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Perfectly Branched Polyamide Dendrons Based on 5-(2-Aminoethoxy)-Isophthalic Acid

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Abstract: Perfectly branched polyamide dendrons based on 5-(2-aminoethoxy)-isophthalic acid have been synthesized up to generation 4 following the convergent approach. This involved a repetitive reaction of 5-(2-t-butoxycarbamylethoxy)-isophthalic acid with the two fold excess of 5-(2-aminoethoxy-hydrochloride)-isophthalic acid dimethyl ester and its analogs of higher generation, respectively, using activation and protection methods from the peptide chemistry. The products were characterized via elemental analysis, different spectroscopic methods, gel permeation chromatograpy, and differential scanning calorimetry. © 1997 Elsevier Science Ltd.

INTRODUCTION

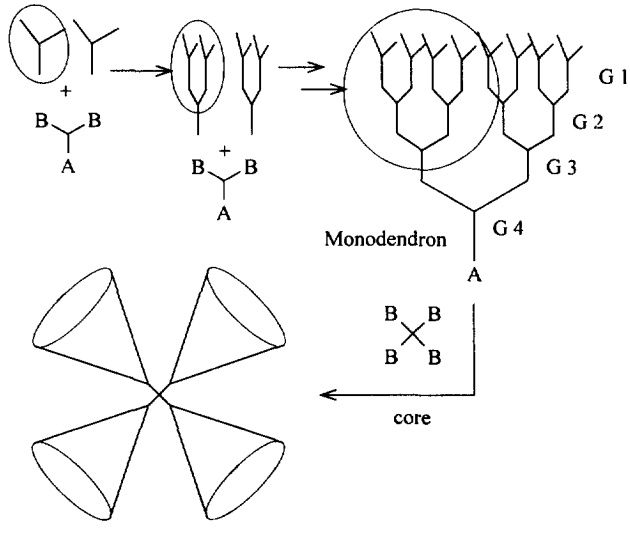
Dendrimers have become one of the most popular topics in polymer chemistry in the last years. The beauty of their perfectly branched structure in combination with unusual properties, such as high solubility, low viscosity, high functionality, and different reactivity compared to linear polymers attracts the interest of many research groups. Using the divergent (from the inside out) or the convergent (from the outside in) approach a very large number of different dendrimers[1] has been synthesized, including poly(amido amine)s[1], poly(ether amides)[2], poly-(ester amide)s[2], poly(amide)s[2-4], and poly(aramide)s[5-7]. One can state that the dendrimer synthesis is more closely related to modern organic chemistry than to macromolecular chemistry with all the requirements regarding high yield reactions, purification, and exact characterization. This is further supported by the fact that most of the defect free, unimolecular dendrimers are large organic molecules with molar masses below 5000 g/mol since a certain amount of defects and therefore a molar mass distribution can not be fully avoided in dendrimers of high generation. On the other hand, the repetitive use of identical building blocks in order to form large molecules is characteristic for a polymer synthesis. In addition, dendrimers can also be considered as model compounds for hyperbranched polymers, those highly but uncontrolled branched polymers which are synthesized in a one-pot synthesis from AB_x monomers[1,8]. Thus, the knowledge which can be gained from perfectly branched structures allows the better understanding of polymer properties which are related to any kind of branching.

The amide bond is of high interest in the dendrimer synthesis due to its chemical and thermal stability which reduces the danger of side reactions, but also due to the large amount of knowledge accumulated on the stepwise synthesis in peptide chemistry and regarding protective group strategies. Even solid-phase synthesis of dendritic polyamides has been attempted in analogy to the Merrifield approach[9]. In addition, the resemblance of polyamide dendrimers with biopolymers like peptides results in an increasing effort to apply these dendrimers in biochemistry or medicine[1,10,11]. Dendritic polyamides are also very interesting from the materials point of view. Linear polyamides are commonly available as materials with high modulus due to semicrystallinity or high glass transition temperatures (T_g). However, the semicrystallinity and the strong tendency to form hydrogen bonding cause also low solubility and high melt viscosity which limits the processing. A highly branched structure as in dendrimers, which usually leads to an amorphous materials with excellent solubility, might improve the processing of polyamides and therefore, can result in new applications for polyamides. Many of the already synthesized dendrimers

containing amide functions, however, are oily substances at room temperature. This is due to the absence of melt transitions in low T_g dendrimers based on aliphatic repeating units. Perfect dendrimers of low generation can exhibit melt transitions. E.g. a perfect aliphatic polyamide 12-cascade dendrimer[12] has been isolated from solution in a crystalline form which was lost after the first melt process. On the other hand, the synthesis of high generation dendrimers with high glass transition temperatures based on fully aromatic structural units seems to be problematic due to sterical hindrance in the early stage of dendrimer growth or incomplete reaction of aryl amines with aryl acid chlorides[5]. First results on highly branched polyaramides[13-15], however, give evidence that high molar masses can be achieved in combination with good solubility and T_g above room temperature.

Our goal is the synthesis of perfect dendrimers built up by amide formation without sterical crowding but with glass transition temperatures above room temperature. An additional requirement is the presence of reactive functional groups on the dendrimer surface which should allow further modification reactions. As mentioned above, two different routes are available for the synthesis of perfect dendrimers: the divergent and the convergent approach. The introduction of functionalities on the dendrimer surface is more easily obtained by the divergent approach where the synthesis is started at a central, multifunctional core and the dendritic structure is formed in generations around this core using building blocks with a branch site. However, this synthetic approach requires that from generation to generation a rapidly increasing number of functional groups reacts quantitatively. Conversion below 100% results in defects and therefore, extensive purification in order to remove molecules with a small number of defects from the perfect dendrimers is necessary to avoid that the defect is progressing.

In contrast to this, in the convergent synthesis of dendrimers only a low number of functional groups (4 in the case of AB_2 building block) has to react in each branching step (compare scheme 1) and therefore, purification of the product is facilitated. In order to avoid uncontrolled reaction of the AB_2 building blocks, selective protection - deprotection or activation - deactivation of the groups A and B, respectively, is necessary. This leads in general to functional groups on the surface of the dendrimer which are still protected and thus, have to be activated before further modification is possible. In addition, one obtains so called monodendrons with a focal functionality which can be combined to dendrimers in a subsequent reaction.



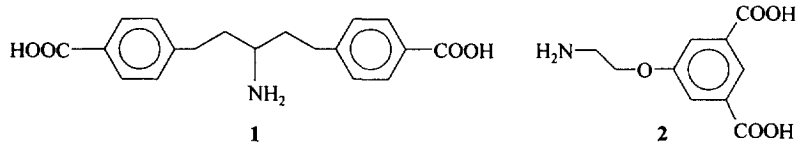
G 4 Dendrimer

Scheme 1

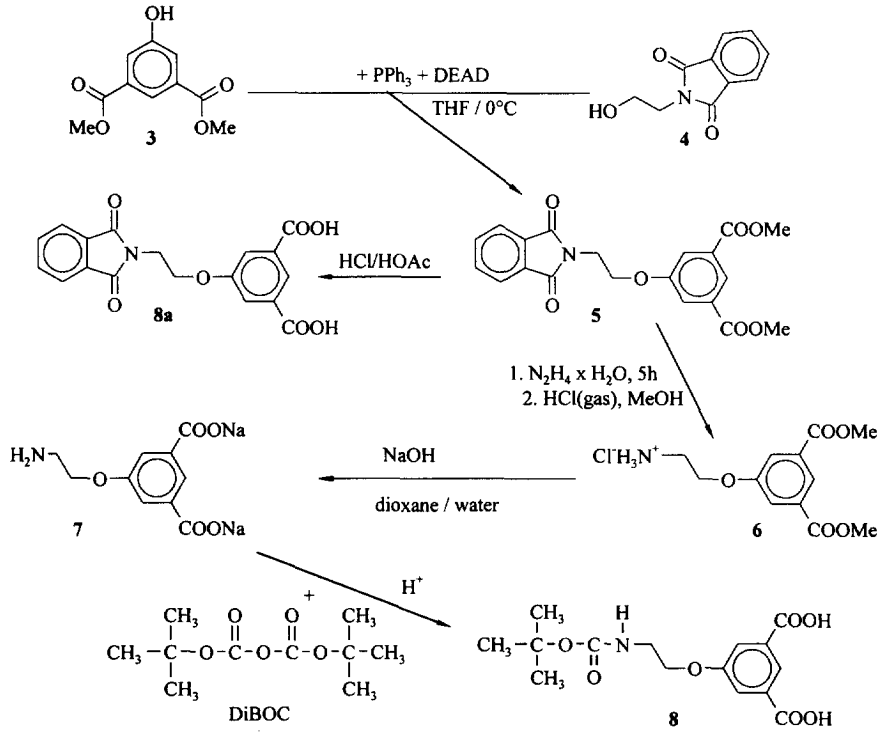
The design of a suitable AB_2 building block to achieve our goal by the convergent approach, the synthesis of polyamide monodendrons up to generation 4, and the characterization of these dendritic structures will be discussed in the following. The combination of several monodendrons towards dendrimers using a core molecule is still in progress.

RESULTS AND DISCUSSION

Dendritic polyamides with a glass transition temperature above room temperature but without sterical crowding should be achievable using an aromatic-aliphatic building block. The convergent approach requires AB_x monomers, e.g. a molecule with one amino function and two acid groups or vice a versa. First, we attempted to use 3-amino-1,5-bis-(4-carboxyphenyl)-pentane **1** (Scheme 2) which was synthesized starting from 4-formylmethylbenzoate, reaction with acetone, catalytic reduction of the carbonyl function and the double bonds[16], and subsequent conversion of the hydroxy group to an amine. However, low yields in the synthesis and problems to free the amine function in the last reaction step forced us to look for alternatives. 5-(2-Aminoethoxy)-isophthalic acid **2** was found to be more readily available.



Scheme 2



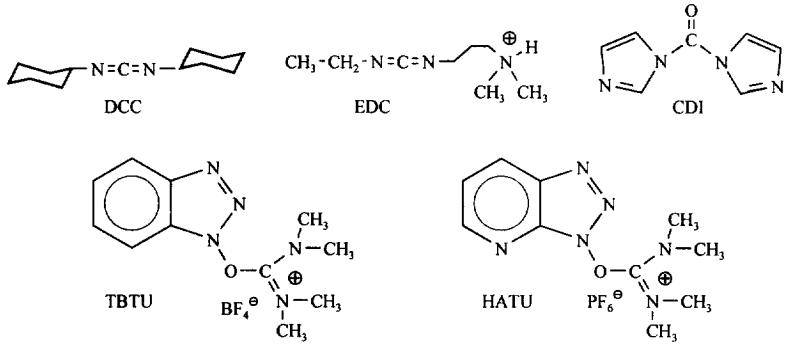
Scheme 3

The synthesis of **2** started from the commercially available 5-hydroxyisophthalic acid which was converted in the dimethyl ester **3**. In the meantime, ethanolamine was reacted with phthalimide at elevated temperature to

form hydroxyethyl phthalimide **4**. The dimethyl ester **3** was condensed with hydroxyethyl phthalimide **4** to **5** under Mitsunobu conditions[17] (Scheme 3). The Mitsunobu reaction proved to be the most efficient way to form the ether linkage. The phthalimide protected amine **5** could be purified easily by recrystallization from ethanol. The formation of dendrimer segments based on the building block **2** requires selective removal of the amine protecting group, e.g. the phthalimide group, without the loss of the methyl esters. This was achieved by treatment of **5** with hydrazine hydrate to yield the ammonium salt **6**.

On the other hand, it is necessary to selectively keep the amine function protected and free the acid groups. The reaction of the phthalimide protected amine **5** with hydrochloride acid and acetic acid under reflux led to the selective hydrolysis of the methyl esters (compound **8a**). However, during the dendrimer synthesis it has been found that the phthalimide group is not suitable as amine protection group since its removal was not quantitative at higher generations. Therefore, the compound **6,** which was purified by precipitation from methanol solution into diethyl ether, was further treated with sodium hydroxide in dioxane/water to yield the amine **7**. The intermediate **7** was then protected with DiBOC (Scheme 3). In the following, the resulting 5-(2-t-butoxycarbamylethoxy)-isophthalic acid (**8**) was generally used as amine protected $A'B_2$ building block in the dendrimer synthesis. In addition, the acid protected ammonium salts, e.g. **6,** were converted into the amines in DMF at 0 °C using triethylamine *in situ* before the coupling with diacid building block **8**.

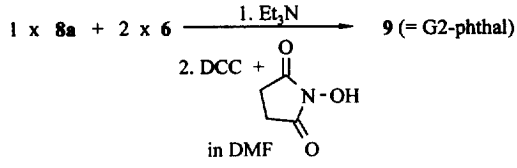
The coupling of amines with acids needs activation techniques in order to obtain high yields. Mild reaction conditions in combination with high yields are usually achieved with activation reagents[18,19] from the peptide chemistry, e.g. with dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), carbonyldiimidazole (CDI), or with uroniums salts such as O-(benzotriazole-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate (TBTU) or O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (HATU) (Scheme 4).



Scheme 4

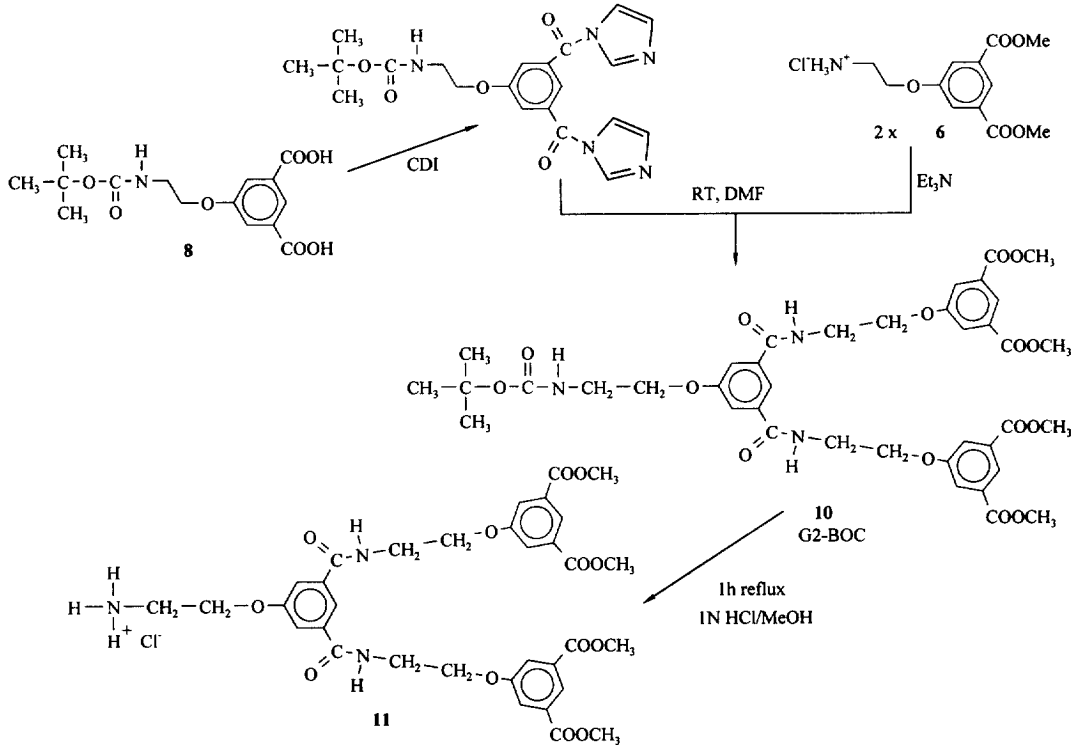
The components **8** or **8a** and **6** were now combined to form the monodendron of the next generation. In order to simplify the numbering, the original building block (**6** or better **6-BOC** which is obtained from **6** by treatment with DiBOC) is considered as monodendron of generation 1 and the first combination product will be called generation 2, being aware that different numbering systems are also used in the dendrimer literature[1].

The reaction conditions as well as the activation and the protecting techniques have been varied in order to find the optimum in yield and selectivity. The reaction of **8a** with **6** (excess) in DMF, using triethylamine for *in situ* conversion of the ammonium group into the amine and DCC and N-hydroxysuccinimide as coupling reagents yield G2-phthal **9** in 59% yield after purification of the product (Scheme 5).



Scheme 5

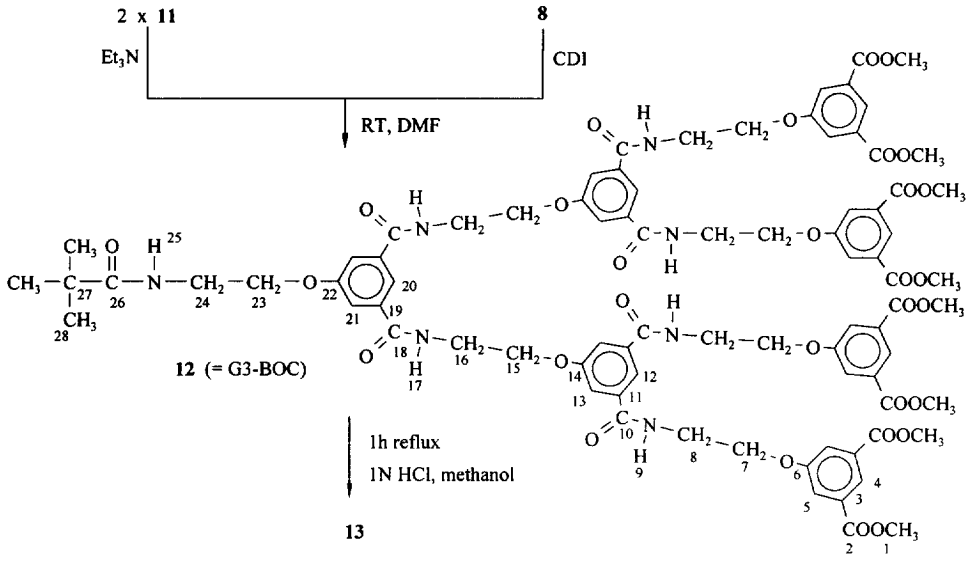
However, removal of the phthalimide protecting group in **9** without some loss of methyl esters was not possible. Therefore, in the next attempt the BOC-protected compound **8** was reacted with **6** (excess) to form the monodendron **10** (Scheme 6). EDC instead of DCC was added since the reagent was more easily removed from the reaction mixture and no additional activation with N-hydroxysuccinimide was necessary. G2-BOC (**10**) was obtained under these conditions in 59% yield. The reaction could be further improved to 81 % by using the activation via carbonyldiimidazole (CDI) where *in situ* the diimidazolide of the diacid **8** is formed as active intermediate (Scheme 6).



Scheme 6

The BOC protecting group in **10** was removed with 1 N HCl in methanol under 1 h reflux. The overall yield from **8** to the ammonium chloride **11** using CDI activation was 75 %. The compound **11** could be readily purified and was obtained as white crystals. Similarly, the CDI activation was used to synthesize G3-BOC from **11** (excess)

and **8** (Scheme 7). Again, DMF had to be used as solvent. The yields were with 79% after purification quite high, and the ammonium chloride G3-NH_3Cl (**13**) could be isolated as white powder.



Scheme 7

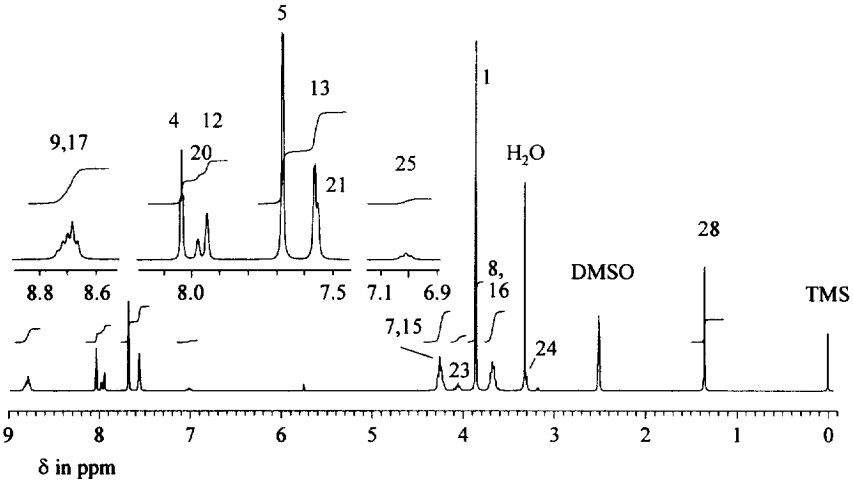


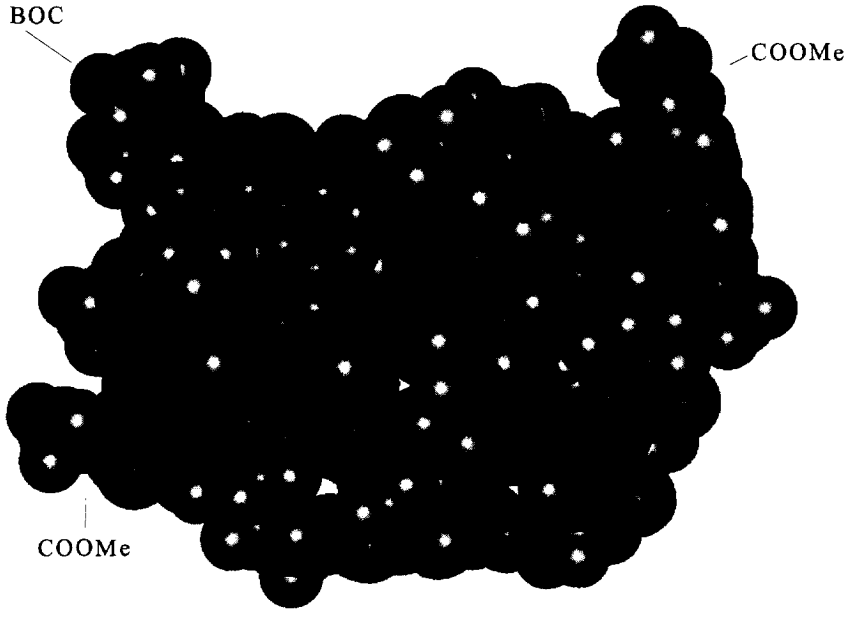
Fig. 1: ^{1}H NMR spectrum of **12** (G3-BOC) in DMSO-d_6 (assignment compare Scheme 7)

All the products up to generation 3 were characterized by FT-IR, ^{1}H and ^{13}C spectroscopy, elemental analysis and mass spectroscopy. The characterization proved the chemical structure as well as the purity. For the elemental analyses of the ammonium salts G2-NH_3Cl (**11**) and G3-NH_3Cl (**13**) one had to consider one respectively two moles of crystal water in order to obtain good agreement between the theoretical and the calculated values. FAB mass spectroscopy on G2-BOC (**10**) and G3-BOC (**12**) proved that there were only the molecules of the calculated molar masses present, and all signals in the NMR spectra could be clearly assigned to the corresponding protons and carbons. Fig. 1 shows the ^{1}H NMR spectrum of **12** in DMSO-d_6. It is very interesting to note that the signals of the aromatic protons 4, 20, and 12 (compare Scheme 7) can be clearly distinguished, however, their NMR shifts are differently as expected. The protons 4 in the outermost layer between the two methyl esters show a signal at 8.03 ppm, the signal of the protons 12 is shifted to 7.96 ppm, however, the signal of 20 is again at 7.99 ppm.

2 x **13** → **8**

Et_3N

DMF, 58 h ↓ HATU, RT



14 (= G4-BOC)

↓ 1h reflux
1N HCl, methanol

15

Scheme 8 (CPK model of **14**, molecular dynamics for 930 ps at 300 K)

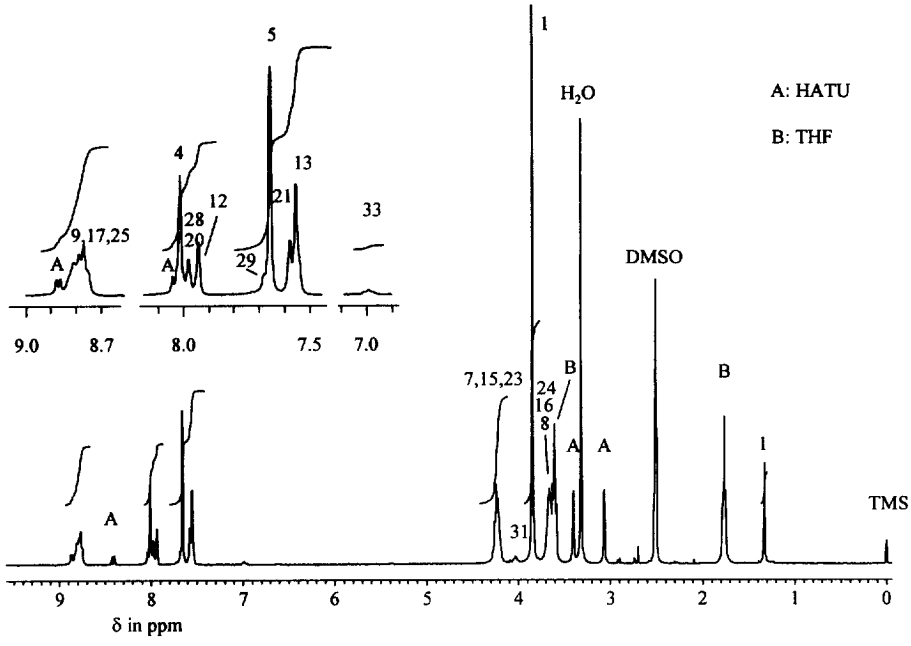


Fig. 2: ^{1}H NMR spectrum of **12** (G3-BOC) in DMSO-d_6 (assignment compare Exp. Part).

Unfortunately, the reaction conditions which had been used successfully for the synthesis of the G3 monodendron, had to be changed again for the next reaction step. The coupling of **13** with **8** using CDI did not result in pure G4-BOC monodendron (**14**). In the ^{1}H NMR spectrum of the product the integral of the signal related to the BOC function compared to that of the methyl esters was too low. Therefore, the uronium salts HATU and TBTU, which are known to work very well for the synthesis of sterical hindered peptides[19], were applied as activation agents. The use of HATU finally led to the successful synthesis of **14** (Scheme 8). The NMR analysis of the product proved the existence of the desired product, even though signals of the residual HATU and of THF, which was used as solvent during purification, could still be detected (Fig. 2). It was even still possible to distinguish in the proton NMR spectra of **14** the signals for the aromatic protons in different generations. Further purification of **14** via column chromatography, however, was not successful up to now. The dense, polar structure of **14** favors the inclusion of low molar mass compounds, e.g. solvent molecules. Even the formation of an adduct between the monodendron and the solvent molecules has to be discussed, since intensive drying of the product in order to clean the product at least from the solvent was also unsuccessful.

However, removal of the BOC protecting group and isolation of the ammonium salt **15**, which could be washed thoroughly with methanol, led to a clean product. In the ^{1}H NMR of **15**, the protons of the focal ammonium chloride group are found as a broad signal at 8.16 ppm whereas the signals of the amide NH protons of the different generations can be found at 8.83 ppm, 8.89 ppm, and 8.94 ppm (compare Experimental Part). Due to the loss of the BOC group in **15**, however, a comparison of the integrals of the signals for the ester function and the focal BOC function is no longer possible. With our equipment non-destructive FAB mass spectroscopy was not possible on this compound which has a theoretical molar mass of 3450 g/mol (**14**). Here, it will be necessary to use new techniques, e.g. MALDI-TOF mass spectroscopy, for the final proof of a defect free monodendron.

The molecular modeling of the G4-BOC (**14**, Scheme 8) gave indications that the structure is dense but not crowded. Especially it was found that the focal BOC unit is located on the surface of the molecule and therefore, further reaction of this function should be possible. This was confirmed experimentally since the BOC function was removed completely without any problems. However, one has to consider that the modeling is done in vacuum and therefore the structure of the molecule might be quite different in the realistic reaction medium.

The dendritic molecules were all fully soluble in organic solvents in high concentrations. However, their solubility behavior changed, as expected, with increasing molar mass. The compounds **8** and **10** are fully soluble in THF, methylene chloride, or ethyl acetate. G3-BOC (**12**) is no longer soluble in methylene chloride or ethyl acetate, and in THF only in dilute solutions. Solvents of high polarity, especially amidic solvents like dimethylformamide (DMF) or dimethylacetamide (DMAc) dissolve excellently the monodendrons of generation 3 and 4 which was expected due to the polyamide character of these dendritic structures.

Table 1: GPC[1] and DSC[2] Results for the Monodendrons G1 to G4

compound	$M_{theor.}$ in g/mol	$\bar{M}_n$ in g/mol	$\bar{M}_w/\bar{M}_n$	T_m in °C	T_g in °C
6-BOC[3] (G1-BOC)	353	463	1.00	82	-
10 (G2-BOC)	796	788	1.01	113	40
12 (G3-BOC)	1680	1370	1.02	111	96
14 (G4-BOC)	3450	2348	1.06	-	93
13 (G3-NH_3Cl)	1617	498	1.32	-[4]	-[4]
15 (G4-NH_3Cl)	3390	1252	1.31	-[4]	-[4]

[1] molar masses of **6-BOC**, **10**, **12**, and **14** determined in THF, polystyrene standards; molar masses of **13** and **15** determined in DMF, poly(ethyleneglycol)-poly(ethyleneoxide) standards

[2] heating rate 20K/min

[3] the amine function of compound **6** was protected using DiBOC in order to obtain a molecule which represents G1-BOC

[4] not measured

The monodendrons G1 to G4 were also characterized by Gel Permeation Chromatography (GPC) and by Differential Scanning Calorimetry (DSC). Fig. 3 shows the molar mass distributions of the monodendrons as they have been determined via GPC in THF as eluent. As one can see the molar mass distributions are small and monomodal and only the GPC trace of **14** seems to be somewhat broadened. For this measurement the sample **14** (G4-BOC) prepared via CDI activation has been used which was not 100% pure (the amount of **14** which was obtained using HATU was too small to carry out all characterization) and therefore, impurities or even a small amount of unreacted G3 might be the reason for the broadening of the GPC trace. It is also possible that the bad solubility of **14** in THF causes the broadening and therefore, it will be necessary to switch to an amidic solvent like DMF or DMAc. First GPC measurements in DMF on the ammonium salts **13** and **15** (prepared from the HATU sample) showed that the polyamide dendrons have a tendency to aggregate in this solvent (compare Table 1) which can be only avoided by the addition of salt as described by Kim[13]. In addition, the results in DMF are not comparable to those in THF due to strong differences in the polarity of the solvents and the use of GPC columns of different pore size. Therefore, GPC studies in DMF have to be done for all samples in order to be able to compare the results.

Table 1 summarizes the GPC and DSC results. As expected, the theoretical molar masses and the experimental values for $\overline{M}_n$ differ at higher molar masses, since a calibration of the GPC with linear polymer standards is not suitable for highly branched molecules.

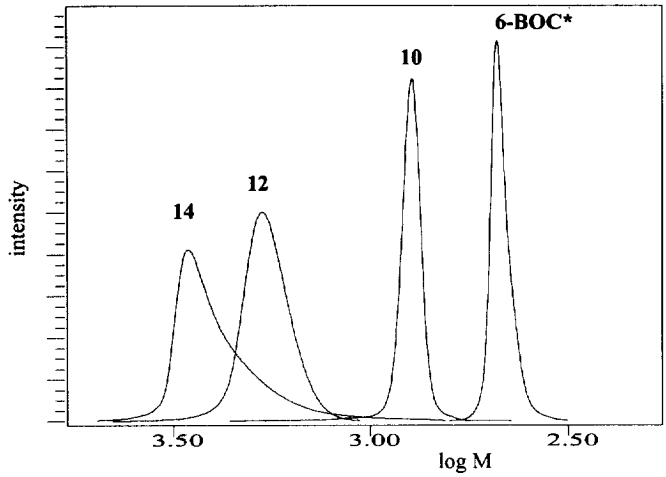


Fig. 3: Molar mass distributions determined by GPC in THF (polystyrene calibration) for G1 (**6-BOC**) to G4 (**14**) (* the amine function of compound **6** was protected using DiBOC in order to obtain a molecule which represents G1-BOC)

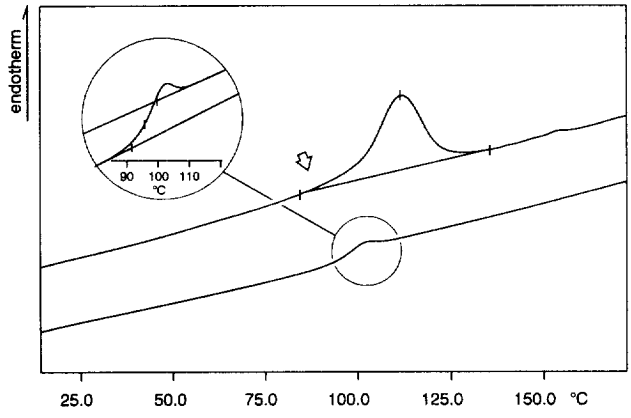


Fig. 4: DSC trace of **12** (G3-BOC), first (top) and second heating (arrow: T_g hidden under the melting endotherm in the first heating)

The DSC measurements revealed that these polyamide monodendrons can crystallize from solution up to generation 3 since a melting endotherm could be found for **6-BOC**, **10** and **12** at least in the first heating. For **12** it was not possible even by annealing to recrystallize the material after the first melting, similarly as it has been observed by Newkome and coworkers[12] for polyamide cascade dendrimers. This behavior is an indication that the crystallization might be dependent on interactions with the solvent. The highly branched structure does not favor

crystallization, and therefore, a glass transition was observed already at generation 2 (**10**) which was shifted to higher temperatures for larger molecules. Generation 4 (**14**) exhibited only a T_g at 93 °C and seemed to be fully amorphous, whereas for **10** and for **12** a glass transitions (T_g = 40 and 96 °C, respectively) were observed beside the melting endotherm at about 111 °C (Fig. 4). It is also surprising that the melting exotherm for **12** is that close to the glass transition. Therefore, more detailed studies of these thermal characteristics, especially of the partial crystallinity in **12** are necessary.

CONCLUSION

The results described here show that it is possible to develop a suitable synthetic procedure to aliphatic-aromatic polyamide monodendrons based on protection-deprotection techniques as used in the peptide chenmistry. The dendritic structures up to a molar mass of 3450 g/mol could be fully characterized and their ideal structure was proven. However, an intensive optimization of the reaction conditions was necessary in order to obtain perfect molecules of reasonable molar masses. First results on solubility and also molecular modeling experiments indicate that the synthetic scheme should be applicable to the synthesis of polyamide monodendrons of even higher generations. The reactivity of the focal functionality is reduced at higher generation but optimization of the reaction conditions and the use of very potent activation reagent should allow to overcome this problem. In addition, it was possible to develop rather simple purification methods which allow the synthesis of these dendritic molecules even on a larger scale.

As hoped, dendrimers with a glass transition temperature above room temperature result from the aliphatic-aromatic structure which was chosen for the building block. Furthermore, the monodendrons of low generation exhibit partial crystallinity with melting points in the range of 110 °C. Therefore, the concept to use aliphatic-aromatic structures in order to avoid sterical crowding but with the option to obtain structures which are interesting as models for hyperbranched polyamides based on a similar repeating units and with interesting material properties was successful.

The described monodendrons are now the base for future work on the synthesis of larger polyamide dendrimers, especially with the focus on the combination of several monodendrons to a multifunctional core molecule. The study of their material properties and their chemical reactivity should be an important contribution to the broad field of dendrimers.

EXPERIMENTAL PART

General

All solvents were rectified over a column filled with glass bearings before use and, when necessary (e.g for THF = tetrahydrofuran or DMF = dimethylformamide), were dried following standard procedures and stored over molecular sieves. The chemicals were used as received from Aldrich, Fluka and Merck in p.a. quality. 2-Hydroxyethyl phthalimide **4** was prepared from phthalic acid anhydride and ethanolamine according to the literature[20]. 5-Hydroxyisophthalic acid dimethyl ester **3** was prepared from 5-hydroxyisophthalic acid following standard esterification procedures[21].

A dendrimer nomenclature developed by Kahovec[22] based on the IUPAC polymer nomenclature has been used.

Instruments

The NMR spectra were recorded with a Bruker ARX 300 (^{1}H NMR: 300 MHz; ^{13}C NMR: 75.5 MHz). Two

GPC systems were used for the determination of the molar masses; eluent THF: Waters pump 510 (0.5 mL/min), UV detector 486, RI detector 410, Ultrastragel columns 7 μm (100 and 500 Å), calibration with polystyrene standards; eluent DMF: Knauer HPLC pump 64 (0.5 mL/min), Knauer UV and RI detectors, Waters Styragel HR5E column, calibration with poly(ethyleneglycol)-poly(ethyleneoxide) standards. The thermal analysis was carried out with a DSC7 from Perkin Elmer (20K/min) and the FT-IR spectra were recorded on a Bruker IFS 55 (KBr pellets). A MAT CH5 DF mass spectrometer with Iontech ion source (8 kV accellerating voltage) and xenon as carrier gas was used for the FAB mass spectra. The elemental analyses were done at the analytical laboratory of the Institute for Organic Chemistry of the Technische Universität München (H. Richter). Molecular modeling has been done using the program Insight II from Biosym Technologies, San Diego, CA, USA and a Iris Silicon Graphics computer.

Synthesis of 5-(2-phthalimidoethoxy)-isophthalic acid dimethyl ester (5)

At 0° C 34.8 g (0.2 mol) diethylazodicarboxylate were added over one hour to a suspension of 38.2 g (0.2 mol) 2-hydroxyethyl phthalimide (**4**), 44.2 g (0.21 mol) 5-hydroxyisophthalic acid dimethyl ester (**3**) and 52.5 g (0.2 mol) triphenyl phosphine in 300 mL THF. The mixture was stirred for 48 h at room temperature, the precipitated product was isolated by filtration, washed with cold THF and dried in vacuum. After removing the solvent from the filtrate by evaporation, additional product was isolated which had to be recrystallized from ethanol.

Yield: 68 g (88 % based on hydroxyethyl phthalimide)

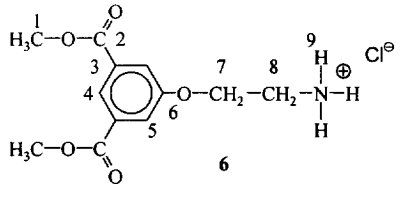
^{1}H NMR ($CDCl_3$), δ in ppm: 3.91 (s, 6H), 4.15 (t, 2H), 4.34 (t, 2H), 7.70 (s, 2H), 7.74 (m, 2H), 7.87 (m, 2H), 8.25 (s, 1H)

^{13}C NMR ($CDCl_3$), δ in ppm: 37.2, 52.4 (2C), 65.3, 119.9 (2C), 123.5 (3C), 131.9 (2C), 132.0 (2C), 134.1(2C), 158.4, 166.0 (2C), 168.1(2C)

Synthesis of 5-(2-aminoethoxy-hydrochloride)-isophthalic acid dimethyl ester (6)

19.2 g (0.05 mol) **5** and 3 g (0.06 mol) hydrazine hydrate (100%) were dissolved in 300 mL methanol, heated to reflux for 5h, and stirred for additional 19 h at room temperature. The intermediate was collected by filtration, washed with a small amount of cold methanol and dried (19.9 g, 0.048 mol). Then it was heated to reflux in 250 mL methanol with 2.7 g (0.075 mol) HCl (gas) for 5 h and kept an additional 19 h at room temperature. The mixture was filtered to remove the precipitated phthalylhydrazide, and the filtrate was reduced in volume until the product started to crystallize. The precipitation of the product was completed by pouring the concentrated methanol solution into 5 to 10 times volume diethyl ether. The product was collected by filtration, washed with diethyl ether until neutral, and dried in vacuum at room temperature.

Yield: 12.8 g (88 % based on **5**)



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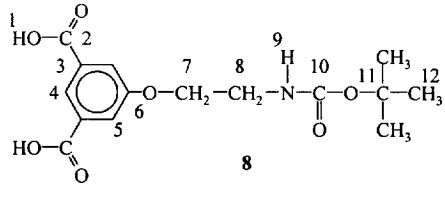


8

^{1}H NMR (DMSO-d_6), δ in ppm: 3.24 (m, 2H, 8), 3.91 (s, 6H, 1), 4.37 (t, 2H, 7), 7.74 (s, 2H, 5), 8.10 (s, 1H, 4), 8.50 (b, 3H, NH_3Cl, 9)

^{13}C NMR (DMSO-d_6), δ in ppm: 38.5 (8), 53.5 (2C, 1), 63.6 (7), 118.6 (2C, 5), 121.4 (4), 130.3 (2C, 3), 157.0 (6), 164.6 (2C, 2)

Synthesis of 5-(2-t-butoxycarbamylethoxy)-isophthalic acid (8)

14.5 g (0.050 mol) **6** were mixed with 10 g NaOH in 150 mL water and 50 mL dioxane and refluxed for 3 h. in order to form **7**. After cooling to room temperature 50 mmol HCl in 50 mL water and additional 350 mL dioxane were added to the reaction mixture. When the mixture became homogeneous upon further cooling to 0°C 12 g (0.055 mol) di-t-butylpyrocarbonate were added and it was stirred for 2 h at room temperature. The dioxane was evaporated almost completely in vacuum, the remaining aqueous mixture was cooled to 0°C, and acidified with approximately 0.2 mol aqueous $KHSO_4$. At pH 3 the product precipitated, was collected by filtration, washed neutral, recrystallized from ethyl acetate, and dried in vacuum at room temperature.

Yield: 14.6 g (90 % based on **6**, white crystals)

^{1}H NMR (DMSO-d_6), δ in ppm: 1.27 (s, 9H, 12), 3.22 (q, 2H, 8), 3.98 (s, 2H, 7), 6.91 (t, broad, 1H, 9), 7.54 (s, 2H, 5), 7.97 (s, 1H, 4), 13.13 (s, broad, 2H, 1)

^{13}C NMR (DMSO-d_6), δ in ppm: 29.0 (12), 40.2 (8), 68.0 (7), 78.6 (11), 120.1 (2C, 5), 123.2 (4), 133.4 (2C, 3), 156.5 (10), 159.4 (6), 167.2 (2C, 2)

Elemental analysis ($C_{15}H_{19}NO_7$, M = 325.32 g/mol)

calc.	C 55.38	H 5.89	N 4.31
found	C 55.12	H 6.09	N 4.50

Synthesis of 5-(2-t-butoxycarbamylethoxy)-isophthalic acid dimethyl ester (6-BOC)

The synthesis of **6-BOC** was carried out analogeous to that of **8**.

Yield: 9.1 g (71% (based on **6**)

^{1}H NMR ($CDCl_3$), δ in ppm (assignment compare **6** and **8**): 1.45 (s, 9H, 12), 3.57 (m, 2H, 8), 3.90 (s, 6H, 1), 4.11 (s, 2H, 7), 4.98 (b, 1H, 9), 7.74 (s, 2H, 5), 8.31 (s, 1H, 4)

^{13}C NMR ($CDCl_3$), δ in ppm: 28.7 (12), 40.8 (8), 52.8 (2C, 1) 68.2 (7), 77.6 (11), 120.2 (2C, 5), 123.7 (4), 132.2 (2C, 3), 159.0 (2C, 6,10), 166.4 (2C, 1)

Synthesis of 5-(2-phthalimidoethoxy)-isophthalic acid (8a)

15 g (0.039 mol) of **5** were heated to reflux for 3 h in 50 mL HCl conc. and 100 mL acetic acid (100%). After cooling the mixture was poured into 750 mL water. The product precipitated, was collected by filtration, washed neutral with water, and dried in vacuum at 50 °C.

Yield: 8.3 g (60 % based on **5**)

^{1}H NMR (DMSO-d_6), δ in ppm: 4.00 (t, 2H), 4.34 (t, 2H), 7.60 (s, 2H), 7.88 (m, 4H), 8.05 (s, 1H), 13.26 (b, 2H)

^{13}C NMR (DMSO-d_6), δ in ppm: 36.8, 65.3, 119.1 (2C), 122.5, 123.1 (2C), 131.5 (2C), 132.6 (2C), 134.4(2C), 157.2, 166.1 (2C), 167.7 (2C)

Synthesis of α-[5-(2-phthalimidoethoxy-(3,5-biscarbonylphenyl)]-ω-(tetra-oxymethyl)-poly[(iminoethoxy-(3,5-bis(carbonylphenyl))] = G2-phthal (9)

2.5 g (0.025 mol) triethylamine were added at 0°C to 6.0 g (0.021 mol) **6**, dissolved in 100 mL DMF. After addition of 3 g (0.0084 mol) **8a** and 5 g (0.043 mol) N-hydroxysuccinimide the mixture was cooled to -20 °C and 4.1 g (0.02 mol) dicyclohexylcarbodiimide (DCC) dissolved in 25 mL DMF were added. The mixture was stirred 12 h at -15 °C, and additional 7 h at room temperature. Then, 10 g silica gel 60 (40-63 μm) were added, the solvent removed in vacuum at 35 °C, and the product loaded silica gel was eluated in a column with hexane/ethyl acetate. The product was isolated from the eluate after evaporation of the solvent.

Yield: 4.1 g (59 % based on **8a**)

^{1}H NMR ($CDCl_3$), δ in ppm: 3.86 (q, 4H), 3.91 (s, 12H), 4.07 (m, 2H), 4.19 (t, 4H), 4.26 (t, 2H), 7.19 (t, 2H), 7.50 (s, 2H), 7.65 (s, 4H), 7.68 (m, 2H), 7.79 (m, 2H), 8.02 (s, 1H), 8.20 (s, 2H)
^{13}C NMR ($CDCl_3$), δ in ppm: 36.9 (2C), 39.7, 52.4 (4C), 65.2 (2C), 67.1, 116.7 (2C), 118.3, 119.7 (4C), 123.4 (4C), 131.8 (6C), 134.1(2C), 135.8 (2C), 158.5 (3C), 165.9 (4C), 166.9 (2C), 168.1 (2C)

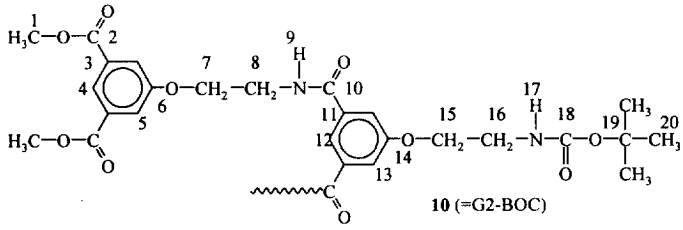
*Synthesis of α-[5-(2-t-butoxycarbamylethoxy)-(3,5-biscarbonylphenyl)]-ω-(tetra-oxymethyl)-poly[(iminoethoxy-(3,5-bis(carbonylphenyl))] = G2-BOC (**10**)*

EDC activation

Under inert atmosphere 7.25 g (0.025 mol) **6**, 250 mL dry methylene chloride, and 10 mL triethylamine were heated to reflux for 1 h until the mixture became homogeneous. After cooling to room temperature, 3.25 g (0.010 mol) **8** were added, and the mixture was cooled to - 20 °C before 5.75 g (0.03 mol) 1-ethyl-3-(3-dimethyl-aminopropyl)-carbodiimide (EDC) was also added. The mixture was stirred 1 h at -20 °C and 23 h at -10 °C before it was warmed to room temperature. The solvent volume was then reduced to 100 mL by rotary evaporation and the organic phase was washed with aqueous Na_2CO_3, water, diluted aqueous citric acid, and again with water. The organic phase was dried over Na_2SO_4, and the product was isolated from this phase after removal of the solvent.
Yield: 4.7 g (59 % based on **8**)

CDI activation

6.5 g (0.04 mol) carbonyldiimidazole (CDI) were added to 6.5 g (0.02 mol) **8**, dissolved in 50 mL dry DMF. In a separate flask 14.5 g (0.05 mol) **6**, suspended in 150 mL DMF and cooled to 0°C, were mixed with 7.6 g (0.075 mol) triethylamine. Both mixtures were stirred for 1 h at room temperature, then combined and kept at room temperature for 24 h under stirring. The purification procedure was similar as described above.
Yield: 12.9 g (81 % based on **8**)
$C_{39}H_{45}N_3O_{15}$, M = 795.79 g/mol; FAB-MS (in thioglycerin): 819 (M+ $Na^{\oplus}$), 740 (M - butene), 696 (M - BOC).



10 (=G2-BOC)

^{1}H NMR (DMSO-d_6), δ in ppm: 1.37 (s, 9H, 20), 3.65 (m, 4H, 8), 3.88 (s, 12H, 1), 4.05 (m, 2H, 15), 4.28 (m, 4H, 7), 7.02 (m, 1H, 17), 7.53 (s, 2H, 13), 7.71 (s, 4H, 5), 7.94 (s, 1H, 12), 8.08 (s, 2H, 4), 8.77 (t, 2H, 9) (signal 16 hidden under the H_2O signal at about 3.3 ppm)
^{13}C NMR (DMSO-d_6), δ in ppm: 29.0 (3C, 20), 39- 41 (3C, 8,16), 53.4 (4C, 1), 67.6 (2C, 7), 67.8 (15), 78.6 (19), 116.7 (2C, 13), 119.8 (12), 120.3 (4C, 5), 122.7 (2C, 4), 132.4 (4C, 3), 136.6 (2C, 11), 156.5 (18), 159.1 (14), 159.6 (2C, 6), 166.0 (6C, 2,10)

*Synthesis of α-[5-(2-aminoethoxy-hydrochloride)-(3,5-biscarbonylphenyl)]-ω-(tetra-oxymethyl)-poly[(iminoethoxy-(3,5-bis(carbonylphenyl))] = G2-NH$_3$Cl (**11**)*

12.9 g (0.016 mol) **10** were dissolved in 300 mL methanol which contained 11 g (0.3 mol) HCl_{gas} and refluxed for 2 h. The product precipitated, was collected by filtration, and washed neutral with diethyl ether.
Yield: 11.9 g (overall 75 % based on **8**)
^{1}H NMR (DMSO-d_6), δ in ppm (assignment compare **10**): 3.24 (t, 2H, 16), 3.69 (m, 4H, 8), 3.88 (s, 12H, 1), 4.28

(m, 6H, 15+7), 7.62 (s, 2H, 13), 7.71 (s, 4H, 5), 8.07 (s, 3H, 12,4), 8.17 (s, broad, 3H, NH_3Cl, 17), 8.92 (t, 2H, 9)

Elemental analysis ($C_{34}H_{38}ClN_3O_{13}$ x H_2O, M = 750.15 g/mol)

calc.	C	54.44	H	5.37	N 5.60
found	C	54.46	H	5.28	N 5.39

Synthesis of α-[5-(2-t-butoxycarbamylethoxy)-(3,5-biscarbonylphenyl)]-ω-(octa-oxymethyl)-poly[(iminoethoxy-(3,5-bis(carbonylphenyl))] = G3-BOC (12)

The synthesis of **12** was similar as described for **10** with CDI activation. Amounts: 2.4 g (7.5 mmol) **8** and 2.4 g (14.8 mmol) CDI in 20 mL dry DMF; 13.2 g (18 mmol) **11** in 230 mL DMF; 3.4 mL (25 mmol) triethylamine. The stirring at room temperature was extended to 48 h.

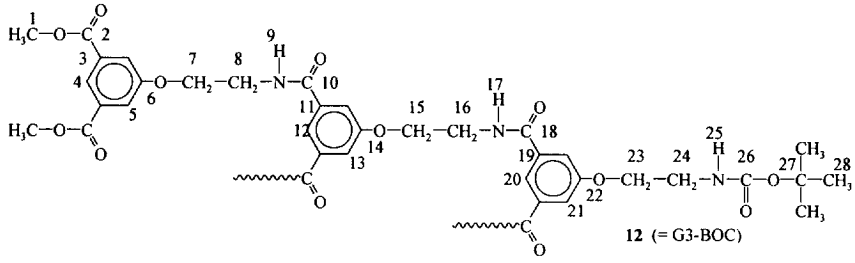
For purification the reaction mixture was reduced in volume to 50 mL and poured into 500 mL methanol. The precipitated product was collected by filtration, washed thoroughly with methanol, and dried.

Yield: 9.9 g (79 % based on **8**)

$C_{83}H_{89}N_7O_{31}$, M = 1681g/mol; FAB-MS (in 4-nitrobenzylalkohol): 1702 ($M+ Na^{\oplus}$), 1580 (M - BOC).

^1H NMR (DMSO-d_6), δ in ppm: 1.36 (s, 9H, 28), 3.68 (m, 12H, 8,16), 3.87 (s, 24H, 1), 4.06 (m, 2H, 23), 4.26 (m, 12H, 7,15), 7.02 (m, 1H, 25), 7.58 (m, 6H, 13,21), 7.68 (s, 8H, 5), 7.96 (s, 2H, 12), 7.99 (s, 1H, 20), 8.03 (s, 4H, 4), 8.78-8.83 (m, 6H, 9,17), (signal 24 partially hidden under the H_2O signal at about 3.3 ppm)

^{13}C NMR (DMSO-d_6), δ in ppm: 28.1 (3C, 28), 38- 42 (7C, 8,16,24), 52.4 (8C, 1), 66.4, 66.7, 66.9 (7C, 7,15,23), 77.7 (27), 115.8, 118.9, 119.3, 121.8 (21C, 4, 5, 12, 13,20,21), 131.4, 135.7 (14C, 3,11,19), 155.5 (26), 158.1, 158.6 (7C, 6,14,22), 165.0, 165.7 (14C, 2,10,26)



12 (= G3-BOC)

Synthesis of α-[5-(2-aminoethoxy-hydrochloride)-(3,5-biscarbonylphenyl)]-ω-(octa-oxymethyl)-poly-[(iminoethoxy-(3,5-bis(carbonylphenyl))] = G3-NH_3Cl (13)

The BOC group of **12** (5g, 3 mmol) leading to **13** was removed as described for **11** using 3.6 g HCl (gas) in 100 mL methanol.

Yield: 3.6 g (75 % based on **12**)

^1H NMR (DMSO-d_6), δ in ppm (assignment compare **12**): 3.25 (t, 2H, 16), 3.67 (m, 12H, 8,16), 3.86 (s, 24H, 1), 4.28 (m, 14H, 7,15,23), 7.58 (s, 4H, 13), 7.63 (s, 4H, 21), 7.68 (s, 8H, 5), 7.99 (s, 2H, 12) 8.04 (s, 4H, 4), 8.09 (s, 1H, 20), 8.14 (s, broad, 3H, NH_3Cl, 25), 8.84 (t, 4H, 9)

Elemental analysis ($C_{78}H_{82}ClN_7O_{29}$ x $2H_2O$, M = 1653.01 g/mol)

calc.	C	56.68	H	5.24	N 5.93
found	C	56.58	H	5.24	N 5.96

*Synthesis of α-[5-(2-t-butoxycarbamylethoxy)-(3,5-biscarbonylphenyl)]-ω-(hexadeca-oxymethyl)-poly[(iminoethoxy-(3,5-bis(carbonylphenyl))] = G4-BOC (**14**)*

CDI activation

189 mg (0.58 mmol) **8** and 186 mg (1.15 mmol) CDI were stirred in 10 mL DMF for 1 h at room temperature. At the same time a suspension of 2.81 g (1.74 mmol) **13** and 1 mL triethylamine in 10 mL dry DMF was stirred at 0 °C for 30 min. The suspension was warmed to room temperature, 80 mL DMF were added and the mixture was stirred again for 30 min. Then the two solutions were combined and stirred at room temperature for 48 h. The reaction volume was reduced to 30 mL below 35 °C and the concentrated solution was precipitated into 500 mL methanol. The white product was isolated by filtration, washed with methanol and dried.

Yield: 1.48 g (74% based on **8**, not pure)

HATU activation

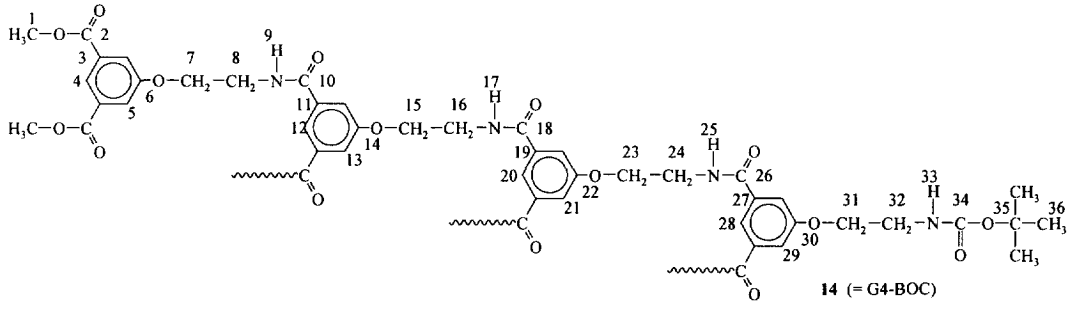
25 mL dry DMF, 438 mg (0.271 mmol) **13**, 0.7 mL triethylamine, 42.3 mg (0.130 mmol) **8** and 400 mg (1.2 mmol) HATU (= O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium-hexafluorophosphate) were combined and stirred for 48 h at room temperatures. The reaction mixture was then slowly poured into 250 mL methanol, the product was isolated by filtration, washed with methanol and dried.

Yield: 310 mg (70% based on **8**, contains impurities: DMF, HATU)

In order to purify the product, the reaction product was dissolved in 100 mL THF, heated to reflux for 2 h, hot filtered, the residue was washed with methanol and dried in high vacuum for 48 h.

Yield: 200 mg (45 % based on **8**, contains impurities: THF, HATU)

Further purification by chromatography was not successful up to now.



14 (= G4-BOC)

^{1}H NMR (DMSO-d_6), δ in ppm: 1.32 (s, 9H, 36), 3.3 (under the H_2O signal, 32), 3.66 (m, 28H, 8,16,24), 3.84 (s, 48H, 1), 4.03 (m, 2H, 31), 4.24 (m, 28H, 7,15,23), 6.99 (m, 1H, 33), 7.55 (m, 8H, 13), 7.58 (m, 4H, 21), 7.65 (m, 16H, 5), 7.68 (m, 2H, 29), 7.94, 7.98, 8.00 (m, 15H, 4,12,20,25), 8.77 (m, 14H, 9,17,25); in addition: 1.76, 3.58 (THF); 3.02, 3.4, 8.02, 8.41, 8.87 (HATU)

^{13}C NMR (DMSO-d_6), δ in ppm: 29.0 (3C, 36), 38- 52 (15C, 8,16,24,32), 53.3 (16C, 1), 67.3, 67.6, 67.8 (15C, 7,15,23,31), 78.6 (35), 116.7, 119.8, 120.2, 122.7 (45C, 4,5,12,13,20,21,28,29), 132.3, 136.6 (30C, 3,11,19,27), 156.5 (34), 159.0, 159.1, 159.5 (15C, 6,14,22,30), 165.9, 166.6 (30C, 2,10,18,26)

*Synthesis of α-[5-(2-aminoethoxy-hydrochloride)-(3,5-biscarbonylphenyl)]-ω-(hexadeca-oxymethyl)-poly[(iminoethoxy-(3,5-bis(carbonylphenyl))] = G4-NH_3Cl (**15**)*

In 25 mL methanol which contained 0.9 g HCl_{gas} 100 mg of **14** were dissolved and refluxed for 5 h. The product precipitated, was isolated by filtration, washed with methanol and dried.

Yield: 0.078 g (80% based on **14**)

^{1}H NMR (DMSO-d_6), δ in ppm (assignment compare **14**): 3.66 (m, 30H, 8,16,24,32), 3.84 (s, 48H, 1), 4.24 (m,

30H, 7,15,23,31), 7.57-7.68 (m, 30H, 5,13,21,29), 7.98 - 8.09 (m, 15H, 4,12,20,28), 8.16 (s, broad, 3H, NH_3Cl, 33), 8.83 (m, 8H, 9), 8.89 (m, 4H, 17), 8.94 (m, 2H, 25)

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