Preparation of Hyperbranched Aliphatic Polyester Derived from Functionalized 1,4-Dioxan-2-one

Xiang-hua Yu,[†,§] Jun Feng,[‡,§] and Ren-xi Zhuo*[,‡]

School of Material Science and Engineering, Wuhan Institute of Chemical Technology, and Key Laboratory of Biomedical Polymers (The Ministry of Education), Department of Chemistry, Wuhan University, Wuhan, 430072, China

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Introduction. Poly(1,4-dioxan-2-one) (PDON), generally prepared by ring-opening polymerization of 1,4-dioxan-2-one (DON), has been widely used as biodegradable monofilament suture material. Currently, the improvement of polymer structure and property has dominated the investigation about PDON. However, copolymerization with other cyclic monomers such as lactones is the most popular strategy for such an aim, and the study about direct modification of DON and PDON architectures has been seldom reported.[1]

This paper first describes the synthesis of a hydroxyl-functionalized DON substitute, 6-hydroxymethyl-1,4-dioxan-2-one (HDON), through relatively simple steps (Scheme 1). It is known that hyperbranched structure may endow the polymer with unique mechanical and rheological properties.[2,3] Therefore, HDON was further designed for the preparation of hyperbranched polymer by self-condensing ring-opening polymerization (SCROP). Because of the repeating units of poly(HDON) consisting of glycerol and glycolic acid, it may be biodegradable and biocompatible. More interestingly, a large number of hydroxyl groups at the side chains of this hyperbranched polyester allow further surface modification and facilitate covalent prodrug attachment.

Experimental Section. a. General Procedures. 2,2-Dimethyl-1,3-dioxolane-4-methanol was synthesized from glycerol according to the literature; bp 72−73 °C/8 mm.[4] Toluene was dried over sodium before use. All other reagents were of analytical grade.

The ^{1}H NMR spectrum of HDON was recorded on a Varian Mercury-VX 300 MHz NMR spectrometer operating at 300 MHz. All other NMR spectra were recorded on a Varian INOVA 600 MHz NMR spectrometer equipped with ^{1}H and ^{13}C inverse probes, operating at 600 MHz for ^{1}H and 150 MHz for ^{13}C at 25 °C. $CDCl_3$ or DMSO-d_6 was used as solvent and TMS as internal standard. The gHSQC spectrum was recorded using the standard pulse programs. The quantitative ^{13}C spectrum was recorded at 150 MHz using a NOE suppressed, inverse gated proton-decoupling technique.

The FTIR spectrum was recorded on a Perkin-Elmer-2 spectrometer. The sample was film-cast in $CHCl_3$ onto sodium chloride. GPC analysis was carried out on a Waters high-performance liquid chromatographic system equipped with a 2690D separation module, a 2410 refractive index detector, and Shodex K803 and K805 columns. DMF was used as the eluent at a flow rate of 1.0 mL/min.

b. Synthesis of 6-Hydroxymethyl-1,4-dioxan-2-one (HDON). 2,2-Dimethyl-1,3-dioxolane-4-methanol (13.35 g, 0.101 mol) and anhydrous toluene (150 mL) were placed in a 250 mL flask with a vigorous stirring. Fresh sodium (2.37 g, 0.103 mol) was added within 0.5 h. The resulting mixture was then cooled to room temperature and treated with sodium chloroacetate (11.65 g, 0.100 mol). After refluxed with stirring for further 2 h, toluene was removed under reduced pressure. The residue was washed thoroughly with ethyl ether and then acidified by concentrated HCl. After stirring for 48 h, the mixture was concentrated and washed with THF. The filtrate was combined, concentrated, and distilled to give the crude product. Redistillation with $MgCO_3$ and successive fractional distillation for two times gave a slightly yellow liquid (8.03 g, yield: 60.8%); bp 118−122 °C/0.1 mm. FTIR (NaCl plates, cm^{-1}): 3445 (ν-OH), 1744 (νC=O). ^{1}H NMR ($CDCl_3$, ppm) (Figure 1b): δ 3.36 (1H, broad s, −O*H*), 3.71−3.88 (3H, m, CH_2−OH and 5-H$_a$), 3.94−3.99 (1H, q, 5-H$_e$), 4.22−4.41 (2H, d, d, 3-H$_a$ and 3-H$_e$), 4.60−4.66 (1H, m, 6-H). ^{13}C NMR ($CDCl_3$, ppm) (Figure 1c): δ 61.22 (*C*H$_2$−OH), 63.60 (5-C), 65.66 (3-C), 79.49 (6-C), 168.27 (2-C).

c. Polymerization of HDON. The SCROP of HDON was performed in bulk at 110 °C. The monomer and catalyst of Sn(Oct)$_2$ in toluene solution were placed in a dried flask with a magnetic stirring. The vessel was degassed by several vacuum−purge cycles to remove the solvent introduced from the initiator solution. The flask was then sealed under vacuum and immersed in an oil bath at 110 °C for a predetermined reaction time. The product was dissolved in methanol and then poured into a great amount of dichloromethane. The precipitated polymer was dried in a vacuum at 25 °C for 24 h.

Results and Discussion. a. Monomer Synthesis. The synthetic pathway for the preparation of HDON is shown in Scheme 1. Though theoretically there existed two possible products according to ring-closure route, six-membered 6-hydroxymethyl-1,4-dioxan-2-one (HDON) was finally obtained rather than seven-membered 6-hydroxyl-1,4- dioxapan-2-one (HDOX), judging by the analysis of the NMR spectrum (Figure 1).

We have employed the gHSQC spectrum to attribute the methine and methene chemical shift of HDON (Figure 1a). The assignments of protons and carbons are shown in Figure 1b,c. As Shown in Figure 1b, the signal of the 6-CH proton was found at the lowest field (at 4.60−4.66 ppm) for the deshielding effect of the carboxyl bond. It was multiple-peaked due to the coupling of the 5-CH_2 and CH_2OH methene protons. If the seven-membered HDOX would exist, two quartet signals given by an AMX system should have been found at the lowest field, which would be assigned to two 7-CH_2 protons owing to the deshielding effect of the carboxyl bond. Since the carbon which was present at the lowest field correlated with one but not two protons in gHSQC spectrum, it was confirmed that the monomer shoud be six-membered HDON but not seven-membered HDOX. The 3-CH_2 protons (at 4.22−4.41 ppm) showed an isolated AB system with $^2J_{3Ha,3He}$ of −17.4 Hz, which was in agreement with that of other DON substitutes

[†] Wuhan Institute of Chemical Technology.
[‡] Wuhan University.
[§] Equal contribution.
* To whom correspondence and reprint requests should be addressed: Fax (+86) 27-68754509; e-mail pibmp@public.wh.hb.cn.

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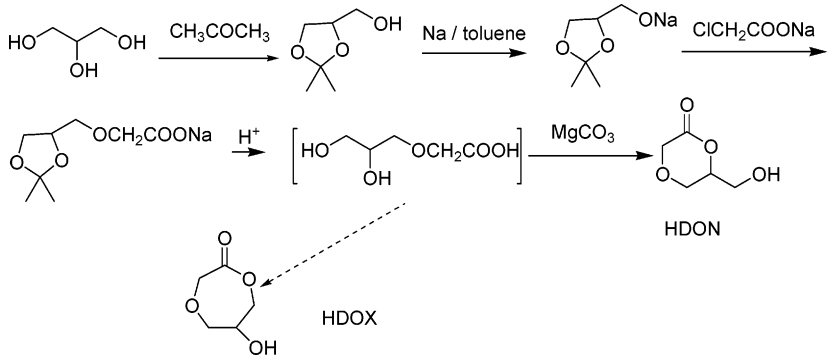
Scheme 1. Synthetic Pathway for Glycerol-Based Functionalized Monomer HDON



reported.[5−7] The 5-CH_2 protons with 6-CH proton as well as the CH_2OH methene protons with 6-CH protons formed two AMX systems. The signal of one of the 5-CH_2 protons was found at 3.94−3.99 ppm ($^2J_{5Ha,5He}$ was −12.6 Hz and $^3J_{5He,6H}$ was 3.6 Hz). The signal of another was overlapped with that of the CH_2OH methene protons. The chemical shift spacing between the signals of two 5-CH_2 protons of HDON was broad because the preferred half-chair conformation of six-membered DON substitute aroused great nonequivalence of the axial and equatorial protons.[5,7,8]

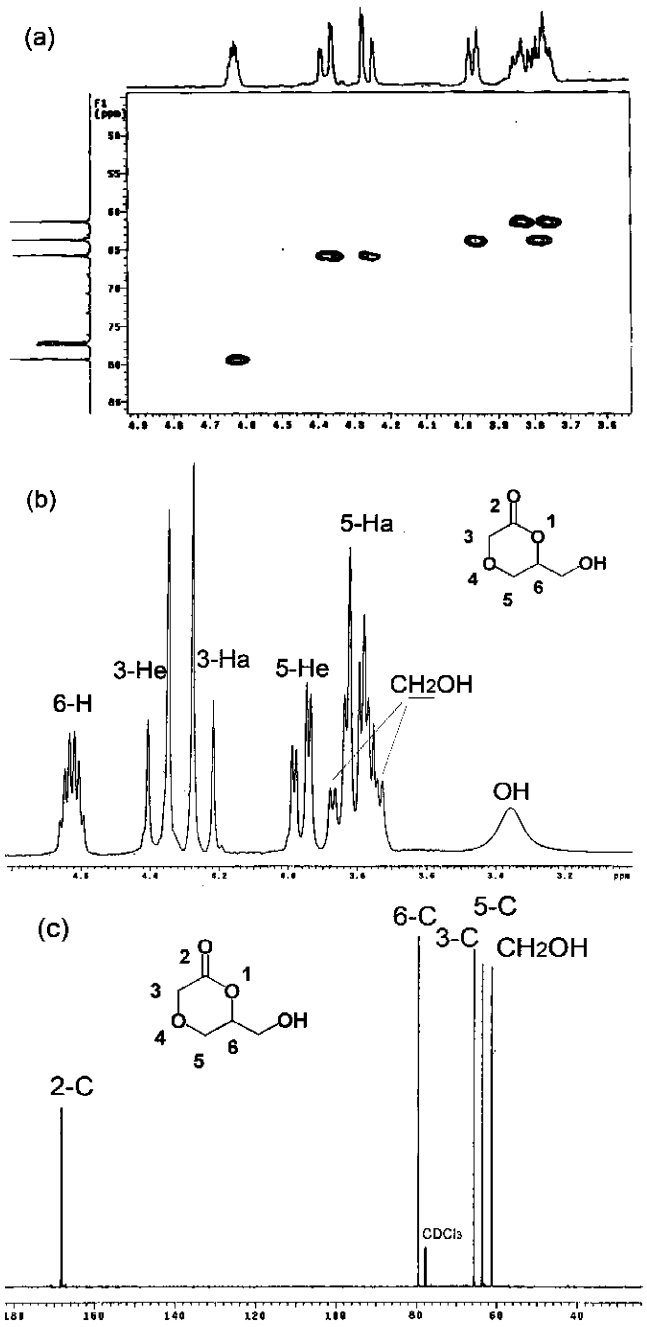


Figure 1. NMR spectra of HDON (a, gHSQC; b, ^{1}H NMR; c, ^{13}C NMR, $CDCl_3$).

Table 1. SCROP of HDON Using $Sn(Oct)_2$ as Catalyst[a]

entry	[M]/[I][b]	time (days)	M_n	M_w/M_n	yield (%)
1	100	6	9 500	2.5	95
2	800	6	7 800	3.0	95
3	400	1	22 800	2.1	97
4	400	2	25 600	2.0	98
5	400	4	23 300	2.1	96
6	400	6	23 700	2.2	98
7	400	8	22 600	2.2	96

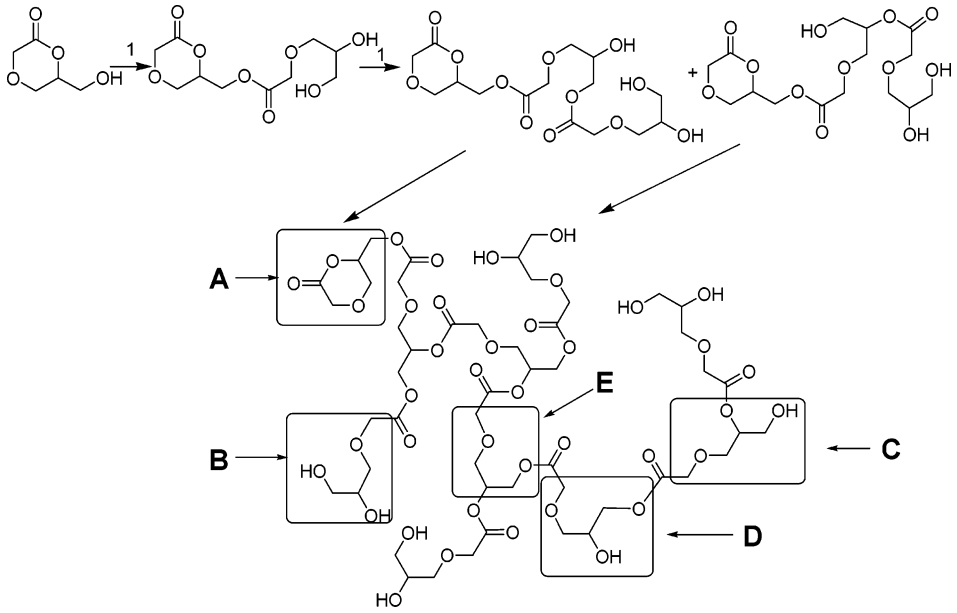
[a] Polymerization temperature: 110 °C, in bulk. [b] Molar ratio of monomer to catalyst.

b. Ring-Opening Polymerization of HDON. Polymerization of HDON in the presence of $Sn(Oct)_2$ produced hyperbranched poly(HDON) with M_n of 7800−25 600 g/mol and polydispersities of 2.0−3.0 (Table 1). The polymerization showed relatively rapid reaction rate when the catalyst concentration was fixed at 1/400 (molar ratio in feed). It was found the monomer conversion had no marked change around 98% as the reaction proceeded after 1day. Once the maximum of the molecular weight reached 25 600 g/mol during 2 days, prolonged reaction time led to a slight decrease in the molecular weight value. Catalyst concentration also had a strong influence on the molecular weight of the product. The data indicated that comparatively too high (1/100) or low $Sn(Oct)_2$ concentration(1/800) cannot afford higher molecular weight during 6 days reaction. The higher molecular weight (M_n = 23 700 g/mol) was obtained at an $Sn(Oct)_2$ concentration of 1/400. Polydispersities of all obtained polymers were comparatively broad, indicating characteristic of self-condensing polymerizations.[9]

The degree of branching (DB) is an important property of hyperbranched polymers. It is defined as DB = (no. of dendritic units + no. of terminal units)/(no. of dendritic units + no. of terminal units + no. of linear units). Both ^{1}H NMR and quantitative ^{13}C inverse gated NMR have been utilized to determine DB.[10,11]

The structure of the polyester included five possible subunits, A, B, C, D, and E (Scheme 2). A and B were terminal units. C and D were linear units while E was dendritic unit. The amount of terminal unit A could be ignored without significantly affecting the DB calculation since it would not be present as a result of the

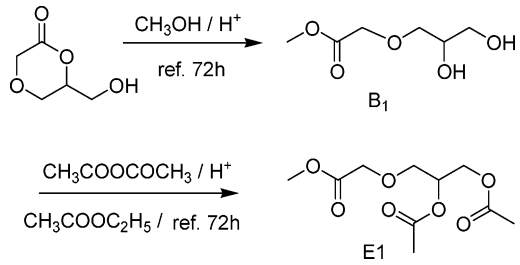
Scheme 2. SCROP of HDON and Possible Subunits in Poly(HDON)



intramolecular side reaction. [12] So the DB of polymer could be calculated from the fraction of subunits as DB = (B + E)/(B + E + C + D).

To facilitate the assignment of ^{13}C NMR signals of poly(HDON), two model compounds B1 and E1 representing subunits B and E were synthesized as shown in Scheme 3. ^{13}C NMR spectra of B1 and E1 and the ^{13}C inverse gated spectrum of poly(HDON) are shown in Figure 2. All related ^{13}C resonances of model compounds B1 and E1 could be found in the spectrum of poly(HDON) with M_n of 25 600, which was assigned to the corresponding carbons of subunits B and E in poly(HDON). The content of linear unit D should be higher than that of linear unit C since the initiating activity of the primary hydroxyl group is higher than that of the secondary one. Therefore, though the ^{13}C resonances of C and D were unknown, both of them can also be easily assigned according to the integral intensity. The DB of hyperbranched poly(HDON) was determined to be 0.40 according to the corresponding integral of each subunit in quantitative ^{13}C inverse gated spectrum.

Scheme 3. Synthetic Pathway for Model Compounds B1 and E1



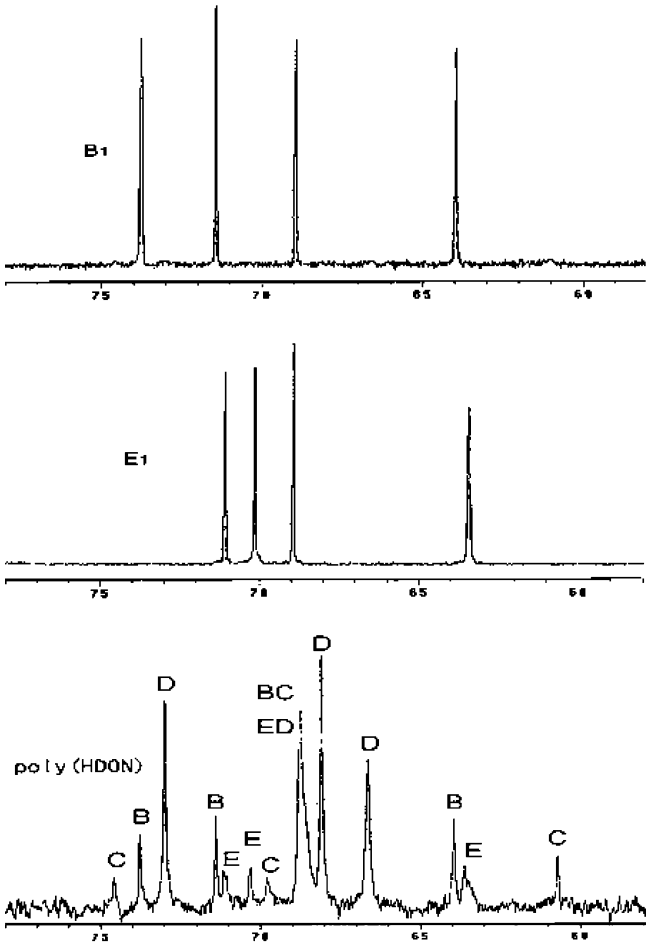


Figure 2. ^{13}C NMR spectra of model compounds B1 and E1 and ^{13}C inverse gated NMR spectrum of poly(HDON) (DMSO-d_6).

Conclusion. A novel cyclic monomer, 6-hydroxymethyl-1,4-dioxan-2-one (HDON), was synthesized with relatively simple steps. SCROP of HDON was performed at 110 °C in the presence of $Sn(Oct)_2$ to afford the corresponding hyperbranched polyester. The degree of branching (DB) of the polyester with M_n of 25 600 was determined to be 0.40 by quantitative ^{13}C inverse gated NMR spectrum analysis.

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Supporting Information Available: NMR spectra of HDON and HDOX, ^1H NMR spectrum of HDON, and struc-

tures of compounds B1−E1 and B−E. This material is available free of charge via the Internet at http://pubs.acs.org.

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