane. Dendrimer-solute ratio = 1:1.*

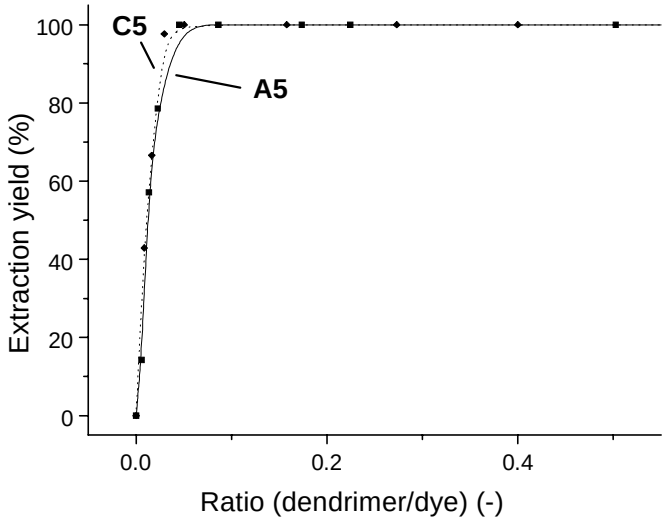


Figure 4.9: *Extraction of **IV** with **A5** and **C5** in dichloromethane as a function of the dendrimer-solute ratio.*

If the experiment is performed at a high dendrimer-to-solute ratio, *i.e.* 62 tertiary amines per solute molecule (dendrimer/dye = 1:1), it can be concluded that the extraction performance is independent of the type of endgroups. Moreover, the extraction of **IV** has been investigated as a function of the dendrimer-to-solute ratio for extractants **A5** and **C5** to determine the maximum load possible (Figure 4.9). The extraction is the same for both extractants, even at very low dendrimer-to-solute ratios. In both cases a large amount of solutes can be extracted per dendrimer. Also for the extraction of other solutes, like Fluorescein (**I**), no large endgroup-effect is observed. As a consequence, the endgroups of the dendrimer seem to have a minor effect on the extraction characteristics, but only important for the solubility of the extractant molecule.

Finally, it is important to note that the different series of dendritic extractants vary in type and shape of the endgroups. Whereas **A5** consists of flexible, linear endgroups, dendrimer **C5** and **D5** contain bulky, rigid endgroups. A study of the amphiphilic properties of these extractant molecules at the air/water interface,[20] indicated that the conformational freedom of the dendrimers changes drastically with **A5** that can invert in shape and **C5** and **D5** that behave as a shape-persistent spheres. Differences between the conformational freedom of dendrimers **A5** compared to **C5** and **D5** do not affect the extraction properties and it is therefore suggested that the uptake of solute molecules at the interface does not require drastic changes in the conformation of the dendritic extractant molecules. The influence on the extraction in all cases is investigated under equilibrium conditions; kinetic effects are not addressed in this study.

4.2.6 Conclusions

In the previous section, the use of poly(propylene imine) dendrimers with an apolar periphery as extractants for anionic solutes is discussed. The extraction can be explained by acid-base interactions between solute and dendrimer and depends strongly on the acidity of the solute and the basicity of the extractant. The host-guest interactions are therefore reversible and depend strongly on pH, resulting in an extraction efficiency which is strongly modulated by the pH of the aqueous medium. The dendrimer generation determines the number of tertiary amine sites, and as a consequence, the amount of solute molecules that can be extracted per dendrimer. For instance for Fluorescein, **I**, only 1-2 dyes per dendrimer can be extracted with a fifth generation dendrimer, but for Rose Bengal, **IV**, it is possible to extract up to 50 molecules, yielding an assembly with a molecular weight of 70 kD, *ca.* 2.5 times the molecular weight of the dendrimer. The results suggest that a maximum of 1:1 complexation of the tertiary amine with the solute should be possible. The endgroups determine the solubility characteristics of the dendritic molecule but have no major effect on the extraction characteristics. A large difference in extraction is observed between a fifth generation dendrimer and a first generation generation or tri-*n*-octylamine (TOA). Moreover, a fifth generation extractant shows a solvent independent behavior in contrast to the solvent dependent properties of a first generation extractant; such solvent dependent properties are commonly observed for other low molecular weight extractants. The absence of the solvent-dependence in case of a fifth generation can be explained by a local micro-environment consisting of a high concentration of the tertiary amine sites.

4.3 Characterization of the Extractant-Solute Complexes

Whereas in Section 4.2 the liquid-liquid extraction with dendrimers is characterized in terms of *extraction yield* or *extractant value*, the focus in this section is the characterization of the dendrimer as host for water-soluble derivatives.

4.3.1 UV/vis Studies

The extraction of anionic solutes, **I-XI**, has been studied at pH = 7 using palmitoyl-functionalized dendrimer **A5** with a dendrimer/dye ratio of 1:1. Figure 4.11 shows the normalized UV-Vis spectra of **II** in an aqueous medium and in the organic medium (dichloromethane).

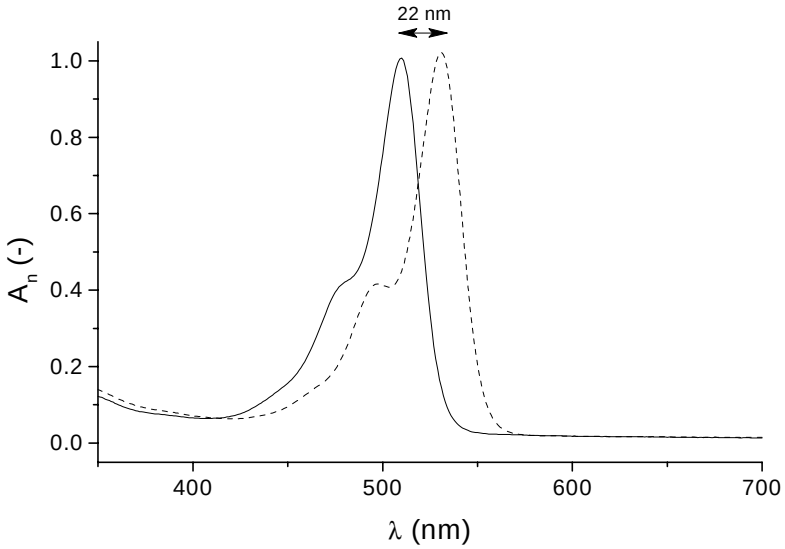


Figure 4.10: *Normalized UV-Vis spectra of **II** in the aqueous layer (——) and in the organic layer (– – –), when extracted with **A5**.*

Table 4.2: *UV/vis data of solutes **I-XI** in various media. Compared are λ_{max} for solutes **I-XI** in aqueous medium (pH = 7) and organic phase using **A5** or TOA as extractant.*

Solute	λ_{max} (nm)		
	H_2O	CH_2Cl_2	
		A5	TOA
I	491	509	(n.e.)
II	510	532	523
III	526	537	534
IV	551	566	556
V	519	533	522
VI	495	514	(n.e.)
VII	576	585	(n.d.)
VIII	464	425	423
IX	507	518	508
X	504	516	518
XI	618	612	(n.e.)

(n.e.) = No extraction takes place, unable to determine λ_{max}. (n.d.) = Not determined

A small solvatochromic shift (~ 20 nm) is observed upon transfer of solute, *i.e.* a xanthene dye, in the organic medium, probably due to the change in polarity of the organic medium and/or the interaction with the dendritic interior (consisting of tertiary amines). Table 4.2 shows the λ_{max} of the solutes in the two media. Similar measurements have been performed for tri-*n*-octylamine (TOA). In almost all cases the

shift in λ_{max} is largest in case of the dendritic extractants. Solute-dendrimer complexes of the highest generation show a rather solvent-independent absorption spectrum, when comparing dichloromethane and toluene, as can be explained from a shielding of the dye from the solvent.

These results have been observed previously in case of the dendritic box in which encapsulation of dyes in the dendrimer yielded a environment-independent absorption and emission profiles of the guest.[35] TOA and lower generation dendrimers show a somewhat smaller shift in λ_{max} and the absorption spectrum is dependent on the polarity of the solvent. Finally, the shifts in λ_{max} (see Table 4.2) are batochromic for most dyes except for Methyl Orange (**VIII**) which shows an hypsochromic shift in λ_{max}.

4.3.2 Small Angle X-ray Scattering Measurements.

UV/vis spectroscopy suggested the shielding of solute-dendrimer interactions for the higher generation dendrimers, but direct evidence on the localization of the solute in the complex is hard to determine. Investigation of the complexes with ^{1}H-NMR studies were unsuccessful probably due to the low relative concentration of the guest molecules compared to dendrimer resonances and due to a decrease in molecular motion. Finally, Small Angle X-ray Scattering (SAXS) measurements in solution have been used to determine the localization of the guest in the dendritic environment. SAXS is a well-known technique in the field of proteins and biochemistry, but relatively unknown in the field of dendrimers.[45–47] DeSimone reported the use of this technique for determining dimensions of the fluorinated extractants in the organic medium and it was shown that no particle aggregation took place. This technique, can be used to obtain detailed information on dimensions of dendritic macromolecules, similar to SANS-studies on dendritic macromolecules.[48, 49] Complexes are studied of host **A5** and guest **II** in THF, and the average load is varied between 0 and 12 molecules of **II** per dendrimer.

A radius of gyration of about 1.3 nm is derived from the scattering data of the unloaded dendrimer. Surprisingly, the radius of gyration is comparable to that of the amine-terminated poly(propylene imine) dendrimers.[50] The explanation is that the contrast between the chains and solvent is much smaller with respect to the contrast between core and solvent and that scattering is essentially arising from the dendrimer core. Thus, structural information is obtained directly from the core of the dendrimer upon addition of the guest. Table 4.3 summarizes the data of these investigations. Guinier plot representations of the scattering data recorded from the solutions are displayed in Figure 4.12. A small upturn at low q indicates that some aggregation takes

place but the predominant species is the single molecule, as also has been shown by Stevelmans *et al*.[19] who used Dynamic Light Scattering.

Table 4.3: *Characteristics of the investigated host-guest systems*

load	MW	rel. MW	I(q→0) [(a)]	R_g (nm) [(a)]
0	22426	1.00	100	1.29
1	22896	1.02	122	1.17
8	25826	1.15	134	1.08
12	27522	1.23	117	1.08

[(a)] data obtained from SAXS measurements, depicted in Figure 4.11

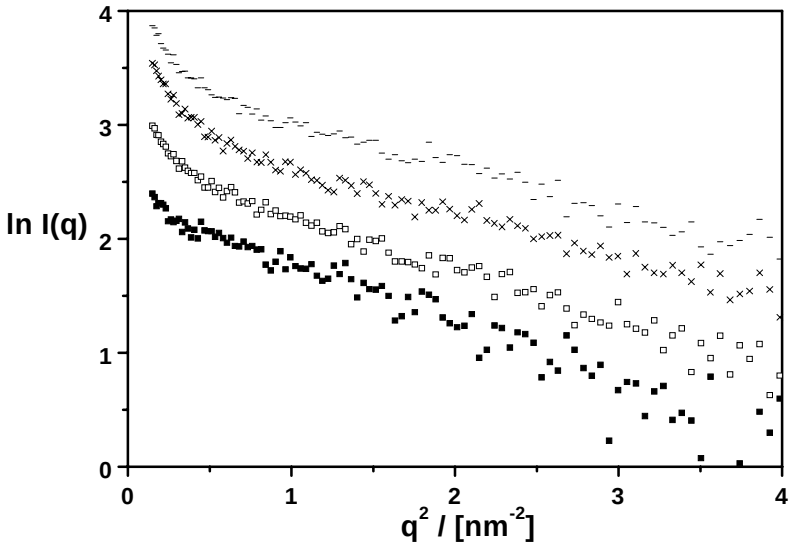
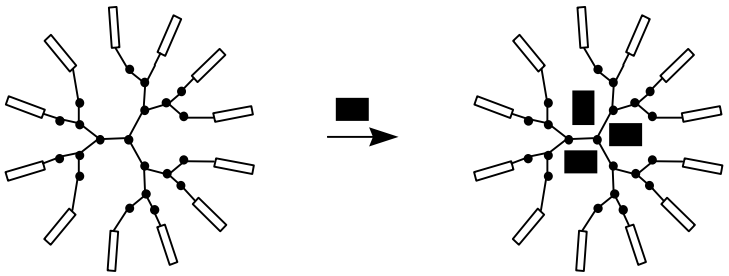


Figure 4.11: *Guinier plot representation of the scattering data of host-guest complexes:* ■ *no guest*, □ *1 guest*, × *8 guests*, – *12 guests*.

Based on the increase in molecular weight only, the forward scattering intensity should display an increase by the same relative values since the scattering intensity scales linearly with the volume (and molecular weight) of the complex, and provided that the scattering contrast remains unchanged. However, the increase in forward scattering appears to be much steeper. This might be connected to the incorporation of the dye molecules, each carrying four chlorine atoms. These electron-rich sites most likely cause a change in scattering contrast $\Delta\rho$, which results in the steeper increase in forward scattering. Although, some aggregation in the solutions takes place which is reflected by an upturn in the Guinier plots at very low q values, it is still possible to deduce the radii of gyration of the different systems, neglecting this region. A small decrease in the radius of gyration is observed with increasing number of dye molecules (Table 4.3). This in contrast to the expected increase in volume of the host-guest system and the subsequent increase of R_g. Whereas the definition of the radius of gyration

$$R_g^2 = \frac{\int_V \rho(r) r^2 \, dV}{\int_V \rho(r) \, dV}$$

reflects the electron density distributions of the systems, it can be concluded that, a decrease in the radius of gyration -despite an increase of the overall molecular weight - would indicate that the electron density in the center of the host-guest complex increases. This suggests a preferential organization of the guest into the interior of the dendrimer, close to the core. A cartoon is depicted in Scheme 4.3. These findings are supported by the distance distribution functions that were carefully calculated on the basis of the scattering pattern.



Scheme 4.3: *Cartoon of the preferential location of dye molecules in the dendrimer as the concentration of the dye is increased. One blue box represents roughly 4 dye molecules.*

Moreover, when guests are complexed by water-soluble oligoethyleneoxy-modified poly(propylene imine) dendrimers, similar results, *i.e.* a decrease in R_g, have been found. More details of this host-guest system and of details of the SAXS-studies will be provided in Chapter 5.

4.4 The Application of Dendritic Extractants

4.4.1 Introduction

The use of (liquid-liquid) extraction has found a wide-spread use in the purification of waste and process streams. Akzo Nobel has developed a commercial MPPE (Macro Porous Polymer Extraction) system,[51] which is a new, highly selective and guaranteed technology for removing hydrocarbons from water and ideal for process, waste and ground water treatment.[52, 53] With this technology up to 99.9999% of dissolved and dispersed hydrocarbons can be removed from the water by the MPPE. The technology consists of a column packed with MPPE-particles (Fig. 4.13) through which the contaminated water is passed. An extraction liquid,[54] *i.e.* an aromatic non-volatile liquid

within the polymer matrix removes the hydrocarbons in a single pass. The purified water passes out of the column to reuse or discharge. Regeneration of the extraction liquid containing particles is accomplished periodically in-situ with low pressure steam. The volatile hydrocarbons are removed by the stripping process, while the immobilized non-volatile extraction liquid is retained in the pores of the polymer.

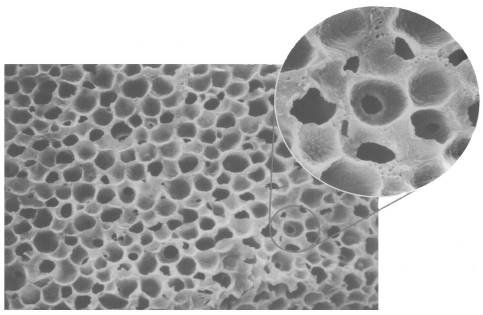
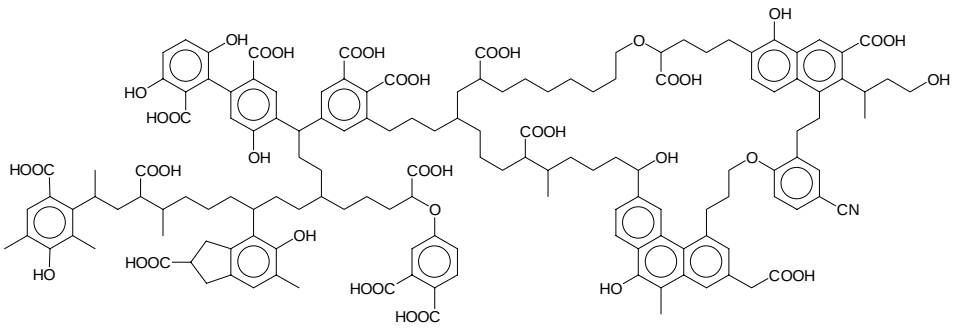


Figure 4.12: *Microscopic picture of MPPE-particle.*

Although the technique shows superior characteristics in the removal of aliphatic and aromatic hydrocarbons, as well as for chlorinated hydrocarbons, PCBs and PAHs, more hydrophilic contaminants like alcohols or ketones, phenolic residues or acids (carboxylic or sulphonic) can not be removed with this technique. Moreover, one of the problems in water treatment is the removal (extraction) of humic acids,[55–58] a biopolymer containing carboxylic acid and phenolic functionalities (Scheme 4.3). Several methods have been used sofar to study the removal of humic acids, including supercritical extractions,[59] however the results have not been satisfactory.



Scheme 4.4: *Proposed structure of the natural polyelectrolyte humic acid*

The similarity in functionality and structure of the humic acid with the xanthene dyes in Section 4.2.3, suggested that dendritic extractants could also be used in extraction of humic acid. As a first step, dendritic compounds are applied in MPPE-systems™, while maintaining the same process scheme (*i.e.* column setup, regeneration procedure). Dendrimer-based MPPE-particles are obtained by dissolving extractant **A5** into the extraction liquid (approximately 1 w/w%).

4.4.2 Characterisation of a Dendrimer-Based MPPE-System

The extraction of 4,5,6,7-tetrachlorofluorescein, **II,** was investigated by dispersing dendrimer-filled MPPE-particles in an aqueous medium. Efficient and full absorption of the solute occurred and the change in color of the particles (shift in λ_{max}), compared to the aqueous medium, was indicative a solute-dendrimer complex (see also 4.3.1). For MPPE-particles containing the extractant liquid but without dendrimer, no absorption takes place. Subsequently, the removal of Erythrosin B, **III**, from aqueous media (pH = 7, buffered) has been studied using the flow scheme as shown in Figure 4.14 (left). Typical mass transfer of **III** through a dendrimer-filled MPPE column is observed (Figure 4.14, right). The flow-rate has an influence on the mass transfer process, indicating that mass transfer resistance plays a significant role in the extraction process. The slower the feed is passed through the column, the more of the solute can be absorbed from the aqueous phase. A break through is observed at 100 ml in case of a flow of 2.5 l/hr or 160 ml in case of a flow of 1.2 l/hr, which indicates that equilibrium has not been fully established.

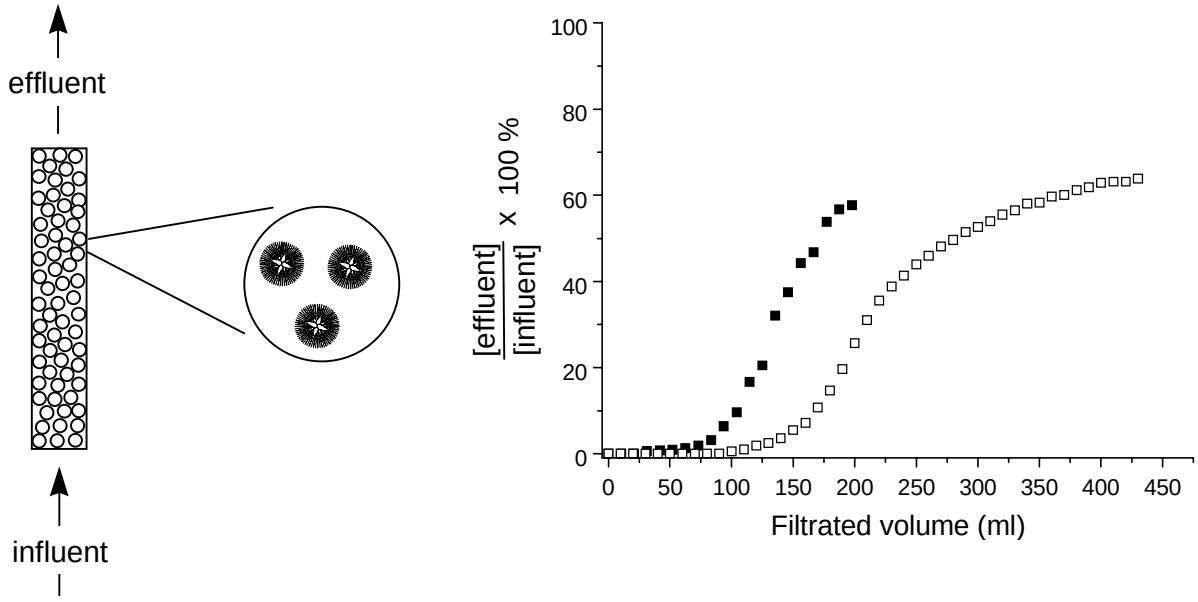


Figure 4.13: *(left) Flow scheme used for dendrimer-filled MPPE columns, (right) Relative concentration of III as a function of the filtrated volume for two different flow speeds:* ■ *2.5 l/hr*, □ *1.2 l/hr.*

The profile of the break through curve can be understood with a so-called 'mass-transfer zone' in the column. At a certain time *t*, an equilibrium exists between dye molecules in the influent and dye-molecules complexed to the dendrimers in the MPP-particles at the inlet at the bottom of the column, whereas in the upper part of the column a 'mass transfer zone' exists where the dendrimers are only partially loaded and with sites available for the complexation of the dye molecules. This zone moves up in

the column, as a function of time and the filtrated volume that is passed through. At a certain moment the 'mass transfer zone' reaches the end of the column and the effluent concentration starts to increase and a break through occurs. The molecular picture is the following: a dendrimer at the end of the column is faced with an increasing amounts of dye molecules, since the bottom part of the column is already saturated. The load of the dendrimer at the end of the column will further increase with a maximum loading that is related to the influent concentration. The maximum loading is obtained when a complete breakthrough is observed: at this point, equilibrium between the organic and aqueous phase is established with respect to partitioning of the dye molecules.

4.4.3 Regeneration Procedure

The regeneration of the dendrimer-filled MPPE particles was investigated using two approaches. Since it was shown in Section 4.2.2 that the solute-dendrimer interactions are dependent on pH, regeneration was studied by flushing the solution with a caustic aqueous solution (pH = 12). Although, initially a fast release of solute-molecules could be observed, not all solute-molecules could be removed, even after flushing with 1000 ml of the basic medium. Besides mass transfer limitations during regeneration, it is also likely that the distribution ratio is not favorable enough for complete regeneration with moderate amounts of basic solvent.

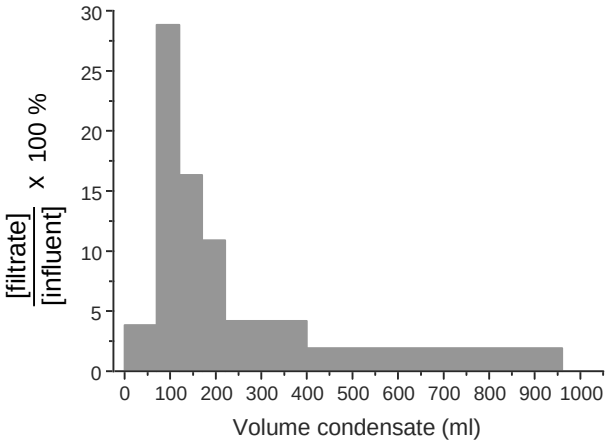


Figure 4.14: *Analysis of the amount of dye **III** relatively to the initial feed concentration used in Section 4.4.2.*

A second regeneration methodology uses low pressure steam, analogously to the current MPPE-process. Again, a fast release of solute molecules was observed and an exponential decrease in the concentration of solute particles could be observed as a function of the volume of condensed steam. (see Fig. 4.11). In contrast to the basic regeneration method, with 1000 ml of condensed filtrate the column was almost completely regenerated. The release can be rationalized by weaker acid-base

interactions between solute and dendrimer at high temperatures. The filtrate was further characterized with UV/Vis spectroscopy which indicated that the absorption spectrum of the filtrate did not reveal a distinct change. This means that decomposition of the dye, due to (partial) hydrolysis into smaller volatile particles, is unlikely. Surprisingly, the extraction performance of the column remained constant over several runs of extraction and regeneration, indicating that also no degradation of the dendritic extractant takes place during short term testing.

4.4.4 Conclusions and Outlook

Initial experiments have shown that a dendrimer-based MPPE-system, allows the removal of anionic xanthene dyes from aqueous (waste) streams. With the development of this modified MPPE-system it should be possible to investigate current water treatment problems, like the extraction of humic acid. However, there is still room for optimization. One can think of increasing the solubility of the dendrimer in the extraction liquid by matching the periphery of the dendrimer with the extraction liquid or to increase the contact area between dendritic extractant and the aqueous medium by reducing the MPPE particle size. Furthermore a quantitative analysis of the extraction system needs to be performed.

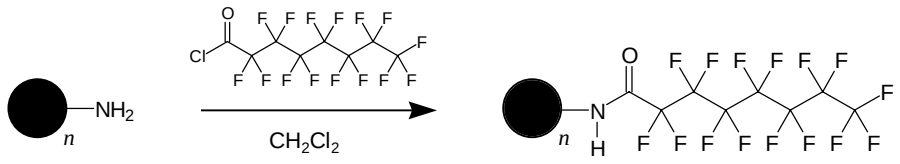
4.5 Extractants for Supercritical Carbon Dioxide

The use of supercritical fluids, like carbon dioxide, instead of organic solvents, in extraction procedures has certain environmental advantages and has become an example of green chemistry.[60] Carbon dioxide is non-toxic, non-flammable, abundant and cheap. Compared to the use of 'unfriendly' organic solvents and their partial solubility in aqueous media that yields considerable problems in industrial processes and water-treatment, supercritical carbon dioxide is an ideal substitute. One of the attractive features is a tuning of its solvating power by appropriate adjustment of the solution density. This allows an easy down-stream separation, through which the product can be separated. Such properties are of common interest in process technology, in an attempt to circumvent rather tedious batch-type and/or small-scale operations like column chromatography and filtration.[61] The major drawback is its difficulty in dissolving polymeric, ionic or highly polar species, but this problem can be resolved through modification of these species with perfluoroalkylunits. Such modification has been applied to obtain CO_2-soluble dendritic extractants, similar to the report of DeSimone *et al*.[21a] Furthermore, this enables a study on the effect of endgroup and

extraction solvent on the extraction properties, by comparing the results for the fluorinated extractants with the 'organic' extractants.

4.5.1 Synthesis

A new series of unimolecular inverted micellar structures has been achieved by reacting the amine-functionalized poly(propylene imine) dendrimer with fluorinated[62] alkylchains. Relatively little[63] was known on the chemistry of fluorinated compounds and the stability of the amide-linkage in the fluorinated dendrimers. Coupling of pentadecafluorooctanoyl chloride with the fifth generation amine-terminated dendrimer yielded a white product with low solubilities in organic solvents due to the extreme difference in polarity between dendritic interior and periphery. Moreover, the fluorinated cover encapsulated reagents, solvent and additives and formed an effective barrier towards water during work-up. The fluorinated dendrimer displayed special properties as was evidenced from the dewetting behavior and coating of glassware. Remarkably, the use of trifluoroacetic acid as a co-solvent increased solubility. Furthermore, these dendrimers could be dissolved in supercritical CO_2.

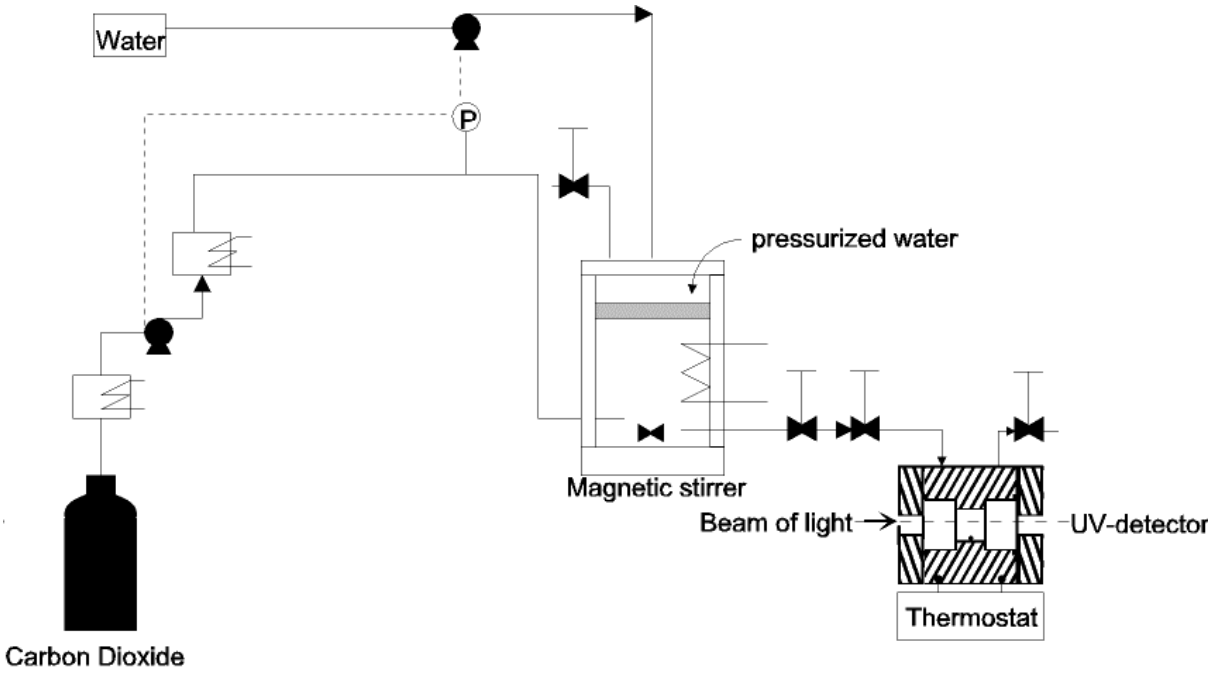


n = 64: **E5**

Figure 4.15: *Modification of a fifth generation poly(propylene imine) dendrimer (n=64) with perfluoroalkyl units.*

4.5.2 Extraction Properties[64]

The fluorinated dendrimer **E5** has been successfully applied to extract anionic solutes, like Methyl Orange **VIII** and Rose Bengal **IV** from water into supercritical CO_2, similar to reports of deSimone.[21a] The setup used and the results for the extraction of **VIII** are depicted in Scheme 4.5 and Figure 4.17. respectively. In case of blank experiments the amount of solute extracted was minimal. The experiments have been performed for different concentrations of **VIII** and the dye/dendrimer ratio in the CO_2-phase represents the maximum of **VIII** that can be absorbed at every concentration. It is shown that with increasing concentration of **VIII** in the aqueous medium, a limiting dendrimer/dye ratio is obtained that is approximately 24–26 for **E5**.



Scheme 4.5: *Reactor set-up for the extraction experiments in supercritical CO_2.*

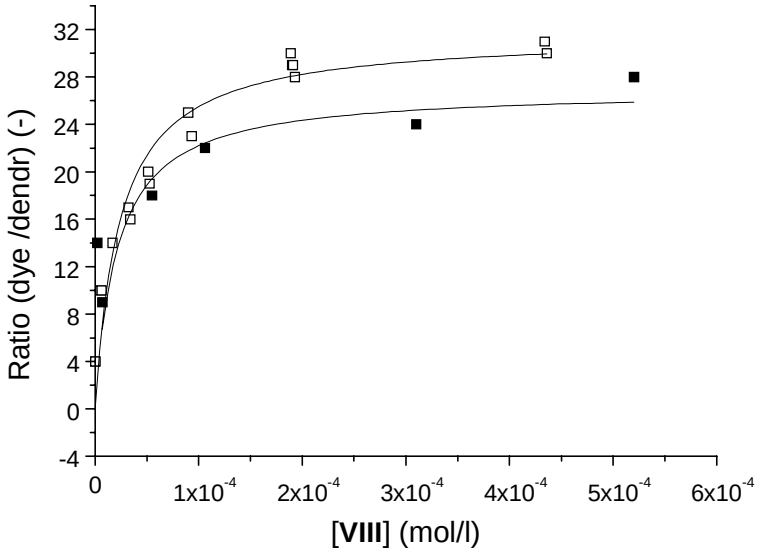


Figure 4.16: *Maximum loading of Methyl Orange* ***(VIII)*** *using* ***E5*** *in supercritical CO_2 (□) and using for* ***A5*** *in tetrachloromethane (■) as a function of the concentration of* ***VIII****. The dendrimer concentration is approximately $1 \cdot 10^{-5}$ M in both cases and equal volumes for the two phase system are used. Experiments are conducted at 40 °C.*

Similarly, the extraction of **VIII** with **A5** and tetrachloromethane was performed. This eluent was chosen in stead of CH_2Cl_2 to study extraction at 40°C and use comparable parameters as for **E5**.In the case of **A5** in tetrachloromethane a maximum loading of 28 is obtained, that agrees well with the 24-26 dyes for **E5**. Despite the difference in dendrimer endgroups and extraction medium used, both series yield similar extraction

performance. Moreover, there is no (large) effect of the different dendrimer series on the observed loading. These observations agree well with results in Section 4.2.3 and 4.2.5, in which the type of endgroup and the medium of the extraction experiment have no major influence on the extraction process. The extraction is mainly determined by dye molecule and dendrimer generation. Furthermore, the difference in pH in the case of extraction with tetra (buffer pH = 6.4) or with supercritical CO_2 (pH ≈ 3, due to equilibrium $CO_2 + H_2O \rightarrow H_2CO_3$) seems not important for the maximum loading as can be understood from Fig. 4.2.

Finally, fluorinated dendrimers are currently investigated as a unimolecular phase transfer catalyst[65] in the nucleophilic displacement of the chloride-anion of benzylchloride with a bromide in supercritical CO_2. This model-reaction was performed in a two-phase system, an aqueous phase with a large amount of KBr and a CO_2-phase with the functionalized poly(propylene imine) dendrimer and benzylchloride, which is not soluble in water.

4.6 Overall Conclusions

Poly(propylene imine) dendrimers with an apolar periphery are very effective extractants of anionic solutes, which can be explained by acid-base interactions between solute and tertiary amine. In all cases, the interactions are highly dependent on the pH used. The high local concentration of tertiary amines in the dendritic interior and the presence of a basic micro-environment, that shield the dendrimer-solute interactions from the solvent, leads to efficiencies that are superior to low molecular weight analogues. Subsequently, application of these extractants in a water-purification technology allows the extraction of anionic solutes. Furthermore, the extraction of solutes in supercritical CO_2 with fluorinated dendritic extractants agrees well with the extraction in organic media. The latter results allow the application of dendritic extractants in an environmental friendly extraction process.

4.7 Experimental Section

Materials

Toluene, dichloromethane (stabilized with 0.2 w% EtOH), chloroform, tetrachloromethane and tetrahydrofuran (THF) were used as received. For the synthesis of dendrimers **A**[19] and **C**[19] you are referred to Chapter 2. The synthesis of dendrimers **B**[19] and **D**[25] are described in literature. Hydrion buffers (Aldrich) were used to maintain constant pH. Tri-*n*-octylamine (98 %) was obtained from Acros Chimica. Fluorescein (**I**), 4,5,6,7-tetrachlorofluorescein (**II**), Erythrosin B (**III**), Eosin (**V**), Rhodamine B (**VII**) and New Coccine (**IX**) were commercially available from Aldrich, Rose Bengal (**IV**), Carboxyfluorescein (**VI**) and Indigocarmine (**XI**) were purchased from Fluka, while Methyl Orange (**VIII**) and Biebrich Scarlet (**X**) were obtained from Acros Chimica. The fifth generation amine-functionalized poly(propylene imine) dendrimer,

DAB-*dendr*-$(NH_2)_{64}$ was kindly provided by DSM Research (Geleen, The Netherlands) and dried *in vacuo* to remove residual amounts of solvents. The MPPE-particles were kindly kindly provided by Akzo Nobel MPP Systems BV (Arnhem, The Netherlands). Property indications: range of (dry) grain diameter 200-1000 mm, range of pore diameter 0.1-100 mm, average porosity 70%.

General Methods

Absorption Spectra in the ultraviolet-visible range (UV/vis) were recorded on a Perkin-Elmer Lambda 3 UV/Vis spectrophotometer or a Perkin-Elmer Lamda 900 UV/Vis/NIR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Bruker AM 400 spectrometer at 400.13 MHz and 100.62 MHz respectively. All δ-values were given in ppm downfield from tetramethylchlorosilane. A Mistral 1000 Centrifuge apparatus was used to separate the two-phase system after stirring. For a detailed experimental discussion on small angle X-ray experiments you are referred to Chapter 5.

Synthesis of DAB-*dendr*-$(NHCO\text{-}C_7F_{15})_{16}$, E3

To a solution of DAB-dendr-$(NH_2)_{16}$ (1.00 g, 0.139 mmol) in THF has been added an equimolar amount of pentadecafluorooctanoylchloride (3.86 g, 8.93 mmol, 64 eq.). The formed precipitate is filtered off and dried *in vacuo*, yielding the fluorinated dendrimer in the protonated form (HCl-salt) as nice white solids. ^{1}H-NMR ($CDCl_3$ / CF_3COO^- = 99:1) indicated coupling of the fluorinated endgroups to the dendritic scaffold δ (CH_2NHCO) = 3.3 ppm. No further characterization was performed.

Liquid-Liquid Extraction Experiments

A centrifuge tube setup, as illustrated in Figure 4.1, was set up at room temperature. Into this setup was placed *x* ml of a solution of extractant in the appropiate organic solvent (CH_2Cl_2, $CHCl_3$, toluene or CCl_4 in case of comparison experiments with supercritical CO_2). Additionally an equal volume (*x* ml) of the aqueous solution with the selected solute, **I-XI**, was added. Typical concentrations of dendrimer and solute were in the order of 10^{-5} M. However, concentration of the extractants depended on the type of experiment. For instance, in case of the selective extraction between **I** and **IV**, the concentrations of both solutions were varied from a 1:1 ratio {2.5×10^{-5} M} to a 10.000 : 1 ratio. After stirring for approximately 5 minutes, the two phases were separated using a centrifuge and both the aqueous and the organic phase were sampled by UV-Vis spectroscopy to determine the extraction yield. The *extraction yield* is defined as the relative extraction of the solute into the organic phase and is determined by measuring the decrease and increase in absorption of the aqueous and organic layer, respectively in UV/Vis. The absorption is determined at λ_{max} in both solvents four all dyes, where a small solvatochromic shift of λ_{max} in organic solvents is observed. In all cases a decrease in absorption of the aqueous layer simultaneously gives a complementary increase in absorption of the organic layer. Simultaneously, control experiments were performed to ensure that no dyes molecules were transferred into the organic layer in the absence of (dendritic) extractants. The *extractant value* is defined as the pH at which 50% of the solute is extracted.

Application of Dendritic Extractants in MPPE™-Experiments

MPPE-particles have been used and loaded with dendritic extractant **B3**. Hereto, the extraction oil that is normally used to construct the MPPE-particles and applied in the process, is replaced by an extraction oil containing 1% w/w of **B3**. First, the dendrimer-based MPPE-particles have been tested for qualitative extraction of **II** and compared with the extraction of MPPE-particles without extraction liquid and standard MPPE-particles with extraction liquid. Secondly, MPPE-particles containing the dendritic extractant were deposited in a heavy-wall borosilicate glass column (Omnifit; effective height 200 mm, inner diameter 25 mm, MPP mass 49.98 g, closed with porous 25 mm polyethylene frits). Prior to use of the column for extraction purposes, the MPPE-column was 'ready-to-use' through a regeneration with steam (100 °C < T < 120 °C; p ~ 1 bar), similar to regeneration methods. Subsequently, the extraction of **III** has been tested for various flow speeds. Regeneration was tested using caustic conditions (pH=12) or steam, similar to the MPPE-process. In all cases the filtrate has been characterized by determining the absorption at λ_{max} using UV/vis spectroscopy (Perkin-Elmer Lambda 3 spectrophotometer).

Application of Fluorinated Dendrimers in Supercritical CO_2-Extractions

The perfluorooctanoyl-functionalized poly(propylene imine) dendrimer ($2.2\ 10^{-6}$ mol/L) (**E5**) was transferred into a high-pressure cell (Scheme 4.5) of 80 mL with two oppostie sapphire windows, a magnetic stirrer bar and a Pt-100 resistance thermometer. The reactor was pressurised with carbon dioxide (Hoek Loos, grade

4.5), to a set-point of 300 bar at 40°C. By adjusting the volume of the reactor using a piston part of the content of the reactor was transferred at constant pressure into a high-pressure viewing-cell of 2.2 mL where 1.1 ml water containing the dye Methyl Orange was present. Methyl Orange was pumped into the reactor with a high-pressure pump (LKB HPLC pump) into the reactor. The extraction yield is defined as the relative extraction of the solute into the carbon dioxide phase and is determined by measuring the decrease in absorption of the aqueous phase (the absorption was determined at λ_{max} on a Spectronic® Genesys 5 spectrophotometer.

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Water-Soluble Dendritic Host–Guest Systems

5

Abstract: *Three different generations poly(propylene imine) dendrimers have been functionalized with tris 3,4,5-tri(tetraethyleneoxy)benzoyl derivatives using a pentafluorophenyl ester coupling strategy. The modified dendrimers were purified from excess ester using biobeads column chromatography and their purity was confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopy, TLC and MALDI-TOF-MS. The dendrimers are soluble in a broad range of solvents from apolar ones, like toluene and dichloromethane to more polar ones, like water, methanol and acetonitrile. The host-guest interactions of anionic solute molecules with the ethylene glycol–functionalized dendrimers are studied, qualitatively by using the ultrafiltration technique and quantitatively by performing UV/vis titrations and SAXS-measurements. The latter is used to show the preferential location of the dye molecules in the core of the dendritic interior. Moreover, the host–guest interactions proved to be dependent on generation, pH and temperature.*

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5.1 Introduction

The highly branched, three-dimensional geometry of dendritic macromolecules,[1–6] make these new molecular architectures to ideal container molecules.[7] It has been suggested that these molecules can be used in a number of applications including those related to controlled release of pharmaceuticals.[8–11] Furthermore, dendrimers with their multiple identical ligands are very attractive for pharmocologists, since such structures can exhibit amplified substrate binding.[12] The use of dendrimers as a polyfunctional skeleton has been particularly useful for diagnostic purposes, and is explained by the possibility of multiplying certain functionalities and hence achieving higher sensitivities. Dendritic substances have made crucial advances and have already been tested in preclinical studies, particularly in the field of contrast media for magnetic resonance imaging. Attachment of the Gd(III) chelates to poly(amidoamine) or poly(lysine) dendrimers[13–19] increases ion relaxivity of the contrast agent, which enhances the efficiency. The dendritic contrast agents have been reported to be more effective contrast agents than other macromolecular chelates attached to albumin, polylysine or dextran.

Several host–guest systems have been developed already, *e.g.* dendritic hosts with unimolecular (inverted) micellar structure,[20–23] the 'dendritic box',[24, 25] crown-ether dendrimers[26, 27] and cyclophane dendrimers.[28, 29] A restricted number of guests, like Bengal Rose, could be encapsulated in the 'dendritic box', *i.e.* a fifth generation poly(propylene imine) dendrimer modified with a dense shell of amino acids,[24] but was only released after chemical modification of the shell.[25] Dynamic hosts in organic media[23, 30, 31] or supercritical CO_2,[32, 33] are based on hydrophobically modified poly(propylene imine) dendrimers and proved efficient extractants of aqueous solutes as described in the previous chapter. The unimolecular nature of dendrimers yields a new type of amphiphiles, with properties that are superior to that of conventional low molecular weight species. The high local concentration of sites and/or the presence of a micro-environment account for unique (dendritic) features with cooperative effects.

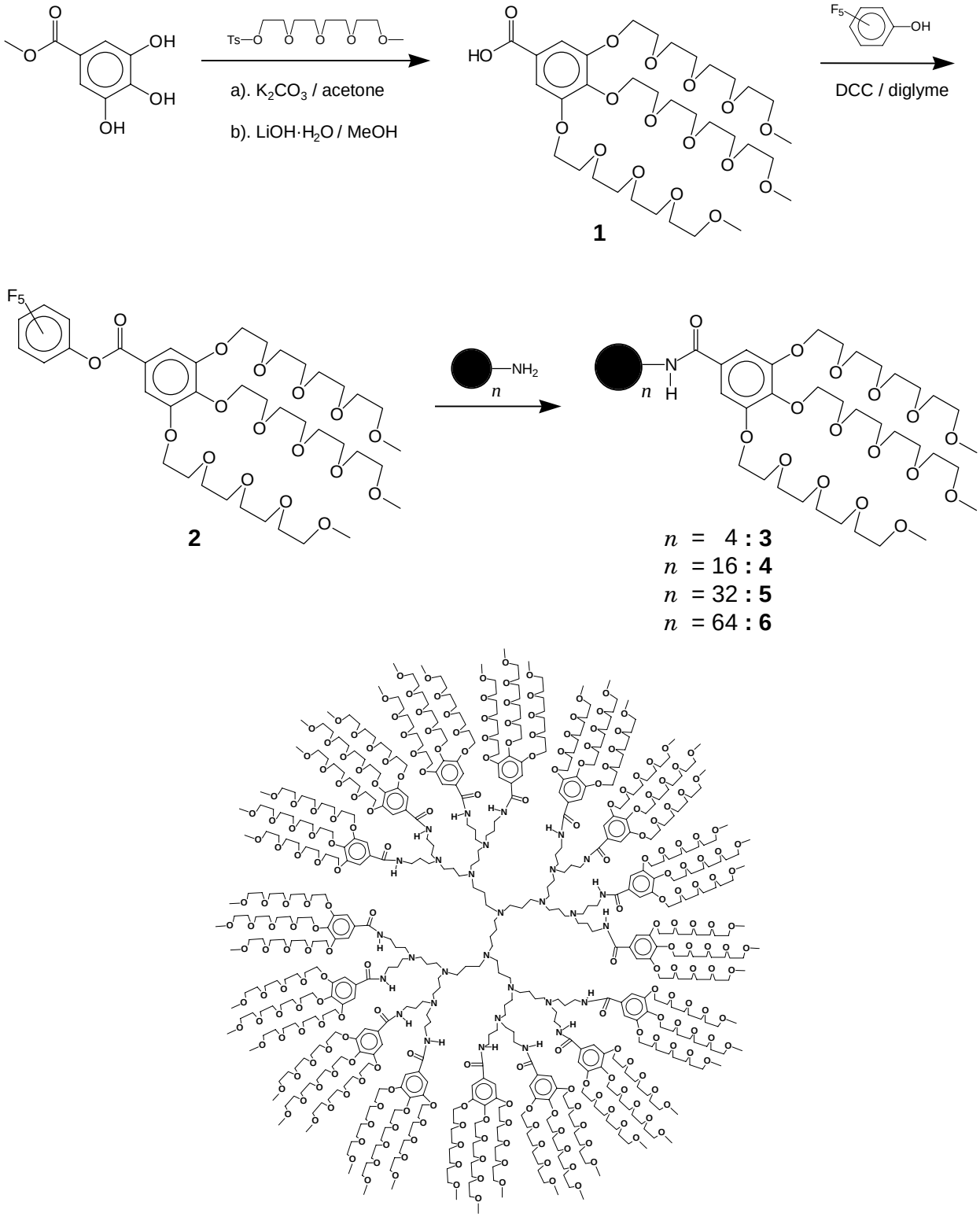
In order to develop dendrimers for diagnostics or biomedical engineering, more attention has been focussed on water-soluble dendritic systems. Functionalization of dendrimers with carboxylate groups is a well-established and easily accessible method to obtain water-soluble dendrimers,[34–37] however the use of toxic ionic endgroups limits their biocompatibility. Also, the synthesis of carbohydrate containing dendrimers, *i.e.* glycodendrimers, is well documented.[38–43] Functionalization with ethylene glycol chains not only generates water-solubility,[44–49] but moreover yields a biocompatible system that due to its low toxicity is interesting for medicinal applications. Recently, Fréchet *et al.*[44] reported the design of a dendrimer-poly(ethylene glycol) conjugate that contains

(extra) reactive sites for the covalent attachment of model drug molecules, like cholesterol and amino acid derivatives. The role of the poly(ethylene glycol) chains is to solubilize the dendritic assembly. Furthermore, Uhrich *et al.*[46] addressed the concept of drug delivery by synthesis of a unimolecular micelle that consists of a hydrophobic core and a poly(ethylene glycol) periphery in order to solubilize hydrophobic molecules. The stability[20, 21] of such unimolecular drug carriers contrasts the instability of conventional micelles. However, a detailed discussion on the host-guest properties of dendritic systems in aqueous media has not been reported.

In this chapter, the synthesis and structural characterization of poly(propylene imine) dendrimers[50] modified with tris 3,4,5-tri(tetraethyleneoxy)benzoyl units is discussed, yielding dendritic structures with a basic interior of tertiary amines and a hydrophilic periphery. Titration experiments with UV/vis spectroscopy using water-soluble dyes showed a strong association with the dendrimers. Moreover, small angle X-ray scattering (SAXS) experiments[51] are used to show that unique interactions lead to a preferential location of guests in the core of these novel unimolecular water-soluble dendritic hosts.

5.2 Synthesis and Characterization

Four different generations of oligoethyleneoxy-functionalized poly(propylene imine) dendrimers, *i.e.* DAB-*dendr*-(NHCO-EG)$_n$ with EG used for the tris 3,4,5-tri(tetraethyleneoxy)benzoyl unit and with n = 4 : **3**, n = 16 : **4**, n = 32 : **5** and n = 64 : **6**, have been synthesized by the reaction of the corresponding pentafluorophenyl ester with the amine-terminated poly(propylene imine) dendrimers. The synthesis of the pentafluorophenyl ester requires three steps, starting from methyl 3,4,5-trihydroxybenzoate. Alkylation of the latter with the tosyl derivative of tetra ethylene glycol monomethyl ether in acetone afforded methyl 3,4,5-tris(tetraethylene glycol monomethyl ether) benzoate, which was purified using column chromatography. Hydrolysis with lithium hydroxide afforded the corresponding benzoic acid derivative **1**. Subsequently, the latter is converted into the pentafluorophenyl ester **2**,[52] using pentafluorophenol and DCC. Although all steps require column chromatography or column filtration, pure **2** is easily accessible in three steps from trihydroxybenzoate methyl ester in an overall yield of 45%; the purity was confirmed by ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, IR and TLC and ESI-MS.



Scheme 5.1: Top: *Synthetic scheme of oligoethyleneoxy-functionalized poly(propylene imine) dendrimers (n = 4 : **3**; n = 16 : **4**; n = 32: **5**; n = 64: **6**); Bottom : Detailed structure of host **4** (n = 16).*

Reaction of **2** with the amine-functionalized dendrimers, DAB-*dendr*-$(NH_2)_n$ (n = 4, 16, 32, and 64) yields pure oligoethyleneoxy-functionalized poly(propylene imine)

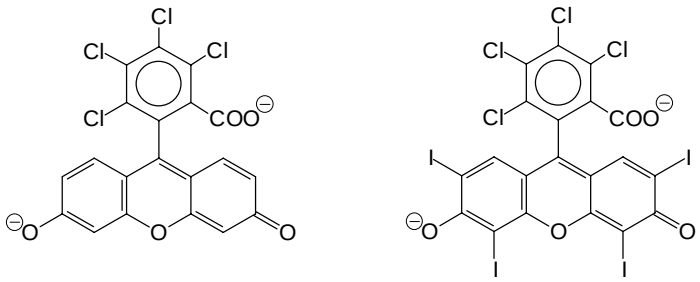
dendrimers, DAB-*dendr*-(NHCO-EG)$_n$ {n = 4: **3**, n = 16: **4**, n = 32: **5**, n = 64: **6**}, after biobeads chromatography, as was evidenced with ^{1}H-NMR, ^{13}C-NMR, TLC and ESI-MS. ^{19}F-NMR indicated a complete removal of excess pentafluorophenyl ester and pentafluorophenol. Complete reaction of all amine-endgroups of the dendrimer was concluded from ^{1}H-NMR spectroscopy; characteristic resonances for the methylene protons adjacent to the primary amine endgroups at δ = 2.8 ppm disappear and shift to δ = 3.4 ppm, indicative of a full conversion and amide formation is observed. Similar conclusions could be drawn from the obtained ^{13}C-NMR spectra. MALDI-TOF MS showed single peaks for compound **3** (n = 4) and **4** (n = 16) with molecular weights of 3206 and 13244 D, respectively, corresponding to the expected mass. This can be expected with (almost) pure amine-terminated poly(propylene imine) dendrimers[53] of the first and third generation and a modification reaction that proceeds with high selectivity. In case of a fourth (**5**) and fifth (**6**) generation functionalized dendrimers, a range of peaks is observed, although the highest peak is observed in the expected mass-range at 26565 D and 53576 D, respectively. The most probable explanation of the distribution of peaks is the presence of defect structures that are already present in the amine-terminated poly(propylene imine) dendrimers. Furthermore, even with the (large) deviations observed, it is possible to determine the selectivity of the modification step, since the mass differences due to one endgroup missing (*ca.* 1 kD) are much larger than the experimental deviations observed (< 0.2 kD).[54] This issue has been discussed previously in Section 2.2.3.

An interesting point is the high solubility of these dendrimers in both apolar and polar (protic) solvents. For instance, the ethylene glycol-functionalized dendrimers are miscible with water in all ratios. At higher temperatures solubility of the dendrimers in water decreases due to LCST-behavior, and aggregation of the dendrimers takes place yielding an increase in turbidity of the solution.[55] The solubility of the ethylene glycol functionalized dendrimers was further investigated with SAXS measurements. In dilute solutions, interactions among the dendrimers are negligible and they reveal maximum dimensions ranging from 5.1–5.6 nm.[56]

5.3 Host-Guest Interactions

5.3.1 UV/vis Spectroscopy

The host-guest properties of these dendritic structures were studied in buffered aqueous media at pH = 7, using two anionic, water-soluble, xanthene dyes (Scheme 5.2) as guest molecules (**I**: 4,5,6,7-tetrachlorofluorescein, **II**: Bengal Rose).



I **II**

Scheme 5.2: *Studied guest molecules: 4,5,6,7-tetrachlorofluorescein (**I**) and Bengal Rose (**II**).*

Titration of a stock solution of **6** to a solution of guests **I** or **II**, yielded in both cases a bathochromic shift in λ_{max}, indicative of an interaction (complexation) between the dendrimer host and the xanthene guest (Fig. 5.1). This complexation is studied by plotting the ratio of absorptions related to complexed and free guest against the guest–host ratio (GHratio) (Fig. 5.2). The λ_{max} of a complexed dye is determined from a UV/vis spectrum of a host-guest sample with a (very) high GHratio. Upon complexation, λ_{max} shifts from 509 to 526 nm and from 547 to 563 nm for guest **I** and **II**, respectively. Figure 5.2 is obtained from the UV/vis spectra in Figure 5.1 by calculating the ratio of absorption at λ_{max} of the complexed guest and the absorption at λ_{max} of the free guest, at each GHratio.

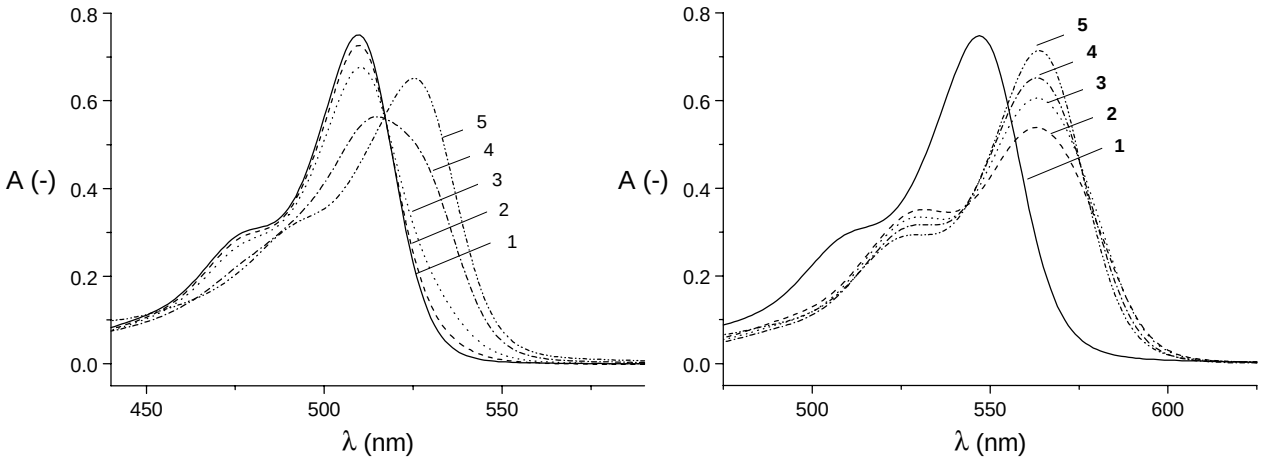


Figure 5.1: *Representative UV/vis spectra obtained from the titration of guest **I** (left) and **II** (right) with **6**. Typical UV/vis spectra are marked from 1 to 5 (see Fig. 5.2).*

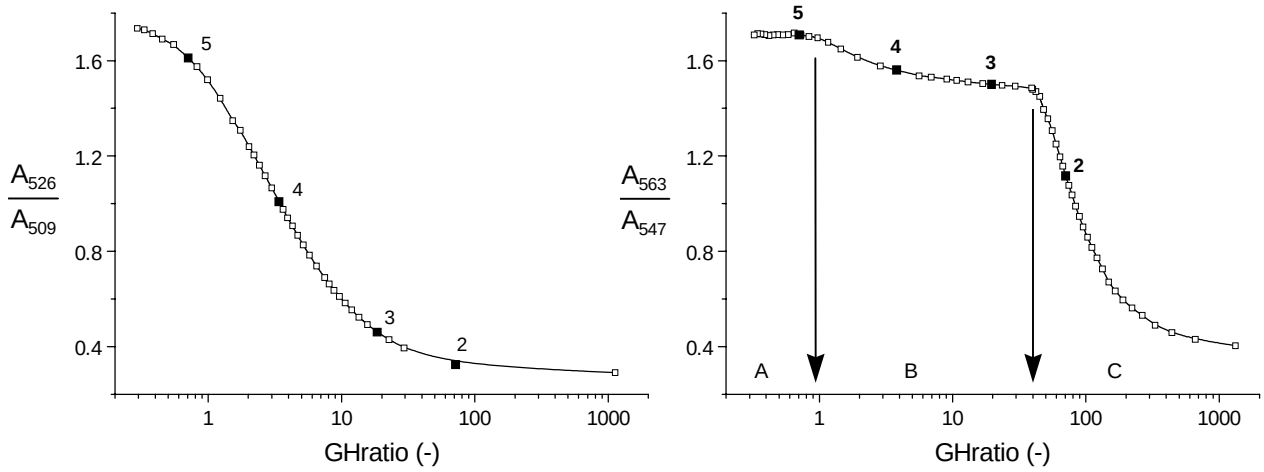
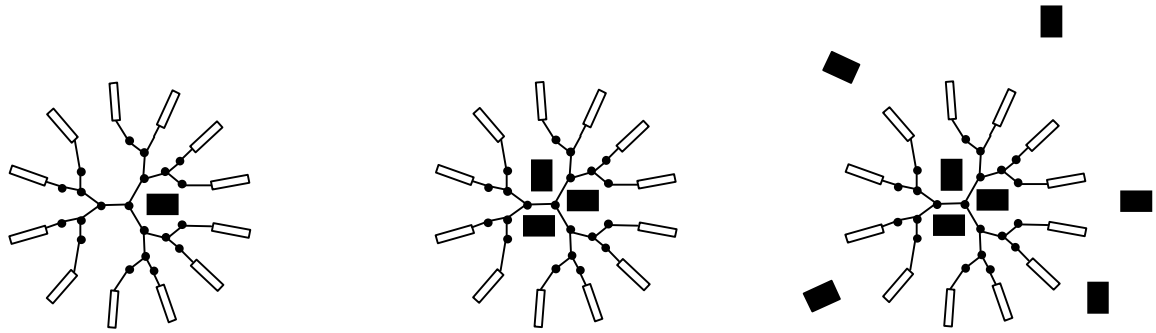


Figure 5.2: *Ratio of absorption of complexed dye to free dye as a function of the GHratio, for guest **I** (left) or guest **II** (right). Numbers 2–5 are used to refer to the UV/vis spectra. Marker 1 at infinite GHratio is omitted.*

In case of guest **II**, the complexation with the dendritic host is much stronger than for guest **I**, with association constants (K_a)[57] of $(5.0 \pm 0.04) \bullet 10^5$ M^{-1} and $(3.0 \pm 0.4) \bullet 10^4$ M^{-1} for guest **II** and **I**, respectively. Upon titration of **I** with **6** the absorption at λ_{max} of the free dye decreases and there is an isosbestic point over the whole titration range, indicative of an equilibrium between free and complexed dye. The single isosbestic points indicates that the λ_{max} of the complexed dye is independent of the number of dyes complexed. More information can be obtained from the titration of **II** with **6** (Figure 5.3, right) where three different regimes and two inflection points (marked by arrows) at GHratios of 1 ± 0.5 and 40 ± 5 can be distinguished. Moreover, beside complexation of the guest, the UV spectra also reveal in this case the effect of dye–dye interactions in one host.[58] Between 0 < GHratio < 1 a strong complexation of the guest takes place, and a constant absorption spectrum is obtained (regime A). Between 1 < GHratio < 40, all guests are strongly complexed up to a load of 40, but due to dye–dye interactions of the guest, within one host molecule, a decrease in the ratio A_{563}/A_{547} is observed (regime B). Finally, for GHratio > 40, an excess of guest is present and the presence of an isosbestic point indicates an equilibrium between free and complexed guest molecules (regime C).



***regime* A** ***regime* B** ***regime* C**

Scheme 5.3*: Schematic representation of host-guest complexes in regime A-C, as is interpreted from Fig.5.1 and 5.2. Short explanation: regime A: All dye molecules are complexed, an excess dendrimer is present, and the average load is less than one; regime B: on the average more than one dye is complexed to the dendrimer, and dye–dye interactions can be observed; regime C: an excess dye is present and dendrimer is fully loaded.*

Effect of generation. The UV/vis titration have been discussed for a fifth generation functionalized dendrimer and the association was much stronger for Bengal Rose (**II**) than for 4,5,6,7-tetrachlorofluorescein (**I**). The host–guest interactions of both guests are compared with a first generation dendrimer and normalized to the G/N ratio, *i.e.* the amount of guests available per tertiary amine. In case of TCF (**I**) a large discrepancy is observed between the first and fifth generation (Fig. 5.4, left). Since the same acid is used in both cases, this can only be explained by a smaller efficiency of lower generation dendrimers for instance due to a lower basicity, and rationalized from a higher local concentration of tertiary amines and a more basic micro-environment in case of the higher generations. In case of Bengal Rose (**II**) (Fig. 5.4, right), the association with the tertiary amines is stronger and, as a result, the effect of dendrimer generation is smaller. A first generation dendrimer shows a similar trend in complexation as a fifth generation dendrimer. However, although a similar numbers of guest **II** can be complexed per tertiary amine, it is evident that the load of guest molecules increases with dendrimer generation.

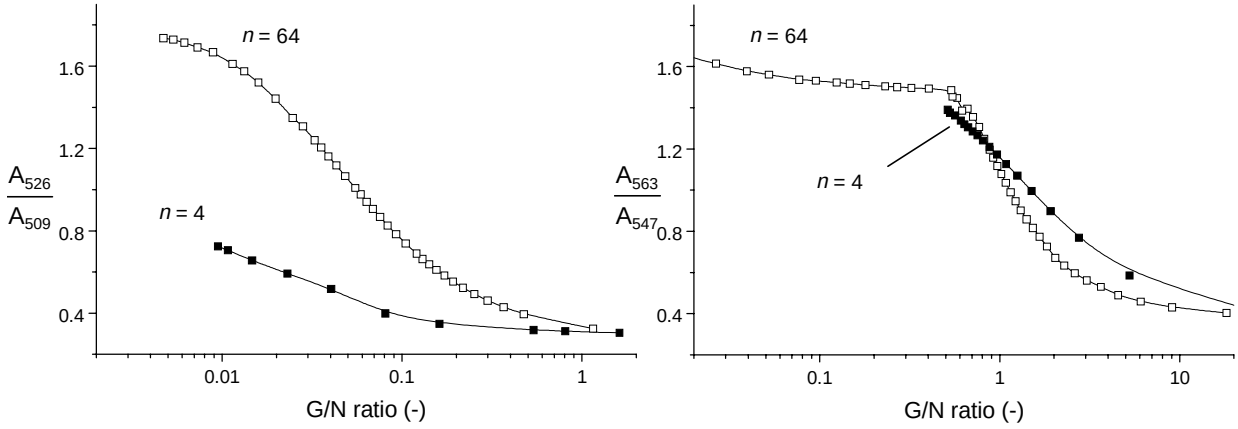


Figure 5.3: *Ratio of absorption of complexed dye to free dye as a function of the G/N ratio, for guest **I** (left) or guest **II** (right).*

pH-Dependence. The association between host and guest described above is explained by acid–base interactions between the anionic functionality of the guest and the protonated tertiary amines of the dendritic host, similar to previously reported host–guest systems.[30, 59, 60] This is also supported by a strong pH-dependent association behavior of **I**. In Figure 5.4 the interaction of **6** and **I** is studied at pH = 7, 11 and 14. The observed decrease in interaction can be explained by a weak acid–base interactions at higher pH, due to the smaller degree of protonation of the dendritic host.[61]

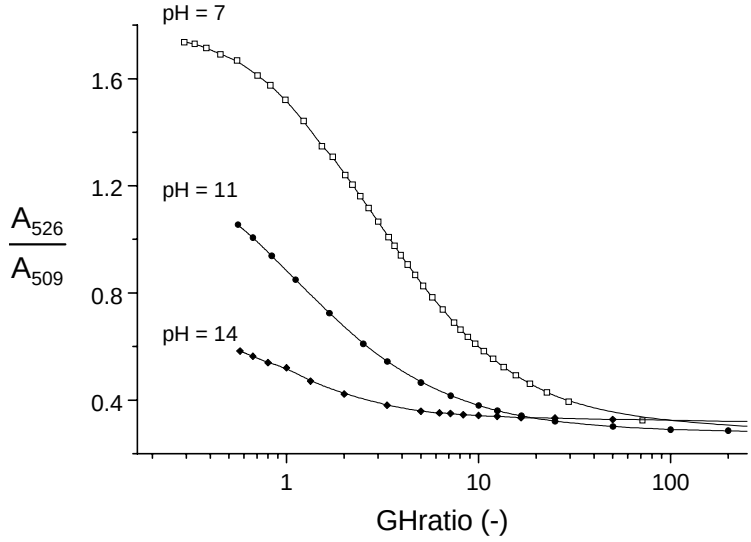


Figure 5.4: *Interactions of **I** with **6** at pH = 7, 11 and 14. Titration curve for pH = 7 is replotted from Fig. 5.3.*

On the contrary, the smaller pH-dependence of **II** (not shown), suggests, however, that not only electrostatic interactions (acid–base), but also other properties, like the high polarizability and hydrophobicity of **II** play an important role in the association process.[62] It has been reported that these interactions increase with increasing halogen substitution.[63]

Temperature Dependence. UV/vis spectra of a sample of **6** and **II** with a GHratio of *ca.* 70 have been investigated at different temperatures. For this sample an equilibrium between free and complexed dye exists (see regime C in Fig. 5.3). The ratio of absorptions of complexed to free dye, *i.e.* A_{563} / A_{547}, decreases from 1.03 to 0.77 when the temperature increases from 20 to 80 °C. Although a linear relationship is observed between A_{563} / A_{547} versus 1000/T (Fig. 5.5), the ratio of absorptions does not represent any thermodyamic quantity and it is therefore not attempted to calculate thermodynamic data.

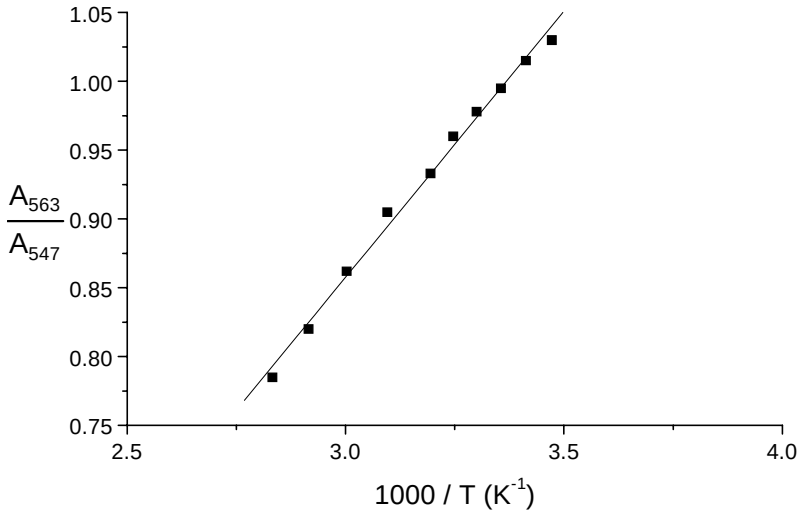


Figure 5.5: *Ratio of absorptions for a complex of **6** and **II** with a GHratio of ca. 70 as a function of temperature. A straight line is drawn to guide the eye.*

Above 80 °C a strong increase in scattering is observed, due to the LCST behavior of the oligo(ethyleneoxy) chains.[55] The decrease in the ratio corresponds with a qualitative picture in which the equilibrium shifts towards an increasing amount of free guest when temperature is increased. Although, it is not attempted to calculate quantitative thermodynamic data, these results illustrate that temperature can be used as a tool to 'release' guest molecules.

Ultrafiltration. So far the host–guest properties are characterized in terms of interactions and the dependence thereof. The ultrafiltration technique, uses a membrane with a molecular weight cut-off of approximately 10 kD, and has been used to demonstrate stability of the system (Figure 5.6) in case of host–guest complexes using either **3** (3 kD) or **6** (53 kD) as host. In case of host **6**, all guest molecules are retained in the filtration cell, indicative of the high molecular weight of the host and a (very) strong association. This behavior is in sharp contrast to a host-guest complex of **3**

which passes through the membrane. The UV/vis spectra of the filtrate indicate that the guest is still complexed to dendrimer **3**, after filtration.

The ultrafiltration results indicate that nanometer dimensions of dendrimers can be used to achieve high retention in membranes, similar to their use as homogeneous catalysts in membrane reactors.[64–66]

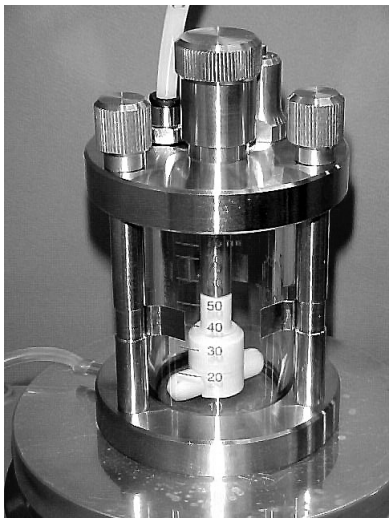


Figure 5.6: *Picture of the ultrafiltration cell with pressure inlet (on top) and flow effluent (on bottom). Picture kindly provided by J. W. Weener.*

5.3.2 Small Angle X-ray Scattering

SAXS measurements[67–69] have been performed in different media to analyze the structure of dendrimer **6** in solution. SAXS and SANS-studies[70, 71]are commonly used to determine the amount of interactions between the dendritic molecules, that assemble due to the formation of aggregates. Since in the case of dilute solutions no specific intermolecular interactions are present and measurements have been performed on dilute solutions of host **6** and guest **II** for different GHratios, with concentrations of approximately 10 mg/ml.[72] In all cases, the SAXS intensity at low q is described using the Guinier approximation and displayed in Figure 5.7.

This plot reveals three features: (i) the forward scattering intensity, $I_h(q\rightarrow 0)$, obtained via extrapolation and the invariant, Q_h, were derived in order to calculate the particle volume via

$$V_h = \frac{2\pi^2 I_h(0)}{Q_h}$$

without absolute scaling of the scattering intensity. This yields V_h = 8.5*10^{-26} m^3 and the molar mass of the host $M_h = V \rho N_A$ is therefore 51.5 kD when assuming a density of 1000 kg/m^3 whereas the actual molar mass is 53.5 kD as measured by MALDI-TOF.

This confirms that the SAXS pattern reflect scattering from individual macromolecules. Additional scattering data, scaled to absolute intensities are shown in the supplementary section. (ii) an increase in forward scattering intensity, I(q→0), with increasing amounts of dye molecules in the dendrimer which not only reflects the change in molecular weight of the complex due to addition of the guest molecules (1 kD) to the dendritic host (53 kD), but also a change in contrast, $\Delta\rho$, since the guest molecules, with chlorine and iodine atoms add a substantial amount of electrons to the system, (iii) a change in slope of the Guinier plots that reveals a significant decrease in the radius of gyration (R_g*) of the complex upon addition of the guest molecules (—•—). If the dyes were uniformly distributed within the dendrimer molecules, a slight increase would be expected in both, the radius of gyration of the complex (· · · □ · · ·) and the maximum dimensions due to the increase in total molecular weight. In the present systems, the maximum dimensions are essentially unchanged, whereas the radius of gyration (Figure 5.8, bottom) decreases with increasing number of guest molecules (up to a ratio of 12). Since the latter reflects the second moment of the (electron) density distribution ρ*(r) within the complex, and not ρ(r) of the dendritic host, this in fact indicates that the dye molecules are preferentially accumulated in the center region of the dendritic hosts. If more guests are complexed to the dendritic hosts, the outer regions fill up and an increase in the R_g is observed. Surprisingly, with an excess of guest, *i.e.* a GHratio of 100, the R_g equals that of the unloaded host (see the cartoon in Figure 5.9).

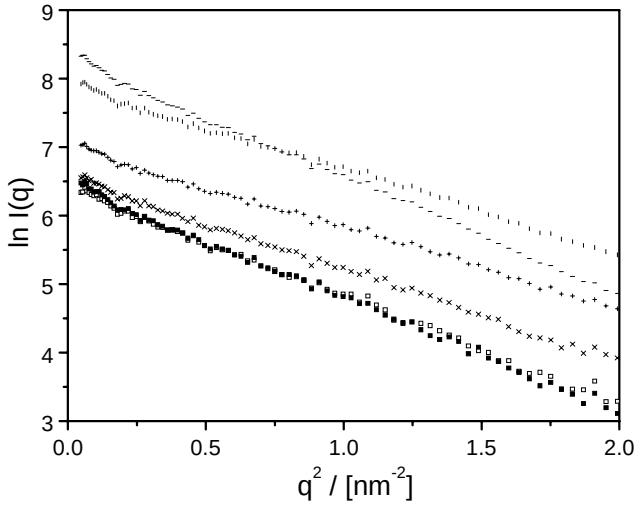


Figure 5.7: *Guinier plots for complexes of* ***6*** *and* ***II*** *for different GHratios;* ■ *no guest,* □ *1 guest,* × *4 guests, + 12 guests, | 32 guests, – 100 guests.*

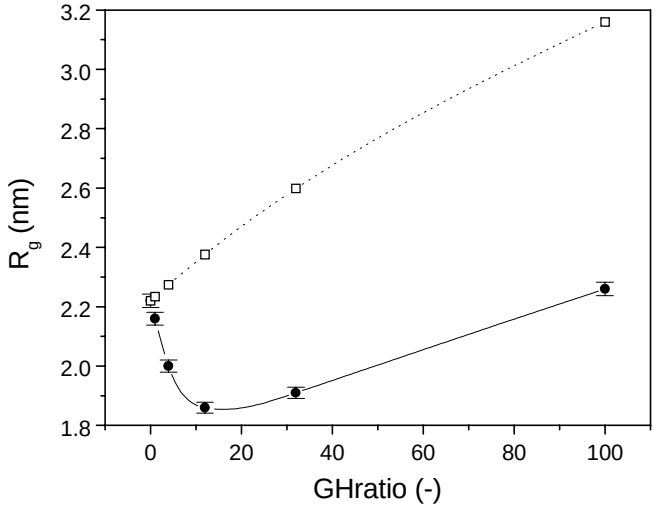


Figure 5.8: *Radius of gyration (R_g) of complexes of 6 and II as a function of the GHratio;* (—●—) *: R_g from experimental data.* (· · · □ · · ·): *Expected radius of gyration of complex is included, assuming homogeneous distribution of guests.*

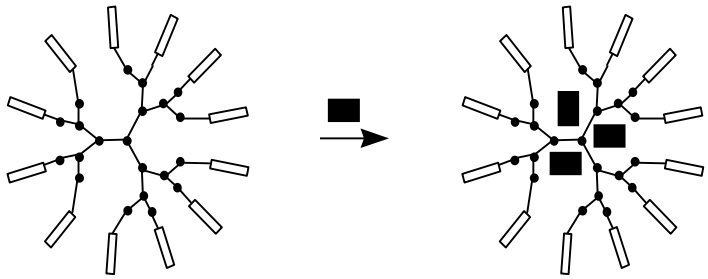


Figure 5.9: *Cartoon of the preferential location of dye molecules in dendrimer* ***6*** *as the concentration of the dye is increased. One black box represents roughly 10 dye molecules.*

5.4 Conclusions

In conclusion, a new host–guest system is developed in an aqueous medium based on oligoethyleneoxy-functionalized poly(propylene imine) dendrimers. The host–guest interactions of guest **I** and **II** differ significantly and cannot be rationalized by differences in electrostatic interactions between host and guest only, but also hydrophobic interactions seem to play an important role. A typical property of dendrimers, *i.e.* their retention in membranes because of their nanometer dimensions, has been shown by ultrafiltration. As there is no aggregation, the SAXS measurements provide strong evidence for the preferential location of the guests in the interior of the dendrimer, which makes the latter ideal containers and suggests their use in drug-delivery applications.

5.5 Experimental Section

Materials

Commercial grade solvents were used without further purification. Methyl 3,4,5-trihydroxybenzoate (98%), tetraethylene glycol monomethyl ether (98%) and *p*-toluenesulfonyl chloride (99+%), lithiumhydroxide monohydrate and potassium carbonate (p.a.) were obtained from Acros Chimica. Pentafluorophenol (99+%) and 1,3-dicyclohexylcarbodiimide (DCC, 99%) and Hydrion dry pH buffers were obtained from Aldrich. The amine-functionalised poly(propylene imine) dendrimers, DAB-*dendr*-$(NH_2)_n$ (n = 4, 16, 32, 64), were kindly provided by DSM Research (Geleen, The Netherlands) and used as received. 4,5,6,7-tetrachlorofluorescein (**I**), Bengal Rose (**III**) was purchased from Fluka. Bio-Beads S-XI Beads (200—400 mesh) were obtained from Bio-Rad Laboratories**.**

General Methods

Absorption Spectra in the ultraviolet-visible range (UV/vis) were recorded on a Perkin-Elmer Lambda 3 UV/Vis spectrophotometer or a Perkin-Elmer Lamda 900 UV/vis/NIR spectrometer. ^{1}H-NMR, ^{13}C-NMR and ^{19}F-spectra were recorded in $CDCl_3$ on a Bruker AM 400 spectrometer at 400.13, 100.62 and 376.49 MHz, respectively. All δ-values were given in ppm downfield from tetramethylchlorosilane for ^{1}H-NMR and ^{13}C-NMR and in ppm downfield from $CFCl_3$, in case of ^{19}F-NMR. Infrared Spectra were recorded on a Perkin-Elmer 1605 Series FT operating between 4400 and 450 cm^{-1} using KBr-pellets. Electrospray mass spectra were recorded on a API 300 MS/MS mass spectrometer (PE-Sciex, Foster City, USA). Preparation and measurement of the samples were performed analogous to the ones in previous publications.[73] The mass spectrometer was used in positive ion mode. MALDI-TOF mass spectra were recorded on a Perspective Biosystems Voyager E-Pro MALDI-TOF mass spectrometer (Accelerating Voltage: 25000 V; Grid Voltage: 74000 %; Guide Wire Voltage: 0.030 %) using α-cyano-4-hydroxycinnamic acid as matrix.

UV/vis Titrations

Stock solutions of 2.5×10^{-5} M ethyleneglycol-functionalized dendrimer **3-5** were added in aliquots of 1–100 µL to a 1.25×10^{-5} M solution of anionic solute **I–III** of a known volume (2–3 mL) in a quartz cell. UV/Vis spectra were recorded after mixing and corrected for dilution. Reverse titration experiments were performed to check specific spectral changes.[57]

Small Angle X-ray Scattering

Small Angle X-ray scattering (SAXS) experiments were performed on the X33 camera of the European Molecular Biology Laboratory at the storage ring DORIS III of the Deutsches Elektronen Synchrotron (DESY), Hamburg.[74, 75] The sample to detector distance was set to 2.5 m, which resulted in an effective q range from 0.1 to 3 nm^{-1}, where $q = (4\pi\sin\theta)/\lambda$; with 2θ, the scattering angle and λ = 0.15 nm, the wavelength. A quadrant detector with delay line readout[76] was used to obtain good statistics, particularly in the high q range. Scattering patterns were collected in series of 20- 30 frames of 60 s each. The raw data were normalized to the intensity of the primary beam, monitored with an ionization chamber, averaged and corrected for the detector response using the SAPOKO program (Svergun and Koch, unpublished results). Background scattering was subtracted and the difference curves were scaled for concentration. Further data processing was performed using the OTOKO program.[77] Calibration of the q-axis was performed with tripalmitin or collagen as standards and the resulting scattering patterns were subsequently used for calculation of the distance distribution functions P(r) which was carried out using a program that is based on the GNOM algorithm.[74, 78]

SAXS experiments were performed on solutions with concentrations up to 500 mg/ml to evaluate the influence of interparticle interactions. In a concentration range up to 50 mg/ml, the forward scattering intensity I(0) is independent of concentration within the accuracy of our experiments. Increasing the concentration results in a decrease in I(0), indicating repulsive interactions, with a well-defined structure factor maximum appearing at the highest concentrations.

Ultrafiltration Experiments

To aqueous solutions of ethyleneglycol functionalized dendrimer 3—5 or TOA were added stock-solutions of anionic solute **II** to yield appropriate dendrimer-to-solute ratios. In a typical experiment, 40 ml of a stock-solution of 2.5×10^{-5} M dendrimers 3—5, was added to 4 ml of a stock-solution of 2.5×10^{-4} M solute. The

mixture was transferred into an ultrafiltration cell (Schleicher & Schuell Stirred Cell SC 75). The cell uses cellulose membranes (Schleicher & Schuell Ultran RC/100) with a temperature limitation of T < 60 °C and within a pH-range of 2 – 12). Membranes used have a cut-off of 10 kD and need to be swollen in aqueous solvent. Pressure can be applied to the ultrafiltration cell to regulate filtration speed. Typically, the cell volume is concentrated by a factor of 4, after which the cell volume is re-adjusted and the filtration experiment repeated. Both the filtrated solution and the residual phase are characterized with UV/Vis spectroscopy.

Synthesis of tris 3,4,5-tri(tetraethyleneoxy)benzoic acid, 1

To a solution of trihydroxybenzoate methylester (3.83 g, 0.0208 mol) in acetone (100 ml) was added finely ground potassium carbonate (28.76 g, 0.2081 mol, 10 eq.) and monomethyltetraethyleneglycol monotosylate[79] (26.4 g, 0.0728 mol, 3.5 eq). The heterogeneous mixture was heated under reflux conditions for 24 h under an argon atmosphere, and the pink reaction mixture was filtrated to remove excess potassium carbonate. Additionally, acetone was evaporated and the crude product dissolved in dichloromethane (125 ml), washed with 100 ml water, 50 ml 1 M HCl and 100 ml water and the solvent evaporated. Additional column chromatography (SiO_2: chloroform/MeOH, 97:3, R_f = 0.36) yielded pure methylester (10.68 g, 68%). ^{1}H-NMR ($CDCl_3$): δ = 3.38 (s, 9H, (OC*H*$_3$)$_3$; 3.53–3.87 (m, 21H, OC*H*$_2$); 3.88 (s, 3H, C*H*$_3$OOC); 4.20 (m, 6H, Ar-(OC*H*$_2$CH$_2$O)$_3$); 7.30 (s, 2H, Ar-*H*); IR (KBr): ν (cm)$^{-1}$ = 2872.4 (C–H sat), 1718.2 (C=O,s), 1586.8 (C–O); ESI-MS: Calcd. for $C_{35}H_{62}O_{17}$: 754.86. Found 777.6 [M + Na$^+$], 793.5 [M + K$^+$]. This ester (10.68 g, 0.014 mol) was added to a solution of LiOH·H_2O (0.75 g, 0.018 mol, 1.25 eq.) in water/MeOH mixture (17 ml, 1:3 v/v) and stirred overnight. The mixture was evaporated *in vacuo*, redissolved in dichloromethane and extracted with water to remove salts. Evaporation of the organic phase under reduced pressure yielded 8.98 g (85%) of pure acid **1** as a viscous oil. ^{1}H-NMR ($CDCl_3$): δ = 3.38 (s, 3H (OC*H*$_3$), 3.40 (s, 6H, (OC*H*$_3$)$_2$; 3.56–3.87 (m, 21H, OC*H*$_2$); 4.22 (m, 6H, Ar-(OC*H*$_2$CH$_2$O)$_3$); 7.38 (s, 2H, Ar–*H*); ^{13}C-NMR ($CDCl_3$): δ = 60.1 (3C, O*C*H$_3$); 69.9 / 70.7 / 71.5-71.9 / 72.9 / 73.5 (24C, O*C*H$_2$); 110.4 (2C, Ar–*C*2/*C*5); 125.7 (1C, Ar–*C*1); 143.7 (1C, Ar–*C*5); 153.2 (2C, Ar–*C*4/*C*6). IR (KBr): ν (cm)$^{-1}$ = 3434.9 (N–H strectch), 2873.9 (C–H sat), 1713.6 (C=O,s), 1586.8 (C–O), 1429.1 (C=O, a); ESI-MS: Calcd. for $C_{34}H_{60}O_{17}$: 740.84. Found 741.1 [M + H$^+$], 763.0 [M + Na$^+$], 779.1 [M + K$^+$].

Synthesis of pentafluorophenyl tris 3,4,5-tri(tetraethyleneoxy)benzoate, 2

A solution of acid **1** (5.95g, 8.031 mmol) and pentafluorophenol (1.5g, 8.64 mmol, 1.07 eq.) was prepared in diglyme (8ml). To the homogeneous solution, which was cooled at 0 °C, 1,3-dicyclocarbodiimide (1.85g, 8.97 mmol, 1.12 eq.) was added. After complete addition of DCC, the temperature of the reaction mixture was allowed to equilibrate to room temperature and after 1 day, the reaction mixture was filtered and the filtrated concentrated *in vacuo*. The product was precipitated in cyclohexane and additional column chromatography (SiO_2: dichloromethane/MeOH, 9:1, R_f = 0.80) yielded pure PFP-ester **2** as a viscous oil (5.67g, 78 %). ^{1}H-NMR ($CDCl_3$): δ = 3.39 (s, 3H (OC*H*$_3$), 3.42 (s, 6H, (OC*H*$_3$)$_2$; 3.56-3.90 (m, 21H, OC*H*$_2$); 4.25 (m, 6H, Ar-(OC*H*$_2$CH$_2$O)$_2$); 4.30 (t, 2H, OC*H*$_2$CH$_2$O); 7.46 (s, 2H, Ar-*H*); ^{19}F-NMR ($CDCl_3$): δ = 20.5 (d, 2F, *J* = 16.9 Hz), 15.1 (t, 1F, *J* = 22.2 Hz), 10.7 (t, 2F, *J* = 20.0 Hz).

Typical Procedure for the Synthesis of oligoethyleneoxy-modified poly(propylene imine) dendrimers: DAB-*dendr*-(NHCO-EG)$_{16}$, 4

To a solution of DAB-*dendr*-(NH_2)$_{16}$ (1.00 g, 5.93·10^{-4} mol) in CH_2Cl_2 (10 ml) is added 8.82 g (9.72·10^{-3} mol, 1.025 eq per NH_2) of the pentafluorophenyl ester of 3,4,5-tri(tetraethylene glycol)benzoic acid. After stirring overnight the reaction mixture is extracted with 0.1 M NaOH and excess active ester is removed by biobeads chromatography (BioRad, SX1) yielding pure **2** (6.28 g, 80%) as a viscous oil. Purity was confirmed by TLC (CH_2Cl_2/MeOH 95/5, R_f = 0). ^{1}H-NMR ($CDCl_3$): 1.40-1.80 (60H, NCH$_2$C*H*$_2$), 2.30–2.60 (84H, NC*H*$_2$), 3.38 (144H, OC*H*$_3$), 3.42 (32H, C*H*$_2$NHCO), 3.45–3.80 (672H, OC*H*$_2$), 4.00–4.16 (96H, Ar–OC*H*$_2$), 7.16 (s, 32H, Ar–*H*), 7.96 (s, 16H, N*H*CO); ^{13}C-NMR ($CDCl_3$): δ = 27.5 (NCH$_2$*C*H$_2$CH$_2$NHCO); 38.9 (*C*H$_2$NHCO), 51.8 - 52.4 (N*C*H$_2$), 59.0 (O*C*H$_3$), 69.0 / 69.8 / 70.7 / 70.8 / 72.1 / 72.6 (O*C*H$_2$), 106.7 (Ar-*C*2, *C*6), 129.7 (Ar–*C*1), 140.8 (Ar–*C*4), 152.3 (Ar–*C*3,*C*5), 167.2 (NH*C*O); MALDI-TOF MS: Calcd. for $C_{632}H_{1136}N_{30}O_{256}$ 13251.9. Found 13243 [M + H]$^+$.

DAB-*dendr*-(NHCO-EG)$_4$, 3

^{1}H-NMR ($CDCl_3$): δ 1.38 (s, 4H, NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N), 1.78 (t, 8H, NCH$_2$C*H*$_2$CH$_2$N), 2.38 (s, 4H, NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N), 2.48 (t, 8H, C*H*$_2$NHCO), 3.38 (36H, OC*H*$_3$), 3.42 (8H, C*H*$_2$NHCO), 3.45-3.80 (168H, OC*H*$_2$), 4.00-4.16 (24H, Ar-OC*H*$_2$), 7.16 (s, 8H, Ar-*H*), 7.61 (s, 4H, N*H*CO); ^{13}C-NMR ($CDCl_3$): δ = 24.5

($NCH_2CH_2CH_2CH_2N$), 27.5 ($NCH_2CH_2CH_2NHCO$); 38.9 (CH_2NHCO), 51.8 – 52.4 (NCH_2), 53.6 ($NCH_2CH_2CH_2CH_2N$), 59.0 (OCH_3), 69.0 / 69.8 / 70.7 / 70.8 / 72.1 / 72.6 (OCH_2), 106.7 (Ar-*C*2, *C*6), 129.7 (Ar-*C*1), 140.8 (Ar-*C*4), 152.3 (Ar-*C*3,*C*5), 167.2 (NH*C*O); MALDI-TOF MS: Calcd. for $C_{152}H_{272}N_6O_{64}$ 3207.8. Found 3207.0 $[M + H]^+$, 3229.2 $[M + Na^+]$.

DAB-dendr-(NHCO-EG)$_{32}$, 5

^{1}H-NMR ($CDCl_3$): δ 1.40–1.80 (124H, NCH_2CH_2); 2.30-2.60 (176H, NCH_2CH_2); 3.38 (288H, OCH_3), 3.42 (64H, CH_2NHCO), 3.45–3.80 (1344H, OCH_2), 4.00-4.16 (192H, Ar-OCH_2), 7.06 (s, 64H, Ar-*H*), 8.02 (s, 32 H, N*H*CO); ^{13}C-NMR ($CDCl_3$): δ = 24.0 ($NCH_2CH_2CH_2N$), 27.0 ($NCH_2CH_2CH_2NHCO$); 38.6 (CH_2NHCO), 51.8 - 52.4 (NCH_2), 53.6 ($NCH_2CH_2CH_2CH_2N$), 58.9 (OCH_3), 69.0 / 69.8 / 70.7 / 70.8 / 72.1 / 72.4 (OCH_2), 106.8 (Ar-*C*2, *C*6), 129.7 (Ar-*C*1), 141.0 (Ar-*C*4), 152.3 (Ar-*C*3,*C*5), 167.1 (NH*C*O); MALDI-TOF MS: Calcd. for $C_{1272}H_{2282}N_{62}O_{512}$ 26644.34. Found 26565.3 $[M + H]^+$.

DAB-dendr-(NHCO-EG)$_{64}$, 6

^{1}H-NMR ($CDCl_3$): δ 1.40–1.80 (252H, NCH_2CH_2); 2.30–2.60 (368H, NCH_2CH_2); 3.38 (576H, OCH_3), 3.42 (128H, CH_2NHCO), 3.45–3.80 (2688H, OCH_2), 4.00–4.16 (384H, Ar-OCH_2), 7.06 (s, 512 H, Ar-*H*), 8.18 (s, 64 H, N*H*CO); ^{13}C-NMR ($CDCl_3$): δ = 27.5 ($NCH_2CH_2CH_2NHCO$); 38.9 (CH_2NHCO), 51.8 - 52.4 (NCH_2), 59.0 (OCH_3), 69.0 / 69.8 / 70.7 / 70.8 / 72.1 / 72.6 (OCH_2), 106.7 (Ar-*C*2, *C*6), 129.7 (Ar-*C*1), 140.8 (Ar-*C*4), 152.3 (Ar-*C*3,*C*5), 167.2 (NH*C*O); MALDI-TOF-MS: Calcd. for $C_{2552}H_{4592}N_{126}O_{1024}$ 53428.8. Found 53576.2 $[M + H]^+$.[54]

5.6 References and Notes

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Liquid Crystalline Dendrimers

6

Abstract: *Three generations poly(propylene imine) dendrimers with 4, 16 and 64 amine endgroups have been functionalized with pentyloxycyanobiphenyl and decyloxycyanobiphenyl mesogens. The liquid crystalline properties of these dendrimers have been studied in detail by differential scanning calorimetry, optical polarization microscopy and X-ray diffraction. All the mesogenic dendrimers orient into a smectic A mesophase. Thermal properties are influenced to a large extent by the spacer length, showing g* $\rightarrow S_A \rightarrow$ *I transitions for the dendritic mesogens with the pentyloxy spacers and K* $\rightarrow S_A \rightarrow$ *I transitions for the ones with a decyloxy spacer. In case of the decyloxy spacer, the temperature range of the mesophase increases with dendrimer generation. The mesophase formation in case of the pentyloxy series is less stable compared to the corresponding decyloxy anologues, considering transition enthalpies. The effect of generation on mesophase formation can not clearly be distinguished, although in case of the fifth generation dendrimer with a decyloxy spacer, microscopic textures could be obtained more easily, compared to the lower generations. X-ray diffraction measurements of oriented samples indicate that the cyanobiphenyl endgroups of both series orient into an anti-parallel overlapping interdigitated structure. The observed* S_A*-layer spacings are independent of the dendrimer generation, for both spacer lengths, indicating that the dendritic backbone has to adopt a completely distorted conformation, even for the higher generations.*

This work has been published: Baars, M. W. P. L.; Söntjens, S. H. M.; Fischer, H. M.; Peerlings, H.W. I.; Meijer, E. W. *Chem. Eur. J.* **1998**, *4*, 2456–2466.

6.1 Introduction

The use of dendrimers[1–9] as well-defined building blocks with nanometer dimensions for the construction of supramolecular architectures attracts many scientific as well as technological attention. The multifunctional and three-dimensional structure allows the use of dendrimers as large homogeneous catalyst systems,[10–12] enzyme mimicking host–guest systems[5, 13–18] or self-assembling modules.[19–22] The monodisperse character of the dendritic molecules and the shape persistence of their three-dimensional conformation play an important role in these applications.

Recently, liquid crystalline dendrimers have proven to be an interesting new family of (polymeric) mesogenic compounds with dimensions and molecular weights in between low molecular weight mesogens,[23–27] such as monomeric,[28–30] dimeric[31, 32] and oligomeric compounds,[33–36] and high molecular weight main-chain or side-chain liquid-crystalline polymers.[37–39] Dendritic properties, like the absence of entanglements and the high local concentration of endgroups, explain the interest in dendritic mesogenic molecules as potential liquid crystalline materials with an interesting balance in viscosity and thermodynamic stability and these intriguing properties are reviewed by various experts in the dendrimer[40, 41] and the liquid crystal field.[42–44]

Percec *et al.*[45–47] showed that incorporation of rodlike units in hyperbranched polymers[45] yielded nematic mesophases, whereas the dendritic analogues showed both nematic and smectic mesophases. Kumar and Ramakrishnan[48, 49] showed, however, that in case of random distribution of mesogenic units in a hyperbranched polymer, liquid crystalline properties were suppressed. Lattermann *et al.*[50] showed that the coupling of 3,4-bis(decyloxy)benzoyl groups onto a poly(propylene imine) dendrimer skeleton induced shape anisotropy, yielding hexagonal columnar mesophases for generation 2 through 4, whereas generation 5 with 64 endgroups showed a different liquid crystalline behavior. The three-dimensional geometry of a fifth generation is likely to surpress the formation of a columnar structure. Percec *et al.* showed that, by variation of the dendritic side-groups, polymer-shape could be controlled yielding either hexagonal columnar mesophases or cubic mesophases.[51–56] Moore *et al.*[57] observed discotic behavior by attachment of flexible ethylene oxide oligomers to a rigid phenylacetylene core, again as a consequence of molecular shape anisotropy. Frey *et al.*[58] and Shibaev *et al.*[59] connected rod-like mesogenic units to the periphery of a multifunctional dendritic carbosilane skeleton; the formation of smectic mesophases was observed. However, for a fifth generation dendrimer with 128 endgroups a change in liquid crystallinity was observed.[60] Moreover, attention has been paid to the effect of spacer length on liquid crystalline properties of these mesogenic dendrimers.[61] Recently, others have also connected rodlike mesogens to poly(amidoamine)[62–64] dendrimers, poly(propylene imine)

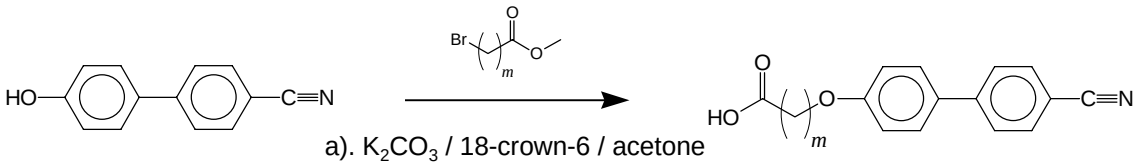
dendrimers and carbosilane dendrimers.[65] From all these studies, it is evident that the geometrical requirements to obtain a well-defined mesophase is highly dependent on (the dimensions of) the dendrimer scaffold and on the type of endgroup used.

Here, a study of cyanobiphenyl mesogenic units coupled in a remote way to the periphery of poly(propylene imine) dendrimers is presented, varying both the spacer length of the cyanobiphenyl mesogens and the dimensions (generations) of the dendrimers. These variations will enable a study of the effect of molecular structure on the self-assembly of the different dendritic mesogens in the liquid crystalline mesophase. It is an intriguing question whether a (symmetrical) dendritic skeleton is able to impede liquid crystalline properties or whether the high local concentration of mesogenic units in a dendritic molecule leads to pre-organization and facilitates the formation of a mesophase. All generations, irrespective of the spacer length, show liquid crystalline properties. DSC measurement, optical microscopy and X-ray diffraction prove smectic A mesophases and the independence of the smectic layer spacings indicates that the mesogenic endgroups dictate the organization of the macromolecules and that the dendritic scaffold is flattened for the higher generations.

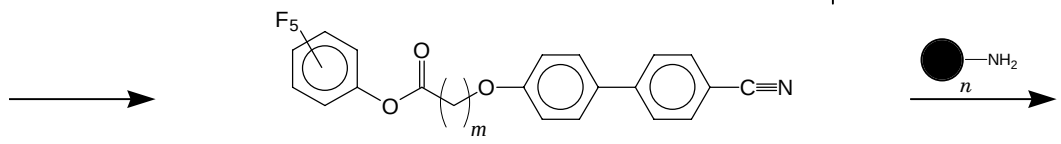
6.2 Synthesis and Characterization

Poly(propylene imine) dendrimers[3] are synthesized with pentyloxy and decyloxy cyanobiphenyl mesogens, and indicated as DAB-*dendr*-(NHCO-C_5-CBPh)$_n$ [66] (n = 1: **3**, n = 4: **4**, n = 16: **5**, n = 64: **6**) and DAB-*dendr*-(NHCO-C_{10}-CBPh)$_n$ [66] (n = 1: **9**, n = 4: **10**, n = 16: **11**, n = 64: **12**), respectively (Scheme 6.1).

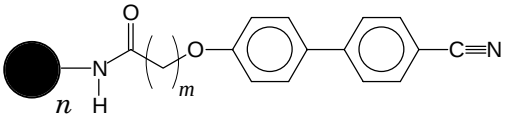
Pentafluorophenyl esters of 6-((4'-cyano(1,1'-biphenyl)-4-yl)oxy)hexanoic acid (**1**) and 11-((4'-cyano(1,1'-biphenyl)-4-yl)oxy)undecanoic acid (**7**)[67] were coupled to different generations of amine-functionalized poly(propylene imine) dendrimers (n = 4, 16 and 64) and to model compound n-propylamine (n = 1) with n being the number of functional groups. In contrast to the pentafluorophenol derivatives **2** and **8**, the corresponding N-hydroxysuccinimidoyl esters[68] proved to be quite unreactive. All dendritic mesogens **3**–**6** and **9**–**12** could be obtained by reacting the amine-functionalized dendrimers with a small excess of the pentafluorphenol derivatives and subsequent precipitation of the dendritic products into a non-solvent, like MeOH or n-hexane.



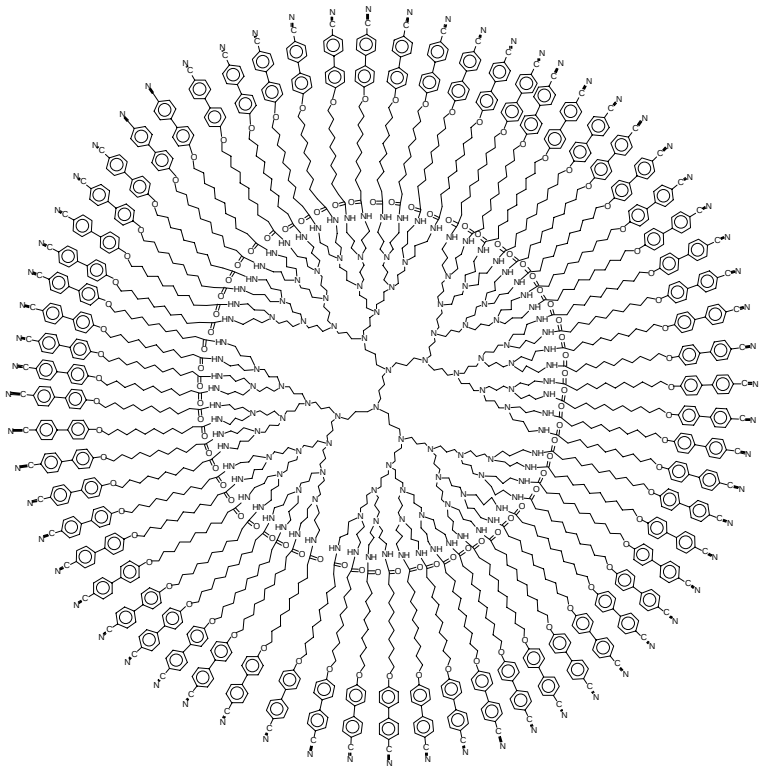
1 | m = 5
7 | m = 10



2 | m = 5
8 | m = 10



Compound	m	n
3	5	1
4		4
5		16
6		64
9	10	1
10		4
11		16
12		64



Scheme 6.1: *Numbers are used to represent compounds. (top): Synthesis of functional cyanobiphenyl substituents (**1**, **2**, **7** and **8**) and of cyanobiphenyl-functionalized poly(propylene imine) dendrimers **3**–**6** and **9**–**12**; (bottom): Detailed structure of host **12** (m = 10, n = 64).*

Mass spectrometry (FAB-MS and MALDI-TOF MS) has been conducted to examine the dendritic structures on defects (incomplete reactions). The amine-functionalized poly(propylene imine) dendrimers, DAB-*dendr*-$(NH_2)_n$ (n = 4–64) have been characterized previously by ESI-MS in detail.[69] DAB-*dendr*-$(NH_2)_4$ shows a purity of an organic compound (96%), while DAB-*dendr*-$(NH_2)_{16}$ contains the pure product (64%) and two defect structures, that can be attributed to dendrimers missing one and two branches, respectively. DAB-*dendr*-$(NH_2)_{64}$ shows a (dendritic) purity of approximately 20% and a calculated polydispersity of 1.002. As a consequence a small number of defects will be present in the fifth generation poly(propylene imine) dendrimer. FAB-MS has been used to characterize the first generation dendritic mesogens, **4** and **10**. The experimental masses ($[M + H]^+$) of 1483 and 1764 D, were in excellent agreement with the calculated masses for **4** and **10** of 1482.9 and 1763.5 D, respectively. No defect structures, due to incomplete coupling, could be detected. MALDI-TOF-MS analysis of the third generation dendrimers, **5** and **11** showed a parent peak ($[M+H]^+$) of 6346.7 (calc. 6348.4) and 7449.3 (calc. 7470.5),[70] respectively. No peaks attributed to dendrimers missing one mesogenic unit were detected, indicating that all primary amine endgroups were modified.[71] The defects that were found originate from defects in the starting material. It proved to be impossible to analyze the fifth generation dendrimer with MALDI-TOF-MS, despite variations in the experimental conditions. This is probably due the high molar mass (30 kD) and hence, the difficulty to yield a considerable ionization in case of dendrimers **6** and **12**. All NMR (^1H and ^{13}C) and IR spectroscopic data of compounds **1**–**12** are in full agreement with the structures proposed. The properties of the functionalized dendrimers were studied in detail by means of differential scanning calorimetry (DSC), polarization microscopy and X-ray diffraction.

6.3 Liquid Crystalline Properties

6.3.1 Differential Scanning Calorimetry

The phase transitions of the pentyloxy substituted compounds **3**–**6** and decyloxy substituted compounds **9**–**12**, have been studied with DSC using heating and cooling rates of 10 K min^{-1}. All samples were dried in a vacuum oven prior to analysis. All dendrimers with a pentyl spacer, **4**–**6**, show liquid crystalline behavior. DSC-traces of these dendrimers are depicted in Figure 6.1.[72] Phase transition temperatures and thermodynamical data of compounds **3**–**6** and reference compound 4-(pentyloxy)-4'-cyanobiphenyl (C_5-CBPh)[73] are summarized in Table 6.1.

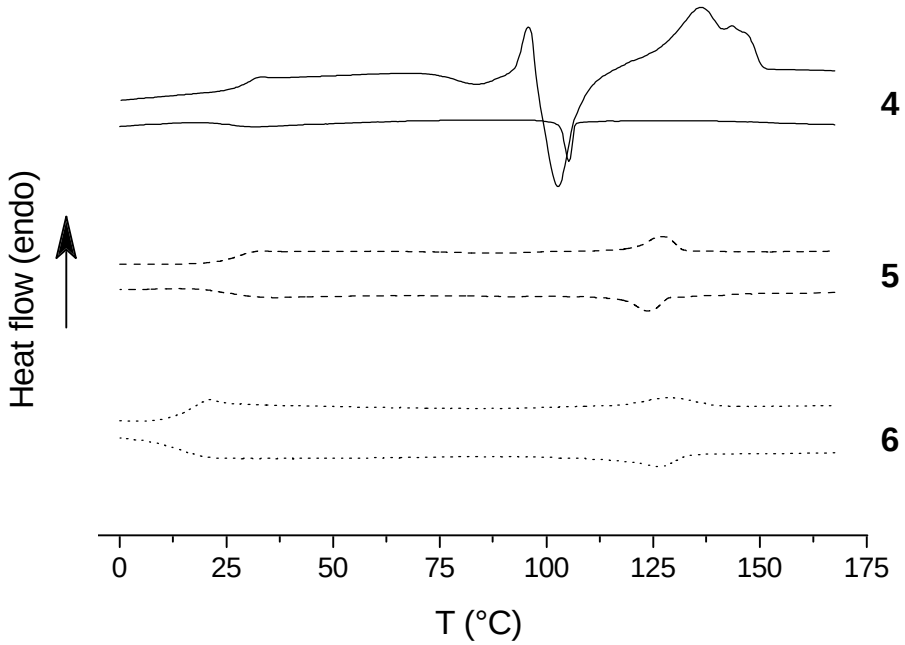


Figure 6.1: *DSC-traces of pentyloxy-cyanobiphenyl dendrimers* **4**, **5**, **6**; *first cooling run (bottom trace), second heating run (top trace).*

Table 6.1: *Transition temperatures and thermal data* [a] *for pentyloxy-cyanobiphenyl compounds (g denotes the glassy state, K the crystalline state, M the mesophase, I the isotropic state, ΔS is the entropy change of the M → I transition).*

Compound	g		K		M		I	ΔS
C_5-BPh			•	50	•	68	•	
				(86; *23*)		(1.8; *0.5*)		1.5
3			•	119			•	
				(69; *23*)				
4	•	31	•	155 [b]	•	{106} [c]	•	
		(0.79; *0.29*)		(–)		(4.8; *1.8*)		4.7
5	•	25			•	127	•	
		(0.49; *0.19*)				(4.9; *2.0*)		5
6		13			•	129	•	
		(0.37; *0.15*)				(3.6; *1.5*)		3.7

(a) Glass transitions are depicted in J g^{-1} K^{-1} or *kJ* mol^{-1} K^{-1}, all other transitions in J g^{-1} or *kJ·mol*$^{-1}$, the entropy changes are depicted in J mol^{-1} K^{-1} (b) Broad (re)crystallization traject from 75 –155 °C (see Fig. 6.1), melting at 155 °C. (c) Compound **10** shows liquid crystalline behavior upon cooling from the isotropic state.

Propylamine derivative **3** remains crystalline up to complete melting and does not show the formation of a liquid crystalline mesophase. In case of the higher generations (n = 16 and 64), a broad mesophase is observed in between glass transition and the transition to isotropic state. The first generation, upon heating also shows a transition from the glassy state into the mesophase, but starts to recrystallize above 75 °C and becomes isotropic at 155°C. This type of complex melting behavior is commonly observed for first generation substituted poly(propylene imine) dendrimers,[74] which is attributed to both inter- and intramolecular hydrogen-bond interactions. Even at low cooling rates (1, 2 or 5 $K\,min^{-1}$) the thermogram remained unchanged and crystallization did not occur. These results indicate that the branched topology strongly impedes crystallization. Dendritic mesogens with a pentyloxy spacer resemble side-chain liquid crystalline polymers with a short spacer between the mesogenic unit and the dendritic scaffold,[38, 39, 75, 76] yielding liquid crystalline behavior in between glassy state and isotropic liquid. The observed results also agree with observations for cyanobiphenyl functionalized carbosilane dendrimers with a short spacer.[58]

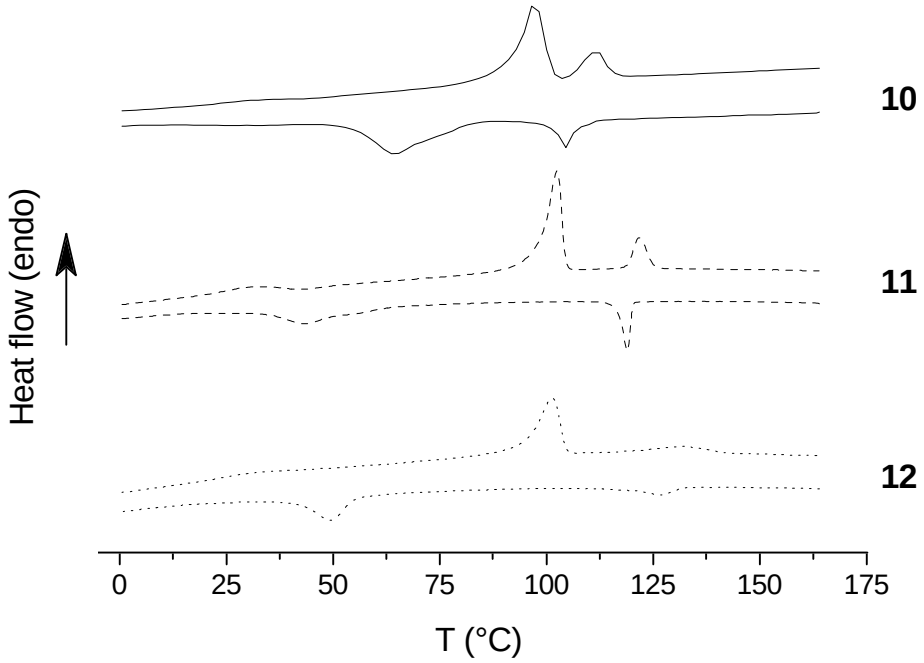


Figure 6.2: *DSC-traces of pentyloxy-cyanobiphenyl dendrimers* **10**, **11**, **12**; *first cooling run (bottom trace), second heating run (top trace).*

The enthalpy of the transition from mesophase into isotropic liquid transition for compounds 4–6 in all cases amounts to 4–5 J g^{-1} (1.5-2.0 kJ mol^{-1}), which hints to a smectic → isotropic transition. Expression of the enthalpy in kJ mol^{-1} relates to the

transition energy per mesogenic unit in the dendrimer and demonstrates an almost generation independent behavior.

Table 6.2: *Transition temperatures and thermal data [(a)] for decyloxy-cyanobiphenyl compounds (g denotes the glassy state, K the crystalline state, M the mesophase, I the isotropic state, ΔS is the entropy change of the M → I transition).*

Compound	g [(b)]		K		M		I	ΔS
C_{10}-CBPh			•	59	•	86	•	
				(98; *33*)		(7.8; *2.6*)		7
9			•	105			•	
				(84; *34*)				
10	•	22	•	106	•	114	•	
		(–)		(34; *15*)		(9.2; *4.0*)		10
11	•	26	•	105	•	124	•	
		(–)		(37; *17*)		(8.8; *4.1*)		10
12	•	22	•	103	•	135	•	
		(–)		(32; *15*)		(8.7; *4.1*)		10

(a) Glass transitions are depicted in J g^{-1} K^{-1} or *kJ* mol^{-1} K^{-1}, all other transitions in J g^{-1} or *kJ* mol^{-1}, the entropy changes are depicted in J mol^{-1} K^{-1}. (b) Dendrimers **10–12** show small glass transitions, that were hardly visible; thermal data was not determined.

The dendrimers with a decyloxy spacer (**10**, **11** and **12**) also show liquid-crystalline behavior for all generations. DSC-traces of dendrimers **10–12** are depicted in Figure 6.2.[72] Phase transition temperatures and thermodynamical data of compounds **9–12** and reference compound 4-(decyloxy)-4'-cyanobiphenyl (C_{10}-CBPh)[73] are summarized in Table 6.2. Propylamine derivative **9** remains crystalline up to complete melting, but does not show a liquid crystalline mesophase. Hydrogen bonding of the amide residue in the melt is likely to account for this behavior. In case of dendrimers **10–12**, upon cooling from the isotropic liquid, a mesophase is entered before a transition into the semi-crystalline state. A (small) glass transition can be detected at lower temperature. Hydrogen bonding is also likely to account for the substantially higher transition temperatures of the dendritic compounds in comparison with C_{10}-CBPh (Table 6.2).

The phase transition temperatures of the mesogenic dendrimers with a decyl spacer are presented in Figure 6.3 and show a slight decrease in melting temperature (T_m) and a distinct increase in clearing point (T_c) as a function of dendrimer generation (molecular weight). This stabilization of the LC phase[77] can be understood from restriction of translational and rotational motions of the mesogenic molecules, when linked to the dendritic scaffold.

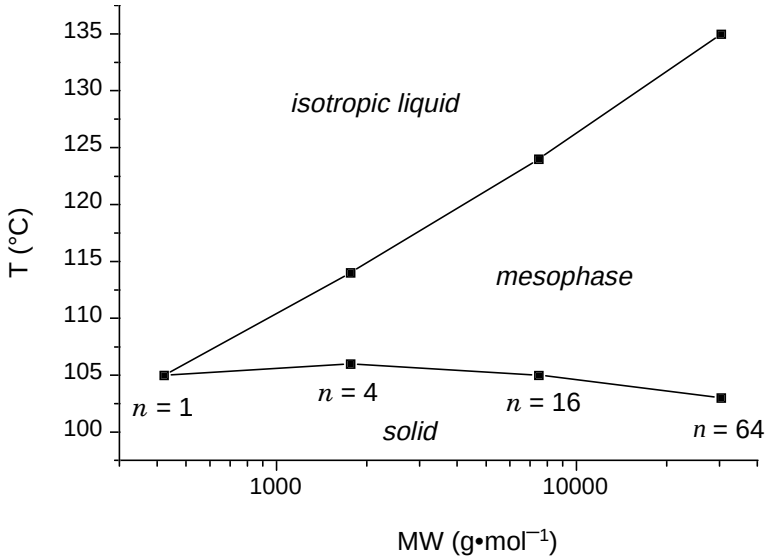


Figure 6.3: *Transition temperatures of cyanobiphenyl dendrimers with a decyl spacer, i.e. DAB-dendr-(NHCO-C$_{10}$-CBPh)$_n$ as a function of molecular weight.*

The transition enthalpy of mesophase to isotropic liquid amounts to 8-9 J g^{-1} (4.0 kJ mol^{-1}) for compounds **10**-**12,** which is of the same order as that of the reference compound (2.6 kJ mol^{-1}). Identical transition enthalpies for dendrimers **10** through **12**, expressed in kJ mol^{-1}, indicate that no distinct effect of generation can be observed, except for the peak transitions that broaden for the higher generations. A detailed study of the broadening of peak transitions in side chain liquid crystalline polymers by Pugh *et al*.[78] revealed that the observed broadening of the peak transitions for the higher generations is not only due to an increase in polydispersity of the dendritic compound, but can also be explained in terms of different microdomains that are present in the liquid crystalline sample.[78] The enthalpies of the crystalline phase to the mesophase transition are of the same order of magnitude for dendritic compounds **10**-**12**, which suggests that crystallization of the mesogenic units is comparable for the different generations and independent of the (dimensions of the) dendritic skeleton. Dendritic mesogens with a decyloxy spacer show a behavior characteristic of a well-defined monodisperse polymer[79] in which the mesogenic unit is (almost) completely decoupled from the dendritic skeleton.

Comparison of both series with a pentyloxy and a decyloxy spacer, respectively, reveals that the length of the spacer has a major influence on thermal properties. Recently, similar trends have been observed by Frey *et al*.[61] The longer the spacer, the more decoupled is the mesogenic unit from the dendritic skeleton. From the DSC traces and the transition enthalpies, it is concluded that the mesophase formation is independent of the dendrimer generation. This is in contrast to the general idea[61] that a larger (spherical) dendrimer distorts liquid crystallinity to a higher extent, and to the

observations of Lattermann.[50] In the latter case, the three dimensional conformation of a fifth generation poly(propylene imine) dendrimer could not adapt to the requirements of the 3,4-bis(decyloxy)benzoyl substituents attached to the core without spacers.

6.3.2. Polarization Microscopy

In order to study the mesophase of the compounds with polarisation microscopy, samples of dendrimers **4–6** and **10–12** were prepared between glass slides. Upon heating, compound **4** shows a broad melting/recrystallization trajectory, in good agreement with the DSC trace. Upon cooling from the isotropic liquid, a mesophase was formed at approximately 110 °C. The structure of the mesophase is converted into a glassy state without any macroscopically recognizable changes. The higher generations showed similar cooling runs, an I → M transition at approximately 130 °C and a M → g transition at room temperature, whereas heating runs showed the reverse behavior, g → M → I. The observed results indicated liquid crystalline behavior from glass transition to isotropisation[58] and were in good agreement with DSC-data. Formation of bâtonettes[23] suggested a smectic A mesophase. Typical textures for compounds **4–6** were grown by slowly cooling the isotropic liquid (0.5 K min^{-1}), an example is presented in Figure 6.4 (left) for a sample of compound **6**. It can clearly be seen from the image that the optical textures grown were very small and initially yielded formation of bâtonettes. Further growth into larger domains proved to be impossible, even after annealing for longer periods. The majority of the image consisted of confocal textures, representing small birefringent regions of 10 µm in dimension.

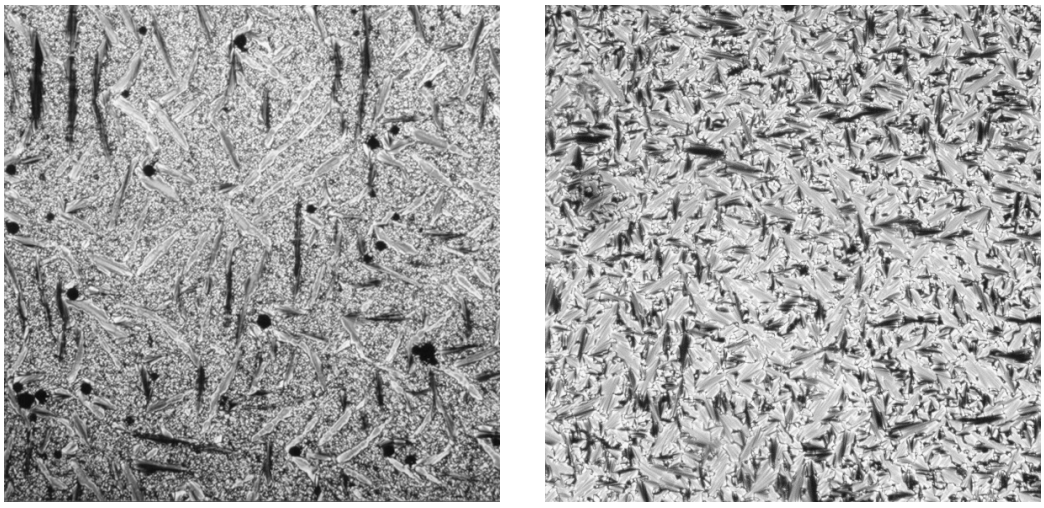


Figure 6.4: *Left: Optical texture of **6** at 120 °C (crossed polarizers, enlargement 200 x); Right: Optical texture of **12** at 130 °C (crossed polarizers, enlargement 200 x).*

Compounds **10–12** showed the formation of mesophases, in good agreement with the DSC traces. At approximately 105 °C a transition from the semi-crystalline state into the mesophase takes place followed by a transition into the isotropic liquid at higher temperature. Again, typical textures could be grown by slowly cooling the isotropic liquid (1 K min^{-1}). A focal-conic fan-shaped texture,[23] indicative of a smectic A phase is depicted for compound **12** (Figure 6.4, right). The fast reappearance of the liquid crystalline phase at 130 °C upon cooling from the isotropic liquid, indicated a high degree of pre-orientation in the isotropic state, an effect which might be related to the high local concentration of the endgroups in the dendritic structure. Surprisingly, the highest generation gave best results in growing these focal-conic fan structures. This suggested a tighter packing of the mesogens in case of the higher generations.

6.3.3 X-ray Diffraction

The structures of the mesophases of compounds **4–6** and **10–12** were examined in detail by X-ray diffraction. Figure 6.5 shows a flat camera photograph of oriented samples of **5** and **11** at room temperature obtained by quickly cooling from the mesophase. The X-ray diffraction curves of **11** and **12** are depicted in Figure 6.6.

Table 6.3: *X-ray diffraction data obtained for DAB-dendr-(NHCO-C_m-CBPh)$_n$.*

Compound			d-spacings (Å)	
4	m = 5	n = 4	4.4 ± 0.1	36 ± 2
5		n = 16	4.4 ± 0.1	39 ± 2
6		n = 64	4.4 ± 0.1	38 ± 2
10	m = 10	n = 4	4.4 ± 0.1	45 ± 2 (a)
11		n = 16	4.4 ± 0.1	44 ± 2 (a)
12		n = 64	4.4 ± 0.1	45 ± 2 (a)

(a) *Spacings are obtained by averaging 1st, 2nd and 3rd order reflections.*

For all mesogenic dendrimers a diffuse wide angle reflection at 4.4 ± 0.1 Å was observed (Table 6.3), typical for the lateral distance between the mesogens. These values are in agreement with literature data on side-chain polymers containing cyanobiphenyl mesogens.[23, 24] The diffuse nature of the reflection indicates the short-range order of the mesogens. X-ray diffraction patterns of compounds **4**, **5** and **6** show sharp small angle reflections (first order) at 36, 39 and 38 Å (Table 6.3), respectively. These reflections are typical for a smectic A mesophase and indicate a defined packing of the dendritic mesogens in layers. Compounds **10**, **11** and **12**, with a decyloxy spacer,

show small angle reflections at 45, 44 and 45 Å (Table 6.3), respectively. Besides sharp, first order, point-like meridian reflections, second and third order reflections are also observed. The observations of higher order reflections is indicative of a long-range longitudinal order and suggests that the packing of the mesogenic dendrimers with a decyl spacer into smectic layers is more defined than the packing of the pentyl series, in which the higher order reflections are abundant.

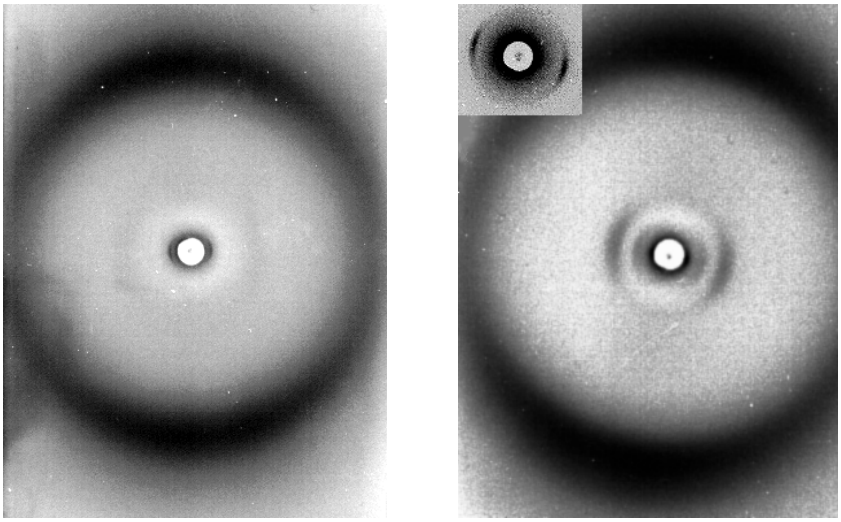


Figure 6.5: *X-ray diffraction pattern of oriented samples of **6** (left) and **11** (right) at room temperature.[80] (left): first order reflection of **6** is located in beam stop; (right): first, second and third order reflections of **11**. First order is located in beam stop, but inset shows reflection at small angle.*

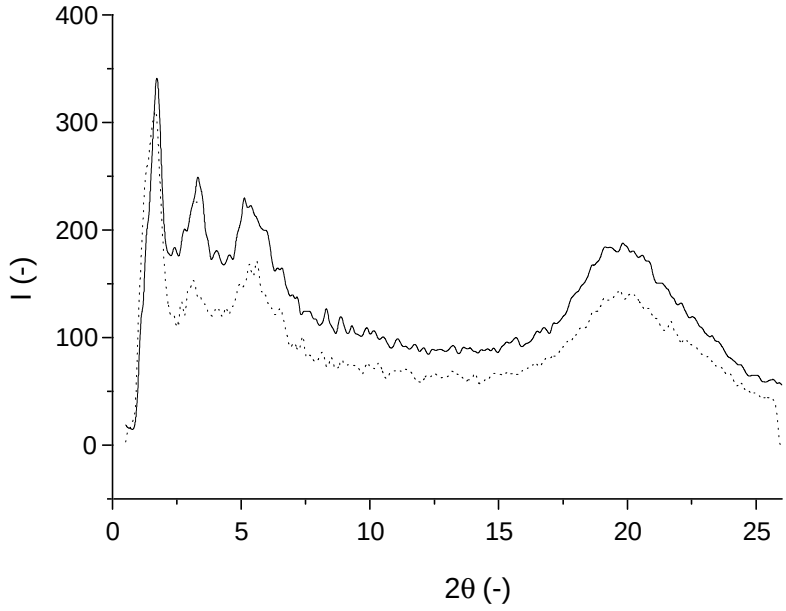


Figure 6.6: *X-ray diffraction curves of decyloxycyanobiphenyl dendrimers **11** (—) and **12** (·····).*

The formation of smectic mesophases can be explained by a phase separation between the anisometric rigid units and the flexible skeleton (alkyl spacer and dendritic interior) in combination with a microphase separation between the polar dendritic interior and the apolar mesogenic endgroups. The arrangement of the mesogenic endgroups is predominantly perpendicular with respect to the plane of the smectic layer in which the dendritic backbone is positioned. The mesophase consists of consecutive layers in which the mesogenic units and the dendritic interior are microphase separated. It is known that cyanobiphenyl mesogens, because of their large dipole moment, preferentially orient into an antiparallel overlapping interdigitated structure.[23, 24] The spacings of the smectic layers are (almost) independent of the dendrimer generation, but are dependent on the spacer length of the mesogenic unit. The constant value of the layer spacings indicates that the dendrimer, for all generations, occupies the same thickness in the smectic layers and that the dendritic interior has to adopt a highly distorted conformation for the higher generations. A proposed model is represented in Figure 6.7 (top).

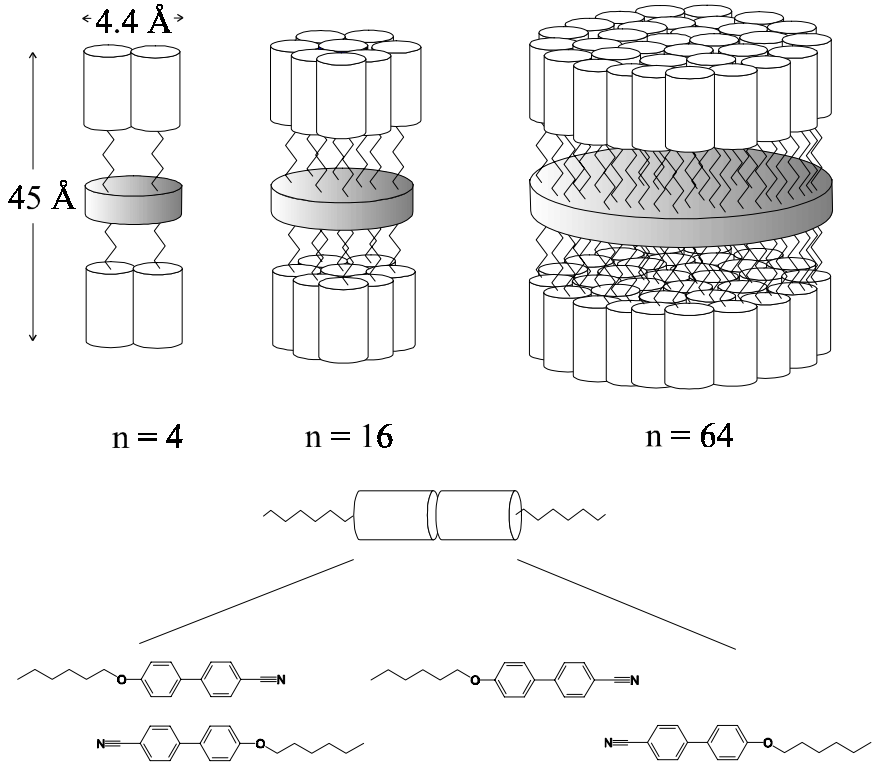


Figure 6.7: *(top) Proposed model for the organization of mesogenic dendrimers into smectic layered mesophases, depicted for the first (n = 4), third (n = 16) and fifth generation (n = 64). Dimensions are shown for the dendrimers with a decyl spacer; (bottom) Cartoon for the possible overlap of the mesogenic fragments in the smectic layers. Choice of alkyl chain length is arbitrary.*

It is difficult however to determine the exact degree of overlap of the cyanobiphenyl units and deformation of the flexible skeleton.[38] Two possible (extreme) cases of overlap are depicted in Figure 6.7 (bottom). An extended decyloxycyanobiphenyl chain occupies a length of 25 Å. To account for the observed layer spacings of approximately 45 Å, and the thickness of the dendrimer layer, the cyanobiphenyl parts (of different dendritic molecules) need to have a considerable overlap. Assuming that this overlap is generation independent, a constant dendrimer thickness seems likely, since for all dendrimer generations, the volume per endgroup is roughly constant.

6.4 Discussion

The spontaneous orientation of the mesogenic units forces the (three dimensional) dendritic skeleton into a highly distorted conformation, an observation which is quite common for side-chain liquid crystalline polymers.[75] Recently, similar results have been obtained for poly(propylene imine) dendrimers modified with an apolar periphery of palmitoyl chains.[22, 81] Transmission Electron Microscopy and X-ray measurements of the dendrimers in bulk and of aggregates of these dendrimers in aqueous media, showed bilayer spacings that were independent of generation. It is assumed that the dendritic interior occupies the same thickness for all generations and has to adopt a highly distorted conformation in case of the higher generations. In the case of a poly(propylene imine) scaffold, the volume and shape of the endgroups determine the organization of dendritic macromolecules. Endgroups with an alkyl chain,[22] or alkoxyazobenzene-units[22] organize in the bulk into layered arrangements. Modification with rodlike-mesogens, like alkoxycyanobiphenyl units, leads to such layered arrangement in the form of a smectic A mesophase. The type of linkage used, amide or ester[65] can further be used as a tool to tailor the phase transition temperature.[82] Bulky units like adamantyl[22]- or amino acid-derivatives yield a denser packing of the dendritic surface, in which the conformational freedom is reduced and an overall spherical structure is obtained. In case of pie-shaped mesogenic endgroups, reported by Latterman *et al.*[50] a hexagonal columnar mesophase can be observed. These results show that the poly(propylene imine) scaffold is highly flexible.

Various reports discuss the modification of poly(amidoamine)[62–64] and carbosilane dendrimers[58–61] with rodlike mesogens and show similar liquid crystalline behavior. In most cases, a layered smectic mesophase is observed. However, some difference can be observed between the polar, flexible poly(propylene imine) scaffold and the apolar, stiff carbosilane scaffold even when the periphery is modified with the same endgroups. For instance, in case of a fifth generation carbosilane dendrimer with decyloxy

cyanobiphenyl mesogens no smectic mesophase is observed, whereas the corresponding poly(propylene imine) dendrimer can easily deform into a layered arrangement. Furthermore, Differential Scanning Calorimetry (transition enthalpies), optical microscopy (tectures) and X-ray measurements (diffraction pattern) suggest that the organisation is less well-defined and that with a stiffer skeleton liquid crystallinity is hindered. Furthermore, besides flexibility and rigidity that play a predominant role in liquid crystallinity, also the difference in polarity between interior and periphery is also likely to play a role in the phase separation process. Recently, other studies with poly(propylene imine) dendrimers following our first publication confirm the conclusions made here.[62, 64, 65]

6.5 Conclusions

Amine-functionalized poly(propylene imine) dendrimers have successfully been reacted with pentafluorophenyl esters of alkoxycyanobiphenyl mesogens at the periphery of the dendrimer. Three different generations of mesogenic dendrimers have been synthesized with 4, 16 and 64 endgroups, respectively. The spacer between the mesogenic unit and the dendritic core was varied, *i.e.* pentyl or decyl. Differential scanning calorimetry, polarization microscopy and X-ray investigations indicate the formation of smectic A mesophases for all generations of dendrimers. This is in contrast with observations of other mesogenic poly(propylene imine) dendrimers and the general idea that for the higher generations liquid crystallinity is less readily observed. The cyanobiphenyl dendrimers orient into an anti-parallel arrangement, yielding an interdigitated bilayer. The layer spacings obtained from the X-ray investigations, are generation independent, both for the mesogenic dendrimers with a decyloxy spacer and a pentyloxy spacer, which suggests that the dendrimer adopts a completely distorted conformation, even in case of the higher generations. The mesophase formation in case of the pentyloxy series is more complex than in case of the decyloxy series, because the latter possesses mesogenic units that are more decoupled from the dendritic skeleton.

The results obtained from this study indicate that under the influence of external stimuli (endgroups) the poly(propylene imine) interior can undergo significant changes in the conformation and that the flexibility of functionalized poly(propylene imine) dendrimers, and of functionalized dendrimers in general, is much higher than previously anticipated.

6.6 Experimental Section

General Methods and Materials

All solvents were of p.a. quality and used as received. 4'-Cyano-4-hydroxybiphenyl (TCI, 98%) and 4'-cyano-4-pentyloxybiphenyl (Aldrich, 99%), 6-bromohexanoic acid (Acros, 98%), 11-undecanoic acid (Acros, 99+%) were used as received. 4'-Cyano-4-decyloxybiphenyl (99%) was synthesized by etherification of 4'-cyano-4-hydroxybiphenyl and decyl bromide, analogous to literature procedures.[83] Synthesis of the methyl esters of 6-bromohexanoic acid and 11-bromoundecanoic acid was performed with an acid-catalyzed esterification in MeOH. Poly(propylene imine) dendrimers with amine-endgroups were supplied by DSM Research (The Netherlands). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM 400 spectrometer at 400.13 MHz and 100.62 MHz respectively, unless noted otherwise. All δ-values are given in ppm using TMS as internal standard. IR samples were prepared according the KBr technique and were measured on a Perkin-Elmer 1605 Series FT machine. Elemental Analysis was performed on a Perkin-Elmer 2400 Series CHNS/O analyzer. Fast Atom Bombardment Mass Spectrometry (FAB-MS) was performed at the University of Copenhagen (Denmark). Matrix-assisted laser-desorption ionization/time-of-flight mass spectra (MALDI-TOF-MS) spectra of **5** and **11** were recorded on a Voyager-DE mass spectrometer using a-cyano-4-hydroxycinnamic acid as a matrix (University of California, Berkeley, USA). Thermogravical Analyses (TGA) were performed on a Perkin-Elmer TGA7 machine to determine thermal stability of the samples. Thermal transitions of compounds **2-7** and **9-12** were determined by Differential Scanning Calorimetry on a Perkin-Elmer DSC7 or a Perkin-Elmer Pyris 1 under a nitrogen atmosphere with heating and cooling rates of 10 K•min^{-1} unless otherwise noted. The optical properties were studied with a Jenaval polarisation microscope equipped with a Linkam THMS 600 heating device, with crossed polarizers. Glass slides were used as received. X-ray diffraction patterns of oriented and non-oriented samples were recorded using a flat film camera at room temperature (Ni filtered, $Cu_{K\alpha}$ radiation (λ = 1.542 Å).

Synthesis of 6-((4′-cyano(1,1′-biphenyl)-4-yl)oxy)hexanoic acid, 1[84]

A mixture of 18-crown-6 (0.51 g, 2 mmol), finely ground potassium carbonate (6.5 g, 47 mmol), 4'-cyano-4-hydroxybiphenyl (5.02 g, 25.7 mmol) and methyl-6-bromohexanoate (7.05 g, 33.7 mmol) in acetone (80 ml) was stirred vigorously and heated under reflux for 16 h. The mixture was concentrated *in vacuo* and recrystallised from MeOH yielding methyl 6-((4'-cyano(1,1'-biphenyl)-4-yl)oxy)hexanoate (7.90 g, 95%) as a white solid. M.p. 127.2°C; ^{1}H-NMR ($CDCl_3$): δ = 7.69 (d, *J* = 8.1 Hz, 2 H, H-3'), 7.64 (d, *J* = 8.2 Hz, 2 H, H-2'), 7.53 (d, *J* = 8.9 Hz, 2 H, H-2), 6.98 (d, *J* = 8.8 Hz, 2 H, H-3), 4.02 (t, 2 H, CH_2CH_2O), 3.69 (s, 3 H, $COOCH_3$), 2.37 (t, 2 H, CH_2CH_2COO), 1.84 (m, 2 H, C_2CH_2O), 1.73 (m, 2 H, CH_2CH_2COO), 1.53 (m, 2 H, $CH_2CH_2CH_2O$); ^{13}C-NMR ($CDCl_3$): δ = 174.3 (CH_2COO), 159.9 (*C*-4), 145.5 (*C*-1'), 132.6 (*C*-3'), 131.8 (*C*-1), 128.3 (*C*-2), 127.1 (*C*-2'), 119.1 (*C*N), 115.1 (*C*-3), 108.8 (*C*-4'), 67.8 (OCH_2CH_2), 51.5 ($COOCH_3$), 34.0 (CH_2COO), 28.9, 25.6, 24.7 ($(CH_2)_3$); IR (KBr): ν (cm^{-1}) = 2946 (CH_2), 2221 (C≡N), 1721 (C=O). This ester (6.47 g, 20 mmol) was added to a sodiumhydroxide solution (100 ml, 3 M). Consequently THF (ca. 15 ml) was added until a homogeneous suspension was formed. The reaction mixture was stirred at room temperature for 4 days, during which the reaction was monitored with TLC. In case of complete hydrolysis the suspension was neutralised with a solution of hydrochloric acid (ca. 5 M) at 0 °C. This furnished the crude product as a white precipitate which was filtered off and washed with diethyl ether and water. The crude material was recrystallised twice from EtOH to yield pure acid **1** (4.72 g, 60%) as white needles. M.p. 89.5°C; ^{1}H-NMR (CD_3OD): δ = 12.04 (bs, 1 H, CH_2COOH), 7.86 (d, *J* = 8.4 Hz, 2 H, H-3'), 7.82 (d, *J* = 8.4 Hz, 2 H, H-2'), 7.68 (d, *J* = 8.7 Hz, 2 H, H-2), 7.03 (d, *J* = 8.7 Hz, 2 H, H-3), 4.00 (t, 2 H, CH_2CH_2O), 2.23 (t, 2 H, CH_2CH_2COO), 1.73 (m, 2 H, CH_2CH_2O), 1.56 (m, 2 H, CH_2CH_2COO), 1.43 (m, 2 H, $CH_2CH_2CH_2O$); ^{13}C-NMR (CD_3OD): δ = 174.5 (CH_2COO), 159.3 (C-4), 144.3 (C-1'), 132.8 (C-3'), 130.3 (C-1), 128.3 (C-2), 126.8 (C-2'), 119.0 (*C*N), 115.1 (C-3), 109.1 (C-4'), 67.5 (OCH_2CH_2), 33.6 (CH_2COO), 28.4, 25.2, 24.3 ($(CH_2)_3$); IR (KBr): ν (cm^{-1}) = 3449 (O–H), 2938 (CH_2), 2227 (C≡N), C=O (1702); Anal. calcd. for $C_{19}H_{19}NO_3$ (MW 309.36): C 73.76, H 6.19, N 4.53. Found: C 73.8, H 6.3, N 4.5.

Synthesis of pentafluorophenyl-6-((4′-cyano(1,1′-biphenyl)-4-yl)oxy)hexanoate, 2

A solution of acid **1** (4.10 g, 13.3 mmol) and pentafluorophenol (2.98 g, 14.3 mmol) was prepared in dry DMF (100 ml). To the homogeneous solution, which was cooled at 0 °C, DCC (2.72 g, 13.3 mmol) in DMF (2 ml) was added in portions. After complete addition of DCC, the temperature of the reaction mixture was allowed to equilibrate to room temperature and after 4 days the reaction mixture was filtered and the

filtrate was concentrated *in vacuo*. The product was recrystallised from EtOH to yield crude **2** (5.16 g, 84%) as a crystalline solid (purity > 95% from ^{1}H-NMR). Additional column chromatography (SiO_2: heptane/$CHCl_3$, 35:65, R_f = 0.36) yielded pure **2** (3.69 g , 60%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ = 7.69 (d, *J* = 8.2 Hz, 2 H, H-3'), 7.64 (d, *J* = 8.2 Hz, 2 H, H-2'), 7.55 (d, *J* = 8.8 Hz, 2 H, H-2), 6.99 (d, *J* = 8.8 Hz, 2 H, H-3), 4.04 (t, 2 H, CH_2CH_2O), 2.73 (t, 2 H, CH_2CH_2COO), 1.88 (m, 4 H, $OCH_2CH_2CH_2CH_2CH_2COO$), 1.64 (m, 2 H, $OCH_2CH_2CH_2CH_2CH_2COO$); ^{13}C-NMR ($CDCl_3$): δ = 169.9 (CH_2COO), 160.2 (C-4), 145.8 (C-1'), 133.1 (C-3'), 132.0 (C-1), 128.9 (C-2), 127.6 (C-2'), 119.6 (*C*N), 115.6 (C-3), 110.7 (C-4'), 68.2 (OCH_2CH_2), 33.8 (CH_2COO), 29.4, 26.0, 25.1 (($CH_2)_3$); IR (KBr): ν (cm^{-1}) = 2878 (CH_2), 2224 (C≡N), 1795 (C=O); Anal. calcd. for $C_{25}H_{18}F_5NO_3$ (MW 475.42): C 63.16, H 3.82, N 2.95. Found: C 63.2, H 3.8, N 2.9.

Synthesis of propyl-NHCO-C_5-OCBPh, 3

n-Propylamine (0.2 g, 3.4 mmol) was slowly added to a solution of activated ester **2** (1.00 g, 2.10 mmol) in CH_2Cl_2 (40 ml). After stirring for 1 day, the solution was diluted with CH_2Cl_2 and MeOH and extracted with a saturated sodium carbonate solution and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases consequently were washed with de-mineralized water, dried with sodium sulfate and concentrated *in vacuo* yielding pure **3** (660 mg, 90%) as a white solid. M.p. 119; ^{1}H-NMR ($CDCl_3$): δ = 7.69 (d, *J* = 8.5 Hz, 2 H, H-3'), 7.63 (d, *J* = 8.5 Hz, 2 H, H-2'), 7.52 (d, *J* = 8.8 Hz, 2 H, H-2), 6.99 (d, *J* = 8.8 Hz, 2 H, H-3), 5.43 (bs, 1 H, N*H*CO), 4.01 (t, 2 H, CH_2CH_2O), 3.22 (q, 2 H, CH_2CH_2NHCO), 2.21 (t, 2 H, $NHCOCH_2CH_2$), 1.84 (m, 2 H, CH_2CH_2O), 1.73 (m, 2 H, $NHCOCH_2CH_2$), 1.53 (m, 4 H, CH_2CH_2NHCO and $CH_2CH_2CH_2O$), 0.93 (t, 3 H, $CH_3CH_2CH_2NHCO$); ^{13}C-NMR ($CDCl_3$): δ = 172.7 (CH_2CONH), 159.7 (C-4), 145.2 (C-1'), 132.5 (C-3'), 131.3 (C-1), 128.3 (C-2), 127.1 (C-2'), 119.1 (*C*N), 115.0 (C-3), 110.0 (C-4'), 67.8 (OCH_2CH_2), 41.2 (CH_2CH_2NH), 36.7 (CH_2CH_2CO), 29.0, 25.8, 25.5 (($CH_2)_3$), 22.9 ($CH_3CH_2CH_2NHCO$), 11.3 ($CH_3CH_2CH_2NHCO$); IR (KBr): ν (cm^{-1}) = 2990 (CH_2), 2222 (C≡N), 1635 (C=O); FAB-MS *m*/*z*: 351 [M + H^+]: $C_{22}H_{25}N_2O_2$ (349.45).

Typical Procedure for the Synthesis of pentyloxycyanobiphenyl-functionalized dendrimers : DAB-*dendr*-(NHCO-C_5-CBPh)$_{16}$, 5

A solution of DAB-*dendr*-$(NH_2)_{16}$ (203.0 mg, 0.120 mmol) in CH_2Cl_2 (2 ml) was added slowly to a solution of activated ester **2** (1.00 g, 2.10 mmol) in CH_2Cl_2 (40 ml). After stirring for 4 days, the solution was diluted with CH_2Cl_2 and MeOH and extracted with a saturated sodium carbonate solution and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried with sodium sulfate and concentrated *in vacuo*. The crude product was taken up in CH_2Cl_2 and precipitated twice by slowly adding *n*-heptane. The precipitate was dissolved in CH_2Cl_2, washed with demineralized and dried over sodium sulfate yielding **5** (250 mg, 34%) as a pale brownish solid. g 25°C M 127°C I; ^{1}H-NMR ($CDCl_3$): δ = 7.64 (d, *J* = 8.6 Hz, 32 H, H-3), 7.57 (d, *J* = 8.6 Hz, 32 H, H-2), 7.46 (d, *J* = 8.9 Hz, 32 H, H-2'), 7.12 (t, 16 H, CH_2NHCO), 6.91 (d, *J* = 8,8 Hz, 32 H, H-3'), 3.94 (t, 32 H, CH_2CH_2O), 3.27 (br. d, 32 H, CH_2CH_2NHCO), 2.36 (br. s, 84 H, $NCH_2CH_2CH_2N$ and $NCH_2CH_2CH_2CH_2N$), 2.24 (t, 32 H, $NHCOCH_2CH_2$), 1.79 (m, 32 H, CH_2CH_2O), 1.71 (m, 32 H, $NHCOCH_2CH_2$), 1.60 (m, 56 H, $NCH_2CH_2CH_2N$), 1.50 (m, 32 H, $CH_2CH_2CH_2O$), 1.45 (bs, 4 H, $NCH_2CH_2CH_2CH_2N$); ^{13}C-NMR ($CDCl_3$): δ = 173.4 (16C, $NHCO-CH_2$), 159.6 (32C, C-4'), 144.5 (16C, C-1), 132.5 (32C, C-3), 130.3 (16C, C-1'), 128.2 (32C, C-2'), 126.9 (32C, C-2), 119.0 (16C, *C*N), 115.0 (32C, C-3'), 110.0 (32C, C-4), 67.8 (16C, OCH_2CH_2), 54.5 (2C, $NCH_2CH_2CH_2CH_2N$), 52.1 (24C, br., $NCH_2CH_2CH_2N$), 51.3 (16C, $NCH_2CH_2CH_2NHCO$), 37.8 (16C, $CH_2NHCOCH_2$), 36.3 (16C, $NHCOCH_2$), 29.0, 25.8, 24.3 (48C, ($CH_2)_3$), 27.0 (16C, $NCH_2CH_2CH_2NHCO$), 24.5 (14C, $NCH_2CH_2CH_2CH_2N$ {2C} + $NCH_2CH_2CH_2N$ {12C}); IR (KBr): ν (cm^{-1}) = 2992 (CH_2), 2225 (C≡N), 1639 (C=O); MALDI-TOF-MS *m*/*z*: 6348.4 [M + H^+] : $C_{472}H_{640}N_{46}O_{32}$ (6346.7).

DAB-*dendr*-(NHCO-C_5-CBPh)$_4$, 4

^{1}H-NMR ($CDCl_3$): δ = 7.67 (d, *J* = 6.5 Hz, 8 H, H-3'), 7.61 (d, *J* = 6.5 Hz, 8 H, H-2'), 7.50 (d, *J* = , 8.8 Hz, 8 H, H-2), 6.95 (d, *J* = 8.8 Hz, 8 H, H-3), 6.51 (t, 4 H, $CH_2NHCOCH_2$), 3.97 (t, 8 H, CH_2CH_2O), 3.29 (q, 8 H, CH_2CH_2NH), 2.40 (t, 8 H, $NCH_2CH_2CH_2NH$), 2.35 (bs, 4 H, $NCH_2CH_2CH_2CH_2N$), 2.21 (t, 8 H, CH_2CH_2CO), 1.81 (m, 8 H, $CH_2CH_2CH_2O$), 1.71 (m, 8 H, $NHCOCH_2CH_2CH_2$), 1.62 (m, 8H, $NCH_2CH_2CH_2N$), 1.51 (m, 8H, $CH_2CH_2CH_2O$), 1.39 (bs, 4 H, $NCH_2CH_2CH_2CH_2N$); ^{13}C-NMR ($CDCl_3$): δ = 173.0 (4C, $NHCO-CH_2$), 159.6 (8C, C-4), 145.1 (4C, C-1'), 132.5 (8C, C-3'), 131.3 (4C, C-1), 128.2 (8C, C-2), 126.9 (8C, C-2'), 119.0 (4C, *C*N), 115.0 (8C, C-3), 110.0 (8C, C-4'), 67.8 (16C, OCH_2CH_2), 53.7 (2C, $NCH_2CH_2CH_2CH_2N$), 51.8 (4C, $NCH_2CH_2CH_2NHCO$), 38.1 (4C, $CH_2NHCOCH_2$), 36.5 (4C, $NHCOCH_2$), 29.0, 25.8, 24.3 (12C, ($CH_2)_3$), 27.0 (16C, $NCH_2CH_2CH_2NHCO$), 24.5 (14C, $NCH_2CH_2CH_2CH_2N$ {2C} + $NCH_2CH_2CH_2N$ {12C}); IR (KBr):ν (cm^{-1})

= 2992 (CH_2), 2224 (C≡N), 1638 (C=O); FAB-MS *m/z*: 1483 [M + H^+]: $C_{92}H_{108}N_{10}O_8$ (1481.93).

DAB-*dendr*-(NHCO-C_5-CBPh)$_{64}$, 6

^{1}H-NMR ($CDCl_3$/CD_3OD, 95:5, 333K): δ = 7.59 (d, J = 8.0 Hz, 128 H, H-3'), 7.53 (d, *J* = 8.0 Hz, 128 H, H-2'), 7.42 (d, *J* = 8.4 Hz, 128 H, H-2), 6.87 (d, *J* = 8.5, 128 H, H-3), 3.91 (t, 128 H, CH_2CH_2O), 3.20 (br. d, 128 H, CH_2CH_2NHCO), 2.39 (br. d, 372 H, $NCH_2CH_2CH_2N$ and $NCH_2CH_2CH_2CH_2N$), 2.21 (t, 128 H, $NHCOCH_2CH_2$), 1.76 (m, 128 H, CH_2CH_2O), 1.68 (m, 128 H, $NHCOCH_2CH_2$), 1.61 (m, 248 H, $NCH_2CH_2CH_2N$), 1.49 (m, 128 H, $CH_2CH_2CH_2O$); ^{13}C-NMR ($CDCl_3$/CD_3OD, 95:5, 333K): δ = 173.9 (64C, $NHCO-CH_2$), 159.5 (28C, C-4), 145.0 (64C, C-1'), 132.4 128C, C-3'), 131.1(64C, C-1), 128.4(128C, C-2), 126.9 (128C, C-2'), 118.9 (64C, *C*N), 114.8 (128C, C-3), 109.7 (128C, C-4'), 67.7 (64C, OCH_2CH_2), 51.7 (112C, br., $NCH_2CH_2CH_2N$), 51.0 (64C, $NCH_2CH_2CH_2NHCO$), 37.5 (64C, $CH_2NHCOCH_2$), 36.0 (64C, $CH_2NHCOCH_2$), 28.8, 25.6, 26.0 (192C, $(CH_2)_3$), 27.1 (64C, $NCH_2CH_2CH_2NHCO$), 24.5 (62C, $NCH_2CH_2CH_2CH_2N$ {2C} + $NCH_2CH_2CH_2N$ {60C}); IR (KBr): ν (cm^{-1}) = 2986 (CH_2), 2225 (C≡N), 1640 (C=O).

Synthesis of 11-((4′-cyano(1,1′-biphenyl)-4-yl)oxy)undecanoic acid, 7

A mixture of 18-crown-6 (0.34 g, 1.3 mmol), finely ground potassium carbonate (4.6 g, 33 mmol), 4'-cyano-4-hydroxybipenyl (3.0 g, 15.4 mmol) and methyl-11-bromoundecanoate (5.9 g, 21.1 mmol) in acetone (40 ml) was stirred vigorously and heated under reflux overnight. The mixture was filtered, concentrated *in vacuo* and recrystallised from EtOH yielding **7** as a white solid (4.67 g, 80%). M.p. 103.5 °C; ^{1}H-NMR ($CDCl_3$): δ = 7.69 (d, *J* = 8.6 Hz, 2 H, H-3'), 7.64 (d, *J* = 8.6 Hz, 2 H, H-2'), 7.53 (d, *J* = 8.8 Hz, 2 H, H-2), 6.99 (d, *J* = 8.8 Hz, 2 H, H-3), 4.01 (t, 2 H, CH_2CH_2O), 3.67 (s, 3 H, $COOCH_3$), 2.31 (t, 2 H, CH_2CH_2COO), 1.81 (m, 2 H, CH_2CH_2O), 1.63 (m, 2 H, CH_2CH_2COO), 1.47 (m, 2 H, $CH_2CH_2CH_2O$), 1.34 (br. s, 10 H); ^{13}C-NMR ($CDCl_3$): δ = 174.3 (CH_2COO), 159.8 (C-4), 145.3 (C-1'), 132.5 (C-3'), 131.3 (C-1), 128.3 (C-2), 127.1 (C-2'), 119.1 (*C*N), 115.1 (C-3), 110.0 (C-4'), 68.2 (OCH_2CH_2), 51.4 ($COOCH_3$), 34.1 (CH_2COO), 29.5-29.1, 26.0, 24.9 ($(CH_2)_8$); IR (KBr): ν (cm^{-1}) = 2927 (CH_2), 2223 (X≡N), 1730 (C=O). This ester (3.47 g, 8.8 mmol) was added to a sodiumhydroxide solution (50 ml, 3M). Consequently THF (ca. 50 ml) was added until a homogeneous suspension was formed. This suspension was stirred at room temperature for 3 days, during which the reaction was monitored with TLC. In case of complete hydrolysis the mixture was neutralised with a solution of hydrochloric acid (ca. 5M) at 0°C. The crude product was obtained as a white precipitate, which was filtered off and washed with diethyl ether and water. The crude product was recrystallised from EtOH to yield pure acid **7** (2.56 g, 76%) as a white solid. M.p. 173.7 °C; ^{1}H-NMR ($CDCl_3$): δ = 7.69 (d, *J* = 6.5 Hz, 2 H, H-3'), 7.63 (d, *J* = 6.5 Hz, 2 H, H-2'), 7.52 (d, *J* = 8.7 Hz, 2 H, H-2), 7.99 (d, *J* = 8.7 Hz, 2 H, H-3), 4.00 (t, 2 H, CH_2CH_2O), 2.35 (t, 2 H, CH_2CH_2COO), 1.82 (m, 2 H, CH_2CH_2O), 1.63 (m, 2 H, CH_2CH_2COO), 1.47 (m, 2 H, $CH_2CH_2CH_2O$), 1.31 (bs, 10 H); ^{13}C-NMR ($CDCl_3$): δ = 179.9 (CH_2COO), 159.8 (C-4), 145.3 (C-1'), 132.5 (C-3'), 131.2 (C-1), 128.3 (C-2), 127.0 (C-2'), 119.1 (*C*N), 115.1 (C-3), 110.0 (C-4'), 68.1 (OCH_2CH_2), 33.9 (CH_2COO), 29.5-29.0, 26.0, 24.7 ($(CH_2)_8$); IR (KBr): ν (cm^{-1}) = 3462 (O–H), 2921 (CH_2), 2224 (C≡N), 1703 (C=O); Anal. calcd. for $C_{24}H_{29}NO_3$ (MW 379.50): C 75.96, H 7.70, N 3.69. Found: C 75.9, H 7.7, N 3.7.

Synthesis of pentafluorophenyl-11-((4′-cyano(1,1′-biphenyl)-4-yl)oxy)undecanoate, 8

A solution of acid **7b** (3.8 g, 10 mmol) and pentafluorophenol (2.05 g, 11.1 mmol) was prepared in dry DMF (100 ml). To the homogeneous solution, which was cooled at 0 °C, DCC (2.10g, 10.2 mmol) in DMF (2 ml) was added in portions. After complete addition of DCC, the temperature of the reaction mixture was allowed to equilibrate to room temperature and after 3 days the reaction mixture was filtered and the filtrate concentrated *in vacuo*. The crude product was recrystallised from EtOH to yield crude **9** (4.4 g, 81%) (purity >95% from ^{1}H-NMR). Additional column chromatography (SiO_2: *n*-hexane/$CHCl_3$, 35:65, R_f = 0.36) yielded pure **8** (3.69 g , 62%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ = 7.69 (d, *J* = 4.7 Hz, 2 H, H-3'), 7.64 (d, *J* = 4.7 Hz, 2 H, H-2'), 7.52 (d, *J* = 6.8 Hz, 2 H, H-2), 6.99 (d, *J* = 6.8 Hz, 2 H, H-3), 4.01 (t, 2H, CH_2CH_2O), 2.66 (t, 2 H, CH_2CH_2COO), 1.78 (m, 4 H, CH_2CH_2O), 1.39 (m, 12 H); ^{13}C-NMR ($CDCl_3$): δ = 169.8 (CH_2COO), 159.8 (C-4), 145.3 (C-1'), 132.5 (C-3'), 131.2 (C-1), 128.3 (C-2), 127.0 (C-2'), 119.1 (*C*N), 115.0 (C-3), 110.0 (C-4'), 68.1 (OCH_2CH_2), 33.3 (CH_2COO), 29.4-28.2, 26.0, 24.7 ($(CH_2)_8$); IR (KBr): ν (cm^{-1}) = 2932 (CH_2), 2229 (C≡N), 1785 (C=O); Anal. calcd. for $C_{30}H_{28}F_5NO_3$ (MW 545.55): C 66.05, H 5.17, N 2.56. Found: C 66.4, H 5.3, N 2.5.

Synthesis of propyl-NHCO-C_{10}-CBPh, 9

n-Propylamine (0.2g, 3.4 mmol) was slowly added to a solution of activated ester **8** (1.00 g, 1.83 mmol) in CH_2Cl_2 (40 ml). After stirring for 5 days, the solution was diluted with CH_2Cl_2 and MeOH and extracted

with a saturated sodium carbonate solution and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases consequently were washed with demineralized water, dried with sodium sulfate and concentrated *in vacuo* yielding pure **9** (580 mg, 75%) as a white solid. K 105 I; ^{1}H-NMR ($CDCl_3$): δ = 7.67 (d, *J* = 7.9 Hz, 2 H, H-3'), 7.63 (d, *J* = 8.1 Hz, 2 H, H-2'), 7.52 (d, *J* = 8.9 Hz, 2 H, H-2), 6.99 (d, *J* = 8.8 Hz, 2 H, H-3), 5.43 (br. s, 1 H, CH_2NHCO), 4.00 (t, 2 H, CH_2CH_2O), 3.22 (q, 2 H, CH_2CH_2NH), 2.26 (t, 2 H, CH_2CH_2CON), 1.80 (m, 2 H, CH_2CH_2O), 1.7-1.3 (br. m, 14 H), 0.92 (t, 3 H, $NHCH_2CH_2CH_3$); ^{13}C-NMR ($CDCl_3$): δ = 173.9 (CH_2CONH), 159.8 (C-4), 148.8 (C-1'), 145.3 (C-3'), 132.5 (C-1), 131.2 (C-2), 128.3 (C-2'), 127.0 (*C*N), 115.1 (C-3), 110.0 (C-4'), 68.14 (OCH_2CH_2), 41.1 (CH_2NH), 36.9 (CH_2COO), 29.5-29.0, 25.8 (($CH_2)_8$), 22.9 ($CH_3CH_2CH_2NHCO$), 11.3 ($CH_3CH_2CH_2NHCO$); IR (KBr): ν (cm^{-1}) = 2990 (CH_2), 2236 (C≡N), 1637 (C=O); FAB-MS *m*/*z*: 421 [M + H$^+$]: $C_{27}H_{35}N_2O_2$ (419.59).

Typical Procedure for the Synthesis of decyloxycyanobiphenyl-functionalized dendrimers : DAB-*dendr*-(NHCO-C_{10}-CBPh)$_{16}$, 11

A solution of DAB-*dendr*-$(NH_2)_{16}$ (188.1 mg, 0.112 mmol) in CH_2Cl_2 (2 ml) was added slowly to a solution of activated ester **8** (0.98 g, 1.80 mmol) in CH_2Cl_2 (40 ml). After stirring for 5 days, the solution was diluted with CH_2Cl_2 and MeOH, extracted with a saturated sodium carbonate solution and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried with sodium sulfate and concentrated *in vacuo*. The crude product was taken up in CH_2Cl_2 and precipitated twice by slowly adding *n*-hexane, yielding pure **11** (420 mg, 50%) as a tan solid. K 105°C M 124°C I. ^{1}H-NMR ($CDCl_3$): δ = 7.65 (d, *J* = 8.3 Hz, 32 H, H-3'), 7.60 (d, *J* = 8.3 Hz, 32 H, H-2'), 7.50 (d, *J* = 8.7 Hz, 32 H, H-2), 6.96 (br. t, 16 H, $CH_2NHCOCH_2$), 6.95 (d, *J* = 8.7 Hz, 32 H, H-3), 3.96 (t, 32 H, CH_2CH_2O), 3.26 (br. d, 32 H, CH_2CH_2NH), 2.38 (br. s, 84 H, $NCH_2CH_2CH_2N$ and $NCH_2CH_2CH_2CH_2N$), 2.24 (t, 32 H, CH_2CH_2CO), 1.77 (m, 32 H, CH_2CH_2O), 1.5-1.2 (br. m, 280 H); ^{13}C-NMR ($CDCl_3$): δ = 173.7 (16C, $NHCO-CH_2$), 159.7 (32C, C-4), 145.1 (16C, C-1'), 132.5 (32C, C-3'), 131.2 (16C, C-1), 128.3 (32C, C-2), 127.0 (32C, C-2'), 119.0 (16C, *C*N), 115.0 (32C, C-3), 110.0 (32C, C-4'), 68.1 (16C, OCH_2CH_2), 54.5 (2C, $NCH_2CH_2CH_2CH_2N$), 52.1 (24C, br., $NCH_2CH_2CH_2N$), 51.3 (16C, $NCH_2CH_2CH_2NHCO$), 37.7 (16C, $CH_2NHCOCH_2$), 36.6 (16C, $CH_2NHCOCH_2$), 29.6 - 29.4, 29.0, 25.9, 25.8 (128C, $(CH_2)_8$), 27.0 (16C, $NCH_2CH_2CH_2NHCO$), 24.5 (14C, $NCH_2CH_2CH_2CH_2N$ {2C} + $NCH_2CH_2CH_2N$ {12C}); IR (KBr): ν (cm^{-1}) = 2982 (CH_2), 2225 (C≡N), 1639 (C=O); MALDI-TOF-MS *m*/*z*: 7449 [M + H$^+$], 7471 [M + Na$^+$], 7487 [M + K]: $C_{472}H_{640}N_{46}O_{32}$ (7470.54).

DAB-*dendr*-(NHCO-C_{10}-CBPh)$_4$, 10

^{1}H-NMR ($CDCl_3$): δ = 7.68 (d, *J* = 7.9 Hz, 8 H, H-3), 7.63 (d, *J* = 8.2 Hz, 8 H, H-2), 7.51 (d, *J* = 8.8 Hz, 8 H, H-2'), 6.98 (d, *J* = 8.8 Hz, 8 H, H-3'), 6.49 (t, 4 H, $CH_2NHCOCH_2$), 3.99 (t, 8 H, CH_2CH_2O), 3.29 (q, 8 H, CH_2CH_2NH), 2.42 (t, 8 H, $NCH_2CH_2CH_2NH$), 2.36 (br. s, 4 H, $NCH_2CH_2CH_2CH_2N$), 2.16 (t, 8 H, CH_2CH_2CO), 1.79 (m, 8 H, $CH_2CH_2CH_2O$), 1.62 (m, 8 H, $NHCOCH_2CH_2CH_2$), 1.5-1.2 (br. m, 76 H); ^{13}C-NMR ($CDCl_3$): δ = 173.4 (4C, $NHCO-CH_2$), 159.7 (8C, C--4'), 145.2 (4C, C-1), 132.5 (8C, C-3), 131.1 (4C, C-1'), 128.2 (8C, C-2'), 127.0 (8C, C-2), 119.0 (4C, *C*N), 115.0 (8C, C-3'), 110.0 (8C, C-4), 68.0 (16C, OCH_2CH_2), 53.6 (2C, $NCH_2CH_2CH_2CH_2N$), 51.7 (4C, $NCH_2CH_2CH_2NHCO$), 38.0 (4C, $CH_2NHCOCH_2$), 36.7 (4C, $NHCOCH_2$), 29.5-29.2, 26.0, 25.9 (32C, $CH_2)_8$), 26.9 (4C, $NCH_2CH_2CH_2NHCO$), 24.7 (2C, $NCH_2CH_2CH_2CH_2N$); IR (KBr): ν (cm^{-1}) = 2990 (CH_2), 2225 (C≡N), 1639 (C=O); FAB-MS *m*/*z*: 1764 [M + H$^+$]: $C_{112}H_{148}N_{10}O_8$ (1762.46).

DAB-*dendr*-(NHCO-C_{10}-CBPh)$_{64}$, 12

^{1}H-NMR ($CDCl_3$, 333K): δ = 7.59 (d, *J* = 8.4 Hz, 128 H, H-3'), 7.55 (d, *J* = 8.2 Hz, 128 H, H-2'), 7.44 (d, *J* = 8.7 Hz, 128 H, H-2), 6.90 (d, *J* = 8.7, 128 H, H-3), 3.93 (t, 128 H, CH_2CH_2O), 3.23 (br. d, 128 H, CH_2CH_2NHCO), 2.38 (br. d, 372 H, $NCH_2CH_2CH_2N$ and $NCH_2CH_2CH_2CH_2N$), 2.17 (t, 128 H, $NHCOCH_2CH_2$), 1.73 (m, 128 H, CH_2CH_2O), 1.60 (m, 128 H, $NHCOCH_2CH_2$), 1.41 (m, 248 H, $NCH_2CH_2CH_2N$), 1.49 (br m, 1024 H); ^{13}C-NMR ($CDCl_3$): δ = 174.0 (64C, $NHCO-CH_2$), 159.7 (128C, C-4), 145.0 (64C, C-1'), 132.5 (128C, C-3'), 131.2 (64C, C-1), 128.3 (128C, C-2), 127.0 (128C, C-2'), 119.0 (64C, *C*N), 115.0 (128C, C-3), 110.0 (128C, C-4'), 68.0 (64C, OCH_2CH_2), 52.0 (112C, br., $NCH_2CH_2CH_2N$), 51.1 (64C, $NCH_2CH_2CH_2NHCO$), 37.5 (64C, $CH_2NHCOCH_2$), 36.6 (64C, $CH_2NHCOCH_2$), 29.7 - 29.5, 29.2, 26.1, 26.0 (512C, $(CH_2)_8$), 27.1 (64C, $NCH_2CH_2CH_2NHCO$), 24.5 (62C, $NCH_2CH_2CH_2CH_2N$ {2C} + $NCH_2CH_2CH_2N$ {60C}); IR (KBr): ν (cm^{-1}) = 2986 (CH_2), 2226 (C≡N), 1639 (C=O).

6.7 References and Notes

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70. Although in the case of compound **9** the observed mass deviates from the calculated one, it was observed that changing of experimental conditions yielded a slight shift of the parent peak. However, there are no indications that the dendritic structure decomposes during analysis.
71. Reactivity of the secondary amines towards pentafluorophenol esters has been also observed for other substituents. These sites however are not reactive towards the corresponding N-hydoxysuccinimidoyl derivatives, see Chapter 2.
72. Differential Scanning Calorimetry data were obtained in the second heating run and / or first cooling run.
73. Thermal data of the reference compounds C_5-CBPh and C_{10}-CBPh are in good agreement with literature data, see: Landolt-Börnstein, *Numerical Data and Functional relationships in Science and technology*, Series IV/7a 'Liquid Crystals'. ed. by O. Madelung, **1988** Berlin, Springer-Verlag.
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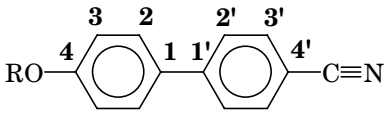


Development of a Dendrimer-Based Electro-Optical Switch

7

Abstract: *A dendrimer-based electro-optical switch is developed based on light scattering. This technology does not require the use of polarizers, in comparison with traditional (twisted) nematics displays. Blends of cyanobiphenyl-functionalized (**1**) or palmitoyl-functionalized poly(propylene imine) dendrimers (**2**) and nematic liquid crystal, E7, have been prepared and investigated with Differential Scanning Calorimetry and electro-optical measurements. These blends scatter light and their transparency can be tuned by the application of a voltage. Blends containing **1** reveal a complex, voltage dependent, switching behavior, that is probably due to the presence of two liquid crystalline phases with different switching characteristic. Blends containing **2** show a fast switching behavior even when compared to a 'state of the art' PDLC. A drawback is the contrast between the scattering and the transparent state, which needs to be optimized further.*

Part of this work will be published: Baars, M. W. P. L.; van Boxtel, M. C. W.; Bastiaansen, C. W. M.; Broer, D. J.; Söntjens, S. H. M.; Meijer, E. W. *Adv. Mater.* submitted.

7.1 Introduction

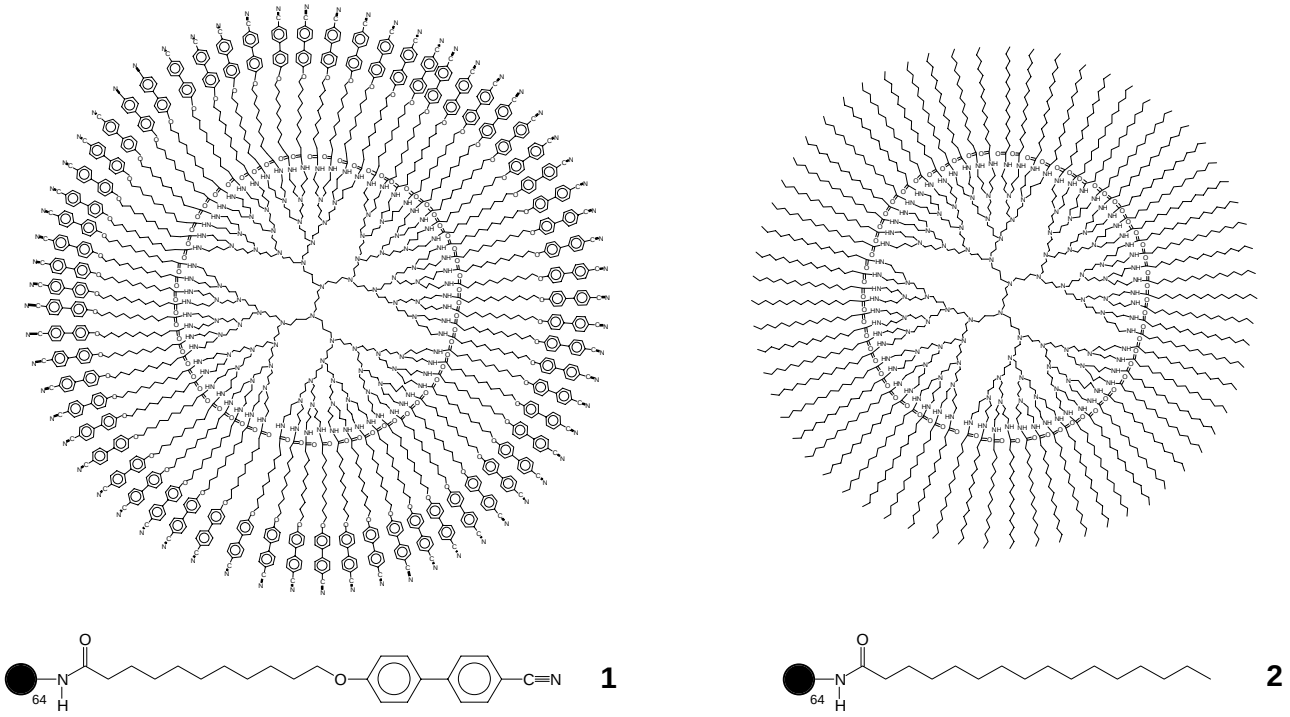
Almost all commercially significant liquid crystal displays use polarized light which is modulated by twisted nematic layers, the so-called TN-displays.[1] An electrical field alters the polarization direction of the transmitted light, and enables switching between the transparent and the dark state. This concept, however, suffers from many drawbacks, like the need for polarizers resulting in a major loss of light intensity, difficult processing and restriction to small-area applications.

The design of liquid crystal displays based on light scattering has been an active area of research due to possible applications in large area display technology[2–4] and the absence of polarizers. Presently, the scattering originates from either (i) dispersing solid particles, *e.g.* inorganic aerosil[5–9] or rigid polymeric particles,[10, 11] in a filled nematic LC-matrix, the so-called Polymer Filled Nematics (PFNs) or (ii) dispersing small droplets of nematics in a solid continuous polymer matrix, the so-called Polymer Dispersed Liquid Crystals (PDLCs).[12–15] The reversible switching between the scattering and the transmittance mode is caused by an optical heterogeneity–homogeneity change upon applying a variable ac field. Although these composites show efficient contrast ratios, the high switching voltages required and the presence of hysteresis effects are a drawback for applications. Furthermore, in the case of a PDLC or PFN, the refractive index of the solid phase requires a careful matching with the ordinary refractive index of the liquid nematics or visa versa. Interfacial interactions[16] play an important role in these scattering displays and further optimization of these interactions is a prerequisite for satisfying electro-optical characteristics.

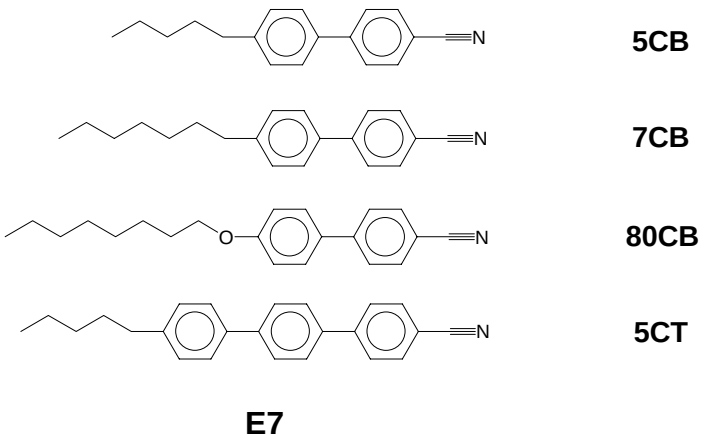
A new, molecular approach to scattering displays is based on the addition of low-molecular weight gelling agents to liquid crystals. These gelling agents organize into a continuous network, thereby dividing the nematic phase into many small domains, and a highly scattering state is obtained.[17, 18] So far only low molecular weight compounds have been used to prepare anisotropic gels in LC-matrices. Dendritic molecules[19, 20] consisting of a branched, three-dimensional geometry are also known to assemble in various types of organization based on secondary interactions between the (endgroups of the) dendrimers.[21–23] Although the combination of dendrimers and liquid crystals has received much attention recently,[24–29] and an example is discussed in the previous Chapter, no attention has been paid to the application of these highly branched structures in a liquid crystal display device.

In this chapter, the development of an electro-optical switch based on the addition of dendrimers to a continuous liquid crystalline matrix is discussed.[30] Two types of dendrimers are used as additive (Scheme 7.1): a fifth generation cyanobiphenyl-functionalized poly(propylene imine) dendrimer,[28] *i.e.* DAB-*dendr*-(NHCO-C_{10}-CBPh)$_{64}$,

1, and a fifth generation palmitoyl-functionalized poly(propylene imine) dendrimer,[31, 32] *i.e.* DAB-*dendr*-(NHCO-$C_{15}H_{31})_{64}$, **2**. Their synthesis has been described in Chapter 6 and 2, respectively. E7, a mixture of cyanobiphenyls and cyanoterphenyls (Scheme 7.2), has been used as the nematic liquid crystal matrix (g 61.5 N 59.9 I).[33]



Scheme 7.1: *DAB-dendr-(NHCO-C_{10}-CBPh)$_{64}$, **1** (left) and DAB-dendr-(NHCO-$C_{15}H_{31})_{64}$, **2** (right). Top: detailed molecular structure, bottom: simplified notation.*



Scheme 7.2: *Components of nematic liquid crystal E7. 5CB = 5-pentylcyanobiphenyl, 7CB = 7-pentylcyanobiphenyl, 8OCB = 8-octyloxycyanobiphenyl, 5CT = 5-pentylcyanoterphenyl.*

7.2 Dendrimer–Liquid Crystal Blends

Compound **1** shows a transition from a semi-crystalline state into a S_A mesophase at 104 °C, followed by a transition into the isotropic phase at 135 °C.[28] Compound **2** shows a transition from a semi-crystalline state into the isotropic phase at 72 °C.[31, 32] Blends of **1** and E7 with weight percentages of **1** between 0 and 10% and blends of **2** and E7, containing 0–50% of **2** with weight percentages of **2** between 0 and 50% have been prepared. Heating of the blends above the phase transition of the dendritic compounds yields an isotropic fluid of low viscosity. Upon cooling, an opaque white paste is formed, the viscosity of which increases with the amount of dendrimer. At room temperature blends containing as low as 3.5% of dendritic additive (**1** or **2**) yield stable samples without flow.

7.2.1 Differential Scanning Calorimetry

Blends of **2** and E7 have been investigated with Differential Scanning Calorimetry (Fig. 7.1) and show two transitions, the nematic–isotropic transition of E7 and the crystalline–isotropic transition of **2** at higher temperatures. The crystalline-isotropic transition of **2** at 72 °C is roughly constant over the whole concentration regime.

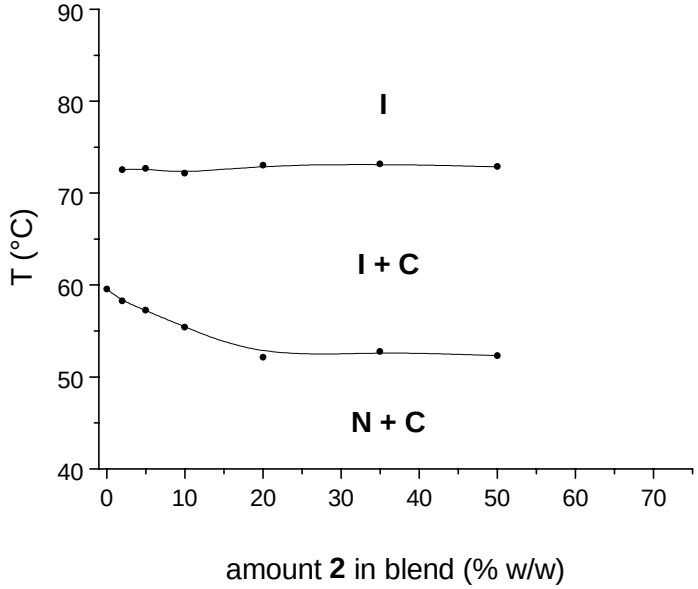


Figure 7.1: *Phase diagram of blends of **2** and E7. (N = nematic phase of E7; C = 'crystalline' state of **2**; I = isotropic phase).*

However, the nematic–isotropic transition of E7 shows an initial decrease with increasing amount of **2** in the blend, but reaches a constant value for higher amounts of **2**. It is well known that a system with dilute disorder undergoes the nematic–isotropic

transition at a lower temperature than the pure system.[34] The incorporation of dendrimers distorts the nematic phase and leads to the formation of poorly correlated domains, containing the liquid crystal. All these domains undergo the phase transition separately, yielding a broadening of the transitions in the DSC traces. Investigation of blends of **1** and E7 yield comparable results, although for dendrimer **1** both a crystalline–liquid crystalline transition and a liquid crystalline–isotropic transition are observed. The nematic-isotropic transition of E7 shows a decrease upon addition of **1**, similar to blends of **2** and E7, and the crystalline–liquid crystalline transition of **1** in the blends is considerably lower than that of pure **1**.

7.2.2 Optical Microscopy

Figure 7.2 shows optical microscopy pictures, taken at room temperature, of blends in between a sandwich cell containing 0, 3.5 and 10% of **1**, respectively. The rubbed polyimide layers of the cell induce a planar alignment of E7 (0% of **1**; left) yielding a black picture when the director is chosen to be parallel to one of the polarizers. The addition of 3.5% of **1** (middle) induces a full distortion of the planar alignment. Increasing the amount of **1** up to 10% (right) yields a decrease in the apparent domain size. These results suggest that the dendrimer is able to form (a stable network of) agglomerates, thereby dividing the nematic phase in many domains. Rotation of the sandwich cell between crossed polarizers indicates that the domains are randomly oriented.

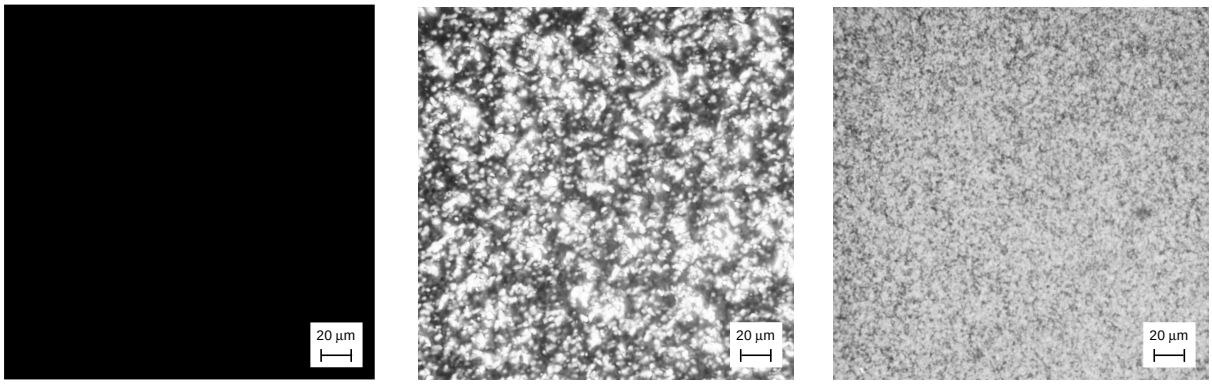


Figure 7.2: *Optical Microscopy pictures of the dendrimer/liquid crystal blends (left, 0% **1** and 100% E7; middle, 3.5% **1** and 96.5% E7; right, 10% **1** and 90% E7).*

Similarly, the addition of a small amount of **2** yields a strong distortion; however, the compatibility of **1** with the nematic mixture, E7, seems to be more effective at lower concentrations. This can be related to the presence of the mesogenic endgroups in the dendritic compound.

7.3 Electro-Optical Switch

7.3.1 Electro-Optical Measurements

The observation that the prepared blends have a low transmittance indicates that visible light is efficiently scattered, and thus a static scattering state is obtained if no voltage is applied. This prompted us to study the electro-optical properties of these blends. Figure 7.3 shows transmittance characteristics as a function of time, during repeated step-voltage scans (off : 0 V, on : 10 V), of 6 μm thick sandwich cells containing 10 % of **1** in E7 (left) and 10 % of **2** in E7 (right), respectively. In Figure 7.4 transmission-voltage characteristics for the same blends, *i.e.* 10 % of **1** in E7 (left, 0 – 120 V) and 10 % of **2** in E7 (right, 0 – 20 V) are depicted.

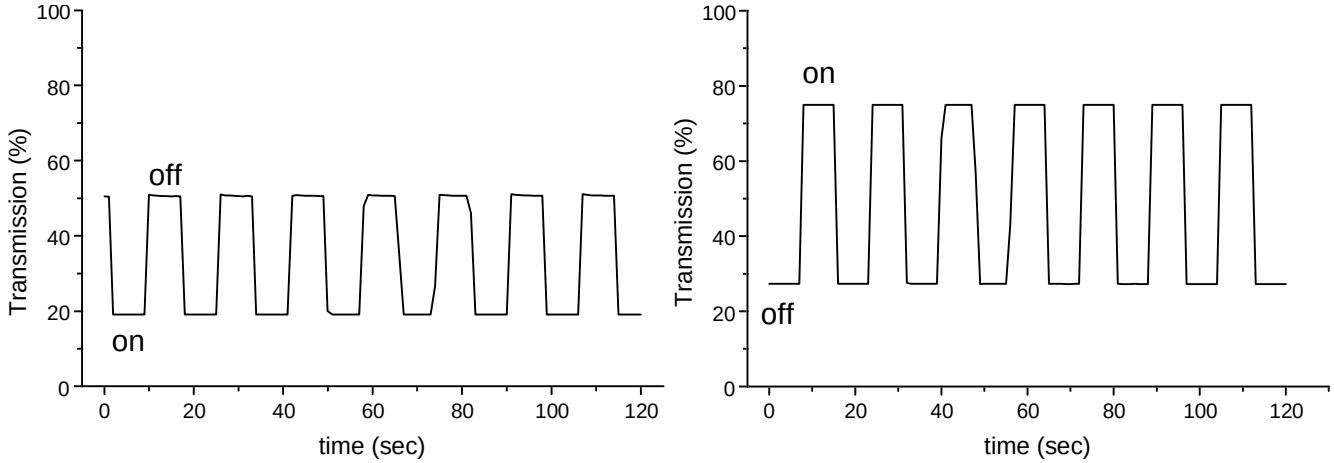


Figure 7.3: *Transmission characteristics of blends containing 10% of **1** in E7 (left) and 10% of **2** in E7 (right) as a function of time using step-voltage scans (off = 0 V, on = 10 V).*

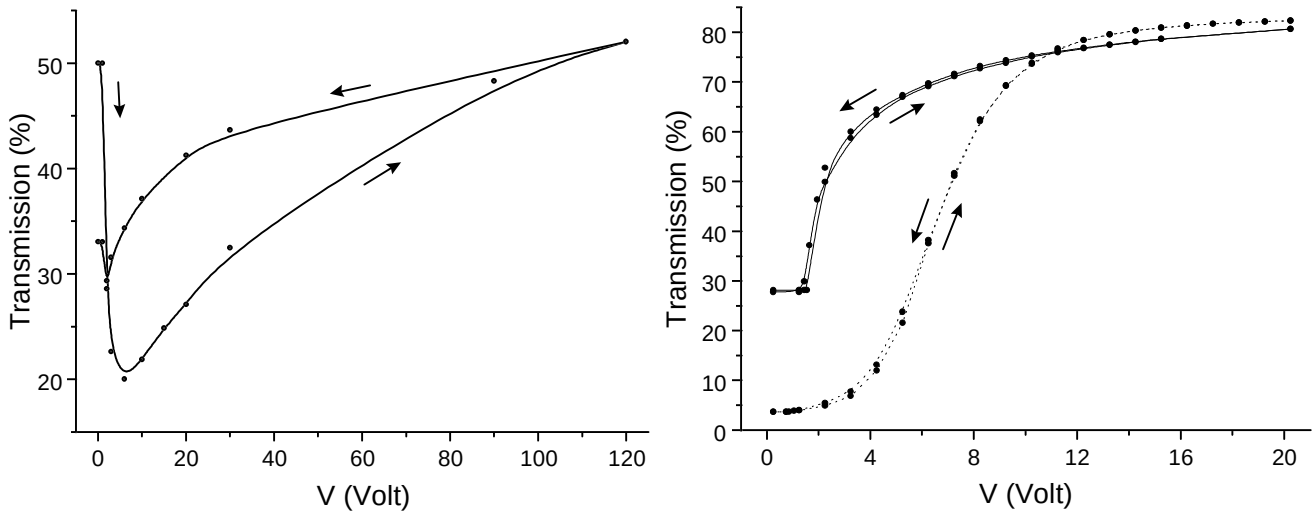


Figure 7.4: Transmission – voltage characteristics of blends containing 10% of 1 in E7 (left, 0 – 120 V) and 10% of 2 in E7 (right, 0 – 20 V, solid lines). Included is a 'state of the art' PDLC (right, dashed lines).

The transmission in the scattered state depends strongly on the sample–detector distance and the collection angle of the optical setup, which were estimated at 9.5 cm and 12°, respectively. A reference measurement on a 'state of the art' PDLC[35] is provided in Figure 7.4 (right). Whereas blends of **2** and E7 give rise to an expected decrease in scattering with 10 V–20 V applied, the blends of **1** and E7 show an unexpected increase in scattering from 50% to 20%. Characteristic are the low threshold voltages for both blends and the absence of hysteresis when low voltages (V < 10 V) are applied. The threshold voltage is approximately 1 V, which is similar to that of pure E7. Most of the PDLC's, PFN's or aerosil-based scattering[5] displays show considerably larger threshold voltages, even for a 'state of the art PDLC'. Furthermore, often hysteresis effects play a significant role in most of these displays. The transmittance measurements of a blend, containing **2**, show reversible switching between a transmittance of 30% (off-state, 0 V) and 80% (on-state, 20 V). The switching from scattering to transparent state agrees well with literature reports[5, 10] that use similar experimental conditions, *i.e*. planar cells with E7 as the nematic liquid crystal, although the observed contrast ratio is smaller than that of the PDLC. The switching can be explained by polydomain formation in the off-state and homeotropic alignment of the nematic liquid crystal in the on-state. The observed transmittance in the on-state of 80% (the transmission of a sandwich cell filled with E7, but without dendrimer is around 85%) indicates that indeed a highly transparent state is obtained in which no large refractive index mismatch between the two phases exists. Figure 7.5 depicts the transmission in on- and off-state as a function of the amount of **2** in the blends and a maximum transmission window is obtained for blends containing ca. 10–20% of **2**.

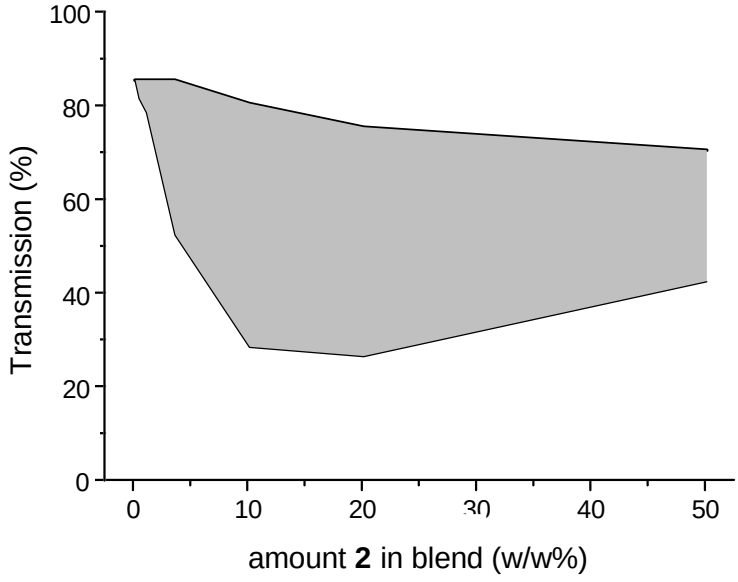
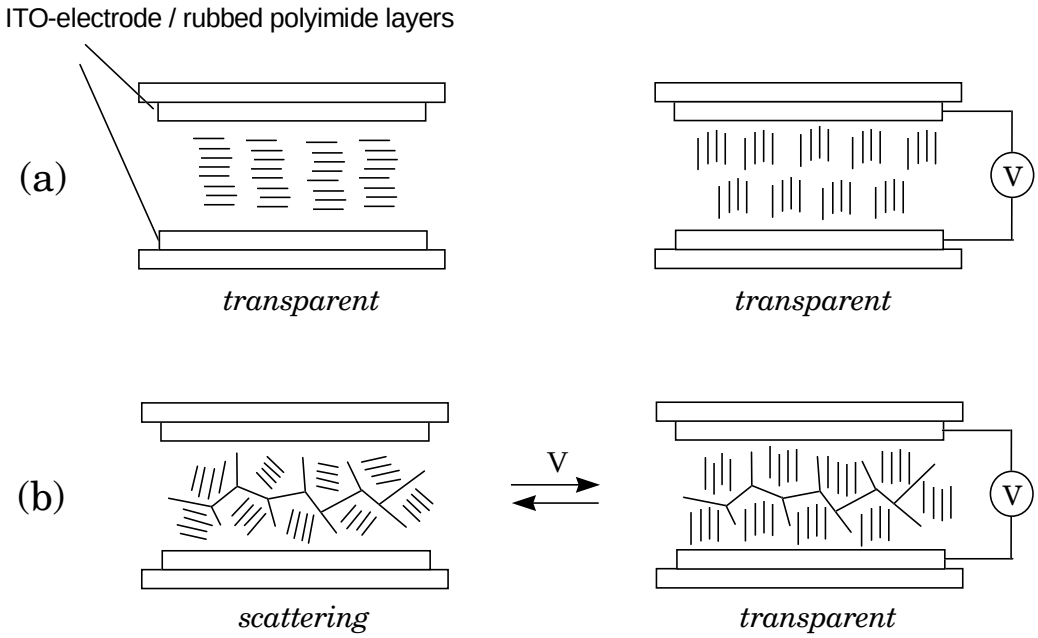


Figure 7.5: *Transmission characteristics of blends of **2** and E7 as a function of the amount of **2** (off, 0 V, scattering state; on, 10 V, transparent state).*

7.3.2 Discussion

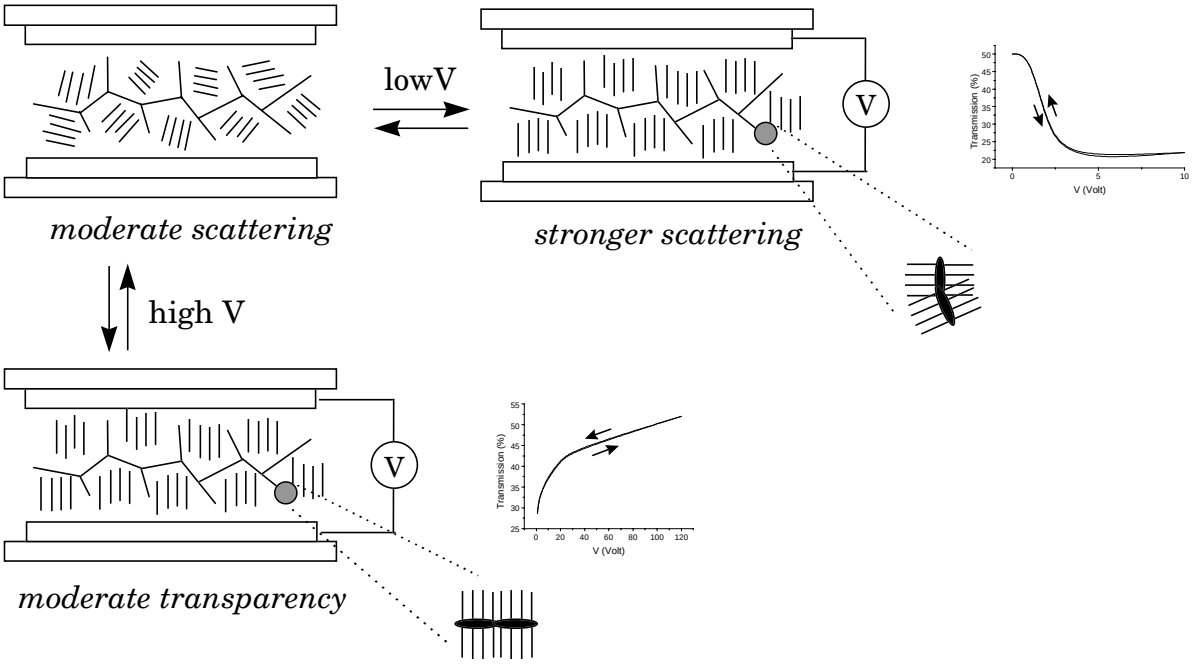
In Section 7.3.1 a dendrimer-based electro-optical switch based on light scattering has been discussed. The sandwich cells contain a rubbed polyimide layer, that yields a planar organization of liquid crystalline molecules, like E7 as is depicted in Scheme 7.3a (no voltage or dendrimer). This yields a large mono-domain and as a consequence a transparent state when no voltage is applied. Upon applying a voltage, the mesogens orient into a homeotropic arrangement and the cell remains transparent. If, however, a blend of **2** and E7 is prepared, the addition of dendrimer disturbs the uniform arrangment of the mesogens and many small domains with random directors are formed. It is proposed that the dendritic additives, because of their large specific area, stabilize the boundaries of the domains. The large optical anisotropy of the liquid crystal material results in scattering of visible light (Scheme 7.3, (b), no voltage), similar to silica[8] or polymer filled nematics.[10] Upon applying a voltage, the nematics can be switched to a homeotropically aligned, tranparent state.



Scheme 7.3: *Schematic diagram to explain the switching properties of pure E7 (a) and of blends containing E7 and dendrimer* ***2****.*

In contrast to PDLC's no phase separation takes place and therefore matching between the refractive indices of the nematic liquid crystal and the dispersed material is not necessary. Furthermore, due to the high volume fraction of the nematic phase, the (non-liquid crystalline) dendritic additives have no large influence on the optical properties of the display. The observed transparency of a blend of **2** and E7 with applied

voltage is almost similar to the transparency of pure E7 (Fig. 7.5). Apparently, the most efficient switch can be obtained if 10–20% of **2** are added. In this concentration regime the highest off-state scattering state is obtained. Since the domain size further decreases for higher amounts of **2**, scattering becomes less effective and an increase in transparency is observed in the off-state. As the on-state transparency decreases, a smaller contrast ratio is observed for higher amounts of **2**. Most remarkably, all blends containing **2** show an unprecedented small hysteresis effect, even in the first voltage scan (see for instance Fig. 7.4, right).



Scheme 7.4: *Proposed diagram for the switching properties of blends containing dendrimer 1 and E7. Schematically, a change in dendrimer arrangement is depicted for high and low voltage regimes. For convenience, the transmittance-voltage scans are depicted and taken from Fig. 7.4, left.*

In case of blends of **1** and E7, the observed behavior (Fig. 7.4, left) is complex, but a schematic diagram is proposed (Scheme 7.4). Two liquid crystalline compounds are present with different switching characteristics. Addition of dendrimer **1** yields a scattering state though not as effective as blends of **2** and E7. At low voltages, the nematics switch into an homeotropic arrangement, but the organization of the dendrimer at the boundary is unchanged and possibly of the E7-molecules that are in its direct vicinity. Due to the anisotropy between dendrimer and nematic phase, scattering increases (Fig. 7.4, left) and a reversible switching pattern is observed between a moderate scattering and a stronger scattering state (Fig. 7.3, left). High voltages change the organization of the liquid crystalline dendrimer into a stable

homeotropic arrangement, even when no voltage is applied and since this organization, due to the smaller refractive index difference, a decrease in scattering is observed. If no voltage is applied, the nematics reorient into a random state, and a decrease in transparency is observed. For the subsequent scans, the behavior resembles that of blends containing **2**, with switching from a moderate scattering to moderate transparent state.

7.4 Conclusions and Outlook

The results presented above indicate that dendritic additives, which are compatible with the LC-matrix, can be used in the development of a promising electro-optical switch. For blends containing liquid crystalline dendrimer **1**, the switching properties are complex and two regimes can be distinguished dependent on the applied voltage. However, the absence of hysteresis and the low voltage required for the switching process of blends containing **2**, offers (clear-cut) advantages compared to Polymer Filled Nematics and Polymer Dispersed Liquid Crystal systems. Experiments are underway to improve the contrast ratio of the electro-optical switch by a further optimization of the (liquid crystalline) dendritic additives.

7.5 Experimental Section

Materials

The nematic liquid crystal used was LC E7 (Merck Ltd.; n_0 = 1.5216, n_e = 1.7462, Δn = 0.2246), a mixture of cyanobiphenyls and a cyanoterphenyl. A fifth generation cyanobiphenyl-modified poly(propylene imine) dendrimer, **1**, and a fifth generation palmitoyl-modified poly(propylene imine) dendrimer, **2**, were used as dendritic additive. The syntheses of **1**[28, 27] and **2**[31, 32] are described in Chapter 6 and 2, respectively. A acrylate-based 'state of the art' PDLC was kindly provided by Philips Research (Eindhoven, The Netherlands). Sandwich cells have been used as received (1×1 cm, spacings 6 μm).

Preparation of the Blends and the Sandwich Cells

Dendrimer/liquid crystal blends were obtained by weighing the nematic liquid crystal (E7) with **1** or **2** in an appropriate ratio and dissolving the mixture in chloroform. After evaporation of the solvent *in vacuo*, the blend was heated till an isotropic fluid was obtained and consequently allowed to cool down. The sandwich cells were filled by applying a droplet of the blend on a pre-heated sandwich cell using capillary suction.

Differential Scanning Calorimetry

Thermal transitions of the blends were determined on a Perkin-Elmer Pyris 1 under a nitrogen atmosphere with heating and cooling rates of 5 $K \cdot min^{-1}$.

Optical Microscopy

The optical properties of the blends in the sandwich cells were studied with a Jeneval Polarization Microscope equipped with a Linkam THMS 600 heating device, using crossed polarizers.

Electro-Optical Measurements

ITO (indium tin oxide) glass sandwich cells (1 cm) coated with polyimide layers, in which the rubbing direction of the two surfaces was anti-parallel, were used for the electro-optical measurements on blends. An electrical field was applied to the sample by use of a Black Star Jupiter 500 0.1 Hz - 500 kHz function generator. Transmission of the blends was determined on a Lambda UV/vis/nearIR spectrometer at λ = 600 nm. All measurements were referenced against air. A reference sandwich cell filled with E7 shows a transmittance of 85%.

7.6 References and Notes

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The Design of a Novel Dendritic Host-Guest Motif

8

Abstract: *Poly(propylene imine) dendrimers functionalized with apolar endgroups and urea linkages, can be used as template for binding ('clicking') guest-molecules within the periphery of the dendrimer. The latter is rationally designed and consists of a carboxylic acid moiety and an urea-linkage. The complexation is stabilized by strong electrostatic interactions between the carboxylic acid of the guest and the tertiary amine of the dendritic host and by hydrogen-bonding interactions between host and guest. The complexes are prepared by mixing host and guest in chloroform and purification from excess guests is performed by biobeads column chromatography, showing the stability of the complex. For a fifth generation dendrimer a maximum of ca. 32 guests can be complexed which suggests that the bis(propylurea)amine unit at the dendritic periphery serves as an ideal pincer for the complexation of the guest molecules.* ^{1}H, ^{1}H*-NOESY-NMR spectroscopy is used to prove the close proximity between host and guest and the localization of these guest at the periphery of the dendrimer. NMR relaxation measurements indicate that a dense shell is formed upon complexation of the dendrimer. The 'clicking' concept represents a new and fast method for the endgroup-functionalization of the dendritic periphery through secondary interactions and opens a plethora of possibilities in the field of catalysis, drug-delivery and modular chemistry.*

Part of this work will be published: Baars, M. W. P. L.; Karlsson, A.; de Waal, B. F. M.; Meijer, E. W., *to be published.*

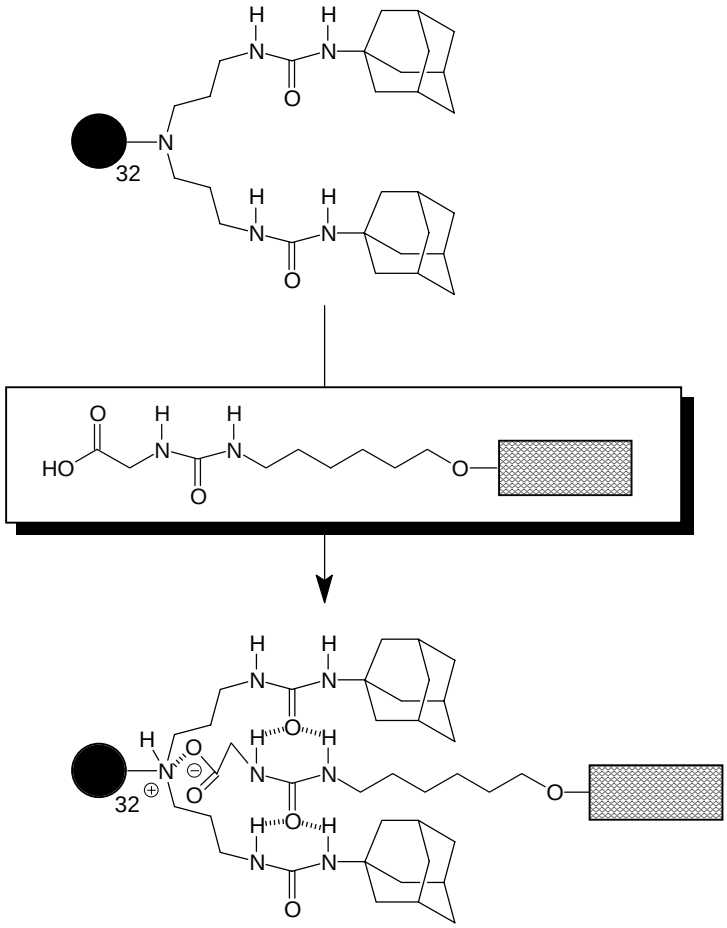
8.1 Introduction

The role of dendrimers in supramolecular chemistry is a topic of great current interest. Their properties as macromolecular hosts[1, 2] with nanometer dimensions have been well-documented and also their (self)-assembly in different media has been addressed.[1, 3] A translation of the design rules of supramolecular chemistry to the area of dendritic host-guest systems has shown that in most cases the molecular recognition is based on clathration of the guest and/or using electrostatic interactions, hydrogen-bonding and hydrophobic interactions between host and guest. It is also known from supramolecular chemistry that a combination of these interactions enables a stronger and more selective recognition.[4] Several examples have shown that the dendritic scaffold yields cooperative effects in the recognition of guest molecules. Astruc *et al.*[5, 6] disclosed higher generation dendrimers that show an increased selectivity for the recognition of inorganic anions, like Cl^- and $H_2PO_4^{2-}$. In Chapter 4 and 5 the assembly of acidic dyes by functionalized poly(propylene imine) dendrimers becomes more effective with generation, especially for the complexation of weak organic acids.[7]

Many investigation makes use of dendrimers as a (multi)functional template. The monodisperse nature of dendrimers and their dimensions makes these dendrimers to ideal building blocks or modules.[8, 9] Zimmermann *et al.*[10] discussed the assembly of acid-functionalized dendritic wedges into a hexameric cluster using multiple hydrogen-bonding interactions. Newkome *et al*.[11] have reported the construction of dendrimers in which four 2,6-diamidopyridine units are incorporated in the interior. Such moieties allow the use of dendrimers as a template for the anchoring of complementary units.[12] Recently, Crooks *et al.*[13] discussed the complexation of fatty acids to the primary amine dendritic scaffold yielding an unimolecular micellar structure based on electrostatic interactions. The assembled dendrimer shows interactions that are comparable to the covalent counterparts.[7, 14] The use of metal-coordination is also a common methodology to assemble metal-ions at the dendritic periphery. For instance, Newkome[15, 16] and Constable[17] used a tridentate 2,2':6',2"-terpyridine (tpy) unit as a strong transition-metal binding ligand to facilitate and control the assembly of molecular architectures. This ligand enables the development of a key and lock principle that allows a step-by-step construction of dendritic assemblies. Another example is the work of Bosman *et al.*[18] who used amine-terminated poly(propylene imine) dendrimers for the complexation of various transition metals, such as Cu(II), Zn(II), Co(II) and Ni(II). The metal-ions are complexed at the periphery by the bis(3-aminopropyl)amine moiety, that serves as an ideal pincer for complexation. Furthermore, amine-functionalized poly(propylene imine) dendrimers can be used as a module for the assembly of rigid Troger's base dizinc(II)

bis-porphyrin receptor molecules, yielding a self-assembled spherical superstructure encapsulating the dendrimer.[19]

In this Chapter, the use of dendrimers as a well-defined nano-sized module is introduced with a short historical perspective, where the encapsulation procedure of the dendritic box is investigated with a modular approach. Subsequently, a new modular approach to the modification of dendrimers is presented, that is based on the design of a dendritic host-guest motif. Through a rational design of guest molecules a strong and selective association with the dendrimer motif can be obtained that is based on electrostatic and hydrogen-bonding interactions (Scheme 8.1).[20]

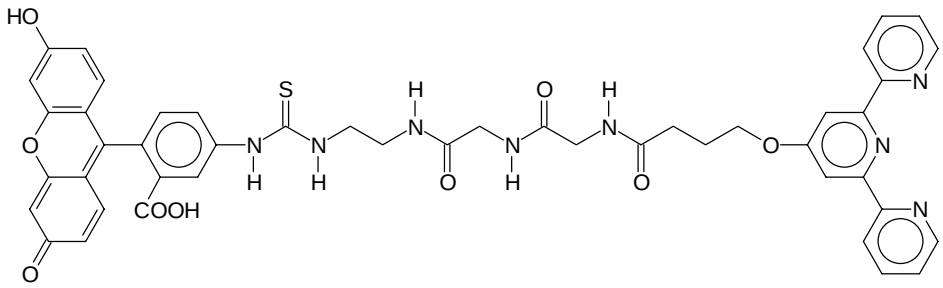


Scheme 8.1: *Complexation of guest-molecules to a fifth generation adamantyl-dendrimer by secondary interactions. The black sphere represents the dendritic interior. The box represents a probe moiety that is used for analysis purposes, and is aimed to introduced functionality.*

The carboxylic acid moiety and urea-linkage of the guest in combination with the bis(propylurea)amine pincer of the host will account for the cooperative interactions observed. The 'clicking' concept represents a new, and easily accessible method for the functionalization of a dendritic periphery through secondary interactions and opens new synthetic possibilities in the dendrimer field.

8.2 Historical Perspective

In Chapter 1 the concept of the dendritic box is discussed, i.e. a poly(propylene imine) dendrimer functionalized with an amino acid endgroup that possesses a unimolecular compartmented structure in which guest molecules, like xanthene dyes can be physically locked.[21–24] *A restricted number of dye molecules can be encapsulated per box; e.g. a maximum number of four was found in the case of Rose Bengal and Fluorescein. Furthermore, a shape-selective liberation of guests can be accomplished by a two-step process.*[25] *In 1995 it was further envisaged that the binding between guest and the dendritic box could be used as a new tool in modular chemistry. New (large) guest-molecules were designed, that consisted of three parts. A xanthene moiety, that could be encapsulated in the box. A spacer unit, containing a diglycine unit for compatibility with and interdigitation through the hydrogen bonding shell of the (perforated shell of the) dendritic box, and a functional part that should stick outside the dendritic box. A particularly interesting endgroup is the terpyridine-motif (tpy), developed by Newkome that allows use in the key-and-lock approach. The functionality of four as the maximum number of several encapsulated guests in combination with the tpy-unit should lead to modular chemistry at the nanoscopic level. The designed 'click'-molecule*[26] *is depicted in Scheme 8.2 and the synthesis could be accomplished in three steps, starting from 4-tpy-butyric acid*[27] *and via condensation with diglycine unit, addition of excess ethylenediamine and reaction with fluorescein-4-isothiocyanate.*



Scheme 8.2: *Designed of 'clicking' molecule for modular chemistry based on the guest-encapsulation procedure of the dendritic box.*

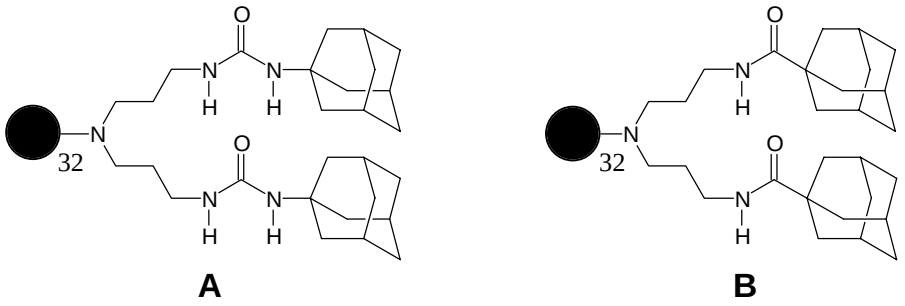
However, with the availability of a new series of poly(propylene imine) dendrimers that had been synthesized in toluene in stead of MeOH, and as a result with a completely different conformation micro-polarity of the dendritic interior, the encapsulation procedures became more delicate, even though many experiments have been performed and experimental conditions varied. It was further realized that the development of this appealing modular approach required an even more detailed knowledge on the dendritic scaffold used. This initiated more thorough investigation of the poly(propylene imine) scaffold (Chapter 3). It is now believed that the encapsulation procedure is a very delicate process, highly dependent on micropolarity (conformation) of the dendrimer. Later, it became evident that the encapsulation experiments

could be explained by acid-base interactions; the latter are also determining the extraction process. From this moment on the irreversible physical encapsulation process of the dendritic box was replaced by reversible dendritic host-guest systems based on secondary interactions. Such hosts have been discussed previously in Chapter 4 and 5 and will be the scope of this chapter.

8.3 Rational Design of Host–Guest Motif

8.3.1 Selection of the Dendritic Hosts

The synthesis of poly(propylene imine) dendrimers with an apolar moiety have been discussed in Chapter 2. Two series have been obtained, with rigid bulky adamantyl and linear, flexible alkyl chains. Moreover, two types of linkages, amides and ureas, are available. The extraction of anionic solutes by alkyl-chain modified poly(propylene imine) dendrimers have been discussed in Chapter 4,[7] and it was illustrated that the (amide) linkage does not play a significant role on the extraction properties. However, in Chapter 3, the hydrogen-bonding properties as a function of the type of linkage and the dimensions of the endgroup have been discussed. The endgroups with an urea-linkage shows in IR-spectroscopy that all N–H-protons are hydrogen-bonded, while in the case of the amide-linkage, the N–H bonds are partially hydrogen-bonded with the highest ratio for the fifth generation due to the high local concentration. The differences between the adamantyl and palmitoyl series arises from differences in shape: the bulkiness of the adamantyl-dendrimers prohibits ideal hydrogen-bonding interactions, while the palmitoyl-series, due to better packing, are able to form highly ordered arrays. A fifth generation adamantyl-functionalized dendrimer with urea-linkages (**A**, Scheme 8.2, left) is therefore selected since it is expected that linear guests can penetrate through the adamantyl-periphery, and that, with a proper rational design of the guest, more effective hydrogen-bonding interactions are possible. Finally, adamantyl-dendrimers with an amide-linkage (**B**) are used in a competition experiment (Scheme 8.2, right).



Scheme 8.3: *Schematic representation of the fifth generation dendritic hosts investigated. Host **A**: adamantyl-functionalized dendrimer with urea-linkage. Host **B**: adamantyl-functionalized dendrimer with amide-linkage.*

8.3.2 Selection of the Guests

Guest molecule, **1**-COOH, has been rationally designed aiming at optimal complexation by the dendritic host as depicted in Scheme 8.1. The guest molecule consists of a carboxylic acid moiety and urea-linkage. Furthermore a linear spacer is introduced to allow an easy penetration though the dendrimer periphery and a cyanobiphenyl moiety for characterization purposes. The synthesis of **1**-COOH is outlined in Scheme 8.4, and can be obtained via synthesis of 6-((4'cyano(1,1'-biphenyl)-4-yl)oxy)aminohexane (**1**-NH_2). The latter is obtained through coupling of 4'-cyano-4-hydroxybiphenyl with 6-bromohexylphthalimide, followed by cleavage of the protecting group with hydrazine. The amine-functionality can be converted into the isocyanate using di-*tert*-butyl tricarbonate[28] and is in situ reacted with glycine methyl ester hydrochloride to yield **1**-$COOCH_3$. Hydrolysis with $LiOH{\cdot}H_2O$ in a THF/H_2O-mixture yields **1**-COOH.

Furthermore three reference compounds are selected, *i.e.* **1**-$COOCH_3$, **1**-OH and **2**-COOH (Scheme 8.5). Compound **1**-$COOCH_3$ is an intermediate in the synthesis of **1**-COOH. Compound **1**-OH can be obtained from the reaction of **1**-NH_2 using di-*tert*-butyl tricarbonate and *in situ* reaction with ethanolamine. Compound **2**-COOH is already discussed and characterized in Chapter 6. Important to note is the use of similar spacings between carboxylic acid and cyanobiphenyl moiety. The purity of all compounds are confirmed with a combination of ^{1}H-NMR and ^{13}C-NMR spectroscopy, IR-spectroscopy, GC-MS and Elemental Analysis. The solubilities of compounds **1**-COOH and **1**-OH in chloroform are small.

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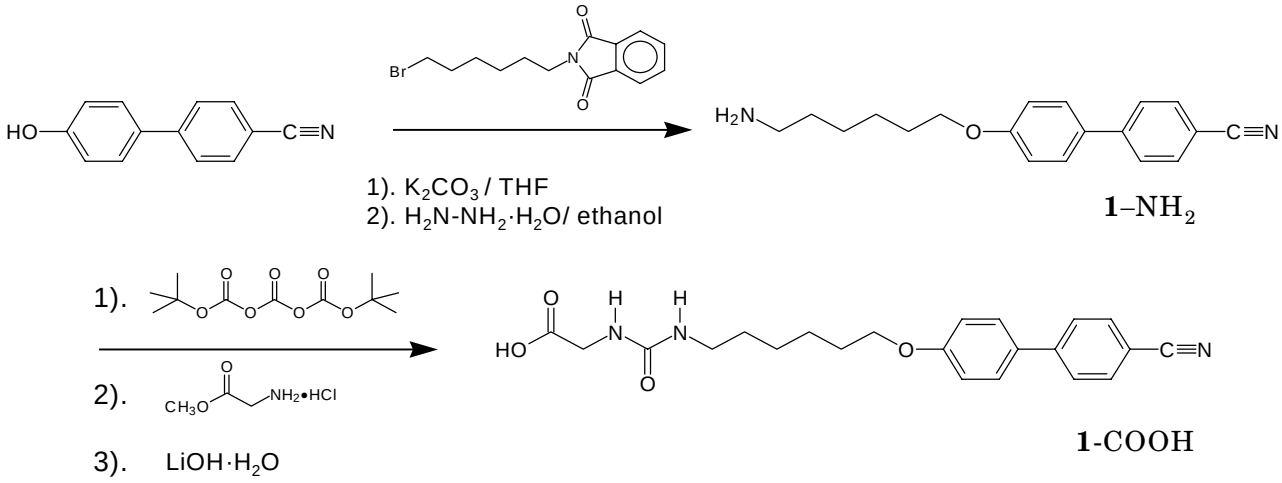
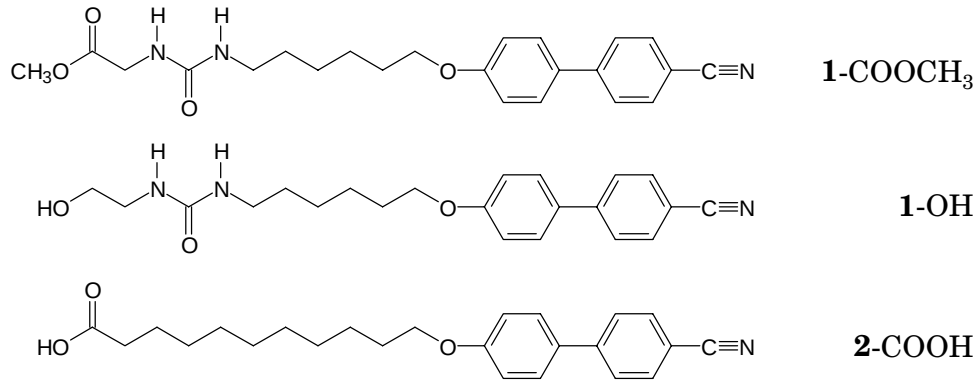


Scheme 8.4: *Synthetic route for compound **1**-COOH.*



Scheme 8.5: *Structure of compounds **1**-OH, **1**-$COOCH_3$ and **2**-COOH*[29]

8.4 Characterization of the Host-Guest Complexes

Mixtures of host **A** and compounds **1**–COOH, **1**–OH, **1**–$COOCH_3$ and **2**–COOH in $CHCl_3$ have been prepared in ratios of *ca.* 1 : 16 (mol/mol). Chemical shifts in ^{1}H-NMR spectroscopy have been used to verify interactions with the dendritic host. No changes in chemical shifts have been observed for complexes of guest **1**–OH and **1**–$COOCH_3$. However, urea-protons of the dendritic scaffold show a downfield shift for guests **1**–COOH and **2**–COOH, which is indicative of a change in hydrogen-bonding interactions between the urea-protons in the dendritic host, due to the incorporation of guests. Furthermore, in case of **1**-COOH, a downfield shift of the methylene protons adjacent to the tertiary amines of the host from *ca.* 2.3 ppm up to 2.9 ppm is observed, which is indicative of protonation of the tertiary amine nitrogens. However, when using guest **2**–COOH, no shift is observed in this region, which indicates that no protonation takes place for this guest.

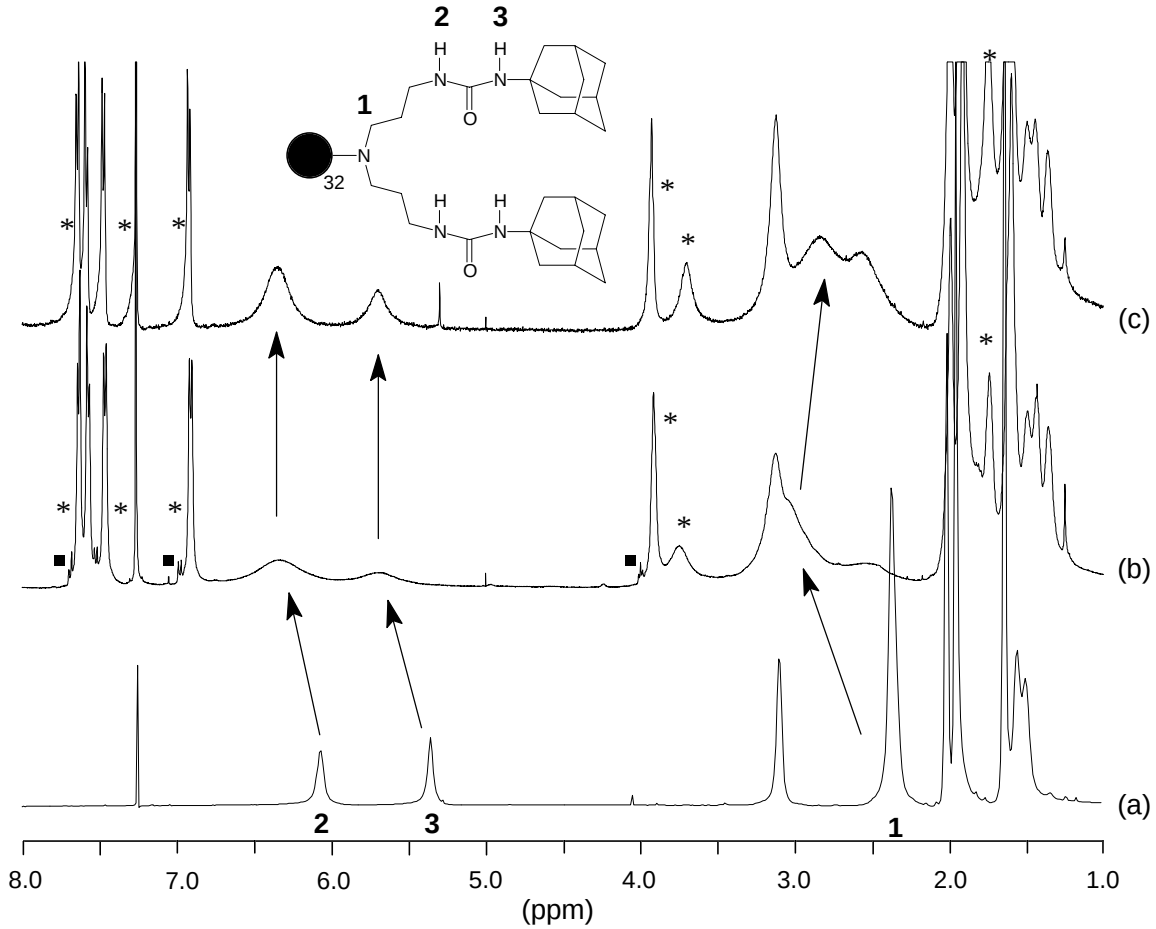


Figure 8.1: *^{1}H-NMR spectra of host A (a), a complex of host A and excess **1**-COOH before biobeads (b) and a complex of host A and guest **1**-COOH after biobeads (c). Guest signals are characterized by an asterisk. Dendrimer-structure is depicted and typical resonances are marked (**1**, **2** and **3**). Adhered guests are marked by ■.*

Subsequently, biobeads chromatography was used to study the stability of the host-guest complexes. A complex of **1**-COOH (excess) and host **A** was prepared and purified with biobeads chromatography. Various spectra are depicted in Fig. 8.1. Spectrum (a) represents host **A** without any guest. Spectrum (b) depicts the spectrum of host **A** with an excess of **1**-COOH before biobeads chromatography, while spectrum (c) shows the spectrum of the complex after biobeads chromatography. Comparison of spectra (b) and (c) with spectrum (a) reveal a shift in resonances of the host due to protonation and stronger hydrogen-bonding interactions upon addition of the guest. A first biobeads-column is used to remove excess guests as is observed when comparing spectrum (b) and (c). In the latter spectrum all adhered guests (■) are removed. After subsequent biobeads filtrations, the host-guest ratio of the complex with **1**-COOH remains constant, as is determined from the integral ratios in the ^{1}H-NMR spectrum. The results indicate that strong complexation takes place, and (almost) no dissociation is observed after performing several biobeads purifications. On the contrary, mixtures of dendrimer **A**

and compounds **1**-OH and **1**-$COOCH_3$ and **2**-COOH, can be separated by biobeads chromatography, using similar experimental conditions. The number of guests **1**-COOH, that can be complexed is restricted and independent of the amount of excess used. In all cases a maximum of *ca.* 32 ± 2 guests after biobeads is found for the fifth generation poly(propylene imine) dendrimers. This (maximum) ratio of guest **1**-COOH and host A, *i.e.* the GHratio, is determined from the integral ratios in the ^{1}H-NMR spectrum.[30] A loading of 32 can be explained by the host-guest motif that is depicted in Scheme 8.1; guests are clicked to the dendrimer periphery and the carboxylic acid moiety interacts with the outer shell of tertiary amines and the urea-linkage with the hydrogen-bonding shell of the dendritic host. A fifth generation dendrimer contains 32 outer shell tertiary amines. Excess guests (■), observed in spectrum (b) before biobeads, adhere to the dendritic assembly probably via hydrogen-bonding interactions yet the association is much weaker and these adhered guests can be removed by biobeads chromatography.

Titration Experiments. A fully loaded dendrimer, with 32 guests complexed to one host, is titrated with an empty dendrimer. The titration experiment is depicted in Fig. 8.2 for methylene protons adjacent to tertiary amines, **1**, and urea protons, **2** and **3** of the dendritic host A. In all cases, the titration-data (▫) agree well with those of pre-prepared host-guest complexes (■). The latter are prepared by direct solubilization of **1**-COOH in appropiate host-guest ratios, in the chloroform solution containing the adamantyl-dendrimer.

Since, the obtained ^{1}H-NMR spectrum shows one single resonance for each proton, it can be concluded that there is a fast exchange of guests on the NMR time scale. Urea-protons, **2** and **3**, show a downfield shift with increasing guest-host ratio (GHratio), which indicates that the strength of hydrogen-bonding interactions increases due to additional hydrogen-bonding interactions between host and guest. It is furthermore illustrated in Fig. 8.2 that the methylene protons **1** upon 'clicking' shifts downfield from δ = 2.3 ppm to two peaks at 2.6 and 2.9 ppm for a fully loaded dendrimer, respectively. Figure 8.2 only depicts the shifts for methylene protons **1**.The peak at δ = 2.9 ppm shows the influence of protonation of the outer shell of tertiary amines.

The peak at δ = 2.6 ppm is characteristic of all other methylene protons adjacent to tertiary amines, that show a low(er) protonation degree. Since all methylene protons adjacent to the tertiary amines in different shells show resonances that are almost identical, it is difficult to determine the exact mode of binding by following peak **1**, only. ^{15}N-NMR spectroscopy shows a better potential to follow this protonation process[31] in poly(propylene imine) dendrimers[32, 33] as was discussed in Chapter 3 already, but the

technique suffers from the low natural abundance of the ^{15}N-nucleus, which makes it difficult to use the technique experimentally.

The urea-linkages of the guest show hydrogen-bonding interactions with the dendritic scaffold, upon complexation into the dendritic scaffold. The guest 'senses' a strong hydrogen-bonding environment of the urea shell in the adamantyl-functionalized dendrimers. As a consequence the urea-resonances of the guest are observed at *ca.* 6.4 ppm in case of a maximum loaded complex,[34] yielding a value that is much higher than in the case of the reference compound **1**-$COOCH_3$ in the same solvent, that does not interact with the dendrimer, and shows two resonances at 4.77 and 5.04 ppm.

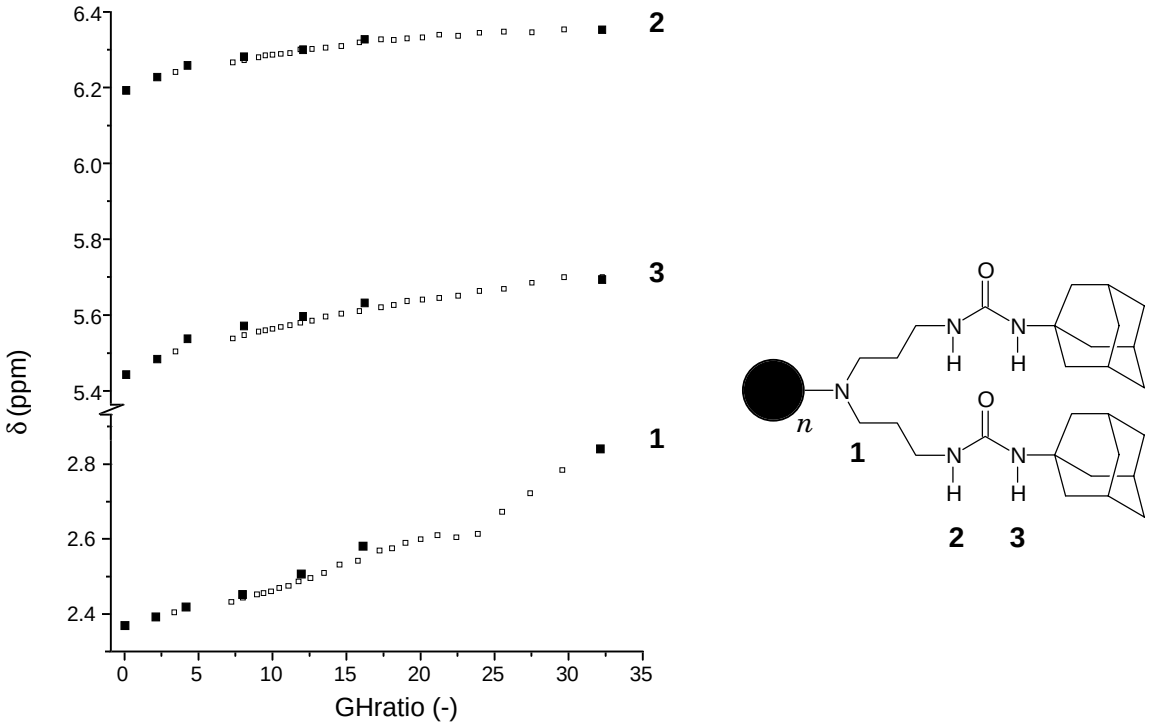


Figure 8.2: *Titration experiment of host-guest complex of A / **1**-COOH with a 1:32 ratio, and host A. Titration data ▫, Pre-prepared samples ■.*

IR-Spectroscopy. The hydrogen-bonding properties have been previously discussed for host A using IR-spectroscopy (Section 3.3.1). All ureas are hydrogen-bonded at 3320 cm^{-1}, and the two NH-units show small differences in wavenumber because their strength is different. Reference compound **1**-$COOCH_3$ shows one resonance at 3450 cm^{-1} (Fig. 8.3) that corresponds with a non-hydrogen bonding urea, and no change is observed when this compound is added to the dendritic host. However, in case of a mixture of **1**-COOH and host **A**, no resonance is observed at 3450 cm^{-1}, which suggests that the urea-linkage of the guest are hydrogen-bonded with the dendrimer shell. Moreover, the resonance of the hydrogen-bonding ureas increases in intensity, and

shifts to smaller wavenumber indicative of stronger hydrogen-bonding interactions, due to participation of the guest-ureas.

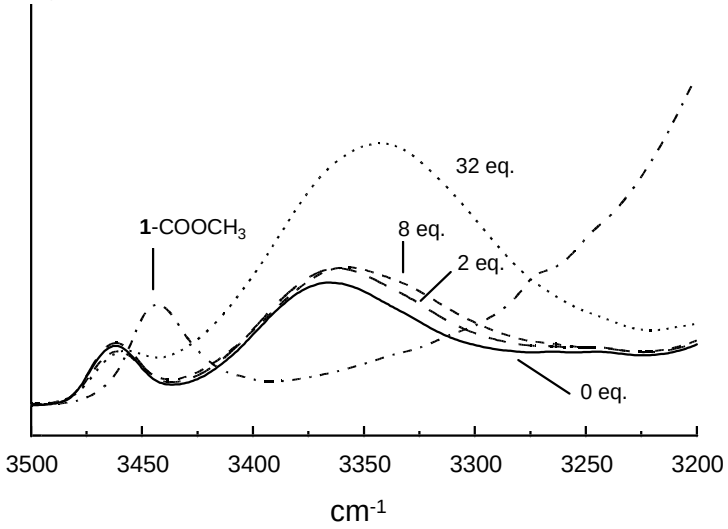


Figure 8.3: NH-region for **1**-$COOCH_3$ and complexes of **B** and **1**-COOH with different GHratios.

NOESY-NMR and NMR-Relaxation Measurements. In a ^1H, ^1H NOESY experiment NOE-interactions are observed between host and guest in $CDCl_3$. The methylene protons adjacent to the carboxylic acid moiety of the guest show an interaction with the propyl-unit in the bis(propylurea)amine pincer.

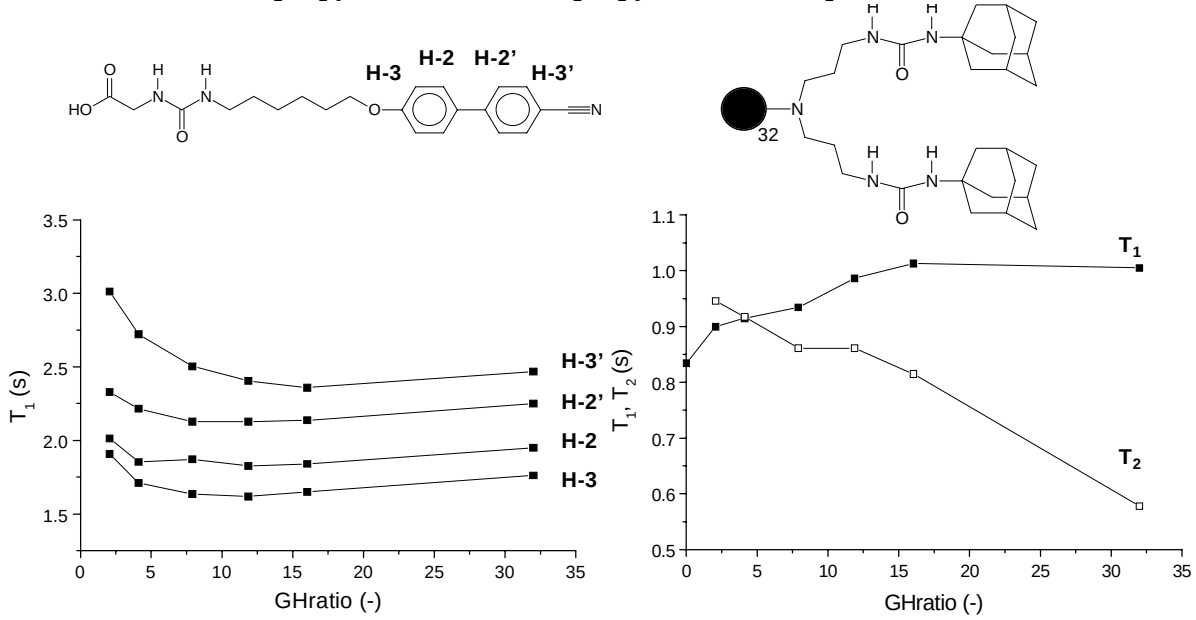


Figure 8.4: *NMR-relaxation times for dendritic host A and guest **1**-COOH as a function of the GHratio. Characteristic signals are marked. (left) T_1 and T_2 relaxation times of dendritic host, (right) T_1-relaxation times of cyanobiphenyl part of guest*

Furthermore, the alkyl-spacer of the guest shows interactions with the dendritic adamantyl-periphery, since the apolar spacer interdigitates through the adamantyl shell. T_1-relaxation times of the guest (Fig. 8.4, left) show an initial decrease with

increasing host-guest ratios, since the guest participates in an assembly with a larger molecular weight. However since the guest motion also becomes more restricted, T_1 increases for larger amounts of guest complexed. The dendritic host (Fig. 8.4, right), with increasing amounts of guests, show a further increase in T_1 and of a decrease in T_2 due to increase in restricted motion, and agrees well with a denser shell packing when more guests are complexed. The effects can be explained by the increase of molecular weight. This agrees well with the results in literature. Jansen *et al.*,[35] showed a decrease in T_2, but an upturn for T_1 with increase in molecular weight of t-BOC-protected L-phenylalanine-modified poly(propylene imine) dendrimers, which is consistent with a solid-like character for the higher generations. Tomalia *et al*.[36] have shown that T_1-values of guests decrease with increasing dendrimer generation. Furthermore, Aida *et al*.[37] showed that T_1-relaxation times of the dendrimer endgroups decreases with generation.

Selectivity. Finally, complexation-properties have been compared for different hosts, by performing a competition experiment. To a 1:1 mixture of adamantyl-dendrimers with an urea-linkage (dendrimer **A**) and amide-linkage (dendrimer **B**), respectively, is added guest **1**-COOH. ^{1}H-NMR spectroscopy is used to investigate the number of guests complexed to the dendrimer and to gain information on which of the two dendrimers is most effective in binding guest **1**-COOH. For small ratios of the guest up to a load of 16 guest per urea-dendrimer, only changes in the resonances of the adamantyl-dendrimer with urea-linkages are observed. Upon further increase of the ratio, also a small downfield shift for the amide-signal of the other dendrimer-series is observed. In Fig. 8.5 a, a ^{1}H-NMR spectrum is depicted of DAB-*dendr*-(NHCONH-Ad)$_{64}$ / DAB-*dendr*-(NHCO-Ad)$_{64}$ / **1**-COOH in a ratio of 1:1:32. The guest signals are marked with an asterisk. Peaks A and B correspond to *one* urea proton of host **A** and the amide of host **B**, respectively. Changes in the resonances of the urea- and amide-protons of the two dendrimers are only due to interaction with guests.

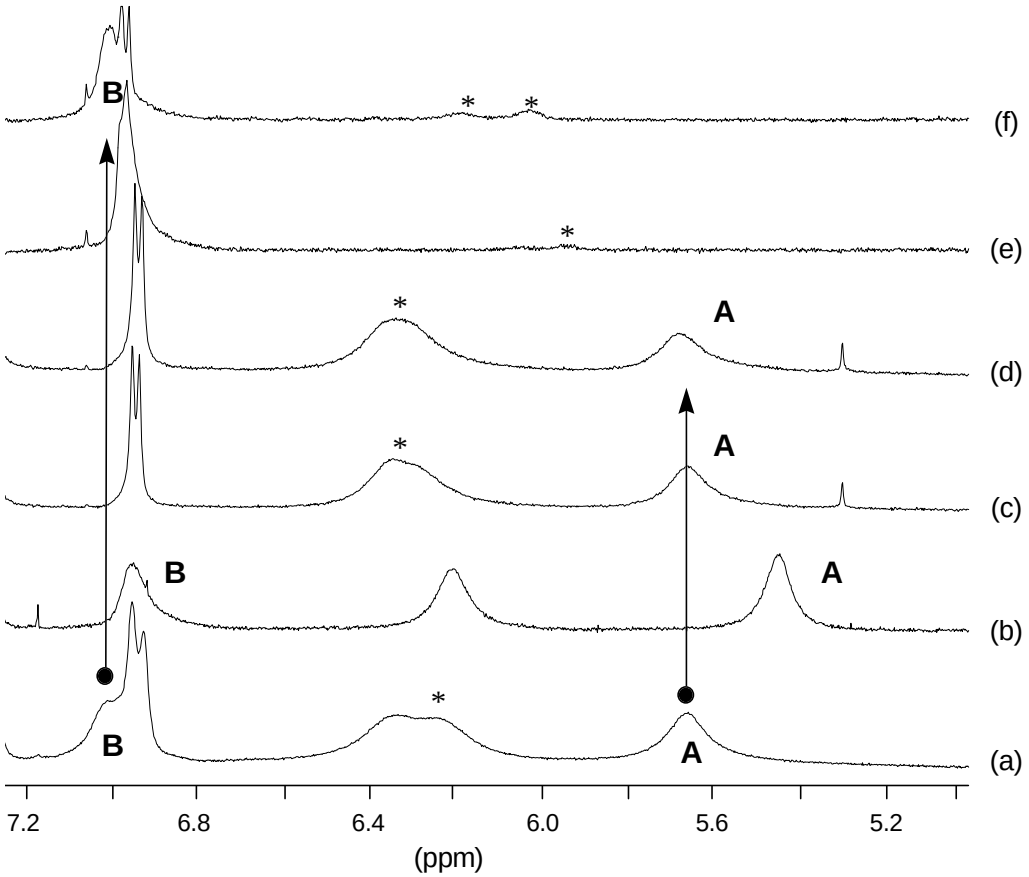


Figure 8.5: *^{1}H-NMR spectra between 5.0 and 7.4 ppm containing: (a) host **A**, host **B** and guest **1**-COOH with a ratio of **A**/**B**/**1**-COOH = 1:1:32. (b) host **A**/host **B** = 1:1, no guest present (c) host **A**/**1**-COOH = 1:24; (d) host **A**/**1**-COOH = 1:28; (e) host **B**/**1**-COOH = 1:4; (f) host **B**/**1**-COOH = 1:8. Marks **A** and **B** are used for one urea-proton of host **A** and of the amide-proton of host **B**, respectively.*

To determine a rough amount of the guests complexed to host **A** and **B**, it is attempted to compare (match) the resonances of spectrum (a) with that of complexes of host **A** / **1**-COOH and host **B** / **1**-COOH, respectively. The position of the urea proton at 5.64 ppm compares nicely with the position in spectrum (c) and (d) that contain *ca*. 24 and 28 guests per urea-dendrimer, respectively. Furthermore, the resonance for the amide-proton at 7.01 agrees with spectra (e) and (f) containing complexes of 4 and 8 guests per adamantyl-amide dendrimer, respectively. This competition experiment indicates that the bis(propylurea)amine pincer is more selective for complexation of guests than the bis(propylamide)amine pincer. It can further be expected that the association strength decreases with loading, since a loaded system has less (free) sites available for complexation than an empty one, which explains that for a certain load of guests, also complexation to the amide-dendrimers are observed.

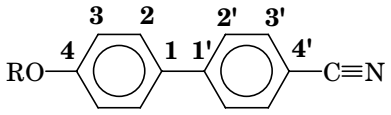
8.5 Conclusions and Outlook

In this chapter, a new concept has been developed for the endgroup-modification by a combination of secondary interactions only. A guest that consists of a carboxylic acid moiety and an urea-linkage complexes strongly with a bis(propylurea)amine-tweezer. This complexation depends strongly on the type of compounds used for complexation studies. Compounds consisting of either a carboxylic unit or an urea-linkage do not show strong complexation with the dendrimer. Furthermore, the complexation efficiency depends strongly on the type of dendrimer used as has been demonstrated in the competition experiment for adamantyl-functionalized dendrimers. The bis(propylurea)-amine pincer shows the highest performance. Presumably interdigitation of the guest through the adamantyl-periphery and interactions of urea-linkages between host and guest yield an increase of the hydrogen-bonding properties of the dendritic shell. Furthermore, initial experiments on the palmitoyl-functionalized dendrimers show no further increase in the hydrogen-bonding interactions, which can be related to the tight packing of the palmitoyl-chains (see Chapter 3). The dendritic host-guest motif allows a fast method for endgroup modification and the use of dendrimer as a nanometer-sized module. Two[38] or more types of endgroups at the dendritic periphery can be easily obtained via a supramolecular approach. Furthermore using this host-guest motif, it should now be possible to perform dendritic combinatorial chemistry, similar to Newkome *et al*.[39]

8.6 Experimental Section

General Methods and Materials

All solvents chloroform, ethanol, acetone, tetrahydrofuran (THF), triethylamine were of p.a. quality. THF was distilled over Na/K/benzophenone under an argon atmosphere, prior to use. Chloroform (p.a. stabilized by amylene; from Biosolve) was stored on acitvated molecular sieves (4 Å). Water was de-ionized before use. Triethylamine (Fluka, p.a) was stored on KOH-pellets. $LiOH{\cdot}H_2O$ (99 %, Acros Chimica), hydrochloric acid (37+ %, Vel), sodium hydroxide (Aldrich), potassium carbonate (Acros, p.a.), hydrazine monohydrate (Fluka), 18-crown-6 (Acros), 1,6-dibromohexane (Acros) were used as received. Melting points were determined on a Büchi Schmelzpunktbestimmungsapparat (nach Dr. Tottoli). GC-MS measurements have been performed on a Shimadzu GC-MS QP5000 using a GC-17A Gas Chromatograph. IR-spectra have been obtained on a Perkin Elmer Spectrum One ATR-FT-IR machine. All measurements were run on a Perkin Elmer 2400 Series CHNS/O analyzer. NOESY-NMR measurements have been performed on a Varian 500 MHz using standard software and mixing times. Biobeads S-XI Beads (200-400 mesh) with a MW cut-off of 14 kD were obtained from Bio-Rad Laboratories. Chloroform was used as the solvent. Di-tert-butyltricarbonate was prepared according to ref. 28. Numbering of the cyanobiphenyl-fragment is as follows.[40]



Procedures for the Synthesis of Click-Molecules:
Synthesis of 6-bromohexylphtalimide

To a solution of 1,6-dibromohexane (358.6 g, 1.47 mol, 6.45 eq) in aceton (400 ml) is added phtalimide potassium salt (38.6 g, 0.228 mol) and 18-crown-6 (240 mg, 0.91 mmol). The reaction was heated under reflux conditions for 20 h and allowed to cool down. The reaction mixture was evaporated *in vacuo* under reduced pressure to remove excess 1,6-dibromohexane. Ethanol (400 ml) was added to the crude product and upon cooling to -20 °C a white precipitate is formed. Filtration and drying under reduced pressure and subsequent crystallization of the residue yielded pure 6-bromohexylphtalimide (54.6 g, 77%). ^{1}H-NMR ($CDCl_3$): δ 1,30-1.90 (m, 8H, CH_2)$_4$), 3.36 (t, 2H, *J* = 7.4 Hz, CH_2Br), 3.65 (t, 2H, *J* = 6.8 Hz, CH_2N), 7.69 (dd, 2H, *J* = 3.2 Hz, Ar-*H*), 7.81 (dd, 2H, *J* = 3.2 Hz, Ar-*H*); ^{13}C-NMR ($CDCl_3$): δ 26.1 / 27.8 / 28.5 ((*C*H$_2$)$_3$); 32.7 (*C*H$_2$Br); 33.8 (*C*H$_2$CH$_2$Br); 37.9 (*C*H$_2$N); 123.3 / 132.2 / 134.0 (*Ph*); 168.5 (*C*=O); IR (KBr): ν (cm^{-1}) = 1770 (C=O, s), 1718 (C=O, a); GC-MS: Calcd. for $C_{14}H_{16}BrNO_2$: 310.19. Found 309 (^{79}Br), 311 (^{81}Br).

Synthesis of 2-NH_2

A mixture of 18-crown-6 (0.34 g, 1.3 mmol), finely ground potassium carbonate (0.6 g, 5.3 mmol), 4'-cyano-4-hydroxybipenyl (1.0 g, 5.12 mmol) and 6-bromohexylphtalimide (1.6 g, 5.16 mmol) in acetone (10 ml) was stirred vigorously and heated under reflux overnight. The mixture was filtered, concentrated *in vacuo* and recrystallised from EtOH yielding **2**-NPht as a white solid (1.54 g, 70%). ^{1}H-NMR ($CDCl_3$): δ 1.40-1.90 (m, 8H, (CH_2)$_4$), 3.72 (t, 2H, *J* = 6.8 Hz, CH_2N), 4.01 (t, 2H, *J* = 7.4 Hz, CH_2O), 7.00 (d, *J* = 8.8 Hz, 8 H, *H*-3'), 7.53 (d, *J* = 8.8 Hz, 8 H, *H*-2'), 7.65 (d, *J* = 8.7 Hz, 8 H, *H*-2), 7.70 (d, *J* = 8.4 Hz, 8 H, H-3), 7.73 / 7.86 (m, 4H, Ar-*H*); ^{13}C-NMR ($CDCl_3$): δ 25.7 / 26.6 / 28.6 / 29.1 (*C*H$_2$)$_4$; 37.9 (*C*H$_2$NPht), 68.0 (O*C*H$_2$CH$_2$), 110.1 (*C*-4'), 115.2 (*C*-3), 119.2 (*C*N), 123.3 / 132.2 / 134.0 (*Ph*), 127.1 (*C*-2'), 128.4 (*C*-2), 131.3 (*C*-1), 132.7 (*C*-3'), 145.3 (*C*-1'), 159.8 (*C*-4), 168.5 (*C*=O); IR (KBr): ν (cm^{-1}) = 1773 (C=O, s), 1718 (C=O, a); Anal. calcd. for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.69; N, 6.60. Found: C, 76.30; H, 5.80; N, 6.57. A solution of **2**-NPht (9.68 g; 22.8 mmol) was dissolved in ethanol (200 ml) and stirred. Then hydrazine monohydrate (29 ml) was added and the reaction is heated to 50 °C. A white precipitate forms and after stirring for 4 h at 50 °C heating was stopped. The reaction mixture was stirred for an additional 16 h at room temperature and evaporated *in vacuo* to yield the crude product. Subsequently, the product was stirred in diluted NaOH (1M, 400 ml), filtered and washed with NaOH (1M, 800 ml) and with demineralized water till the filtrate became neutral. The product was redissolved in chloroform and filtered to remove insoluble compounds. After evaporation *in vacuo*, **2**-NH_2 was obtained as a pure product. M.p. 65-67 °C. ^{1}H-NMR ($CDCl_3$): δ 1.05 (s, 2H, NH_2), 1.37-1.55 (m, 6H, (CH_2)$_3$), 1.70 (q, 2H, OCH$_2$CH_2), 2.85 (t, 2H, *J* = 6.9 Hz, CH_2NH$_2$), 4.00 (t, 2H, *J* = 6.40, OCH_2), 6.99 (d, *J* = 8.8 Hz, 8 H, *H*-3'), 7.50 (d, *J* = 8.8 Hz, 8 H, *H*-2'), 7.63 (d, *J* = 8.7 Hz, 8 H, *H*-2), 7.68 (d, *J* = 8.4 Hz, 8 H, *H*-3); ^{13}C-NMR ($CDCl_3$): δ 26.3 / 27.0 / 29.6 (*C*H$_2$)$_3$, 34.1 (*C*H$_2$CH$_2$NH$_2$), 42.5 (*C*H$_2$NH$_2$), 68.3 (OCH_2), 110.2 (*C*-4'), 115.2 (*C*-3), 119.3 (*C*N), 127.2 (*C*-2'), 128.5 (*C*-2), 131.4 (*C*-1), 132.7 (*C*-3'), 145.4 (*C*-1'), 159.8 (*C*-4); IR (KBr): ν (cm^{-1}) = 2221.0 (C≡N); Anal. calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 76.85; H, 7.51; N, 9.48; GC-MS: Calcd. for $C_{19}H_{22}N_2O$: 294.39. Found 294.

Synthesis of 2-OH

Di-*tert*-butyltricarbonate (0.933 g; 3.55 mmol;) was dissolved in chloroform (50ml) while keeping the setup under a nitrogen atmosphere. A solution of **2**-NH_2 in chloroform (1.0 g; 3.39 mmol in 20 ml) was slowly added over a period of 5 minutes by using a pasteur pipette, and subsequently nitrogen gas was bubbled through the solution. After stirring the solution for 40 minutes at room temperature, dry pyridine (three drops from a pasteur pipette) was added and stirring continued for another 25 minutes, followed by the addition of ethanolamine (0.25 g; 4.09 mmol;) in chloroform (4 ml). Stirring was continued for 6 hours and the turbid reaction mixture was evaporated *in vacuo*, yielding the crude product (1.30 g). The product was dissolved in refluxing chloroform (40 ml), filtered, and the filtrate evaporated *in vacuo*. Then the product was dissolved in refluxing chloroform (20 ml) and allowed to cool down to room temperature. After filtration of the precipitate, washing with ice-cold chloroform (7 ml) and drying at 40 °C under reduced pressure, **2**-OH was obtained as a white powder (1.04 g; 80 %). M.p. 131-132 °C. ^{1}H-NMR (DMSO-d_6): δ 1.25-1.45 / 1.70

(m, 8H, (CH_2)$_4$), 2.95 (m, 2H, NCH_2CH$_2$OH), 3.03 (m, 2H, CH_2NHCONHCH$_2$CH$_2$OH), 4.00 (t, 2H, *J* = 6.4 Hz, OCH_2), 4.65 (t, 1H, *J* = 5.2 Hz, O*H*), 5.80 (t, 1H, NHCON*H*CH$_2$CH$_2$OH), 5.95 (t, 1H, N*H*CONHCH$_2$CH$_2$OH), 7.00 (d, 2H, *J* = 8.4 Hz, *H*-3), 7.68 (d, 2H, *J* = 8.4 Hz, *H*-2), 7.82 (d, 4H, *H*-3' + *H*-2'); ^{13}C-NMR (DMSO-d$_6$): δ 25.8 / 26.7 / 29.6 / 30.5 (*C*H$_2$)$_4$; 39.7 (*C*H$_2$NHCONH), 42.6 (NHCONH*C*H$_2$COOCH$_3$); 61.3 (*C*H$_2$OH), 68.0 (O*C*H$_2$), 119.4 (*C*-4'), 115.4 (*C*-3), 119.3 (*C*N), 127.1 (*C*-2'), 128.6 (*C*-2), 130.5 (*C*-1), 133.1 (*C*-3'), 144.5 (*C*-1'), 158.5 (*C*=O), 159.8 (*C*-4); IR (KBr): ν (cm^{-1}) = 3524 (O–H), 3337 (N–H), 2226.0 (C≡N), 1612 (amide I), 1571 (amide II); Anal. calcd. for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.07; H, 7.09; N, 10.90; GC-MS Calcd. 381.47. Found 381.

Synthesis of 2-COOCH$_3$

A solution of **2**-NH$_2$ (2.0 g; 6.79 mmol) in chloroform (16 ml) was slowly added to solution of di-tert-butylcarbonate (1.87 g; 7.13 mmol; 1.05 eq) in chloroform (100ml). After stirring for 50 minutes at room temperature, a solution of triethylamine (1.37 g; 13.5 mmol) in chloroform (2 ml) and stirring was continued for another 40 minutes. Then a small excess of glycine methylester hydrochloride (0.937 g; 7.46 mmol; 1.1 eq) was added and the reaction was monitored by IR. After 45 minutes no isocyanate peak could be detected and the reaction mixture was evaporated *in vacuo*. The residue was dissolved in chloroform (100 ml) and washed with 0.1 M hydrochloric acid solution, followed by neutralization with water (2 times, 100 ml). The chloroform solution was evaporated in vacuo to yield crude 2-COOCH$_3$. All product was redissolved in 30 ml hot chloroform and allowed to cool down to room temperature. The precipitate was filtered, washed with ice-cold chloroform and dried under reduced pressure to yield pure **2**-COOCH$_3$ (2.03 g, 73%) as a white powder. M.p. 153-155°C. A diluted sample could be analyzed in CDCl$_3$. ^{1}H-NMR (CDCl$_3$): δ 1.38-1.57 (m, 6H, (CH_2)$_3$), 1.80 (q, 2H, OCH$_2$CH_2), 3.20 (q, 2H, *J* = 6.3 Hz, CH_2NHCONH), 3.99 (s, 2H, NHCH_2COOCH$_3$), 4.00 (s, COOCH_3), 4.77 (s, 1H, NHCON*H*CH$_2$COOCH$_3$), 5.04 (s, 1H, N*H*CONHCH$_2$COOCH$_3$), 6.97 (d, *J* = 8.8 Hz, 2H, *H*-3'), 7.50 (d, *J* = 8.7 Hz, 2H, *H*-2'), 7.62 (d, *J* = 8.7 Hz, 2H, *H*-2), 7.65 (d, *J* = 8.6 Hz, 2H, *H*-3); ^{13}C-NMR (CDCl$_3$): δ 26.3 / 27.0 / 29.6 / 30.5 (*C*H$_2$)$_4$; 40.9 (*C*H$_2$NHCONH), 42.5 (NHCONH*C*H$_2$COOCH$_3$); 52.4 (COO*C*H$_3$), 68.3 (O*C*H$_2$), 110.3 (*C*-4'), 115.3 (*C*-3), 119.1 (*C*N), 127.2 (*C*-2'), 128.4 (*C*-2), 131.5 (*C*-1), 132.6 (*C*-3'),145.4 (*C*-1'), 159.8 (*C*-4), 171.7 (*C*OOCH$_3$); IR (KBr): ν (cm^{-1}) = 3333 (N–H), 2937 (C–H), 2219 (C≡N), 1743.1 (amide I), 1579 (amide II); Anal. calcd. for $C_{23}H_{27}N_3O_4$: C, 67.45; H, 6.65; N, 10.26. Found: C, 67.22; H, 6.65; N, 10.10. GC-MS Calcd. 409.48. Found 409.

Synthesis of 2-COOH

A solution of **2**-COOCH$_3$ (1.44 g; 3.52 mmol) and LiOH·H$_2$O (1.0 g; 24.6 mmol) in a THF/H$_2$O mixture (50ml; 1:1 v/v) was stirred for 19 h at room temperature. Subsequently, THF was removed by evaporation *in vacuo*. The suspension was acidified with 50 ml hydrochloric acid (1 M) and the precipitate was filtered (glass filter funnel with suction). Additionally, the residue was washed with 40 ml and consequently with water. Drying under reduced pressure yielded pure **2**-COOH (1.29, 92.6%) M.p. 125-126 °C. ^{1}H-NMR (DMSO-d$_6$): δ 1.25-1.45 (m, 6H, (CH_2)$_3$), 1.70 (q, 2H, OCH$_2$CH_2), 2.96 (t, 2H, *J* = 6.3 Hz, CH_2NHCONH), 3.66 (s, 2H, NHCH_2COOH), 4.00 (t, 2H, 6.28 Hz, CH_2O), 6.01 (s, 1H, NHCON*H*CH$_2$COOH), 6.11 (s, 1H, N*H*CONHCH$_2$COOH); 7.03 (d, *J* = 8.0 Hz, 2H, *H*-3'), 7.67 (d, *J* = 7.9 Hz, 2H, *H*-2'), 7.81 (d, *J* = 8.6 Hz, 2H, *H*-2), 7.85 (d, *J* = 8.6 Hz, 2H, *H*-3); ^{13}C-NMR (DMSO-d$_6$): δ 25.5 / 26.4 / 28.9 / 30.2 (*C*H$_2$)$_4$; 39.1 (*C*H$_2$NHCONH), 41.7 (NHCONH*C*H$_2$COOH); 67.8 (O*C*H$_2$), 109.3 (*C*-4'), 115.3 (*C*-3), 119.2 (*C*N), 127.0 (*C*-2'), 128.5 (*C*-2), 130.5 (*C*-1), 133.0 (*C*-3'), 144.5 (*C*-1'), 158.2 (*C*=O), 159.8 (*C*-4), 172.8 (*C*OOH); IR (KBr): ν (cm^{-1}) = 3318 (N–H), 2932 (C–H), 2235.1 (C≡N), 1696 (amide I), 1624 (amide I), 1582 (amide II); Anal. calcd. for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.65; H, 6.32; N, 10.45; GC-MS Calcd. 395.45. Found 377 (M-H$_2$O).

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Summary

In this thesis the functionalization, characterization and application of poly(propylene imine) dendrimers is described. Dendrimers are well-defined, highly branched macromolecules that emanate from a central core. The branching points of poly(propylene imine) dendrimers can be used as sites for molecular recognition, whereas the endgroups are ideal synthetic handles for modification (Figure 1). The high local concentration of functional sites, the chemical monodispersity and their 'commercial' availability are the motivation for using the poly(propylene imine) dendrimers in this thesis. Attention is focussed on an understanding of the unique features of the dendritic skeleton, in particular with respect to their role in host-guest chemistry and self-assembly in liquid crystalline media.

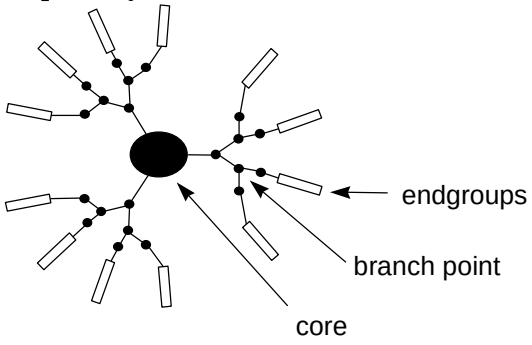


Figure 1: *General representation of a functionalized dendritic structure.*

First, three routes towards endgroup-modification of the poly(propylene imine) skeleton have been discussed and it is shown that such modification proceeds in high yield (Chapter 2). This gives the chemist an ideal control over the incorporation of special functions at the periphery. Furthermore, two characteristic interactions of endgroup-functionalized poly(propylene imine) dendrimers have been unraveled in Chapter 3, *i.e.* electrostatic interactions of the interior tertiary amines with inorganic acids and hydrogen-bonding interactions between the endgroup-linkages consisting of amides or ureas.

Dendrimers with an apolar periphery are used as efficient, selective and reversible extractants of anionic solutes from water into an organic phase (Chapter 4). The interactions, that are based on electrostatic interactions between host and solute are superior for the dendritic extractants in comparision with their low-molecular weight analogues. Here, the three-dimensional dendritic skeleton displays promising features like a high local concentration of sites and a micro-environment that reduces solvent-effects. These promising properties motivated the application of dendritic extractants in

supercritical CO_2-extractions, an 'environmentally friendly' technique and the MPPE-technology, a commercial water-purification technique.

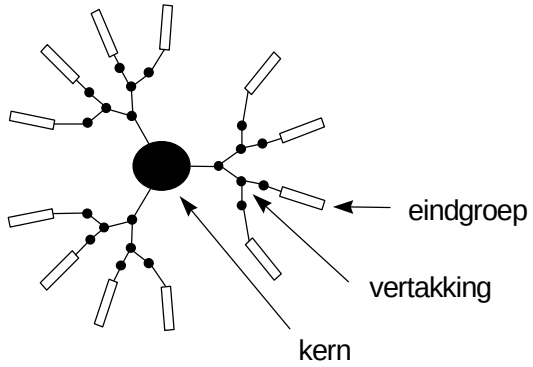
The knowledge gathered in the previous chapters, has been applied in the development of a water-soluble oligoethyleneoxy-based dendritic host and interactions have been studied with anionic guests using SAXS measurements and UV/vis titrations (Chapter 5). These experiments indicate that unique interactions lead to a specific location of the guests in the core of the dendrimers. Such water-soluble host-guest systems might be applied in 'controlled release' of pharmaceuticals.

Self-assembly of dendritic molecules is illustrated in Chapter 6 and 7. First, poly(propylene imine) dendrimers are modified with mesogenic endgroups and their properties characterized. All dendrimers show liquid crystalline behavior and organize into lamellar S_A-mesophases, which indicates that the dendritic interior is able to adopt a pancake-like structure. These liquid crystalline dendrimers and comparable analogues without mesogenic endgroups have been applied in the development of an electro-optical switch that is based on light scattering. Especially in case of dendrimers without mesogenic endgroups unprecedented small switching voltages are observed, even when compared to 'state of the art' systems using the same scattering-principle; however, the contrast between on- and off-state is rather small. The development of 'light-scattering'-based electro-optical switches is relatively new and these studies represent the first example on the use of (liquid crystalline) dendrimers in such systems.

Finally, Chapter 8 discusses a regio-selective complexation of guests at the dendritic periphery by the development of a dendritic host-guest motif that uses a combination of electrostatic and hydrogen-bonding interactions. The bis(propylurea)amine pincer shows a strong complexation with guests that are equipped with a carboxylic acid and a urea-moiety. This host-guest motif enables a new, fast and selective method for endgroup-modification through secondary interactions that might be applied to dendritic catalysts and combinatorial chemistry. Moreover, this chapter stresses that the presented host-guest motif could only be designed based on the understanding of characteristic interactions of the dendritic skeleton; such a rationalization was the main focus of several chapters in this thesis.

Samenvatting

In dit proefschrift worden de functionalizering, karakterisering en toepassing van poly(propylene imine) dendrimeren beschreven. Dendrimeren zijn goed gedefinieerde, boomvormig vertakte macromoleculen, die gesynthetiseerd worden vanuit een kern. De vertakkingspunten kunnen gebruikt worden voor moleculaire herkenning, terwijl de eindgroepen een ideaal synthetische 'handvat' vormen voor modificatie met de gewenste groepen. (Figuur 1). De hoge locale concentratie functionele groepen, het monodisperse karakter van dendrimeren en hun commerciële beschikbaarheid vormen de belangrijkste beweegredenen om poly(propylene imine) dendrimeren te gebruiken in het in dit proefschrift beschreven onderzoek. Aandacht is besteed aan het begrijpen van de unieke eigenschappen van het dendrimere skelet, in het bijzonder met betrekking tot hun rol in host-guest chemie en zelf-organisatie in vloeibaar kristallijne media



Figuur 1: *Algemene weergave van een gefunctionaliseerd dendrimeer.*

Allereerst zijn er drie mogelijkheden naar eindgroep-modificatie van het poly(propylene imine) dendrimeer onderzocht en het is aangetoond dat zulke modificaties in hoge opbrengsten verlopen (Hoofsdtuk 2). Dit stelt de chemicus in staat om iedere gewenste functionaliteit aan het dendrimeer te introduceren. Bovendien, zijn in Hoofdstuk 3 twee karakeristieke interacties van gefunctionaliseerde poly(propylene imine) dendrimeren in kaart gebracht, de electrostatische interacties van tertiare amines in het dendrimere interieur met anorganische zuren en waterstofbruginteracties tussen de amide- en ureum-bindingen naast de eindgroepen.

Dendrimeren met een apolaire periferie worden in Hoofdstuk 4 gebruikt als efficiente, selectieve en reversibele extractiemiddelen voor anionische moleculen vanuit water in een organische fase. De electrostatische interacties, die bij deze extractie een rol spelen, zijn superieur voor de dendritische extractanten in vergelijking met laag-moleculaire analoga. Hier spreidt het drie-dimensionale dendritische skelet veelbelovende eigenschappen ten toon, zoals een hoge locale concentratie van herkenningsplaatsen alsmede de aanwezigheid van een dendritisch micro-milieu dat

oplosmiddel-effecten sterk vermindert. Deze veelbelovende eigenschappen motiveerden de toepassing van de dendritische extractanten in superkritische CO_2-extractie, een milieu-vriendelijke techniek en de MPPE-technologie, een commerciele water-zuiverings proces.

De kennis die in de eerdere hoofdstukken is opgedaan heeft geleid tot de ontwikkeling van een water-oplosbaar dendrimeer, dat als host wordt onderzocht voor anionische gasten (Hoofdstuk 5). De gastmoleculen door unieke interacties met het dendrimeer bevinden zich bij voorkeur in de kern van het dendrimeer, zoals bewezen is met een combinatie van SAXS-metingen en UV/vis titraties. Zulke water-oplosbare systemen kunnen in principe gebruikt worden voor 'gecontroleerde afgifte' van geneesmiddelen.

Zelf-organisatie van het dendrimeer is het onderwerp van Hoofdstuk 6 en 7. Allereerst worden poly(propylene imine) dendrimeren gemodificeerd met mesogene eindgroepen een hun eigenschappen gekarakteriseerd. Alle dendrimeren zijn vloeibaar kristallijn en organiseren in een lamelaire S_A-mesophase, wat aangeeft dat het dendrimere interieur vervormt tot een pannekoek-achtige structuur. Deze vloeibare kristallijne dendrimeren en andere niet-vloeibaar kristallijne dendrimeren zijn toegepast in de ontwikkeling van een electro-optische schakelaar die gebaseerd is op licht-verstrooiing. In het bijzonder voor dendrimeren zonder mesogene eindgroepen worden lage schakel-voltages waargenomen, zelfs wanneer de schakelaar wordt vergeleken met 'state of the art' systemen; echter er dient wel opgemerkt te worden dat het contrast tussen transparente en verstrooiende toestand van de schakelaar nogal klein is en nog verbeterd dient te worden. Deze 'op licht-verstrooiing gebaseerde electro-optische schakelaars zijn relatief nieuw en dit onderzoek is het eerste voorbeeld van het gebruik van (vloeibaar kristallijne) dendrimeren in dit soort systemen tot dusver.

Tot slot wordt in Hoofdstuk 8 een selectieve complexering van gasten aan de buitenkant van het dendrimeer beschreven, dat gebruik maakt van een host-guest motief door middel van een combinatie van electrostatische en waterstofbruginteracties. De in het dendrimeer aanwezige bis(propylurea)amine pincer laat een sterke complexatie zien met gasten die bestaan uit een carbonzuur en een ureum-groep. Dit motief kan gebruikt worden als nieuwe, snelle en selectieve methode voor eindgroep-modificatie van het dendrimeer, op basis van secundaire interacties met toepassingen als dendritische katalysatoren en combinatoriele chemie in het vooruitzicht. Bovendien, toont het onderzoek in dit hoofdstuk aan dat het beschreven motief slechts door een volledig begrip van karakteristieke interacties in dendrimeren ontwikkeld kon worden; het waren juist deze interacties die de hoofdrol vertolkten in vele hoofdstukken in dit proefschrift.

Curriculum Vitae

Maurice Baars werd geboren op 11 september 1972 te Sittard. Na een gymnasium-β opleiding aan het Bisschoppelijk College Schöndeln te Roermond in 1990 met goed gevolg doorlopen te hebben, behaalde hij in dat zelfde jaar de tweede plaats in de Nationale Chemie Olympiade en was een van de vier Nederlandse afgevaardigden voor de Internationale Chemie Olympiade te Parijs. Tevens werd een aanvang gemaakt met de studie Scheikundige Technologie aan de Technische Universiteit Eindhoven alwaar in 1991 het propadeutisch examen behaald werd. Het afsluitend examen werd in juni 1995 met cum laude resultaat afgelegd, met als afstudeeronderzoek "Large scale synthesis of superamphiphiles in de vakgroep Macromoleculaire en Organische Chemie van de Technische Universiteit Eindhoven van Prof. dr. E. W. Meijer. Vanaf oktober 1995 tot oktober 1999 was de auteur van dit proefschrift in dienst van de Nederlandse Organisatie voor Wetenschappelijk Onderzoek en werkte in dezelfde groep aan het in dit proefschrift beschreven onderzoek. Vanaf 1 januari 2000 is de schrijver werkzaam als Research Chemist voor DSM Resins te Zwolle.

Maurice Baars was born in Sittard, the Netherlands on September 11th, 1972. In 1990 he obtained his high school degree at the "Bisschoppelijk College Schöndeln" in Roermond, the Netherlands. In the same year he won the second prize in the National Chemistry Olympics and was one of the Dutch representatives for the International Chemistry Olympics in Paris (France). Furthermore, he started with the study of Chemical Engineering at the Eindhoven University of Technology, the Netherlands and graduated in June 1995. His major was obtained on the topic 'Large scale synthesis of superamphiphiles' in the Laboratory of Macromolecular and Organic Chemistry of Prof. dr. E. W. Meijer. The author of this thesis has been working for the Dutch Foundation for Scientific Research in the same group from October 1995 up to an including October 1999. The highlights of the research are described in this Thesis. The author has started as a Research Chemist at DSM Resins in Zwolle, the Netherlands at January 1st, 2000.

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Eindelijk, na 182 pagina's wetenschap materie is het dan tijd voor 'social talk'. De laatste 7 jaar van mijn leven heeft 'de Vakgroep Macromoleculaire Chemie' een onuitwisbare indruk in mijn geheugen achtergelaten, in het bijzonder de promotie-tijd. Bij deze wil mijn dank uiten aan de mensen die mij gedurende deze periode hebben bijgestaan.

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