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Synthesis of Glycerol Based Hyperbranched Polyesters with Primary Hydroxyl Groups

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Introduction. Dendrimers and hyperbranched polymers (HBP) have gained widespread attention due to their unique three-dimensional architecture and potential applications in the fields of medicine and materials science as well as in homogeneous catalysis.^{1–4} Dendrimers are characterized by perfect monodisperse architecture, but their preparation is generally tedious because of repetitive protection, deprotection, and purification steps, which limits their large-scale application. In contrast to dendrimers, hyperbranched polymers can be conveniently prepared on a large scale in a one-pot procedure. Although hyperbranched polymers contain linear units as insufficient branching, they still inherit the properties of dendrimers such as good solubility, low viscosity, and multifunctionality at end groups. Therefore, hyperbranched polymers, especially hyperbranched polyesters, have been receiving more and more attention in the application of biomaterials.

This paper describes the synthesis of 5-hydroxymethyl-1,4-dioxan-2-one (5-HDON) and its application for preparation of hyperbranched polymers by self-condensing ring-opening polymerization. The repeating unit of the obtained polymer consists of glycerol and glycolic acid residues, which makes it potentially biodegradable and biocompatible. Similar hyperbranched structures were reported recently.^{5–7} Fréchet et al. reported the synthesis of 4-(2-hydroxyethyl)- ϵ -caprolactone and its application for ring-opening polymerization (ROP).⁵ Grinstaff et al. synthesized a biodendrimer based on glycerol and caproic acid using the glycerol benzylidene acetal as a starting material.⁶ Zhuo et al. prepared a HBP based on 6-hydroxymethyl-1,4-dioxan-2-one (6-HDON).⁷ That hyperbranched polymer contained both primary and secondary hydroxyl groups. Another glycerol-based HBP was recently obtained by us from glycerol carbonate.⁸

The unique attribute of the synthesized poly(5-HDON) is the exclusive presence of primary hydroxyl groups. The same reactivity of the primary OH groups enables higher branching degree of the resulting polyester. The OH groups, present in a high quantity on the outer sphere of the macromolecules, can be further modified making the poly(5-HDON) a promising material for drug delivery.

Experimental Section. a. Materials. Ethyl bromoacetate, benzaldehyde, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Aldrich Chemical and used as received. Solvents were purchased from POCh (Gliwice, Poland) and dried prior to use, except for ethyl ether, which was used as received. Glycerol (POCh) was pretreated by azeotropic water removal. Stannous octoate was a gift from LPT (Warsaw, Poland) and was purified as described in ref 9. Compounds **1**¹⁰ and **2**¹¹ were synthesized according to the literature procedures.

b. Instrumentation. IR spectra were recorded on a Biorad FTIR spectrometer as KBr pellets. ¹H NMR and ¹³C NMR spectra were recorded on a Varian VXR 400 MHz spectrometer using tetramethylsilane as an internal standard and deuterated solvents (CDCl₃, DMSO-*d*₆). MALDI-TOF spectra were recorded on a Bruker-Saxonia Reflex IV (Leipzig, Germany) apparatus equipped with a 337 nm nitrogen laser. Measurements of the molecular weight were performed with GPC LabAlliance apparatus using water as an eluent at 35 °C using poly(oxyethylene) glycol for the calibration.

c. Synthesis of 5-Hydroxymethyl-1,4-dioxan-2-one (4). To a one-neck flask equipped with a magnetic stirrer was added 5 g (18.8 mmol) of acetal **2**,¹¹ followed by 20 mL of ethanol and 23 mL of 3% HCl_{aq}. The reaction mixture was stirred for 24 h at room temperature. Reaction progress was monitored by TLC (ethyl acetate/hexane). After the disappearance of the starting material, the reaction mixture was evaporated to dryness. Double distillation (160 °C, 0.5 mmHg) yielded 1.89 g (76%) of **4** as a colorless liquid. ¹H NMR (CDCl₃, 400 MHz): δ (ppm) = 4.50 (d, 1H, COCH₂O, *J* = 17.6 Hz), 4.43 (dd, 1H, COOCH₂CH, *J*₁ = 11.2 Hz, *J*₂ = 16.0 Hz), 4.42 (dd, 1H, COOCH₂CH, *J*₁ = 11.2 Hz, *J*₂ = 12.0 Hz), 4.33 (d, 1H, COCH₂O, *J* = 17.6 Hz), 3.92–3.86 (m, 1H, CH), 3.76 (dd, 1H, CH₂OH, *J*₁ = 4.0 Hz, *J*₂ = 12.0 Hz), 3.68 (dd, 1H, CH₂OH, *J*₁ = 5.1 Hz, *J*₂ = 12.0 Hz), 2.58 (bs, 1H, OH). ¹³C NMR (CDCl₃, 400 MHz): δ (ppm) = 166.7, 72.2, 69.6, 65.7, 61.4. FT-IR (KBr, cm⁻¹): 3400, 1745, 1235.

d. Synthesis of 2-Allyloxyl-1,3-propanediol (5). Part 1. To a flask equipped with a magnetic stirrer was added 6.24 g (0.26 mol) of sodium hydride followed by 100 mL of dry THF. The solution of 40 g of **1** in 100 mL was added dropwise followed by a slow addition of 35.7 g (0.29 mol) of allyl bromide. The reaction mixture was stirred for 24 h at room temperature, and then the solvent was removed under reduced pressure. The remained solid was taken up into 100 mL of dichloromethane, washed with water, and dried with MgSO₄. Then 50 mL of hexanes was added, and the solution was placed in a freezer. The precipitate of 5-allyl-2-phenyl-1,3-dioxane was filtered and dried. Yield: 35.1 g (73%). ¹H NMR (CDCl₃, 400 MHz): δ (ppm) = 7.55–7.50 (m, 2H, H_{Ar}), 7.40–7.30 (m, 3H, H_{Ar}), 6.04–5.92 (m, 1H, =CH=), 5.57 (s, 1H, CHPh), 5.38–5.30 (m, 1H, =CH₂), 5.25–5.19 (m, 1H, =CH₂), 4.38–4.31 (m, 1H, CH₂ cycl), 4.19–4.15 (m, 2H, –CH₂–), 4.10–4.04 (m, 1H, CH₂ cycl), 3.38–3.35 (m, 1H, CHO).

Part 2. The synthesis was performed in analogy to the preparation of compound **4**. Vacuum distillation (0.6 mmHg, 97 °C) gave 2-allyloxyl-1,3-propanediol (**5**) in 96% yield. ¹H NMR (CDCl₃, 400 MHz): δ (ppm) = 5.96–5.85 (m, 1H, =CH=), 5.31–5.24 (m, 1H, =CH₂), 5.21–5.16 (m, 1H, =CH₂), 4.11–4.08 (m, 2H, –CH₂–), 3.79–3.61 (m, 4H, CH₂OH), 3.51–3.45 (m, 1H, CHO), 2.97 (t, 2H, OH, *J* = 6 Hz).

e. Synthesis of Model Compound 6. In a flask equipped with reflux condenser and magnetic stirrer 0.34 g (2.6 mmol) of **5** was placed, followed by 0.26 g (2.6 mmol) of acetic anhydride and 1.4 mg (10 μ mol) of zinc chloride. The mixture was heated at reflux for 0.5 h and stirred at room temperature overnight. Then, it was taken up in ethyl acetate, washed with 10% potassium carbonate and water, and dried with magnesium sulfate. Column chromatography (silica gel, ethyl acetate/hexanes) yielded 0.18 g (40%) of model compound **6**. ¹H NMR

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(d_6 -DMSO, 400 MHz): δ (ppm) = 5.91–5.83 (m, 1H, $-\text{CH}=\text{}$), 5.29–5.09 (m, 2H, $=\text{CH}_2$), 4.20–3.90 (m, 6H, $-\text{CH}_2-$, CH_2O), 3.51–3.45 (bs, 1H, CHO), 2.01 (s, 6H, CH_3). ^{13}C NMR (d_6 -DMSO, 400 MHz): δ (ppm) = 170.9, 136.2, 116.8, 77.7, 70.5, 64.0, 60.7, 21.3.

f. Synthesis of Model Compound 7. In a flask equipped with reflux condenser and magnetic stirrer 0.3 g (2.3 mmol) of **5** was placed, followed by 0.7 g (6.8 mmol) of acetic anhydride and 1.4 mg (10 μmol) of zinc chloride. The mixture was heated at reflux overnight. Then, it was taken up in ethyl acetate, washed with 10% potassium carbonate and water, and dried with magnesium sulfate. Evaporation of solvent yielded 0.44 g (90%) of **7**. ^1H NMR (d_6 -DMSO, 400 MHz): δ (ppm) = 5.80–5.79 (m, 1H, $-\text{CH}=\text{}$), 5.29–5.12 (m, 2H, $=\text{CH}_2$), 4.07–4.04 (m, 2H, $-\text{CH}_2-$), 4.15–4.03 (m, 4H, CH_2O), 3.77–3.72 (m, 1H, CHO), 2.02 (s, 6H, CH_3). ^{13}C NMR (d_6 -DMSO, 400 MHz): δ (ppm) = 170.8, 135.7, 117.2, 74.4, 70.5, 63.3, 20.2.

g. Polymerization of 5-Hydroxymethyl-1,4-dioxan-2-one. 5-Hydroxymethyl-1,4-dioxan-2-one (0.2 g, 1.5 mmol) and the catalyst $\text{Sn}(\text{Oct})_2$ or DBU (3.8 μmol) were placed in a small reactor equipped with a magnetic stirrer and Teflon seal. The solution was flushed with nitrogen for 5 min, and the reactor was closed and heated in an oil bath at 75–110 $^\circ\text{C}$. The reaction mixture was stirred at this temperature for 24–72 h. The resulting polymer was analyzed without further purification.

Results and Discussion. a. Monomer Synthesis. Scheme 1 shows the reaction pathway leading to the monomer **4**. The 5-HDON was synthesized according to the modified procedure previously reported by Broggini et al.¹¹ In the first step, 5-hydroxy-2-phenyl-1,3-dioxane (**1**) was treated with ethyl bromoacetate. We have found that the subsequent basic hydrolysis of the ester group in **2** described in the original procedure¹¹ is not necessary. The hydrolysis of acetal moiety **2** with diluted ethanolic solution of HCl followed by vacuum removal of benzaldehyde and ethanol yields a polymer, which can be converted into pure 5-HDON upon the thermal depolymerization combined with distillation under reduced pressure (160 $^\circ\text{C}$, 0.5 mmHg). The six-membered 5-HDON is formed according to the backbiting mechanism. Although compound **4** was reported previously, no detailed spectral properties were published. Figure 1 shows the ^1H NMR spectrum of 5-HDON.

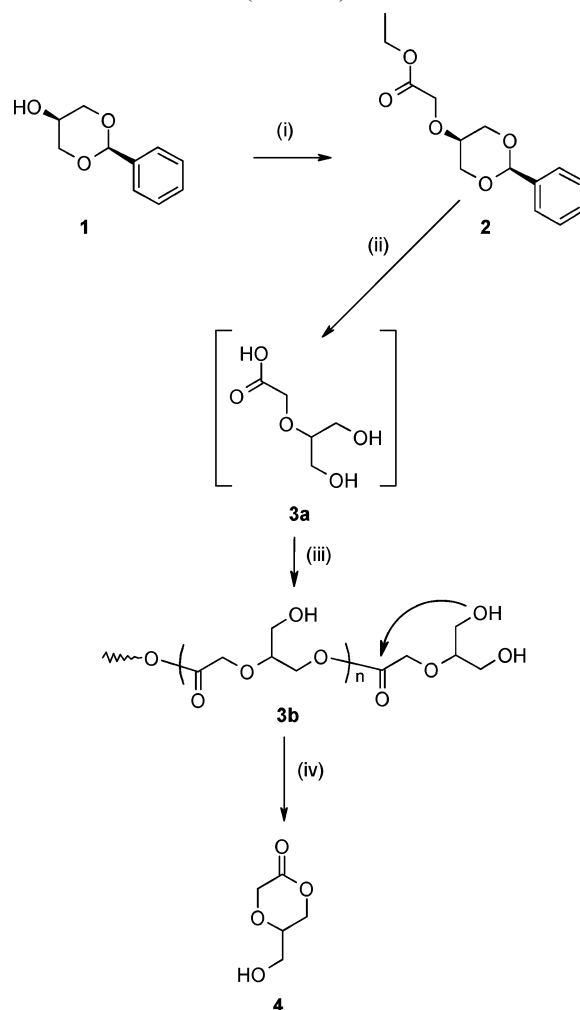
The signals of the hydroxymethyl group protons (7-H) appear as two pairs of doublets in the range 3.65–3.85 ppm, separate for axial and equatorial methylene protons. The isolated methylene protons 3-H give a pair of doublets at 4.52 and 4.35 ppm. The protons of the methylene group (6-H) again appear as two pairs of doublets in the range 4.50–4.39 ppm. A multiplet at 3.9 ppm can be assigned to the 5-H proton. The OH protons are not shown in Figure 1 and appear at 2.21 ppm as a broad singlet.

The presence of carbon atom signals (166.7, 72.2, 69.6, 65.7, 61.4 ppm) in the ^{13}C NMR spectrum, corresponding to five different carbon atoms, additionally confirmed the structure of monomer **4**.

It was found that monomer **4** is unstable at ambient conditions. After 2 weeks at room temperature the formation of oligomers (**P1**) of molecular weight of ~ 6500 Da was observed. The detailed characteristics of this product are given in Table 1 (**P1**). It is noteworthy that the thermal degradation combined with vacuum distillation of these oligomers gives pure **4** with almost quantitative yield.

b. Polymerization. The ring-opening polymerization (ROP) of **4** was carried out in bulk or in solution in the presence of a catalytic amount of $\text{Sn}(\text{Oct})_2$ (coordination polymerization and

Scheme 1. Synthesis of 5-Hydroxymethyl-1,4-dioxan-2-one (5-HDON)^a



^a (i) NaH, $\text{BrCH}_2\text{COOEt}$, toluene, rt, 83%; (ii) 3% HCl_{aq} , ethanol, rt; (iii) vacuum distillation 160 $^\circ\text{C}$, 0.5 mmHg, 76%.

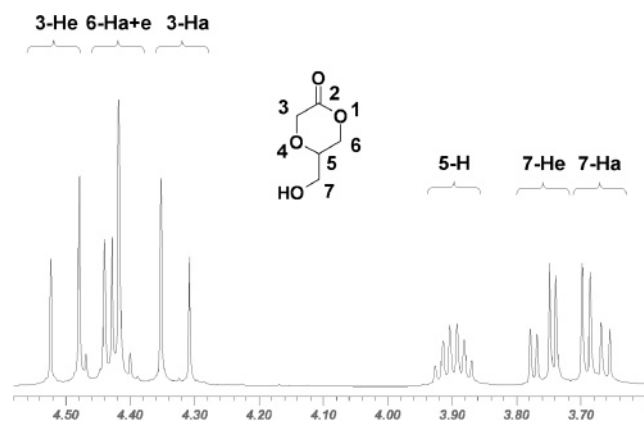


Figure 1. ^1H NMR (CDCl_3 , 400 MHz) spectrum of 5-HDON (**4**).

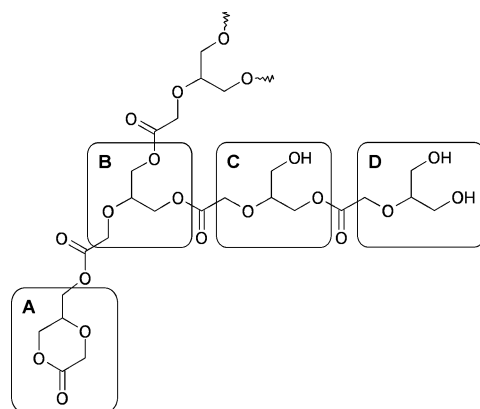
transesterification catalyst^{12,13}) or DBU (typical anionic polymerization initiator¹⁴). In't Veld et al.^{15a} and Kricheldorf et al.^{15b} have demonstrated that during polymerization of cyclic ester monomers carried out below 120 $^\circ\text{C}$ minimal transesterification side reactions take place. In the ring-opening polymerization of monomer **4** the molar concentration of initiating alcohol groups relative to that of $\text{Sn}(\text{Oct})_2$ ($[\text{M}]/[\text{Cat}]$) was kept high (ratio 400:1) to minimize possible transesterification reactions. Table 1 presents the reaction conditions for the polymer synthesis. The products of each experiment were

Table 1. Composition and Conditions of the Polymerization Reactions and GPC Characteristics of the Synthesized Poly(5-HDON)

sample	reactant	catalyst	temp (°C)	solvent	time (h)	M_n	M_w	D
P1	4		rt		336	6450	12 850	1.99
P2	4	Sn(Oct) ₂	75	THF	24	25 160	43 800	1.74
P3	4	DBU	75	THF	24	36 420	67 010	1.84
P4	P1	Sn(Oct) ₂	75	THF	24			
P5	P1	DBU	75	THF	24			
P6	4	Sn(Oct) ₂	110		72	42 400	85 180	2.01
P7	P1	Sn(Oct) ₂	110		72	43 470	87 960	2.02
P8	4		110		168	10 970	21 890	2.00

characterized by means of GPC, ¹H NMR, ¹³C APT NMR, MALDI-TOF spectrometry, and FT-IR spectroscopy.

The theoretical chemical structure of the obtained polymers and oligomers is shown in Figure 2. There are four main

**Figure 2.** Theoretical structure of poly(5-HDON).

subunits characteristic for the hyperbranched polymer. The polymerization starts at the core unit A. The completely substituted subunit B represents the branching points and the subunit C the linear fragment of the molecule. The outer sphere D consists of two unsubstituted hydroxymethyl groups.

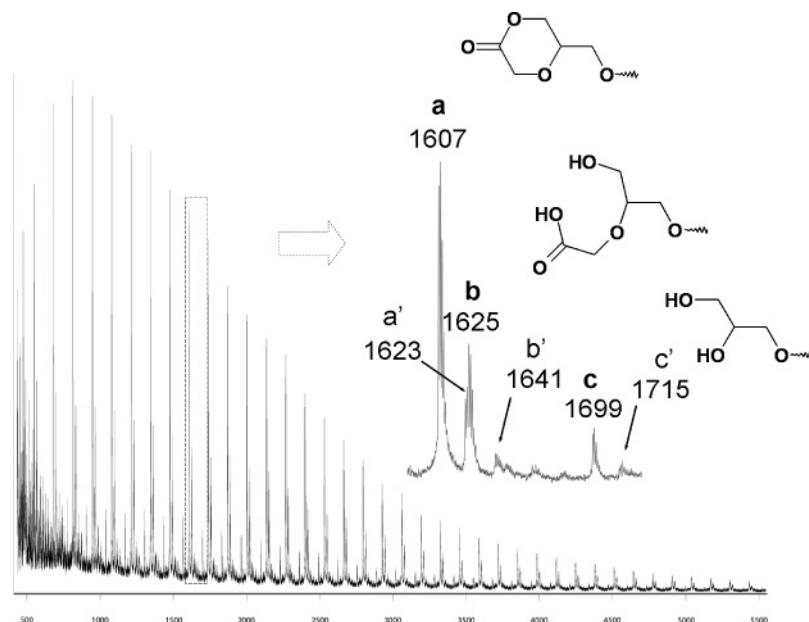
In Figure 3 the MALDI-TOF mass spectrum of the polymer obtained by spontaneous polymerization is shown. In the spectrum there are three series of signals corresponding to polyester macromolecules. The peaks of each series are characterized by a mass increment of 132 Da. This mass increment equals the mass of the repeating unit in polyester

containing glycerol and glycolic acid subunits. The most intensive series of signals (**a**) can be assigned to the sodium cation adduct of the macromolecules containing **4** as the core (residual mass 132 Da). The less intensive series of signals (**b**) corresponds to the macromolecules containing hydrolyzed 5-HDON as the core unit (150 Da). The third series of peaks (**c**) of the smallest intensity corresponds to the macromolecules containing a glycerol core (92 Da). In the mass spectrum besides series of the signals (**a**–**c**), which can be assigned to sodium cation adducts, there are series of the signals (**a'**–**c'**) that correspond to the potassium cation adducts. Similar mass spectra were registered for other obtained polymers.

The GPC analysis showed that the polymerization carried out at 75 °C for 24 h yielded high molecular weight polymers of a relatively low polydispersity (Table 1). It is noteworthy that all the samples contained a low molecular weight fraction of ~400 Da, which could be assigned to the trimeric cyclic oligomers (396 Da) of **4**.

It was found that the polymer obtained using DBU as a catalyst (Table 1, **P3**) is partly soluble in chloroform and completely soluble in DMSO. The fraction soluble in chloroform was isolated and characterized. The GPC experiment showed a molecular weight M_n of ca. 500, which refers to 5–6 repeating units in the molecule. The ¹H NMR spectrum shown in Figure 4 confirms an almost exclusively linear structure of the polymer fraction soluble in chloroform.

The spectrum presented in Figure 4 is similar to the spectrum of monomer **4**. However, because of the presence of chiral 5-C carbon atoms in the polymeric structure, both meso and racemic dyads can be formed during polymerization. The irregular structure of the polymer induces additional splitting of the

**Figure 3.** MALDI-TOF mass spectrum (HABA/MeOH) of poly(5-HDON) (**P1**).

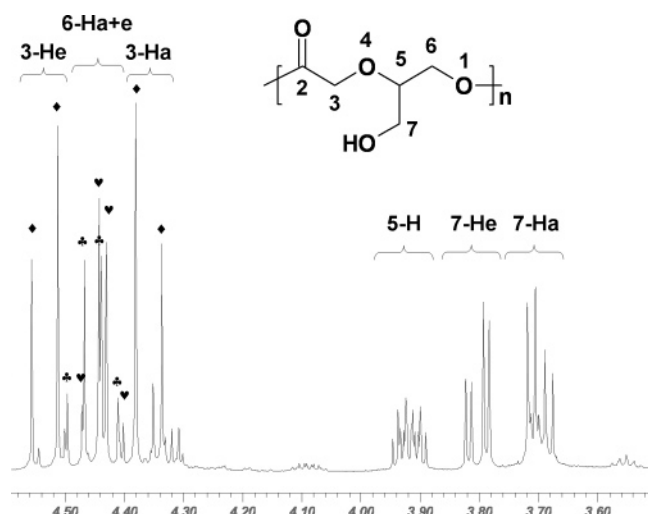


Figure 4. ^1H NMR (400 MHz) spectrum of the linear fraction of poly-(5-HDON) soluble in CDCl_3 .

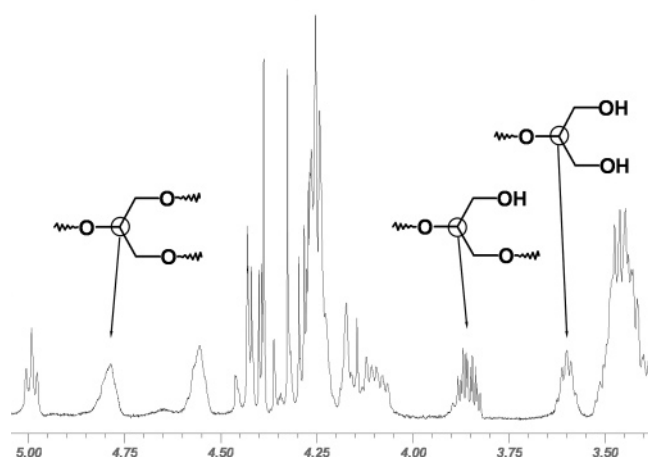


Figure 5. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) spectrum of poly(5-HDON) (P3).

signals corresponding to 5-H and 7-H protons. The OH protons are not shown in Figure 4 and appear at 2.2 ppm as a broad singlet.

In the ^1H NMR ($\text{DMSO}-d_6$) spectrum of the polymer obtained in the presence of DBU there are proton signals corresponding to disubstituted, monosubstituted, and nonsubstituted hydroxymethyl groups which confirms the hyperbranched nature of the molecule. The most significant are the signals of the 5-H protons, which are marked in Figure 5. A similar spectrum was obtained for the fraction insoluble in chloroform.

In addition, in the ^1H NMR spectrum of the “native” polymer **3b** obtained during the synthesis of **4** there are signals at 3.6 ppm corresponding to the terminal CH_2OH groups and 3.85 ppm corresponding to linear units (Figure 4), but there are no signals at 4.8 ppm characteristic for the branching point units observed for the polymer obtained by anionic polymerization of **4** (Figure 5). These results confirm linear structure of **3b**. The integrals ratio indicates a low molecular weight of the polymer **3b**. It was found that higher molecular weight as well as a higher degree of branching precludes thermal depolymerization of the polymer leading to the cyclic monomer.

A closer look into the structure of the polymers gives the ^{13}C APT NMR spectrum shown in Figure 7. To facilitate the assignment of ^{13}C NMR signals of poly(5-HDON), model compounds **5–7** representing subunits B, C, and D were synthesized (Scheme 2).

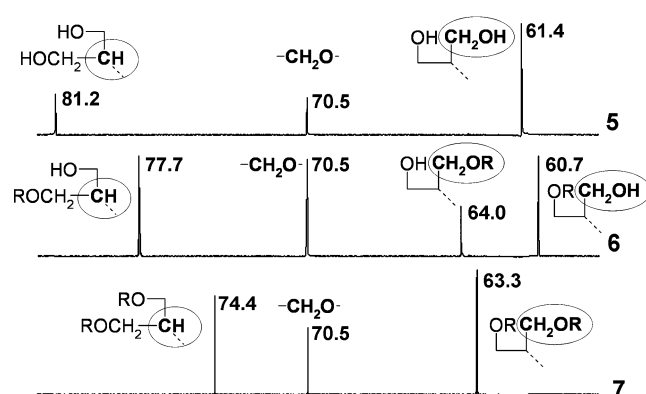


Figure 6. Methylene and methine group region of the ^{13}C NMR (400 MHz, $\text{DMSO}-d_6$) spectra of the model compounds **5–7**.

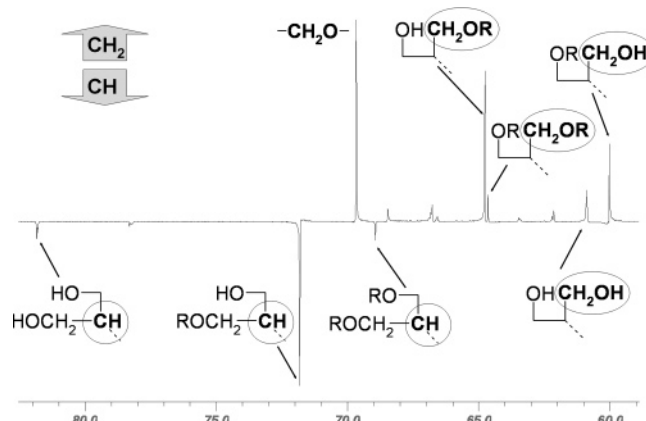
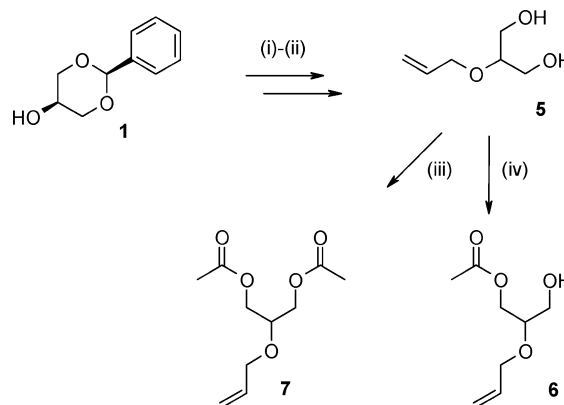


Figure 7. ^{13}C APT NMR (400 MHz, $\text{DMSO}-d_6$) spectrum of the poly-(5-HDON) (P3).

Scheme 2. Synthesis of Model Compounds^a



^a (i) NaH, $\text{BrCH}_2\text{CH}=\text{CH}_2$, THF, rt, 73%; (ii) 3% HCl_{aq} , ethanol, rt, 96%; (iii) acetic anhydride (excess), reflux, 90%; (iv) acetic anhydride (1:1), rt, 40%, column flush chromatography.

Figure 6 shows the chemical shifts of the carbon atoms of the model compounds **5–7** and the related chemical structures. Related ^{13}C resonances of the model compounds can be found in the spectrum of poly(5-HDON) (Figures 6 and 7).

The signals at 60.0 and 60.9 ppm, corresponding to carbon atoms of the CH_2OH group of the linear and terminal units, respectively (Figure 2), can be used to determine the polymer structure depending on the polymerization conditions and the catalyst used.

Figure 8 shows the comparison of intensities of the CH_2OH carbon atom signals for polymer samples obtained under different reaction conditions. The fragment of spectrum (a) shows that the spontaneously formed polymer **P1** contains both

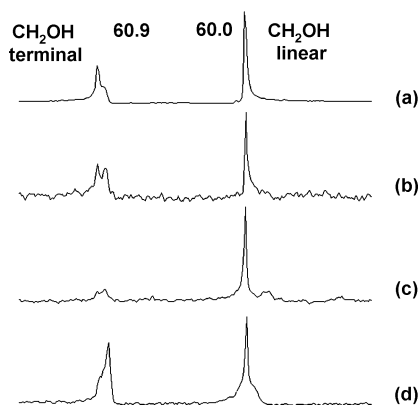
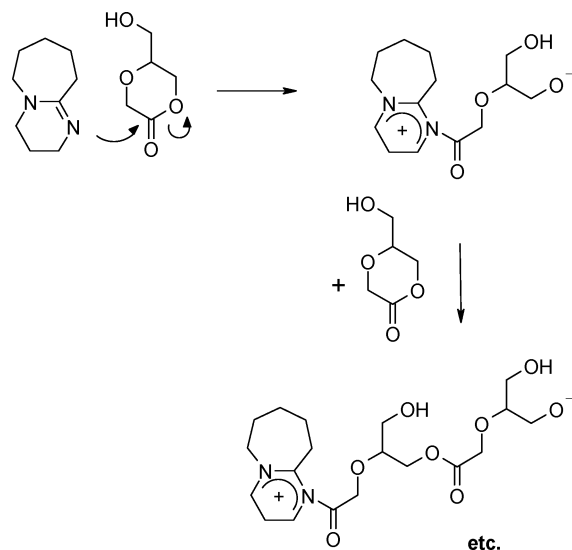


Figure 8. ^{13}C NMR signals of the CH_2OH groups depending on the catalyst used for polymerization: (a) spontaneous polymerization (**P1**), (b) DBU (**P5**), (c) $\text{Sn}(\text{Oct})_2$, 24 h, (**P2**), (d) $\text{Sn}(\text{Oct})_2$, 72 h, (**P6**).

Scheme 3. Mechanism of an Anionic Polymerization of **4** in the Presence of DBU



terminal and linear units (C and D in Figure 2). This confirms the hyperbranched structure of the polymer, as the high concentration of terminal groups must be accompanied by the respective amount of branching substructures (B in Figure 2). If the structure was linear, the intensity of the terminal groups would be negligible. The fragment of the spectrum (b) corresponding to the polymer formed with an anionic catalyst (**P5**), is very similar to the spectrum (a).

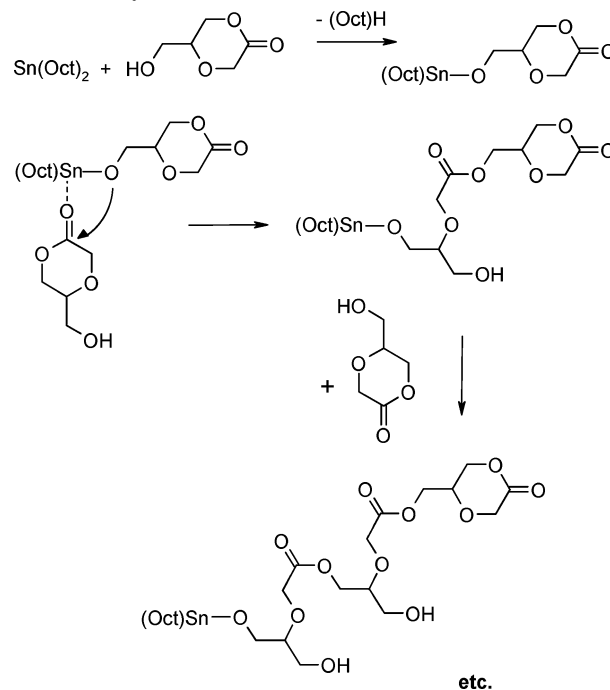
Scheme 3 shows the mechanism of the anionic polymerization of **4** initiated with DBU, analogous to that published by Endo et al.¹⁴

The presence of alcoholate reaction centers makes proton transfer from various OH groups possible, and the polymer with higher amount of B–D subunits can be formed (Figure 2).

In contrast, in the spectrum of the polymer synthesized in the presence of $\text{Sn}(\text{Oct})_2$ as a catalyst (**P2**) (c, Figure 8) at lower temperature (75 °C) the intensive signal which can be assigned to the linear subunit C predominates. Under these conditions monomer **4** undergoes coordination–insertion ROP (Scheme 4).^{9,16}

It is worth mentioning that stannous octoate can also act as a transesterification catalyst. If a sample of a monomer or polymer (**P6**, **P7**) is heated at 110 °C for an extended period of time in the presence of $\text{Sn}(\text{Oct})_2$, the branched structures start to appear (Figure 8d).

Scheme 4. Mechanism of a Coordination–Insertion Polymerization of **4** in Presence of $\text{Sn}(\text{Oct})_2$



Samples **P4** and **P5** did not show much change in the spectrum in comparison to the starting material **P1**.

The most common method for establishing the degree of branching was developed by Fréchet et al.¹⁷ Using the definition of Fréchet, the degree of branching of 0.53 was determined for the polymer obtained in the presence of DBU as a catalyst at 75 °C.

It is important to note that in contrast to polymer obtained from 6-HDON, in which primary and secondary hydroxyl groups of different reactivity are present,⁷ polymerization of 5-HDON leads to more branched and of the higher molecular weight polymer containing solely primary hydroxyl groups.

Conclusions. The monomer 5-hydroxymethyl-1,4-dioxan-2-one was synthesized and used for the ring-opening polymerization yielding a high molecular weight hyperbranched polyester. The chemical structures of the monomer and the polymer were analyzed by means of ^1H and ^{13}C NMR as well as MALDI-TOF spectrometries and GPC chromatography. Depending on the catalyst and reaction conditions, the almost linear or hyperbranched polymers based on glycerol and glycolic acid can be obtained. The unique attribute of the obtained polymers is the presence of primary hydroxyl groups. An abundance of hydroxyl functionality significantly improves the hydrophilicity, a goal long sought for aliphatic polyesters. The same reactivity OH groups, present in a high quantity on the outer sphere of the macromolecules, can be further modified, making the poly-(5-HDON) a promising material for drug delivery.

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