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SYNTHESIS AND PROCESSING OF POLYMERS AND POLYMERIC COMPOSITES

СИНТЕЗ И ПЕРЕРАБОТКА ПОЛИМЕРОВ И КОМПОЗИТОВ НА ИХ ОСНОВЕ

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RESEARCH ARTICLE

Polymerization of D,L-lactide in the presence of Boltorn™ polyester polyol

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Abstract

Objects. *To synthesize monodisperse biodegradable hyperbranched polymers based on D,L-lactide in the presence of Boltorn™ H30 polyester polyol as a macroinitiator.*
Methods. *^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy was used to study the chemical structure of the Boltorn™ H30 polyester polyol and (Boltorn™ H30)-PDLA hyperbranched copolymers. The molecular weight distribution of the polymers was studied by gel permeation chromatography (GPC). In order to study the thermal stability of Boltorn™ H30 polyester polyol, thermogravimetric analysis (TGA) was used. Polymerization of D,L-lactide was carried out in a block in the presence of Boltorn™ H30 polyester polyol.*
Results. *The degree of branching of Boltorn™ H30 polyester polyol was calculated from NMR data, while the TGA method was used to determine the upper operational temperature range. The polymerization of D,L-lactide in the presence of Boltorn™ H30 polyester polyol used as a macroinitiator was studied. The molecular weight characteristics of the obtained copolymers were studied by NMR and GPC.*

Conclusions. *Optimum conditions were determined for the polymerization of D,L-lactide when using Boltorn™ H30 polyester polyol as a macroinitiator. The possibility of synthesizing narrowly dispersed hyperbranched polymers (Boltorn™ H30)-PDLA under the described conditions was demonstrated.*

Keywords: *hyperbranched polymers, biodegradable polymers, polylactide, Boltorn™ polyester polyols*

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НАУЧНАЯ СТАТЬЯ

Полимеризация D,L-лактида в присутствии полиэфирполиола Boltorn™

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Аннотация

Цели. *Синтез узкодисперсных биоразлагаемых сверхразветвленных полимеров на основе D,L-лактида в присутствии полиэфирполиола Boltorn™ H30 в качестве макроинициатора.*
Методы. *Для исследования химической структуры полиэфирполиола Boltorn™ H30 и сверхразветвленных сополимеров (Boltorn™ H30)-PDLA использовали* ^1H *и* ^{13}C *спектроскопию ядерного магнитного резонанса (ЯМР). Молекулярно-массовое распределение полимеров исследовали методом гель-проникающей хроматографии (ГПХ). Для исследования термической стабильности полиэфирполиола Boltorn™ H30 применяли метод термогравиметрического анализа (ТГА). Полимеризацию D,L-лактида в присутствии полиэфирполиола Boltorn™ H30 проводили в блоке.*
Результаты. *По данным ЯМР была рассчитана степень разветвленности полиэфирполиола Boltorn™ H30. Методом ТГА определен верхний температурный диапазон работы с полиэфирполиолом Boltorn™ H30. Исследована полимеризация D,L-лактида в присутствии полиэфирполиола Boltorn™ H30 в качестве макроинициатора. Молекулярно-массовые характеристики полученных сополимеров исследованы методами ЯМР и ГПХ.*
Выводы. *Подобраны оптимальные условия полимеризации D,L-лактида в присутствии полиэфирполиола Boltorn™ H30 в качестве макроинициатора. Показана возможность синтеза узкодисперсных сверхразветвленных полимеров (Boltorn™ H30)-PDLA в этих условиях.*

Ключевые слова: *сверхразветвленные полимеры, биоразлагаемые полимеры, полилактид, полиэфирполиолы Boltorn™*

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INTRODUCTION

Targeted drug delivery has become one of the leading directions of the medical research. While modern methods of treating diseases still employ a wide range of traditional drugs in the form of capsules, tablets, patches, injections, etc., polymer micro- and nanoparticles have been successfully used in the creation of new effective forms of drug delivery, allowing drugs to be delivered purposefully to the focus area of an inflammatory or pathological process [1]. One of the most promising directions in this field involves the use of nanoparticles based on lactide copolymers of varying topologies [2]. Due to the ability to decompose in a living organism without the formation of toxic products, polylactide (PLA) and its copolymers are widely used in surgery, orthopedics and dentistry, as well as in the capacity of carrier polymers for long-acting injectable dosage forms [3, 4].

Today, hyperbranched polymers, which differ significantly from linear, star-shaped and cross-linked analogues, have become increasingly important. As a rule, hyperbranched polymers have a spatially unloaded core, as well as a large number of free functional groups located in the surface layer. A special place among hyperbranched polymers is occupied by the polyester polyols based on 2,2-bis(hydroxymethyl)propionic acid. Such polyesters marketed under the Boltorn™ brand are widely used as auxiliary agents and modifiers in the production of synthetic resins, polyurethanes, organic glasses, etc. These polyesters are widely used in the production of biodegradable copolymers for targeted drug delivery due to the presence of a large number of hydroxyl groups [5, 6].

In recent decades, there has been increasing interest in the synthesis and study of the properties of highly branched polymers, whose main features in comparison with linear analogues are their smaller molecular sizes, higher density macromolecule structure, and lower viscosity values. Such high-molecular substances, which include polymer brushes, dendrimers, star-shaped and hyperbranched polymers, differ significantly in properties from their linear analogues. Their main distinguishing feature lies in the possibility of consistently regulating their structure and concomitant properties. From this point of view, star-shaped and hyperbranched polymers having free reactive functional groups, whose structure-dependent properties can be altered within broad limits, are of particular interest [7–10]. By carrying out additional modification of functionalized polymers, it becomes possible to obtain copolymers with regulated colloidal chemical properties [11–12].

Boltorn™ polyesters marketed under the H20, H30, and H40 product line comprise progressively branching dendrite-like macromolecules differing in molecular weight and average number of hydroxyl groups (16, 32, and 64, respectively) (Fig. 1). As biocompatible and biodegradable polymers, they offer bioavailability, bio-permeability, and low toxicity (LD_{50} = 2000 mg/kg). Although well soluble in some polar solvents, such as dimethylformamide (DMFA), dimethyl sulfoxide (DMSO), acetone, etc., polyester polyols of the Boltorn™ family do not dissolve in methylene

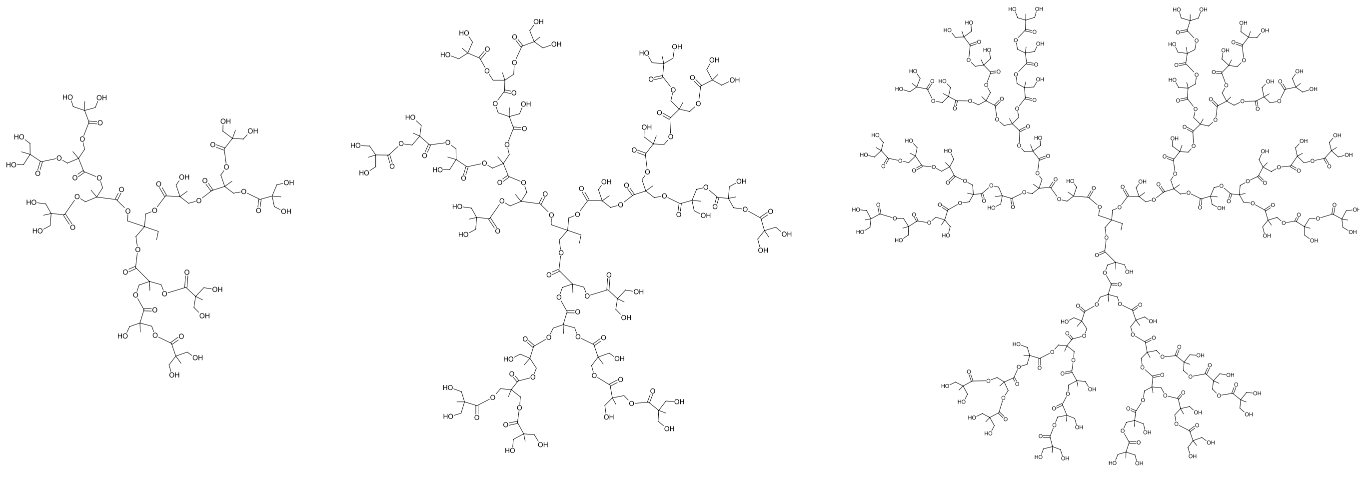

(1) (2) (3)

Fig. 1. Structure of Boltorn™ polyesters: (1) H20, (2) H30, and (3) H40.

chloride, tetrahydrofuran (THF), ethyl acetate, or acetonitrile. The pronounced intramolecular and intermolecular hydrogen bonds of polyester polyols, which persist even at elevated temperatures, is due to the presence of a large number of proton-donating and proton-acceptor groups in their structure [6].

A number of studies have shown that Boltorn™ polyester polyols can be used as a macroinitiator during copolymerization with L-lactide, ε-caprolactone, and glycolide [13–15], allowing macromolecules of high molecular weight to be obtained, along with the possibility of loading the hydrophobic core of the molecule with medicinal substances for targeted delivery. In this paper, studies of polymerization of D,L-lactide in the presence of Boltorn™ polyester have been carried out H30 as a macroinitiator.

EXPERIMENTAL

Boltorn™ H30 polyester polyol (M_w = 3608 g/mol; polydispersity index 1.78; ρ = 1.3 g/cm^3) and 2-ethylhexanoate of tin ($Sn(Oct)_2$) with 97% purity (*Acros Organics*, Belgium) were used without additional purification. D,L-lactide (*Purac*, Netherlands) was recrystallized twice from chemically pure butyl acetate (*Merck*, Germany).

Multiarm block copolymers Boltorn-$[(PDLA)_x]_y$ were synthesized in the block by polymerization with the opening of the cycle (ring-opening polymerization) of D,L-lactide, using Boltorn™ H30 (B32) polyester polyol as a polymerization macroinitiator, tin(II)2-ethylhexanoate ($Sn(Oct)_2$), and tin(II)2-ethylhexanoate ($Sn(Oct)_2$) as a catalyst. The synthesis was carried out as follows: an estimated quantity of macroinitiator (B32), D,L-lactide was loaded into a pre-calcined conical flat-bottomed reaction flask along with a catalyst solution in chemically pure hexane (*Merck*). After evaporating the hexane at reduced pressure, the flask was filled with an inert gas, hermetically sealed and placed in an oil bath. Polymerization was carried out with continuous stirring of the reaction mass for a given time. The obtained copolymers were isolated and purified from the catalyst and monomer residues by double precipitation in the tetrahydrofuran–hexane system, and then dried to a constant mass in a vacuum oven. The synthesis scheme is shown in Fig. 2.

Thermogravimetric studies were carried out on a Pyris 1 TGA device (*PerkinElmer*, USA) in dynamic mode in the temperature range 30–700°C in a nitrogen flow (99.999%) of 100 mL/min using a standard open platinum sample cup holder. The accuracy of temperature determination was 0.1°C, while the accuracy of the scales was up to 0.001 mg. The heating rate was 10°C/min. The experimental data were processed using the Pyris Software Thermal Analysis software package version 10.1.0.0412 (*PerkinElmer*).

Deuterated solvents were used for nuclear magnetic resonance (NMR) assays: 99.96% deuterated chloroform $CDCl_3$ (*Sigma-Aldrich*, Germany) and 99.8% DMSO-d_6 (*Sigma-Aldrich*). The NMR spectra were recorded on the AVANCE DPX high-resolution NMR spectrometer (*Bruker*, Germany).

The molecular mass characteristics of copolymers were determined by gel permeation chromatography (GPC) on the AZURA chromatographic system (*Knauer*, Germany) using a refractometric detector and a Phenogel™ column (*Phenomenex*, USA) with a size of 300 × 7.8 mm and a particle pore size of 10^4 Å and 10^5 Å. The columns were calibrated according to polystyrene standards. The studies were carried out at 40°C with an eluent flow rate of 1 mL/min. A polymer solution in 99.9% tetrahydrofuran for high performance liquid chromatography (*Sigma-Aldrich*) was prepared for the study with a concentration of 2–5 mg/mL. Prior to introduction into the chromatograph, the solution was filtered through a syringe filter with a hydrophobic membrane with a pore size of 0.45 µm.

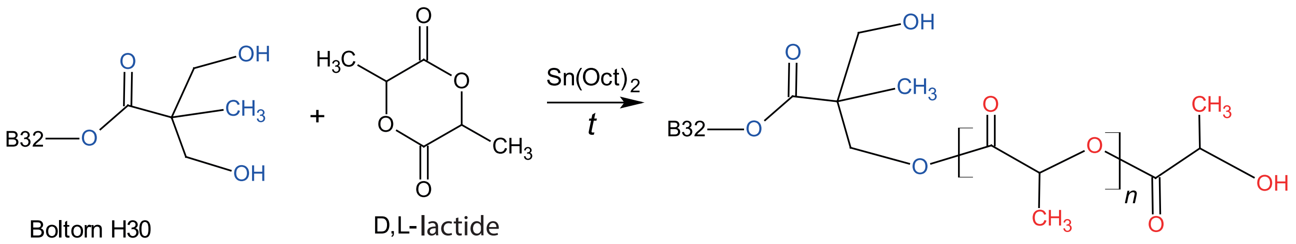


Fig. 2. Scheme for the synthesis of Boltorn™-$[(PDLA)_x]_y$ multiarm copolymers.

RESULTS AND DISCUSSION

The degree of branching of polymer macromolecules, which is closely related to their physicochemical properties, is an important parameter for their characterization. The structure of hyperbranched polyester polyols features not only dendritic (branching) and terminal (terminal) repeating structural units, but also linear links with unreacted functional groups (Fig. 3).

In order to assess the degree of branching of the investigated Boltorn™ H30 polyester polyol, proton and carbon NMR spectra were obtained in deuterated DMSO (Fig. 4). In order to detect weak interactions and improve the resolution of the signal, samples with a low concentration were used in the analysis.

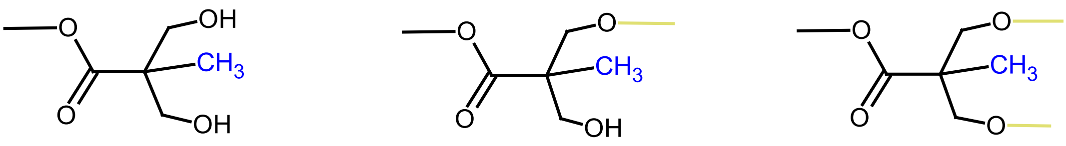
In the ^{1}H NMR spectrum there are signals corresponding to methyl (three types: linear, dendritic, and terminal, a group of signals at 0.95–1.25 ppm), methylene (two types: $–CH_2–OH$ at 3.3–3.6 ppm and $–CH_2–OR$ at 3.9–4.2 ppm) and hydroxyl groups (4.3–5.0 ppm). Since the DMSO contains traces of water, there is a broadening of the signal in the region of 4.3–5.0 ppm.

To describe the structure of hyperbranched polymers, Fréchet [16] introduced the term "degree of branching" (DB) as a function of the ratio between dendritic (D), linear (L) and terminal (T) structural units calculated by the following ratio:

$$\mathrm{DB} = \frac{\mathrm{D}+\mathrm{T}}{\mathrm{D}+\mathrm{L}+\mathrm{T}}$$

Based on the data on the signal intensities of methyl groups of various types of links, we obtain the following ratio of terminal, linear, and dendritic types of links: 24%, 59%, and 17%, respectively. The degree of branching calculated by the formula is 0.4, which corresponds to the literature data for hyperbranched polymers [17].

Block copolymers based on D,L-lactide are usually synthesized in a melt at temperatures above 130°C. In order to study the thermal stability of Boltorn™ H30 polyester polyol, the thermogravimetric analysis (TGA) method was used to set the temperature of the beginning of thermal degradation of the polymer; this also determines the upper temperature range of operation with the polymer. Boltorn™ H30 polyester was studied both in dynamic (heating rate is 10°C/min) and in isothermal mode (160°C, 170°C, and 180°C). According to the obtained thermograms (Fig. 5), thermal oxidative degradation of Boltorn™ H30 polyester is observed at 200–220°C,



Terminal (T)

Linear (L)

Dendritic (D)

Fig 3. Basic repeating building blocks of Boltorn™ polyesters.

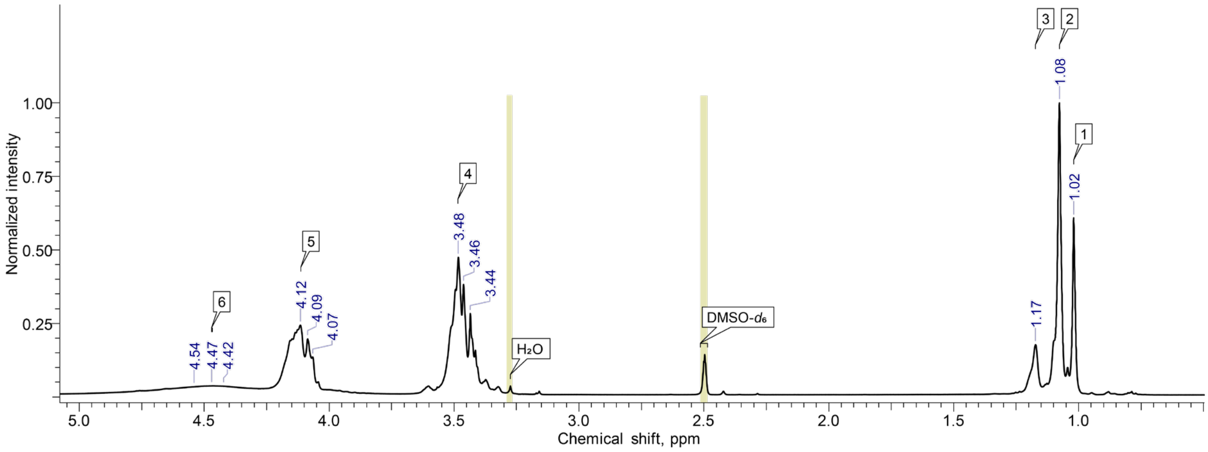


Fig. 4. ^{1}H NMR spectrum of Boltorn™ H30 in DMSO-d_6.

which allows the use of Boltorn™ H30 during copolymerization with lactide at reaction temperatures up to 180–190°C.

In order to select optimal conditions for copolymerization of D,L-lactide (monomer) with Boltorn™ H30 polyester (macroinitiator), the reaction was carried out in the temperature range of 160–180°C with a different molar ratio of monomer/macroinitiator, at a constant concentration of the tin(II) octanoate catalyst of 1400 ppm per monomer. Tin(II) octanoate is widely used as a catalyst in the polymerization of cyclic esters, including for the synthesis of biomedical polymers [18–20].

The reaction conditions, as well as the molecular weight characteristics and polydispersity coefficient of the synthesized copolymers determined by the GPC method, are given in Table.

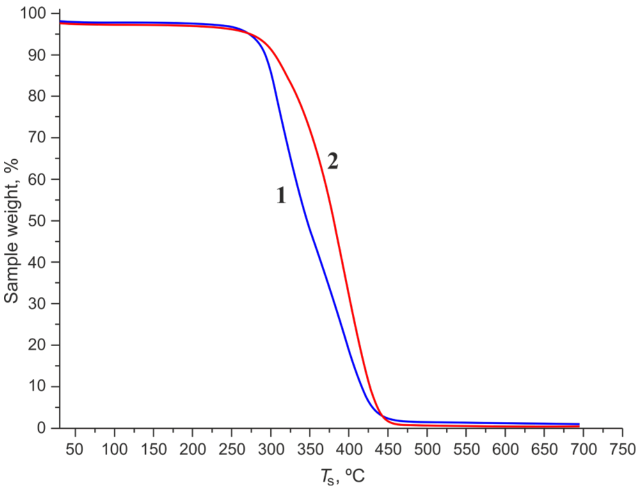


Fig. 5. TGA curves of Boltorn™ H30 polyester obtained in dynamic mode at a heating rate of 10 °C/min: (1) in an open crucible and (2) in a closed crucible.

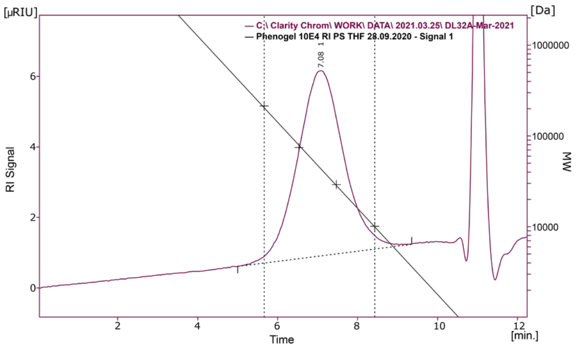
Table. Molecular weight characteristics of copolymers

Sample	**Reaction conditions**				**Molecular weights of copolymers (according to GPC)**		
	***T*, °C**	**τ, h**	***n*(B32), mol**	***n*(D,L-lactide), mol**	M_w	M_n	**PDI**
1	160	1	$2.77\cdot10^{-5}$	$1.04\cdot10^{-2}$	38 029	25 770	1.48
2	160	3	$2.77\cdot10^{-5}$	$1.04\cdot10^{-2}$	42 587	30 298	1.41
3	160	5	$2.77\cdot10^{-5}$	$1.04\cdot10^{-2}$	47 795	28 214	1.69
4	160	24	$2.77\cdot10^{-5}$	$1.04\cdot10^{-2}$	39 790	13 149	3.02
5	170	1	$2.77\cdot10^{-5}$	$1.04\cdot10^{-2}$	29 943	21 227	1.41
6 (DL32A)	170	3	$2.77\cdot10^{-5}$	$1.04\cdot10^{-2}$	52 219	35 534	1.47
7 (DL32B)	170	3	$2.77\cdot10^{-5}$	$2.08\cdot10^{-2}$	73 990	52 514	1.41
8 (DL32C)	170	3	$2.77\cdot10^{-5}$	$3.13\cdot10^{-2}$	121 054	91 812	1.32
9	170	5	$2.77\cdot10^{-5}$	$1.04\cdot10^{-2}$	38 936	28 639	1.36
10	170	24	$2.77\cdot10^{-5}$	$1.04\cdot10^{-2}$	51 143	9 700	5.27
11	180	24	$2.77\cdot10^{-5}$	$1.04\cdot10^{-2}$	41 663	27 407	1.52

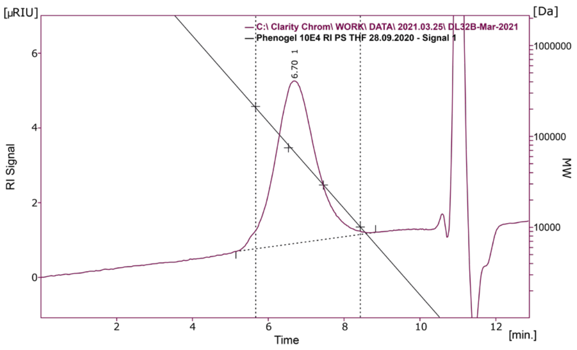
Based on the obtained data, it was found that the optimal copolymerization time of D,L-lactide with Boltorn™ H30 polyester is 3 h at a temperature of 170°C and a catalyst concentration of 1400 ppm. Under these conditions, it is possible to obtain copolymers having a monomodal molecular mass distribution. With an increase in the content of D,L-lactide in the reaction mixture with respect to Boltorn™ H30 from $2.08 \cdot 10^{-2}$ to $3.13 \cdot 10^{-2}$ mol, a bimodal molecular mass distribution is observed on chromatograms (for the DL32C sample, Fig. 6).

The chemical structure of the synthesized copolymers was studied by NMR spectroscopy. Both the proton and carbon spectra have signals corresponding to the functional groups of Boltorn™ polyester and polylactide blocks. The proton NMR spectrum for the DL32B sample is given in Fig. 7. Here, the signals corresponding to the CH groups of the polylactide are in the range of 5.15–5.23 ppm, while the signal of protons of the same groups in the monomer is located in a stronger field: 5.02–5.03 ppm. In the region of 1.65–1.68 ppm, there is a signal of CH_3 group of the residual D,L-lactide monomer, while in the region of 1.55–1.59 ppm, the signal of CH3 groups of D,L-lactide links in the copolymer can be observed. In the range of 5.0–5.30 ppm chemical shifts, signals of CH groups appear, while in the range of 1.50–1.70 ppm, signals of methyl groups are visible. By integrating the peaks, it is possible to obtain the signal intensities of each group, thus forming a basis to calculate the degree of monomer conversion. For all the studied copolymers, the conversion rate was 91.0–96.0%.

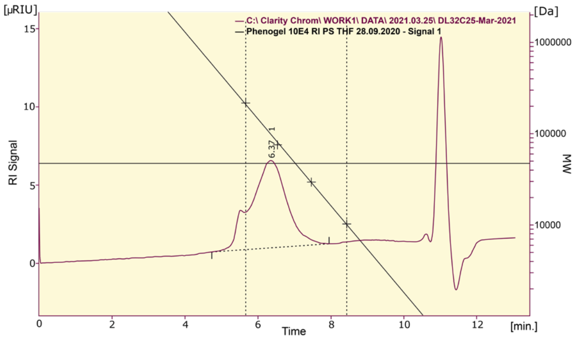
From the carbon spectrum shown in Fig. 8, signals from carbon atoms of the following types can be seen in the structure of the DL32B copolymer: $–CH_3$ groups (16–19 ppm); –C=O groups (171–176 ppm); $–CH_2–OR$ groups (66–70 ppm).



DL32A



DL32B



DL32C

Fig. 6. Chromatograms of hyperbranched copolymers (Boltorn™ H30)-PDLA.

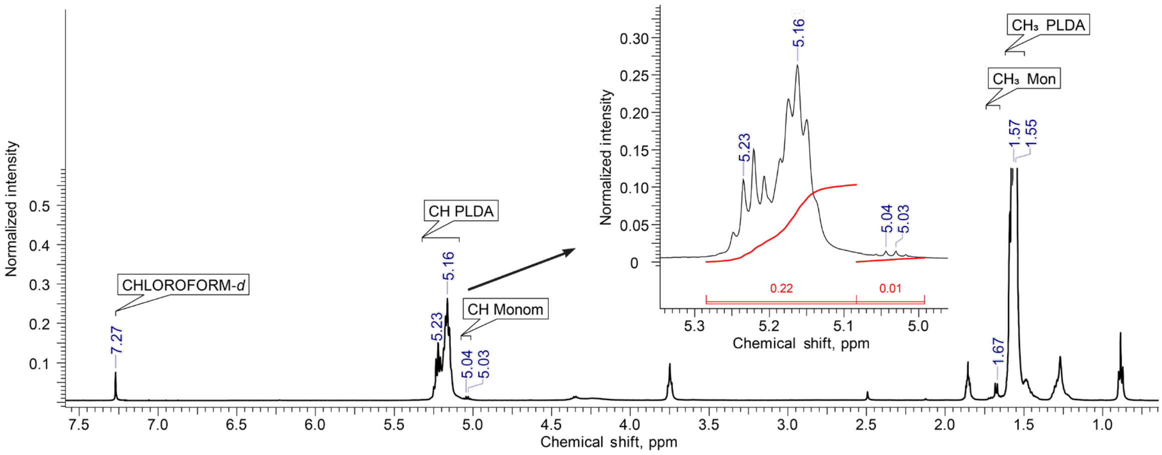


Fig. 7. ^{1}H NMR spectrum of (Boltorn™ H30)-PDLA (sample DL32B).

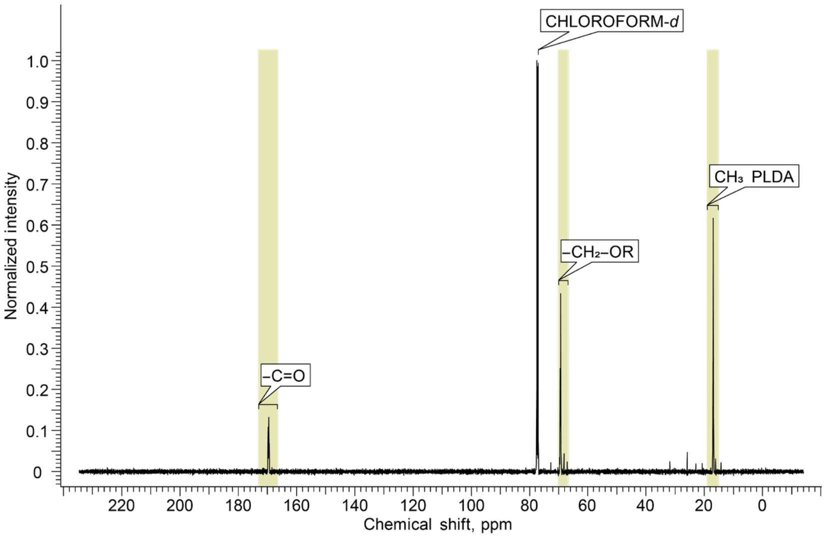


Fig. 8. ^{13}C NMR spectrum of (Boltorn™ H30)-PDLA (sample DL32B).

CONCLUSIONS

The obtained results demonstrate the possibility of synthesizing narrowly dispersed hyperbranched polymers using Boltorn™ H30 polyester polyol as a macroinitiator during polymerization of D,L-lactide. It was found that copolymers with a monomodal molecular mass distribution are formed in 3 h when the content of D,L-lactide and Boltorn™ H30 in the reaction system is $1.04 \cdot 10^{-2}$ and $2.77 \cdot 10^{-5}$ mol, respectively, using tin(II) octanoate taken at a concentration of 1400 ppm at a temperature of 170°C. A further increase in the content of D,L-lactide in the reaction mixture with respect to Boltorn™ H30 leads to the formation of copolymers having a bimodal molecular weight distribution. The synthesized copolymers contain a large number of peripheral hydroxyl groups, which can be further modified with polyethylene oxide to obtain amphiphilic block-copolymers having regulated colloidal chemical properties.

Acknowledgments

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Authors' contributions

V.I. Gomzyak – study idea, literature review, and writing the text of the article;

N.V. Bychkov – conducting experimental research, literature review;

A.S. Aduev – performing NMR spectroscopy of samples;

V.A. Ivanova – performing NMR spectroscopy of samples and analysis of experimental data;

A.D. Koshelev – literature review and writing the text of the article;

S.N. Chvalun – general supervision.

The authors declare no conflicts of interest.

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