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An Approach to Glycerol Dendrimers and Pseudo-Dendritic Polyglycerols

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Macromolecules with a branch-on-branch structure, such as dendrimers and hyperbranched polymers, have attracted increasing interest over the past few years due to their unique molecular features and properties.[1,2] A promising class of these highly branched molecules are aliphatic polyether polyols. Due to their inert building blocks and multiple reactive chain ends they possess promising potential as supports for catalysts and functional organic molecules. In addition, their excellent water solubility and biocompatibility renders them as valuable compounds for polymer therapeutics.[3]

So far, only three examples of aliphatic polyether dendrimers have been reported in the literature.[4] They have been prepared in tedious repetitive multistep syntheses, which are obviously a limiting factor for many applications. Hyperbranched aliphatic polyethers, on the other hand, are conveniently prepared in one step.[5,6] Due to the statistics of the polymerization reaction they are a mixture of isomers, possess a certain polydispersity, and usually contain varying amounts of linear units in addition to dendritic and terminal building units. To date, two monomers for the preparation of hyperbranched aliphatic polyether polyols are known: 3-hydroxymethyl-3-ethyl oxetane[5] and glycidol.[6] Only the latter one is commercially available and permits control in terms of initiator (core) incorporation, molecular weight (M_n: 1000−10000) and low polydispersities ($M_w/M_n < 1.5$).

A challenging issue is the comparison of structure−property profiles of hyperbranched polymers and dendrimers based on the difference in topology and polydispersity.[7,8] To this end, hyperbranched polymers without linear units are required. So far, two strategies have been described in the literature: (i) the use of peculiar monomers, in which the formation of linear units is less favorable than the formation of dendritic ones[9,10] and (ii) the conversion of all linear units into dendritic units by postsynthetic modification.[11] An often faced problem remains the realization of exactly analogous structures[12] and sufficient characterization of the compounds.[8a]

In this contribution we present a new divergent synthesis leading to dendrimers, with glycerol as building unit. Furthermore, we describe a two-step approach to the analogous, perfectly branched structure, designated “pseudo-dendrimer”, by modification of well-defined hyperbranched polyglycerols. This strategy permits a direct comparison between a perfect dendritic molecule and a pseudo-dendritic polymer derived from precisely the same building blocks, i.e., a core unit with only dendritic and terminal units attached.

The synthesis of aliphatic polyether polyol dendrimers requires an efficient strategy for the formation of the ether linkages.[4] Classical Williamson ether synthesis (NaH, alkylhalogenide, DMF) is often incomplete when polyols are used. This problem, however, can be overcome by using a phase-transfer catalyst.[13] For the synthesis of the [G-3] glycerol dendrimer **1** we have selected a simple iterative two-step process (Scheme 1) based on allylation of an alcohol and catalytic dihydroxylation of the allylic double bond. The allylation under phase-transfer conditions reproducibly leads to quantitative formation of the product even when polyols are employed.[14] Catalytic dihydroxylation of the double bond with *N*-methyl morpholine oxide (NMO) as cooxidant[15] completes the sequence and leads to the formation of new glycerol units on every available alcohol functionality (Scheme 1). Both transformations can be carried out in aqueous phase and consume only inexpensive reagents, i.e., allyl chloride and hydrogen peroxide for the recycling of NMO.[15] Starting from trimethylolpropane (TMP) we obtained a [G-3] glycerol dendrimer **1**, with 24 hydroxyl end groups after three cycles (six synthetic steps) in 75% overall yield. Purification by column chromatography was necessary only after the allylation steps. The perallylated intermediates tend to cross-link within several days; therefore, oxygen should be excluded for their storage. The final product **1** was further purified by dialysis in methanol (benzylated cellulose membrane, MWCO = 1000).

The glycerol dendrimer **1** (degree of branching (DB) = 100%) possesses only two types of structural units (dendritic and terminal), while the hyperbranched polyglycerol **2** contains additional linear groups (either bearing primary or secondary hydroxy groups) leading to its lower DB, typically about 60%.[6a] When the above-described allylation and dihydroxylation sequence is applied to the hyperbranched polymer all linear and terminal units are transformed into dendritic units (Scheme 1), and hence, the polymer **3** consists of terminal and dendritic units only. We used a hyperbranched polyglycerol **2** with a molecular weight of $M_n = 1300$ ($DP_n = 15$) with a polydispersity $M_w/M_n = 1.2$ and a degree of branching DB = 58% (thus containing 40% linear units). The material was prepared from TMP in a one-pot synthesis, applying the base-catalyzed ring-opening multibranching polymerization of glycidol on a 500 g scale as described

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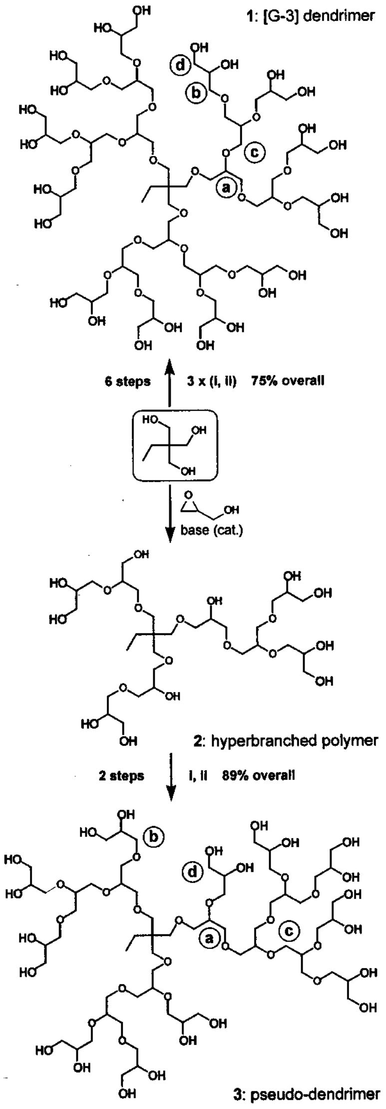
Scheme 1. Synthesis of Glycerol Dendrimer **1**, Hyperbranched Polyglycerol **2**, and Pseudo-Dendritic Polyglycerol **3**[a]



[a] (i) Allyl chloride, NaOH, TBAB, water; (ii) NMO, OsO_4 (cat.), water, acetone, *t*-BuOH. Characteristic carbon signals in the ^{13}C NMR spectra are assigned a, b, c, d.

previously.[6a] Subsequently, all hydroxy groups were converted into allyl ethers while completion of the reaction was monitored by the disappearance of the OH band in the IR spectrum. In the second step all allyl groups were converted into terminal glycerol units, and the conversion was monitored by the disappearance of the allyl signals in the ^{1}H NMR spectrum. The conversions for both reactions were higher than 95%, and the overall isolated yield was 89% after dialysis. SEC (DMF, poly(propylene oxide) calibration) revealed a significant increase in molecular weight (hyperbranched polymer **2** $M_n = 2730$; modified hyperbranched polymer **3** $M_n = 4760$) maintaining the narrow polydispersity of $M_w/M_n = 1.2$.

We have used ^{13}C NMR spectroscopy for a detailed structural characterization of the dendritic polyglycerols. Figure 1 shows the spectra of the glycerol dendrimer **1** and the transformed hyperbranched polymer **3**, confirming the structural perfection of **3**. The signals of both compounds differ only in their line width, which arises from the isomerism and the polydispersity of **3**. On the basis of the structural similarity and the fact that *exactly one* core and exclusively dendritic and terminal units are present we suggest the name "pseudo-dendrimer" for this fully branched polyglycerol **3**.

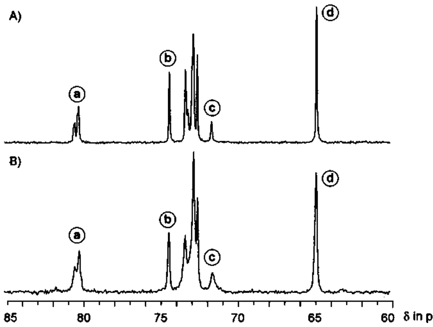


Figure 1. ^{13}C NMR spectra of (A) glycerol dendrimer **1** and (B) pseudo-dendritic polyglycerol **3**. Signals of characteristic carbons are assigned according to Scheme 1. For simplicity, signals of the TMP-core at higher field (43.6, 23.4, 8.1 ppm) are not shown.

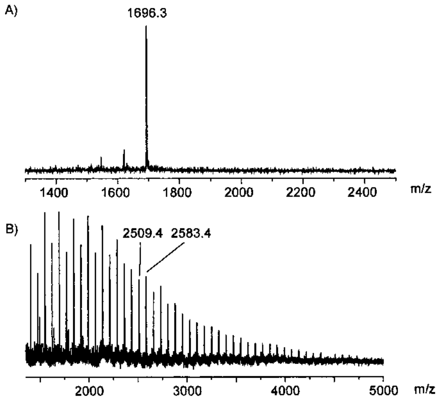


Figure 2. MALDI-TOF mass spectra of (A) [G-3] glycerol dendrimer **1** and (B) pseudo-dendritic polyglycerol **3**. The spectrum of dendrimer **1** contains traces of imperfect dendrimer structures with one and two missing glycerol units (<5% abundance).

Although structural equivalence is proven by NMR, MALDI-TOF spectra show the difference between the two compounds (Figure 2). While the [G-3] glycerol dendrimer **1** shows only one major peak at the expected mass ($m/z = 1690$, i.e., TMP + 21 monomer units), the pseudo-dendrimer **3** exhibits a distribution of molecular weights with the mass of the monomer unit ($M = 74$) as peak distance.

We have developed a new dendrimer synthesis based on chemically stable polyether linkages. By this divergent approach a third generation [G-3] glycerol dendrimer with 24 functional end groups was prepared in an efficient way from inexpensive starting materials and reagents. We also introduced a new strategy to generate a polyglycerol pseudo-dendrimer **3**, which also consists of dendritic and terminal units only, resembling the perfect glycerol dendrimer **1**. The advantages of the second approach are obvious: (i) only three synthetic steps (polymerization, allylation, dihydroxylation) are required to tailor any molecular weight between $M_n = 1000$ and 20 000 with low polydispersities ($M_w/M_n < 1.5$), (ii) the synthesis can be carried out on a multigram scale, (iii) the capacity of 1,2-diols (= terminal units) on the polymer is increased from 4.5 mmol/g for the hyperbranched polymer **2** to 7.1 mmol/g for the fully dendritic structure **3**, and (iv) all reported advantages of the polyether scaffold are preserved.

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Supporting Information Available: Experimental procedures and full characterization (^{1}H, ^{13}C, IR, MS) for all glycerol dendrimers [G-1] through [G-3] and the pseudo-dendritic polyglycerol (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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