Perfectly Branched and Hyperbranched Poly(ether amide)s

Thomas Huber, Brigitte Voit*, Dieter Wolf

Institut für Polymerforschung Dresden e.V., Hohe Strasse 6, D-01069 Dresden, Germany

SUMMARY: Poly(ether amide) dendrimer segments based on 5-(2-aminoethoxy)-isophthalic acid have been synthesized using the convergent approach and mild reaction conditions. The monodendrons were combined to dendrimers via different core molecules and the resulting properties of the molecules were compared to those of the monodendrons. The melt polycondensation of the AB_2 monomers with analog structure resulted first in undefined polymer structures. However, by thermal polyaddition reaction of suitable functionalized oxazoline monomers, well defined hyperbranched poly(ether amide)s with phenol terminal groups could be synthesized.

Introduction

Dendrimers have become a very popular topic in polymer chemistry in the last years due to 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. 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)[2,3)], poly(ester amide)s[2)], poly(amide)s[2-5)], and poly(aramide)s[5-8)]. 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)].

Hyperbranched polyamides, synthesized in a one step reaction from AB_2 monomers and with a less defined structure than dendrimers but with similar properties, are very interesting from

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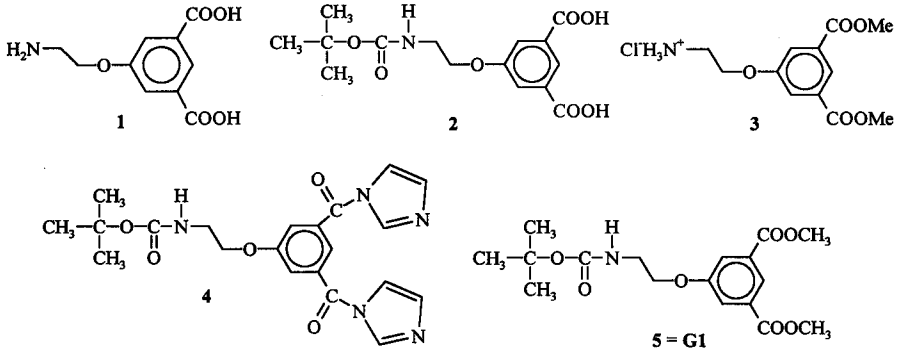
the materials point of view e.g. for blends or coatings. Linear polyamides are commonly available as materials with high modulus due to semicrystallinity or high glass transition temperatures (T_g). However, the semicrystallinity and the strong tendency to form hydrogen bonding causes also low solubility and high melt viscosity which limits the processing. A highly branched structure as in dendrimers or hyperbranched polymers, which usually leads to amorphous materials with excellent solubility, might improve the processing of polyamides and therefore, can result in new applications for polyamides. First results on highly branched polyaramides[12-15] 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 perfectly branched dendrimers and analog hyperbranched polyamides 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.

Results and Discussion

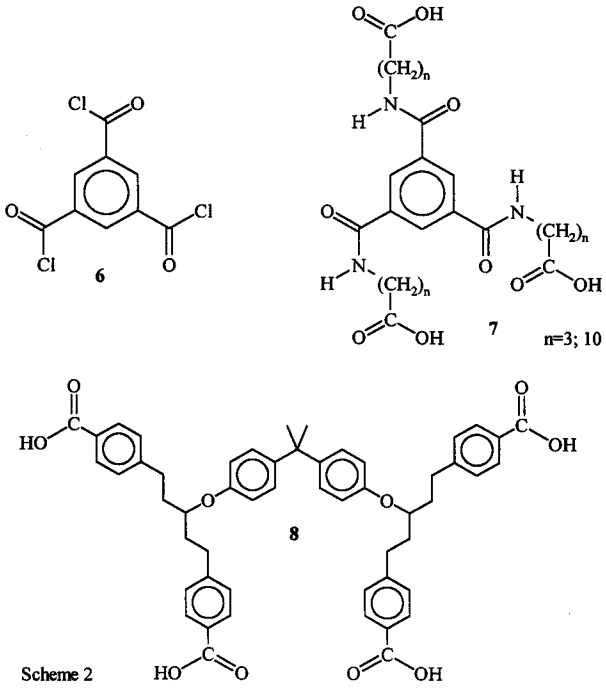
Poly(ether amide) dendrimers

Poly(ether amide) dendrimer segments up to generation 4 have been synthesized based on 5-(2-aminoethoxy)-isophthalic acid **1** as building block and using the divergent approach towards dendrimers[16,17]. A similar approach towards aliphatic-aromatic poly(amide ether) dendrimers but with amino terminal units based on 3,5-(2-aminoethoxy)-benzoic acid has been reported recently by Liskamp et al.[18]. For the repetitive synthesis of the monodendrons of different generation the starting material **1** (obtained via Mitsunobu[19] reaction from 5-hydroxyisophtalic acid) had to be converted into the amino protected compound **2** and the acid protected analogon **3**. One equivalent of **2** was combined with two equivalents of **3** to a monodendron of generation 2 (**G2-BOC**) under mild reaction condition using different coupling reagents like DCC, EDC, HATU, as applied in peptide synthesis. Also very effective was the use of carbonyldimidazole (CDI) which led to the *in situ* formation of the activated intermediate **4** (scheme 1). The BOC-protection group of **G2-BOC** was removed and two equivalents of **G2-Amine** were reacted with one equivalent of **2** to yield **G3-BOC** and so on up to generation 4.



Scheme 1

The structure of the molecules as well as the purity and the theoretical molar masses could be verified by NMR analysis, MS-MALDI-TOF and elemental analysis. Especially MS-MALDI-TOF proved to be very useful for the determination of side reactions or incomplete conversion whereas small deviations in the perfect structure were no longer detectable in the NMR e.g. for **G4**. Even though the perfect structure of the monodendrons could be proven, the removal of small amounts of the activating agents or of the applied solvents was nearly impossible for the larger structures which is an indication for the increasing globular and compact structure of the molecules. Computer modeling and molecular dynamics experiments proved the globular structure[16], but also that no sterical hindrance occurs and further growth should be possible. First attempts to synthesize monodendron **G5** were successful with regard that a compound of the expected molar mass could be isolated but only

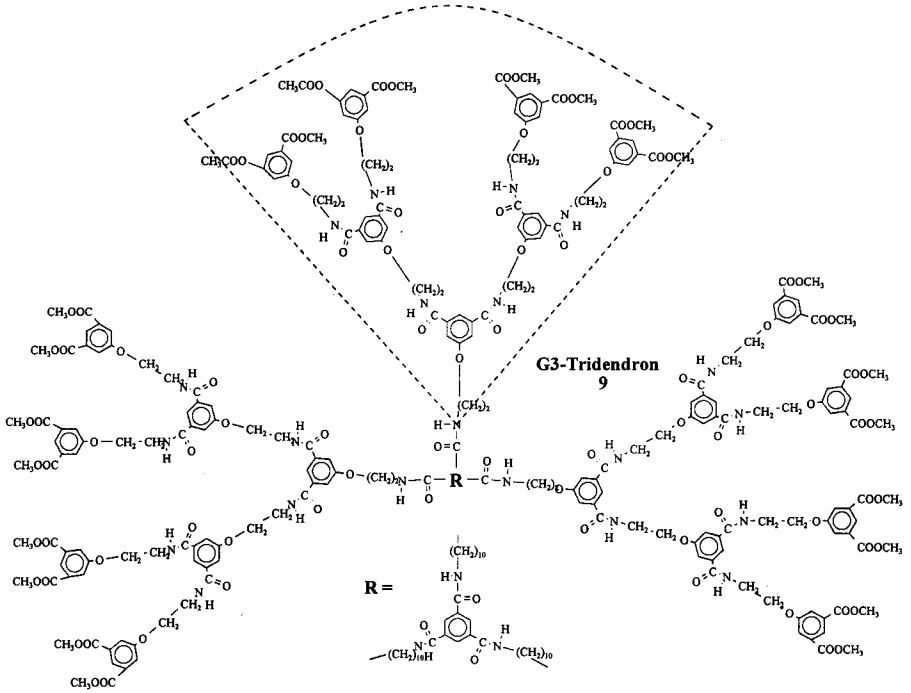


Scheme 2

in low yield.

As multifunctional cores the commercially triacid chloride **6** as well as the more flexible structures **7** (synthesized from **6** via amidation with ω-aminoundecanoic acid methyl ester and subsequent hydrolysis of the ester using potassium carbonate or sodium hydroxid) were applied (Scheme 2). In addition, the tetrafunctional compound **8** was synthesized by Mitsunobu etherification of 1,5-bis(4-methoxycarbonylphenyl)-3-pentanol[20] with bisphenol A and hydrolysis of the methyl ester functions. The very rigid core **6** was reacted with monodendrons **G1** to **G3** but already with generation 2 no complete reaction could be reached due to sterical hindrance at the core. The core molecule **8** – converted to the tetraacid chloride - was already successfully reacted with **G2** monodendrons leading to tetradendrons with a rather large, aliphatic-aromatic core area. The structure could be fully verified by ^{13}C and ^{1}H NMR analysis as well as SEC but further characterization still has to be performed.

The core molecule **7**, with the very flexible spacers, does not lead to sterical hindrance and complete attachment of **G1** to **G3** monodendrons was possible. The structure of the tridendron with **G3** (**9**) is demonstrated in Scheme 3.



Scheme 3

The monodendrons of generation 1 to 3 exhibit in bulk still some crystallinity but the enthalpy value of the melting endotherm in the DSC measurements decreases with increasing generation number. Already **G2-BOC** shows a well distinguishable glass transition at 44 °C which shifts to to about 95 °C for **G3** and **G4**. No crystallinity was observed for **G4** and all other tri- and tetradendrons. Despite of the flexible core molecule the glass transition temperature of **9** was similar to that of **G4-BOC**. However, the solubility behavior changes strongly from **G4** to the tridendron: the monodendron is only soluble in DMF or DMAc and in very low concentration in THF, but **9** exhibits excellent solubility in THF and even in chloroform and methylene chloride.

Table 1: Results for the monodendrons **G1** to **G4** and their products with core **9**

compound	$M_{theor.}$ g/mol[1]	$M_{n(SEC)}$ g/mol[2]	$\eta_{inh.}$ dL/g[3] (c = 0.2g/L)	T_m °C[4]	T_g °C[5]
G1-BOC (**5**)	353	460	-[6]	82	-
G2-BOC	796	790	-[6]	113	44
G3-BOC	1680	1370	0.061	111	97
G4-BOC	3450	2350	-[6]	-	93
G3-tridendron (**9**)	5446	20500	0.250	-	109

[1] theoretical molar mass M_n could be verified for all compounds by MS-MALDI-Tof

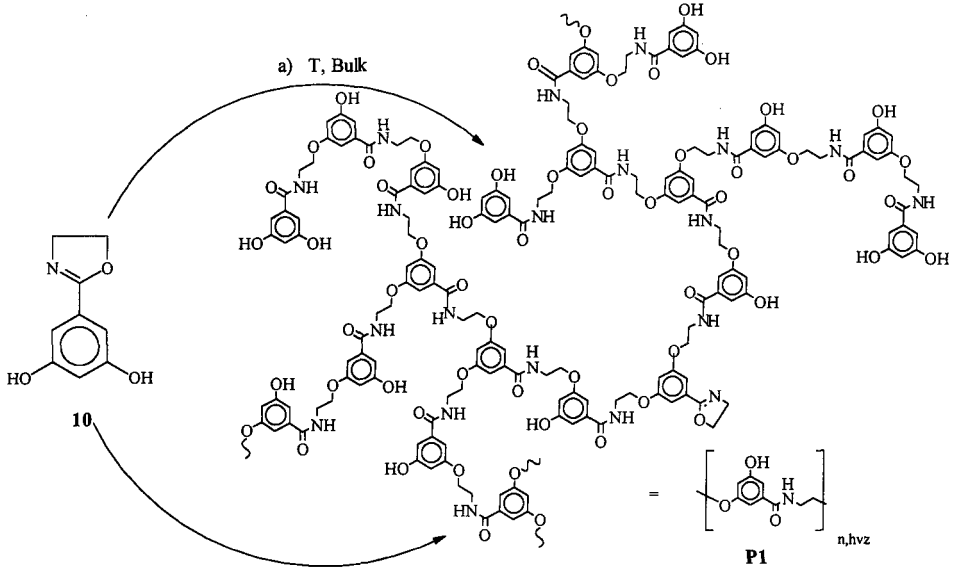
[2] by SEC in THF or DMAc (**9**) calibration with linear polystyrene; [3] measured in DMF; by DSC, 20K/min, 1st heating run; [4] by DSC, 20K/min, 2nd and 3rd run; [6] not measured

As described above, the molar masses were determined successfully by MS-MALDI-TOF. SEC analysis of the monodendrons in THF applying linear polystyrene calibration resulted for the larger molecules in a increasing deviation of the measured molar mass values from the theoretical values which is in agreement with the increasing globular shape of the molecules (Table 1). The SEC molar mass of **9** has been performed in DMAc as a typical solvent for polyamides, again using polystyrene calibration. Surprisingly, the SEC molar mass of **9** is much larger than the theoretical molar mass which is mainly due to the limitation of the polystyrene calibration in polar solvents. However, aggregation of the molecules can also not be excluded. Solution viscosity measurements show a remarkable increase in the inherent viscosity from **G4** to **9** with adding salt to the solvent having no effect. MS-MALDI-TOF, however, clearly exhibit the expected molecule peak for **9**, even though a small impurity of unreacted **G3** and of a side reaction product of the core molecule can also be detected. Further purification of this dendrimer is still in progress.

The methylester end groups can be split off without degradation of the internal amide bonds by selective hydrolysis yielding carboxylic acids, when mild reaction conditions are applied and potassium carbonate is used as base. Thus, reactive functions can be created on the dendrimer surface which are available for further modification reactions.

Hyperbranched poly(ether amide)s

Jikei et. al.[15] described the synthesis of fully aromatic poly(ether amide)s and a first approach towards hyperbranched aliphatic-aromatic poly(ether amide)s of an analogous structure of the above described dendrimers has be published previously[17] by our own group. Both approaches use conventional polycondensation reactions of acids and amines to form the hyperbranched structure. However, using the building block **3** or **5** in a high temperature melt polycondensation process did not result in clean hyperbranched polyamides up to now. Side reaction like partial hydrolysis of the terminal ester groups and alkylation of the amide functions occurred.



Scheme 4

Therefore, a different approach towards hyperbranched polyamides has been undertaken. The nucleophilic ring opening reaction of 2-oxazolines with carboxylic acids, thiols and phenols leads to esteramides[21-23], thioetheramides[24,25] and etheramides[26,27]. The synthesis of linear

poly(ether amide)s in melt and solution of monomers containing a 2-oxazoline and a phenolic group was described by Mülhaupt et al.[28]. We found that the polymerization of an AB_2 monomer with two phenolic groups and one oxazoline function leads to well defined hyperbranched poly(ether amides)[29] (Scheme 4). The structure of the repeating units corresponds well with those of the dendrimers described above with the exception that phenol end groups are obtained instead of methylester or acid functions.

The reactions proceeds best in N-methylcaprolactame as solvent at 190 °C but reaction in bulk at 220 °C was also possible. The products are highly soluble in polar solvents like DMF, DMAc, and DMSO. The ^1H and ^{13}C NMR analysis by means of two dimensional experiments allowed the exact assignment of all signals of the different structural units in the polymer. The ratio of linear, dendritic and terminal units could be determined and a degree of branching of 50% was calculated which is in agreement with a fully statistical branching process. In contrast to observation on linear poly(ether amides) synthesized from p-hydroxyphenyl-2-oxazoline[26], no side reactions could be detected in the hyperbranched system when water was eliminated completely from the reaction medium and the starting materials.

By optimization of the reaction conditions, medium and time, hyperbranched poly(ether amide)s up to a molar mass M_n of 47,500 g/mol could be synthesized. This polymer exhibits an $\eta_{inh.}$ of only 0.305 dL/g (c = 0.2 g/dL) in DMF and a product with M_n = 13500 g/mol of 0.079 dL/g, whereas a linear analog oligomer synthesized from m-hydroxyphenyloxazoline of a molar mass of only 1700 g/mol is much less soluble in DMF and has a η_{inh} of already 0.098 dL/g (c = 0.2 g/dL).

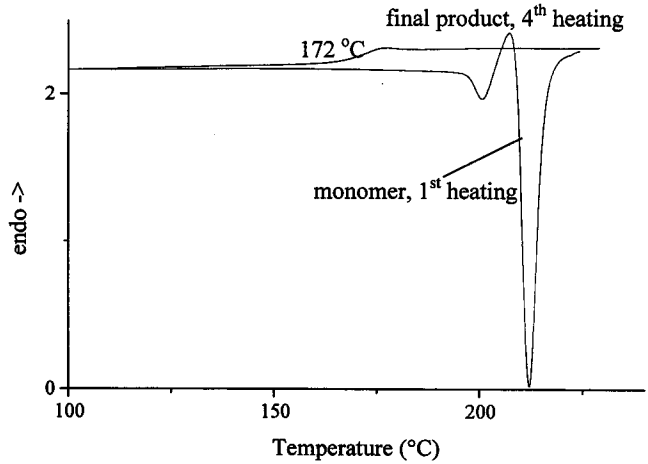


Fig. 1: DSC trace of the AB_2 monomer **10** and the resulting hyperbranched polymer (heating rate: 10K/min)

The thermal reaction of the monomer **10** can be followed by DSC analysis (Fig.1). In the first heating cycle the thermal addition reaction can be observed as a strong exothermic peak which starts directly after melting of the compound is induced. The polyreaction temperature of 190 °C in solution and 220 °C in bulk fits directly into this melting/reaction area. After the first heating cycle the product can be further thermal treated in the DSC experiment by several heating cycles until no more changes occur in the curve (4th heating cycle). The T_g of the resulting polymer can be observed already in the second heating cycle and it shifts up to 172 °C in final heating. Glass transitions temperatures between 170 and 176 °C are also observed for the polyreaction products carried out in the reaction flask.

Thus it was possible to synthesize perfectly branched poly(ether amide) dendrimers and hyperbranched polymers with similar structure. The products are more stable towards hydrolysis than e.g. hyperbranched polyesters, have glass transition temperatures far above room temperature, show high solubility and low solution viscosities.

Experimental Part

Details to the synthesis of the monodendrons G1 to G4 can be found in ref.[16]; the polymerization of **10** is described in ref.[29]. 1,5-Bis(4-methoxycarbonylphenyl)-3-pentanol was synthesized following a patent literature[20]. All products have been characterized by SEC (dendrimers: in THF or DMAc, polystyrene calibration; hyperbranched polymers: in DMAc/LiCl/H_2O, polystyrene calibration; UV- and RI detection). The molar mass of the products has been further verified by MS-MALDI-TOF (HP G2025A MALDI-TOF, measurements in a THF / 2,5-dihydroxybenzoic acid matrix with K^+ - modifier using a laser energy of 5.79 μJ). 500.13 MHz ^{1}H-NMR spectra and 125.74 MHz ^{13}C-NMR spectra were recorded with a Bruker DRX 500 NMR.

Synthesis of the core molecules

Trimesinic acid-tris-(11-carboxyundecylamide) **7**

ω-Aminoundecanoic acid was converted to the methyl ester via standard esterification procedure. The ester (6.4g, 30 mmol) and trimesylchloride (2g, 7.5 mmol) were dissolved in 100 mL dichloromethane. The solution was cooled to 0°C and triethylamine (10 mL, 72 mmol) was added. After 24 h stirring at room temperature the reaction was stopped by addition of 50 mL water and 1g $NaHCO_3$ and a small amount of tributyl ammonium bromide. The organic phase was extracted with diluted HCl, dried over Na_2SO_4, and the product was

isolated by removal of the solvent. The methyl ester function were hydrolyzed using aqueous NaOH or potassium carbonate. The triacid was isolated by adjusting the pH to 2-3 and subsequent filtration. Yield:3.1 g (55% th)

^{1}H NMR (d_6-DMSO, δ in ppm): 1.30, 1.56, 2.23, 3.32, 8.47, 8.69,

^{13}C NMR (d_6-DMSO, δ in ppm): 25.3, 7.3, 29.4, 29.6, 29.7, 29.8, 29.9, 34.5, 129.1, 136.0, 166.2, 175.3

2,2-Bis(4-(1,5-bis(4-carbonylphenyl)-pentyl-3-oxy)phenyl)propane **8**

1,5-Bis(4-methoxycarbonylphenyl)-3-pentanol (7.2g, 20 mmol), 2,2-bis(4-hydroxyphenol)-propane (2g, 8.8 mmol), and triphenylphosphin (5.3g, 20 mmol) were dissolved in 100 mL THF and the solution was cooled to 0°C. Diethylazodicarboxylate (3.5g, 20 mmol), dissolved in 10 mL THF, was added slowly and the solution was stirred 24 h at room temperature. The solvent was removed and 50 mL methanol and 50 mL 1n aqueous NaOH solution were added. The solution was refluxed for 3 h, methanol was removed, the residue was filtered, diluted with 150 mL water, and extracted with 200 mL ethyl acetate. The pH of the aqueous phase was adjusted to 3 and the phase was extracted 3 x with 100 mL ethyl acetate. The combined organic phases were dried over Na_2SO_4. The solvent was removed in vacuum. Yield: 3g (40% th.)

^{1}H NMR (d_6-DMSO, δ in ppm): 1.58, 1.96, 2.75, 4.29, 6.79, 7.09, 7.27, 7.84

^{13}C NMR (d_6-DMSO, δ in ppm): 30.9, 30.7, 34.7, 41.0, 75.8, 115.1, 127.4, 128.3, 128.4, 129.3, 142.6, 147.0, 155.7, 167.0

Tri- and tetradendrons

Reaction with **6**

The monodendrons were dissolved in DMF, triethyl amine and **6** were added and the solution was stirred for 1-2 days. The solvent was removed and the residue was dissolved in ethyl acetate. The organic phase was extracted with aqueous $NaHCO_3$ and diluted HCl. Alternatively, the products were isolated by precipitation in methanol.

Reaction with **7**

Core **7**, **G2-Amine**, TBTU (O-(benzotriazol-1-yl)1,1,3,3,-tetramethyluroniumtetra-fluoroborate), and triethylamine were dissolved in DMF and stirred for 3 days at room temperature. The isolation of the product proceeded similarly as described for **6**.

Reaction with **8**

Core **8**, monodendron-Amine, TBTU (O-(benzotriazol-1-yl)1,1,3,3,-tetramethyluronium-tetrafluoroborate) or HATU (O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium-hexafluorophosphate (HATU), and triethylamine were dissolved in DMF and stirred for 3 days at room temperature. The isolation of the product proceeded similarly as described for **6**.

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