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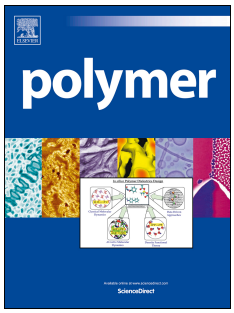

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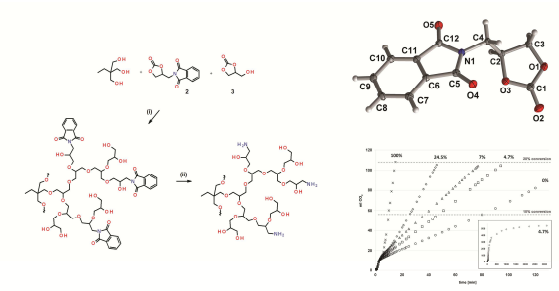

Amine functionalized polyglycerols obtained by copolymerization of cyclic carbonate monomers

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ABSTRACT: Hyperbranched aliphatic polyethers containing hydroxyl and amine end groups were produced from glycerol carbonate (4-hydroxymethyl-1,3-dioxolan-2-one) and cyclic carbonate bearing phthalimide moieties. The new monomer N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide was synthesized in a simple two-step, one-pot process. The structure of the monomer was proved by means of NMR, FTIR and X-ray techniques. Anionic polymerization of cyclic carbonate monomers, which proceeds with simultaneous decarboxylation, was performed using a simple catalyst - potassium carbonate and trimethylolpropane (TMP) or glycerol carbonate as an initiator. The polymerization conditions were investigated and optimized. The polymers were characterized by means of nuclear magnetic resonance, FTIR, MALDI-TOF, GPC and elemental analysis. It was shown that during the process of polymerization an intermediate - glycidol is formed and acts as initiator or monomer.

Key words: glycerol carbonate; hyperbranched polyglycerol; cyclic carbonate monomer; amine groups

1. Introduction

Using biomass for the production of polymers can produce both environmental and economic benefits. In last decades it has been observed a strong desire to replace polymers from fossil fuels with more environmentally friendly polymers generated from renewable resources.

In one of our recent articles we proposed a simple way of synthesis of hyperbranched polyglycerols based on an environmentally benign monomer cyclic glycerol carbonate.[1],

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Glycerol carbonate is easily available with quantitative yield from glycerol and dimethyl carbonate. Since glycerol is produced in large quantities during the biodiesel production, it becomes a non-expensive and easily available starting material for the synthesis of new monomers and polymers.[2] Whereas cyclic carbonate functionality can be attained with the use of carbon dioxide – a cheap, easily available but environmentally burdensome starting material. Therefore glycerol carbonate can be considered an environmentally friendly and "green"chemical.[3],[4] Five-membered cyclic carbonates can be synthesized directly from oxiranes and carbon dioxide, or indirectly in the reaction of vicinal diols with ethylene carbonate or dialkyl carbonates.[5] In combination with diamines bis(cyclic carbonates) provide a convenient way to the formation of non-isocyanate polyurethanes.[6] Moreover, cyclic carbonates bearing substituents containing free hydroxyl groups can alone be a source of many valuable compounds and polymers.

Hyperbranched polymers can be prepared from an AB_n-type monomers according to a single step synthetic procedure.[7] To obtain polymers containing hydroxyl terminal groups glycidol [8], 3-(hydroxymethyl)-3-alkyl oxetanes [9] or glycerol carbonate are typically used in ring opening polymerization reactions. Glycerol carbonate belongs to the class of monomers which is considered a latent AB_2-type monomer since the release of the second B functionality occurs as a result of reaction of the A group.[10] The polymerization of glycerol carbonate occurs with decarboxylation leading to the hyperbranched polyether.[1]

Hyperbranched polyglycerols (HBPGs) are structurally defined, biocompatible macromolecular scaffolds, that have an aliphatic polyether backbone, and possess multiple hydroxyl terminal groups. The hydroxyl groups in polyglycerol not only increase the hydrophilicity of this polymer but also allow for its modification, leading to polymers with carboxyl, amine, and vinyl groups, as well as to polymers with bonded aliphatic and perfluorated chains, sugar moieties, and covalently immobilized bioactive compounds in particular proteins.[11] Cyclic carbonate derivatives of hyperbranched polyethers have also been reported.[12]

Functional HBPGs have recently gained considerable interest due to their potential in biomedical applications.[13],[14],[15],[16],[17], Particularly interesting are branched polymers containing amine groups. A comprehensive review of amine containing hyperbranched polyglycerols as gene carriers was given by Fischer *et al.*[18] However, hyperbranched polymers have also a high potential as additives and modifiers in engineering materials.[19] The specific advantages of the hyperbranched polymers and their influence on mechanical properties in modification of thermoset resin systems have been discussed in

detail by Månson *et al.*[20] For such applications a simple, reliable and environmentally friendly synthetic procedure allowing polymerization in a large scale is needed.

Currently, all of the literature reports concerning synthesis of functional HBPGs, particularly amine containing hyperbranched polyglycerol (A-HBPG) are based on the use of epoxy monomers, mainly products of modification of glycidol based polymers. Various synthetic methodologies were used. The most popular pathway leading to A-HBPGs involves the use of azide intermediates.[21],[22],[23],[24] In this approach polyglycerols were surface modified with amine groups in a three-step protocol involving: mesylation of hydroxyl groups, a nucleophilic substitution with sodium azide and the final reaction with triphenylphosphine.[21] Such architectures containing amine groups showed ability to complex DNA and functioned as cellular delivery systems of low cytotoxicity. A-HBPGs obtained in the same way were also used as coatings for resistant to protein and bacteria attachment polypropylene surfaces.[25] Oupicky *et al.* reported hyperbranched polyglycerol modified with a polyamine shell by the reaction of hydroxyl groups of HBPG activated with phenyl chloroformate with large excess of norspermine or N,N-bisethylnorspermine. [26] Another way to attach amine-functional molecules to the HBPG's outer sphere involved oxidation of hydroxyl groups with sodium periodate followed by the reaction with polyamine.[27]

Majority of literature reports concerning preparation of A-HBPGs includes the modification of existing HBPG macromolecules. The examples of preparation of these structures via copolymerization are particularly rare and based only on epoxy monomers. Such approach was presented by Kim *et al.*[13],[28] The Boc-protected alkylamine glycidyl ether monomers were copolymerized with glycidol through anionic ring-opening multibranching polymerization. The copolymerization and subsequent deprotection chemistry allowed the incorporation of an adjustable fraction of primary amine, hydroxyl and alkyl moieties within the HBPG backbones.

Another method of obtaining HBPGs containing amine functionalities which has just emerged in the literature is the use of the Gabriel synthesis. Phthalimide monofunctional HBPGs were synthesized by applying a (phthalimide)/(potassium phthalimide) initiating system for the anionic ring-opening multibranching polymerization of glycidol.[29] The phthalimide group was then quantitatively cleaved by hydrazinolysis to form a monoamine functional HBPG. Phthalimide functional groups were also introduced to the HBPG structure by post-polymerization modification with N-hydroxy phthalimide.[30] Similar, well-defined, precisely monofunctional hyperbranched polyglycerol-based structures were reported by Frey

et al.[31] For the introduction of the amino functionality the authors used a new initiator - di(benzyl)aminoethanol obtained from ethanolamine and benzyl bromide.

The objective of this work was the synthesis of a new type of hyperbranched polyethers by introduction of amine groups to the polyglycerol via copolymerization of environmentally friendly monomer - glycerol carbonate with a cyclic carbonate monomer bearing phthalimide moiety. Moreover, we expected that the synthesis could be performed using cheap and safe in use catalyst potassium carbonate, instead of burdensome metal alkoxide used in our previous report.[1] We expect that the presence of two types (amine and hydroxyl) of functional groups of different reactivity in the structure of hyperbranched polymer will allow building larger molecular systems with different types of substituents not only for biomedical applications but also as modifiers of mechanical properties of other polymeric materials.

2. Experimental

2.1 Materials

All the reagents were purchased from Sigma-Aldrich (Poznań, Poland) and used as received. Solvents were purchased from POCh (Gliwice, Poland). THF was distilled over potassium benzophenone ketyle and immediately transferred to the reaction vessel under inert atmosphere. DMF was dried using molecular sieves (0.4 nm) for at least 48h and used without further purification. DMSO was dried by azeotropic distillation with toluene and stored over molecular sieves (0.4 nm). Other solvents were used without further purification.

2.2 Instrumentation

FTIR spectra were recorded on a Nicolet iS5 Mid Infrared FT-IR Spectrometer equipped with iD7 ATR Optical Base or Biorad FTS-165 FT-IR Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VXR 400 MHz or Bruker AVANCE 500 MHz spectrometers using tetramethylsilane as an internal standard and deuterated solvents ($CDCl_3$, DMSO-d_6). The average molecular masses of polymers were determined based on integration of signals in ^{1}H NMR spectra. The integral of the CH_3 group signal coming from the core trimethylolpropane (TMP) molecule was used as a reference. MALDI-TOF spectra were measured on a Bruker UltraFlex (Bremen, Germany) spectrometer using DCTB (*trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile) as a matrix and analyzed with flexAnalysis v.3.3 (Bruker Daltonik GmbH) and Polymerix v. 2.0 (Sierra Analytics Inc.) software. Rheological measurements were performed with Malvern Kinexus Pro rheometer in

the parallel plate geometry (φ20 mm, spacing gap 0.5 mm) within the shear rate 0.1–100 1/s. Elemental analysis was performed with Elementar Vario EL III CHNS analyzer. The molar mass and molar mass distribution of acetylated samples of polymers were determined by a GPC on a Viscotek system comprising GPCmax and TDA 305 unit equipped with one guard and two DVB Jordi gel columns (102-107, linear, mix bed) in CH_2Cl_2 as an eluent at 35 °C at a flow rate of 1.0 mL/min using the RI detector and PS calibration.

2.3 Syntheses

N-(2,3-dihydroxypropyl)phthalimide (1) was prepared according to modified patent procedure.[32]

3-Chloro-1,2-propnediol (40 g, 0.362 mol) and potassium phthalimide (80 g, 0.430 mol) were heated to reflux in ethanol (400 ml) for 24 h in a nitrogen atmosphere. The resulting mixture was cooled down and evaporated to dryness. Dichloromethane (400 ml) was added to the residue. The solid salts were filtered off, and the solution evaporated to dryness yielding crude N-(2,3-dihydroxypropyl)phthalimide that was used without further purification.

Yield 80 g (99.9%), mp= 122-124^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.90-7.84 (m, 2H, H_{ar}), 7.78-7.71(m, 4H, H_{ar}), 4.02-3.95 (m, 1H, $CH_2C\underline{H}CH_2$), 3.93 (dd, 1H, $C\underline{H}_2OH$, J_1=14.2 Hz, J_2=5.9 Hz), 3.85 (dd, 1H, $C\underline{H}_2OH$, J_1=14.2 Hz, J_2=5.1 Hz), 3.67 (dd, 1H, $C\underline{H}_2N$, J_1=11.8 Hz, J_2=4.1 Hz), 3.60 (dd, 1H, $C\underline{H}_2N$, J_1=11.8 Hz, J_2=4.8 Hz), 2.24 (bs, 2H, O$\underline{H}$); ^{13}C NMR (400 MHz, DMSO-d_6, δ): 168.1 ($\underline{C}$=O), 134.2 ($\underline{C}_{Ar}$), 131.8 ($\underline{C}_{Ar}$), 122.9 ($\underline{C}_{Ar}$), 68.5 ($\underline{C}$HOH), 64.2 ($\underline{C}H_2OH$), 41.7 ($\underline{C}H_2N$). FTIR (KBr): ν (cm^{-1}) = 3300, 2942, 1780, 1717, 1433, 1392, 1192, 719.

N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide (2)

Crude N-(2,3-dihydroxypropyl)phthalimide (**1**) 80g, 0.361 mol), dimethyl carbonate (DMC) (187 g, 200 ml, 2.075 mol) and potassium carbonate (1.6 g, 11.6 mmol) were placed in a 1000 ml round bottom flask equipped with a reflux condenser. The reaction mixture was heated at reflux for 48h. The excess of DMC and ethanol were removed on a rotary evaporator. Addition of 10 ml of THF caused crystallization of the residue. Crystals were washed with water to remove the catalyst and dried. The product was purified by extraction and crystallization with hot THF performed in a Soxhlet apparatus.

Yield 59.8 g (66.9 %), mp= 178-179°C, ^{1}H NMR (DMSO, 500 MHz, δ): 7.93-7.89 (m, 2H, H_{Ar}), 7.89-7.84 (m, 2H, H_{Ar}), 5.06-4.99 (m, 1H, C<u>H</u>), 4.60 (dd, 1H, OC<u>H</u>$_2$, J_1=8.6 Hz, J_2=8.0 Hz), 4.35 (dd, 1H, OC<u>H</u>$_2$, J_1=8.6 Hz, J_2=6.2 Hz), 3.97 (dd, 1H, NC<u>H</u>$_2$, J_1=14.8 Hz, J_2=6.4 Hz), 3.92 (dd, 1H, NC<u>H</u>$_2$, J_1=14.8 Hz, J_2=4.9 Hz); ^{13}C NMR (DMSO, 125 MHz, δ): 167.8 (N<u>C</u>=O), 154.4 (<u>C</u>=O), 134.6 (<u>C</u>$_{Ar}$), 131.5 (<u>C</u>$_{Ar}$), 123.3 (<u>C</u>$_{Ar}$), 74.2 (O<u>C</u>H), 67.5 (O<u>C</u>H$_2$), 39.4 (N<u>C</u>H$_2$); FTIR (ATR): ν (cm^{-1}) = 1775, 1705, 1390, 1310, 1169, 1046, 716; MALDI-TOF (DCTB, *m/z*): [M + K$^+$] calcd for $C_{12}H_9NO_5K$, 286.012; found 286.015.

4-Hydroxymethyl-1,3-dioxolan-2-one (**3**) **-** Glycerol carbonate was synthesized according to literature procedure.[1]

Determination of the catalyst amount needed for preparation of glycerol carbonate

In a round bottom flask equipped with a reflux condenser, a thermometer and a magnetic stirrer 28,26 g (0.3 mol) of glycerol was placed followed by a certain amount of catalyst - potassium carbonate. The mixture was heated at 40 °C. Then 81g (0.9 mol) of dimethyl carbonate was added. The temperature was then increased up to 70 °C. At 60 °C the dissolution of the catalyst was observed. The time needed for homogenization of the reaction mixture measured from the moment of addition of dimethyl carbonate was registered. A blank experiment without addition of the catalyst showed no reaction progress (no homogenization) after heating for 2h at 70°C.

Determination of the catalyst amount needed for polymerization of glycerol carbonate

To get rid of the catalyst, glycerol carbonate solution in dry ethyl acetate was filtered several times through a bed of silica gel until neutral pH. Then the solvent was removed under vacuum.

In a round bottom flask equipped with a thermometer, magnetic stirrer and a gas outlet connected to a gas burette (filled with CO_2 saturated water) 5g (0,04 mol) of glycerol carbonate was placed and heated at 155 °C. Then a certain amount of catalyst - K_2CO_3 was added and heating continued at 155 °C. The amount of collected CO_2 was measured in time.

General procedure of co-polymerization of glycerol carbonate and N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide

To a 25 mL three-neck round bottom flask equipped with a magnetic stirrer, nitrogen inlet and thermometer, trimethylolpropane (TMP, 1 equivalent, see Tab.1) was added, followed by glycerol carbonate (50-29 equivalents, see Tab. 1) and N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide (**2**) (0-21 equivalents). The reaction mixture was stirred at 80^{o}C to obtain a homogeneous solution, then K_2CO_3 was added and the reaction carried out at 155^{o}C. Reaction progress was monitored by FT-IR spectroscopy. It was finished when the absorption band at 1795 cm^{-1} corresponding to C=O of cyclic carbonate groups disappeared, usually after 24-48 h. Copolymers **HBPG0-HBPG9** were obtained as brown viscous oils. Exact amounts of reagents are placed in Table 1. The method of calculation of molecular weights by ^{1}H NMR is provided in supplementary materials.

Table 1. Amounts of reagents used for polymerization and the reaction yields.

Polymer	TMP / g.c.* / **1**	TMP	Glycerol carbonate	Monomer **1**	Monomer **1**	K_2CO_3	Yield	Yield	M_n NMR calc. value Da	M_n theoret. calc. value Da
	molar ratio	g	g	mol %	g	mg	g	%		
HBPG-0	1/50/0	0.160	6.99	**0**	0	41	4.49	98.8	3800	3800
HBPG-1	1/47/2	0.167	6.98	**4.7**	0.73	9	4.73	91.9	3800	4100
HBPG-2	1/46/4	0.148	5.99	**7.0**	0.97	8	4.66	99.0	4200	4300
HBPG-3	1/46/5	0.150	6.01	**8.9**	1.26	39	4.76	96.0	4300	4400
HBPG-4	1/43/6	0.158	5.99	**12.3**	1.80	40	4.77	88.4	4000	4600
HBPG-5	1/41/8	0.165	6.01	**16.3**	2.51	42	5.65	94.2	4600	4900
HBPG-6	1/40/10	0.170	6.02	**19.6**	3.14	45	5.39	82.5	4300	5200
HBPG-7	1/37/12	0.182	6.00	**24.5**	4.19	28	6.29	85.2	4600	5400
HBPG-8	1/33/17	0.239	7.60	**31.0**	7.33	13	9.79	88.7	5500	6200
HBPG-9	1/29/21	0.270	7.60	**38.5**	10.26	14	11.96	88.8	5900	6700

* g.c.- glycerol carbonate

General procedure of hydrazinolysis of copolymers of glycerol carbonate and N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide

The amine groups of the HBPG polymers were deprotected using modified literature procedures.[33],[34],[35] In a 100 ml round bottom flask equipped with a magnetic stirrer and a reflux condenser 5 g of HBPG copolymer followed by approx. 25 ml of ethanol were placed. The mixture was heated at reflux to dissolve the polymer. Then 25% molar excess (in respect to the amount of phthalimide groups) of hydrazine hydrate 65% water solution was added and

the resulting solution stirred at reflux for 20 h. The mixture was cooled down to room temperature, evaporated to dryness and re-dissolved in methanol. Diluted hydrochloric acid was added drop-wise to a stable acidic pH. The mixture was then heated at reflux for an additional 30 min. The resulting precipitate was filtered off. The filtrate was condensed almost to dryness under reduced pressure and the residue was dissolved in water. Any white precipitate was filtered off and the clear aqueous solution was made alkaline (pH = 10) by addition of Na_2CO_3. The solvent was removed using rotary evaporator. The residue was purified by multiple precipitation from methanol/ethanol mixture to remove any inorganic salts. Amounts of the reagents and yields are given in Table 2.

Table 2. Amounts of reagents used for hydrazinolysis and the reaction yields.

Polymer	Polymer	Phthalimide content	Hydrazine	65% hydrazine hydrate	Ethanol	Yield	Yield
	g	mmol	mmol	g	ml	g	%
A-HBPG-1	5.20	2.37	3.00	0.15	26	3.47	71
A-HBPG-2	5.00	3.36	4.20	0.21	25	3.14	69
A-HBPG-3	2.72	2.27	2.84	0.14	14	1.72	71
A-HBPG-4	3.48	3.88	4.85	0.24	17	2.17	73
A-HBPG-5	4.83	6.87	8.59	0.42	24	2.63	67
A-HBPG-6	5.30	8.78	11.0	0.54	27	3.02	73
A-HBPG-7	5.35	10.6	13.3	0.66	27	1.52	68
A-HBPG-8	5.00	11.9	14.9	0.73	25	2.23	65
A-HBPG-9	5.25	14.6	18.3	0.90	26	2.22	67

2.4 Crystallography

The X-ray measurement of OE was performed at 100(2)K on a Bruker D8 Venture Photon 100 CMOS diffractometer equipped with a mirror monochromator and a CuKα INCOATEC IμS micro-focus source (λ = 1.54178 Å). A total of 3052 frames were collected with Bruker APEX2 program [36]. The frames were integrated with the Bruker SAINT software package [37] using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 1897 reflections to a maximum θ angle of 67.99° (0.83 Å resolution), of which 1895 were independent (average redundancy 1.001, completeness = 98.8%, R_{sig} = 1.77%) and 1756 (92.66%) were greater than $2\sigma(F^2)$.The final cell constants of $\underline{a}$ = 6.9447(5) Å, b = 17.0186(12) Å, c = 9.1872(7) Å, β = 104.177(2)°, V = 1052.76(13) Å^3, are based upon

the refinement of the XYZ-centroids of 9920 reflections above 20 σ(I) with 10.39° < 2θ < 136.5°. Data were corrected for absorption effects using the multi-scan method (TWINABS) [38]. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7450 and 0.7960.

The structure was solved and refined using the Bruker SHELXTL Software Package [39, 40], using the space group $P2_1/n$, with $Z = 4$ for the formula unit, $C_{12}H_9NO_5$.The final anisotropic full-matrix least-squares refinement on F^2 with 163 variables converged at $R1 = 3.10\%$, for the observed data and $wR2 = 7.93\%$ for all data. The goodness-of-fit was 1.065. The largest peak in the final difference electron density synthesis was 0.261 $e^-/Å^3$ and the largest hole was -0.175 $e^-/Å^3$ with an RMS deviation of 0.041 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.560 g/cm^3 and $F(000)$, 512 e^-.

The crystal is twinned by pseudomerohedry with two domains. Some of the reflections are separated whereas the other are overlapped. At the initial stages structure was refined with HKLF 5 option. The refined ratio of the twin components is equal to 0.643(2):0.357(2). After the refinement converged data were processed using WinGX software [41] to regular HKLF 4 format.

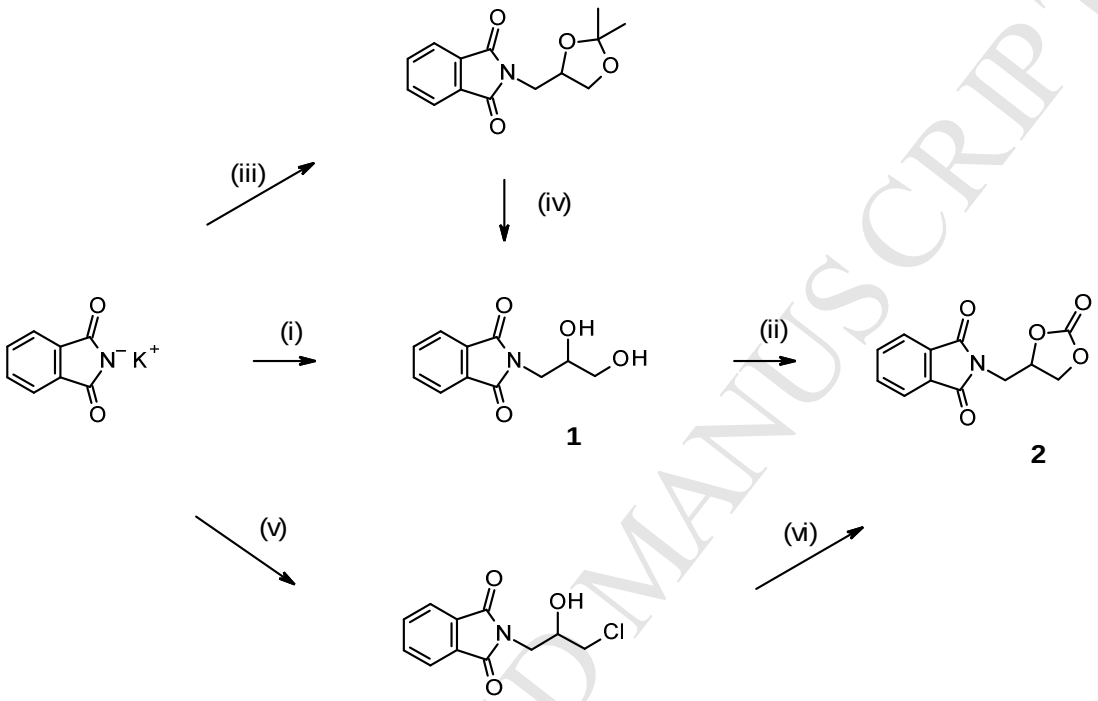
The non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed in calculated positions and refined within the riding model. The temperature factors of hydrogen atoms were not refined and were set to be equal to 1.2 times larger than U_{eq} of the corresponding heavy atom. The atomic scattering factors were taken from the International Tables [42]. Molecular graphics was prepared using program Diamond 3.2. [43] Thermal ellipsoids parameters are presented at 50% probability level.

3. Results and discussion

3.1 Monomer synthesis and characterization

Glycerol carbonate is one of the most valuable derivatives that could be obtained from glycerol and CO_2 and it is considered a green chemical with a broad spectrum of uses, for instance a substitute for petro-derivative compounds such as ethylene or propylene carbonate. This monomer and its derivatives are also key compounds in the synthesis of multiple cyclic carbonates which are used for preparation of non-isocyanate polyurethanes [6] or polyglycerols.[1]

The number of functional five-membered cyclic carbonates that could be co-polymerized with glycerol carbonate is very limited. In majority those compounds posses aliphatic or aromatic hydrocarbon side groups, however a chloromethyl, vinyl, allyl or methacrylic ester derivatives were also reported.[5] So far there were no reports on five-membered cyclic carbonates containing protected amine substituents.



Scheme 1. Synthesis of N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide; (i) 3-chloro-1,2-propanediol; (ii) DMC, K_2CO_3, overall (i+ii) yield 67%; (iii) 4-chloromethyl-2,2-dimethyl-1,3-dioxolane, 31%; (iv) H^+, H_2O, 18%; (v) phthalimide, epichlorohydrin, DMF, 58%; (vi) $NaHCO_3$, DMSO, 16%.

In this work we proposed a synthesis of a new cyclic carbonate monomer N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide (**2**) that allows production of amine containing hyperbranched polyglycerol (A-HBPGs) using Gabriel synthesis. N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide cannot be considered a "green chemical". However, it allows easy functionalization of polyglycerol obtained from glycerol carbonate. There are two main synthetic routes leading to five-membered cyclic carbonates: the reaction of a respective oxirane with carbon dioxide or 1,2-diol with dialkyl or diphenyl carbonate. Instead of carbonic acid esters, phosgene or its derivatives can also be used.[44]

We tried several approaches to synthesize monomer **2** shown in Scheme 1. The preferred synthetic way consisted of two solvent free steps: a reaction of potassium phthalimide with 3-chloro-1,2-propanediol followed by transesterification of crude product **1** with excess of dimethyl carbonate in presence of potassium carbonate. Since the final product **2** readily crystallized and was relatively easy to purify, there was no need to purify the intermediate **1**. The monomer **2** was synthesized with the overall yield 67%.

The halohydrin pathway [45] (v+vi, Scheme 1) was less preferred due to the low effectiveness. It required the use of difficult to remove polar aprotic solvents (DMSO, DMF), extended reaction times and multiple step purification procedures. Intermediate **1** was also available via protection-deprotection procedure using ketal derivative (4-chloromethyl-2,2-dimethyl-1,3-dioxolane). However, since we had realized that final product **2** could be reached from crude compound **1** the synthetic steps iii and iv (Scheme 1) became no longer relevant.

Monomer **2** has been characterized using NMR, FT-IR, X-ray and MALDI-TOF techniques.

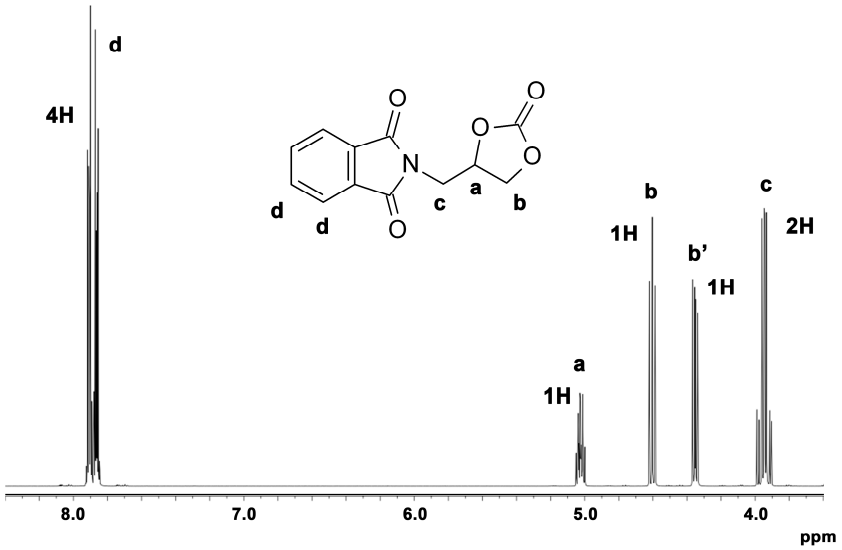


Figure 1. ^{1}H NMR spectrum of N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide (**2**).

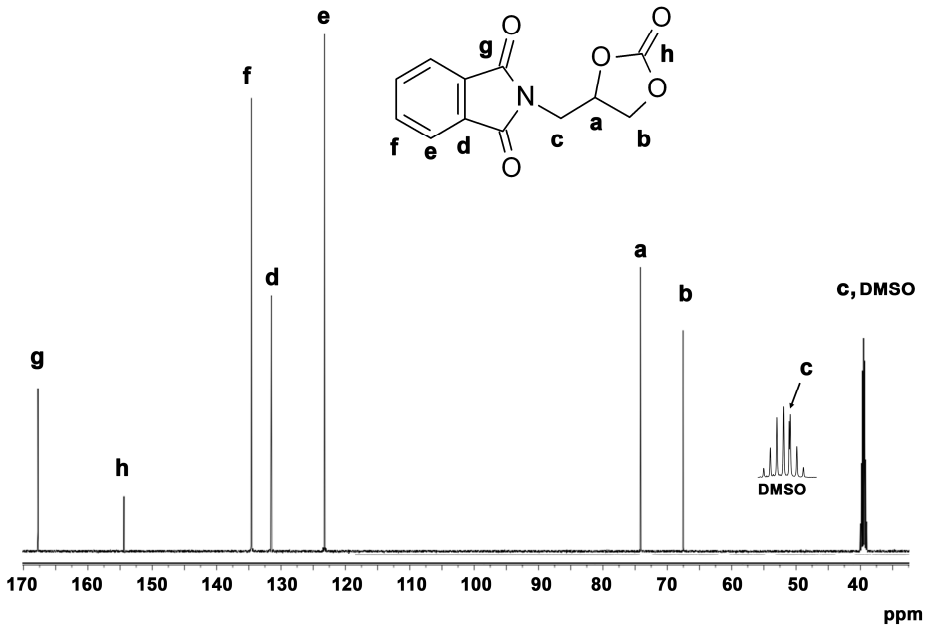


Figure 2. ^{13}C NMR spectrum of N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide (**2**).

Figures 1 and 2 show high resolution ^{1}H and ^{13}C NMR spectra of monomer **2**. The ^{1}H NMR spectrum of **2** contains two symmetrical multiplets (**d**, Fig.1) at approx. 7.9 ppm that were assigned to aromatic protons of phthalimide ring. The protons of aliphatic part of the molecule are represented by a pattern consisting of five groups of signals, typical for unsymmetrically substituted glycerol derivatives, where each proton can be assigned to a separate signal group due to the presence of the asymmetry center in the molecule. The **c** protons of the methylene group linked to a nitrogen atom show two overlaping doublets of doublets at approx. 3.9 ppm with the coupling constants equal 14.8, 6.4 and 4.9 Hz, grouped in a symmetrical multiplet. The methylene group of the 1,3-dioxolan-2-one ring (**b**, **b'** protons at 4.7-4.3 ppm) is also represented by two doublets of doublets. However in this case one pair of doublets appears as a triplet due to the overlapping of peaks. The coupling constants are equal 8.6, 8.0 and 6.2 Hz. The **a** proton signal of the 1,3-dioxolan-2-one ring appears at approx. 5.0 ppm as a multiplet. ^{13}C NMR spectrum shown in Fig. 2 confirmed that the final product contained two types of carbonyl carbons: an imide one at 167.8 ppm and a five-membered cyclic carbonate at 154.4 ppm, three types of aromatic carbons (134.6, 131.5, 123.3 ppm) and three types of aliphatic carbons (74.2, 67.5, 39.4 ppm) which is in agreement with the designed structure.

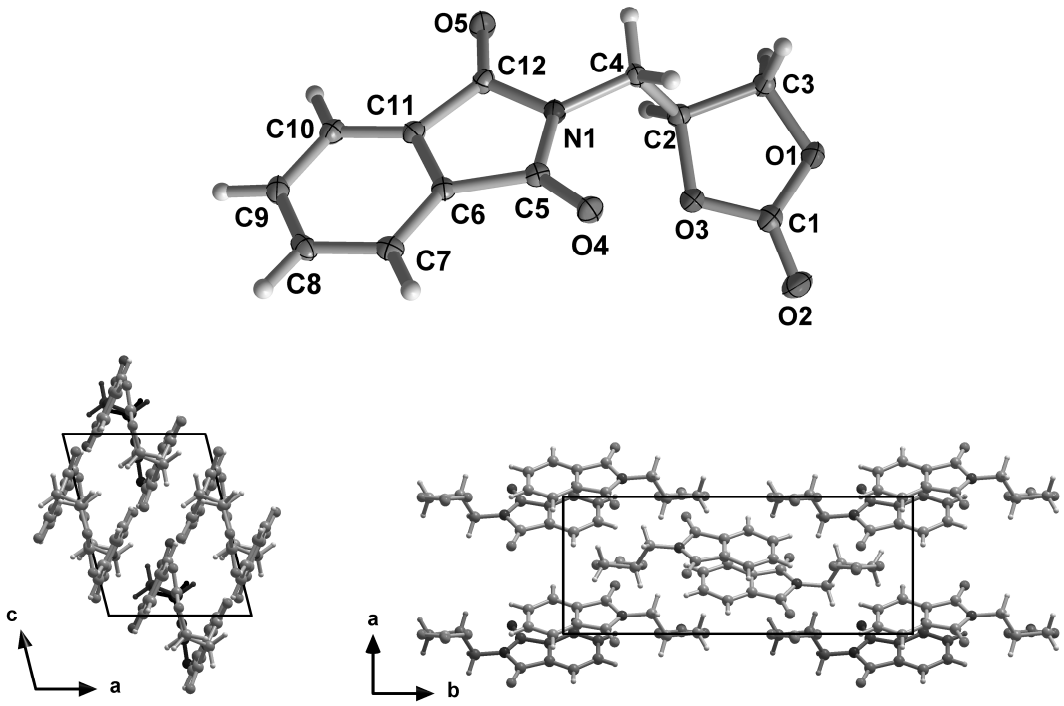
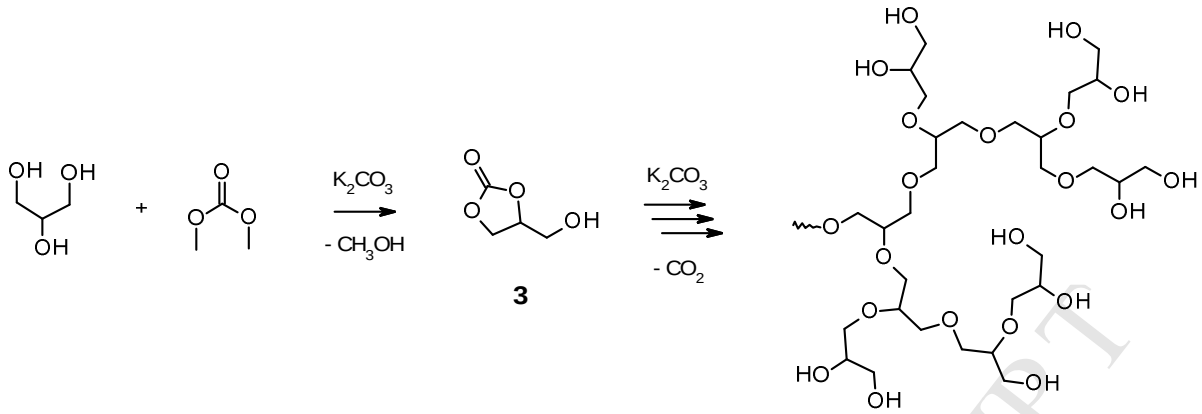


Figure 3. X-Ray structure of N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide (**2**).

Figure 3 shows the X-Ray crystal structure of **2**. The structure of **2** was determined by single crystal X-ray diffraction. Single crystals of **2** were obtained by recrystallization from the ethyl acetate solution by slow evaporation of the solvent. Monomer **2** crystallized in a monoclinic crystal system with space symmetry $P2_1/m$. In the crystal phase phthalimide structures were parallel to each other and formed planes.

The FT-IR spectrum of **2** showed multiple absorption bands below 2000 cm^{-1}. The presence of the carbonyl absorption band at 1775 cm^{-1} confirmed formation of the five-membered cyclic carbonate ring, while the 1705 cm^{-1} presence of the imide ring. The molar mass of **2** was measured with MALDI-TOF spectrometer using CDTB as a matrix. The measured value of 286.015 m/z was in agreement with the molecular formula: $C_{12}H_9NO_5K$, where K stands for potassium ionization cation.

3.2 Determination of the catalyst amount needed for polymerization of cyclic carbonates



Scheme 2. Process of production of hyperbranched polyglycerols.

By now, synthesis of hyperbranched polyglycerols starting from glycerol carbonate has been performed using strong base catalysts: potassium methoxide [1] or sodium hydroxide.[46] However, we have found that the process can be completed using easily available, cheap and safe in operation potassium carbonate. The use of K_2CO_3 is also convenient from the technological point of view, since the same catalyst is used for glycerol carbonate synthesis. (Scheme 2)

To match glycerol carbonate and subsequent polyglycerol syntheses, the amount of catalyst was optimized. In case of glycerol carbonate synthesis the fastest reaction rates were obtained for K_2CO_3 to glycerol molar ratio equal 0.01 and higher. This stands for 0.33g of K_2CO_3 in 100g of the reaction mixture containing glycerol and dimethyl carbonate in the molar ratio 1 to 3.

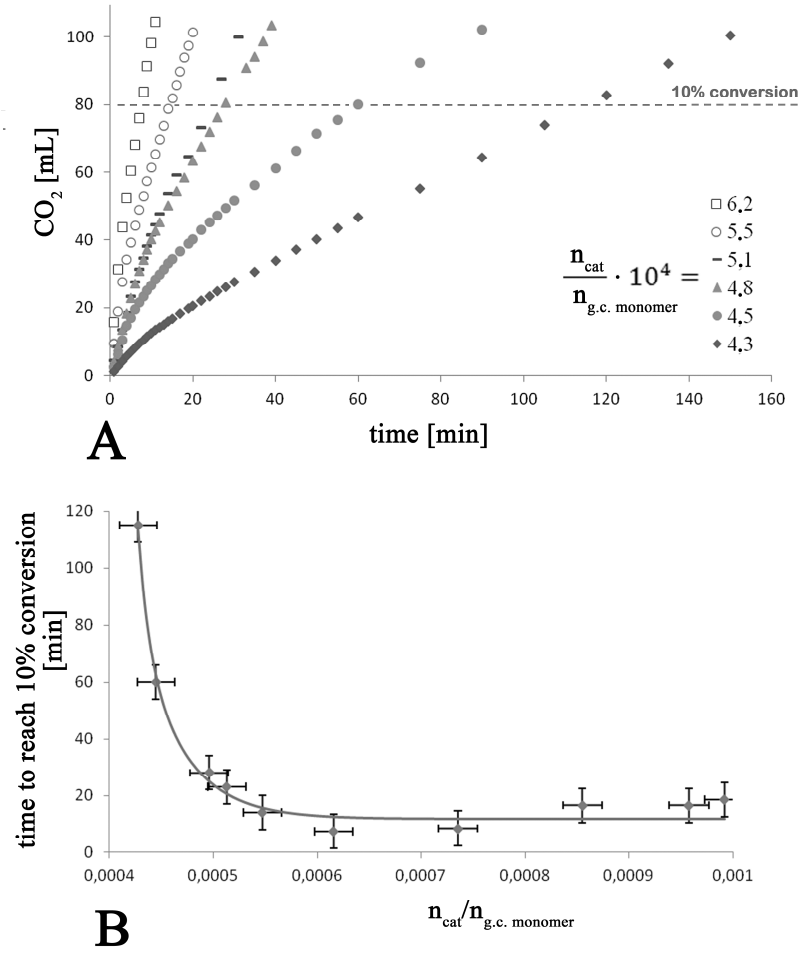
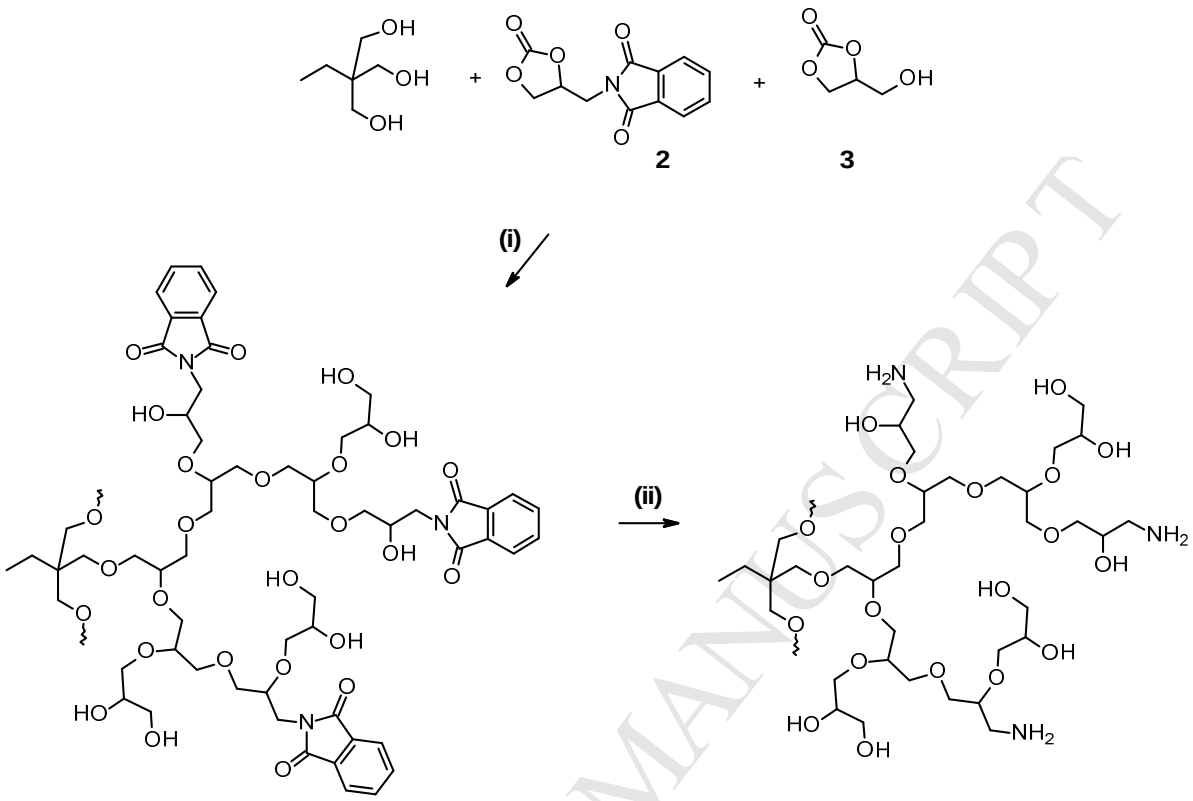


Figure 4. Changes in the amount of CO_2 released during polymerization of glycerol carbonate in time, depending on the amount of catalyst (A); Time needed to reach 10% conversion depending on the amount of catalyst (B); g.c.=glycerol carbonate.

To follow the reaction of polymerization of glycerol carbonate, a setup containing a gas burette connected to the polymerization reactor was applied. The polymerization of glycerol carbonate took place with decarboxylation. Its rate could be estimated by the amount of CO_2 released in time. The fastest reaction rates were reached for the 0.00055 potassium carbonate to glycerol carbonate molar ratio and higher (see Fig. 4) This stands for 0.06%$_{wt}$ of the catalyst in glycerol carbonate, which is a lower value than in case of glycerol carbonate synthesis. This result opens a way to a one-pot production of polyglycerols from glycerol and dimethyl carbonate with a single catalyst common for both synthetic steps, added once, at

3.3 Co-polymerization of glycerol carbonate with N-[(2-oxo-1,3-dioxolan-4-yl)methyl]-phthalimide (2)



Scheme 3. The synthesis of amine containing hyperbranched polyglycerols; (i) TMP, K_2CO_3, 155 °C, 83-91%, (ii) 65% hydrazine hydrate, ethanol, *reflux*, 24h, 65-73%.

Amine functionalized polyglycerols were synthesized in a simple two-step procedure shown in Scheme 3. In the first step monomer **2** was copolymerized with glycerol carbonate **3** in a ring opening polymerization-decarboxylation process using trimethylolpropane (TMP) as a core molecule (initiator) and potassium carbonate as a catalyst. Application of a core molecule (TMP) made it possible to control the molar masses of the products and helped to reduce the dispersity of the molar masses of hyperbranched polymers.[47],[48] Presence of the ethyl group in the core allowed determination of an average molar mass using ^{1}H NMR spectroscopy (Tab.1). The resulting polymers containing phthalimide groups were then reacted with hydrazine hydrate to yield final hyperbranched amino-polyglycerols.

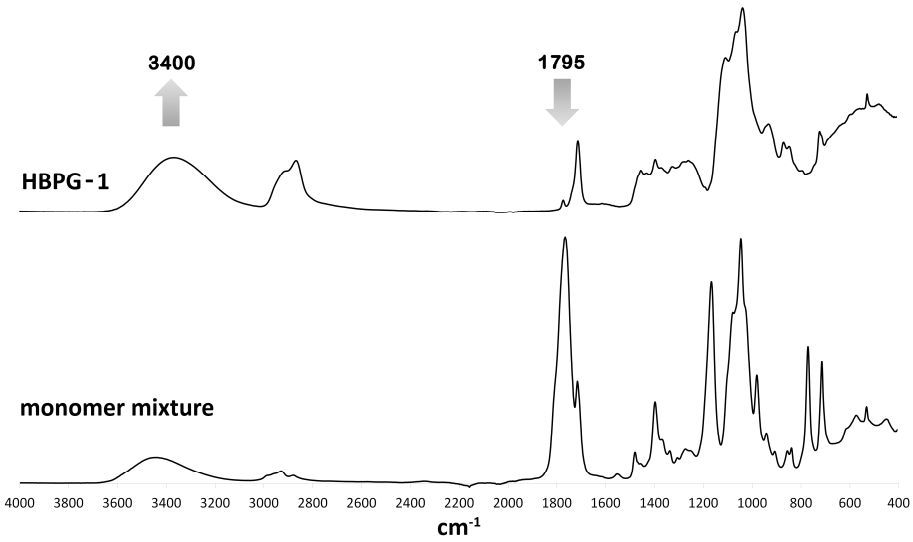


Figure 5. Changes in FT-IR spectra during synthesis of polymer **HBPG-1** containing 4.7% of phthalimide monomer units.

Hyperbranched polymers **HBPG-0–HBPG-7** were prepared by a modified procedure previously reported by us.[1] However, to allow the CO_2 release studies the slow addition of monomers was not used. Such methodology in case of hyperbranched polymers usually results in high dyspersity index of the product. The ring-opening copolymerization of **2** and glycerol carbonate was carried out in bulk, in the presence of TMP and a catalytic amount of potassium carbonate at 155 ^{o}C. The molar ratio of the carbonate monomers to TMP was equal 50 to yield in the final step A-HBPGs of the average molar mass of approx. 3800 g/mol that could be easily characterized with spectroscopic methods. For analytical purposes, mainly to simplify MALDI-TOF spectrograms, samples without the core molecule were also synthesized. The progress of the reaction was monitored by disappearance of the cyclic carbonate absorption band at 1795 cm^{-1} in the FT-IR spectrum. (Fig. 5) The process was usually finished within 48h. Copolymers **HBPG-0–HBPG-9** were obtained as dark yellow viscous oils.

The copolymerization rate was dependent on the content of **2** in the mixture with glycerol carbonate. Fig. 6 shows the amount of carbon dioxide released from the reactor in time for the reaction system containing from 0 to 100%$_{mol}$ of **2** and constant amount of catalyst.

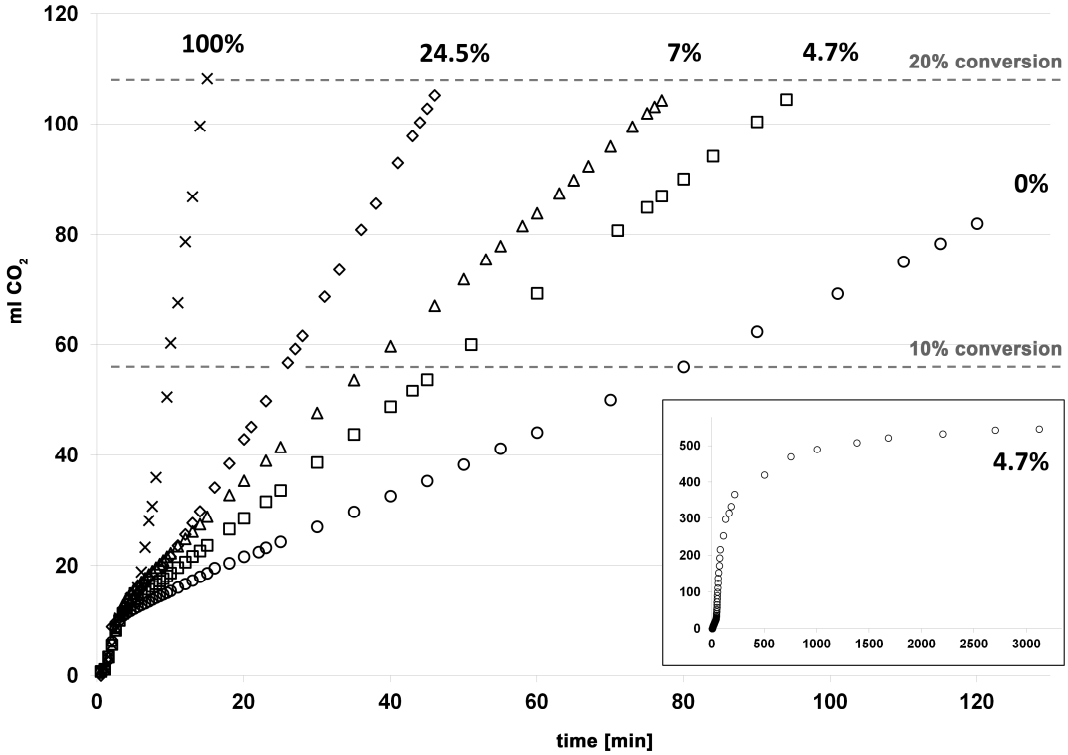


Figure 6. The CO_2 release during copolymerization of glycerol carbonate and monomer **2** in time, depending on the amount of **2** in the reaction mixture (molar per-cents of **2** given); inset shows a full CO_2 release curve for **HBPG-1** polymer containing 4.7% of **2**.

Surprisingly, the highest polymerization rates were observed for samples containing highest amounts of sterically hindered monomer **2**. It seems that electron withdrawing effect of imide nitrogen atom, activating the cyclic carbonate ring is of large importance.

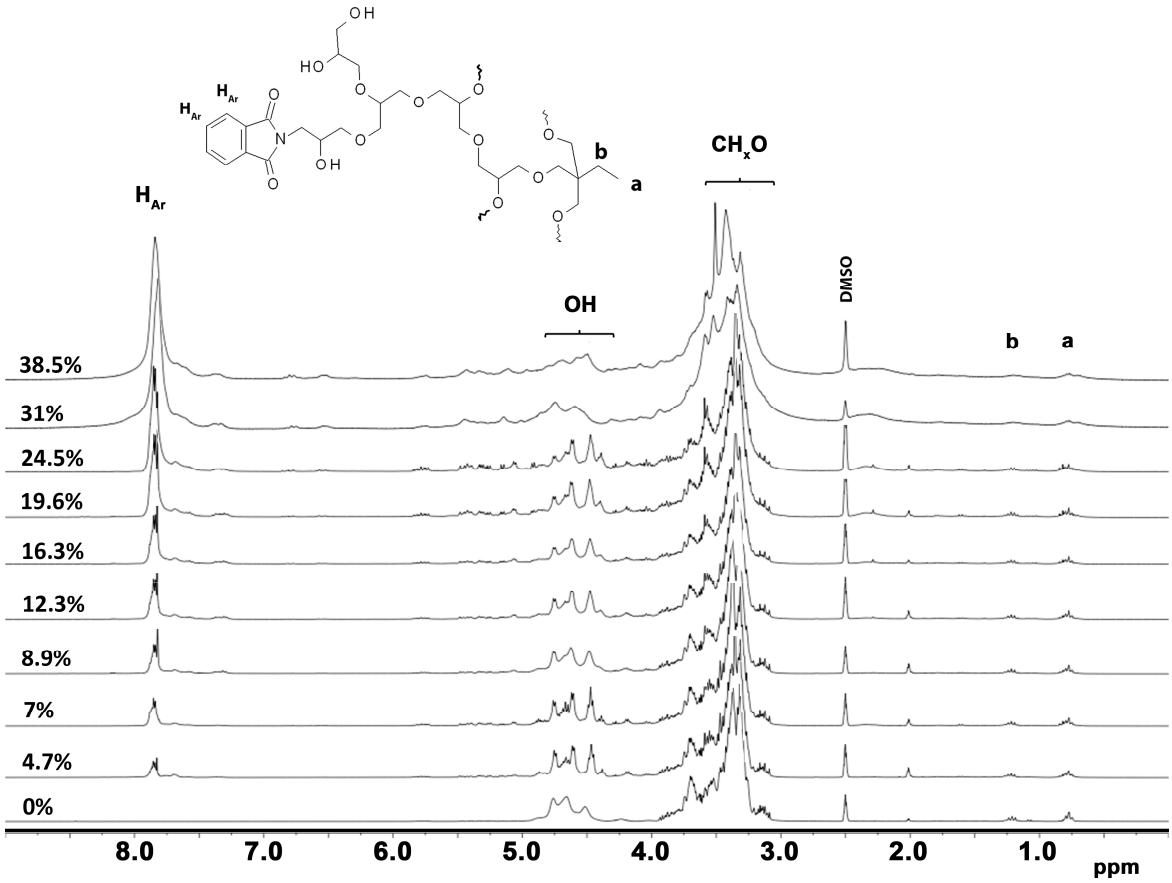


Figure 7. ^{1}H NMR (400MHz, DMSO-d_6) spectra of the **HBPG-0-HBPG-9** polymers. Theoretical amount of phthalimide monomer **2** shown.

Fig. 7 shows a comparison of ^{1}H NMR spectra of synthesized polymers. They show no signals of unreacted monomer **2**. The **a** and **b** peaks located between 1.5 and 0.5 ppm are assigned to the ethyl group of the core molecule (TMP). The integrals ratio of other signals to these signals allowed to calculate the average molar mass of the polymers and their composition. The calculated values of molar masses placed in Tab.1 may be overestimated. As shown below, due to the occurrence of autoinitiation, it is not guaranteed that every polymer molecule bears a TMP moiety. The phthalimide aromatic ring signals are located at approx. 8 ppm. Their intensity grows with the growing amount of the monomer **2** in the post-reaction mixture. The signals in the range of 3.7 to 3 ppm are assigned to methylene and methine groups attached to oxygen atoms and are overlapping. The signals in the range of 5 to 4.3 ppm are assigned to the hydroxyl groups.

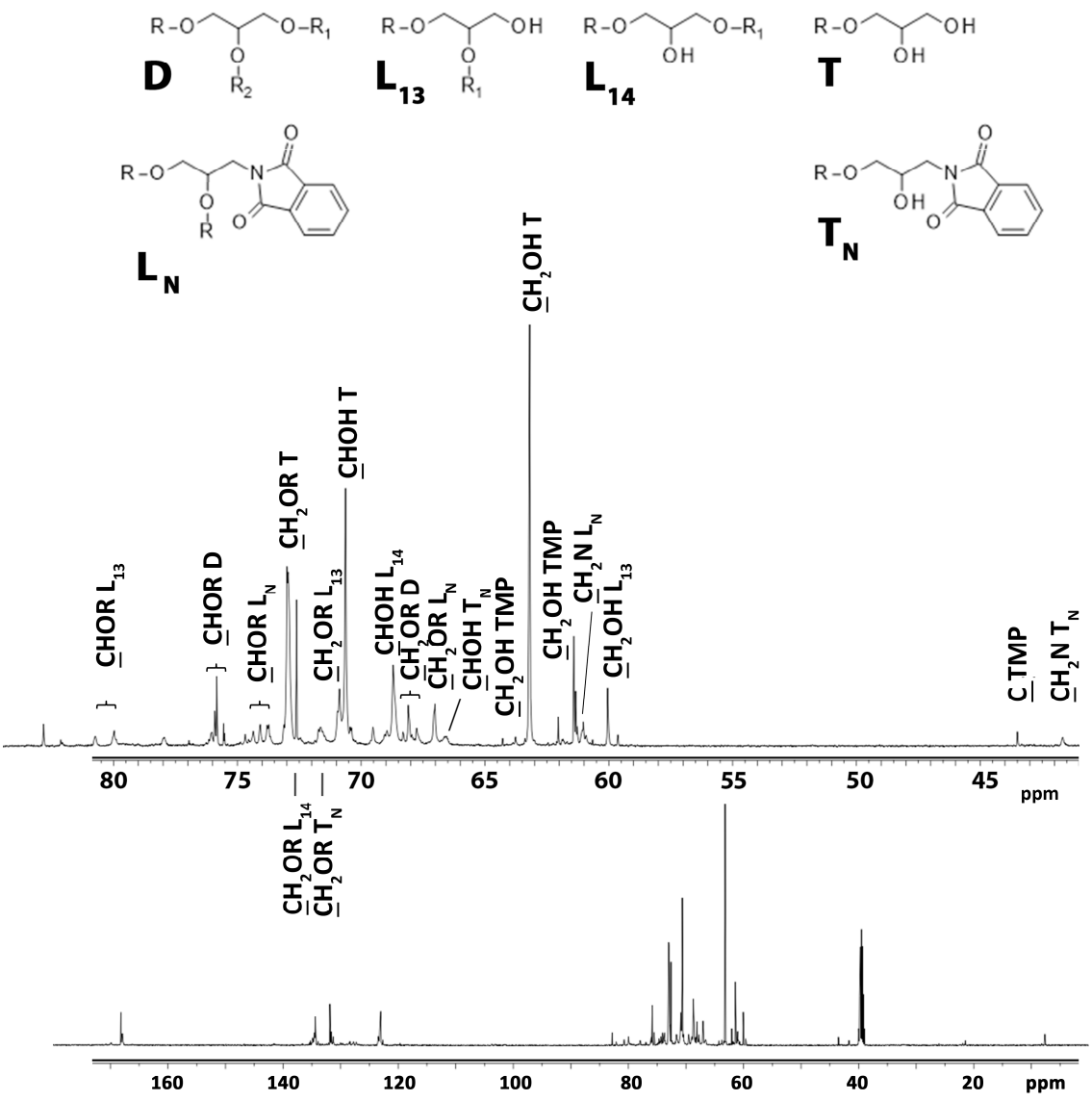


Figure 8. ^{13}C NMR (400MHz, DMSO-d_6) spectra of the **HBPG-8** polymer.

The ^{13}C NMR spectrum shown in Fig. 8 confirmed the incorporation of phthalimide monomer into the structure of the polymer. Due to a high complexity of the structure of hyperbranched polymers (presence of core, linear, branching and terminal units) precise assignment of signals in the ^{13}C NMR spectra was difficult. The signals in Fig. 8 were assigned according to a publication by Sunder *et al.*[8] containing detailed chemical shifts of carbons in the polyglycerol structure and confirmed by the HSQC and HMBC analyses (see supplementary materials Figures 5s-7s). Fig. 8 shows the structures of possible repeating units and their signals in the range of 80-40 ppm. In addition to the units typical for polyglycerol the spectrum contains the signals of phthalimide containing repeating units. The most intense

signals in the spectrum come from linear and terminal units while the dendritic subunits are in minority. It may be caused by the sterical hindrance of the bulky phthalimide residues.

MALDI-TOF technique allows to observe the mass of repeating units of the polymers and their end groups. In case of homo-polymers, the analysis of the spectrum is usually simple. However, when copolymers and products of polymer modifications are considered the analysis becomes tedious.[49] To simplify the MALDI-TOF spectrum a copolymer of **2** and glycerol carbonate (molar ratio 1:2) was synthesized without the TMP core molecule.

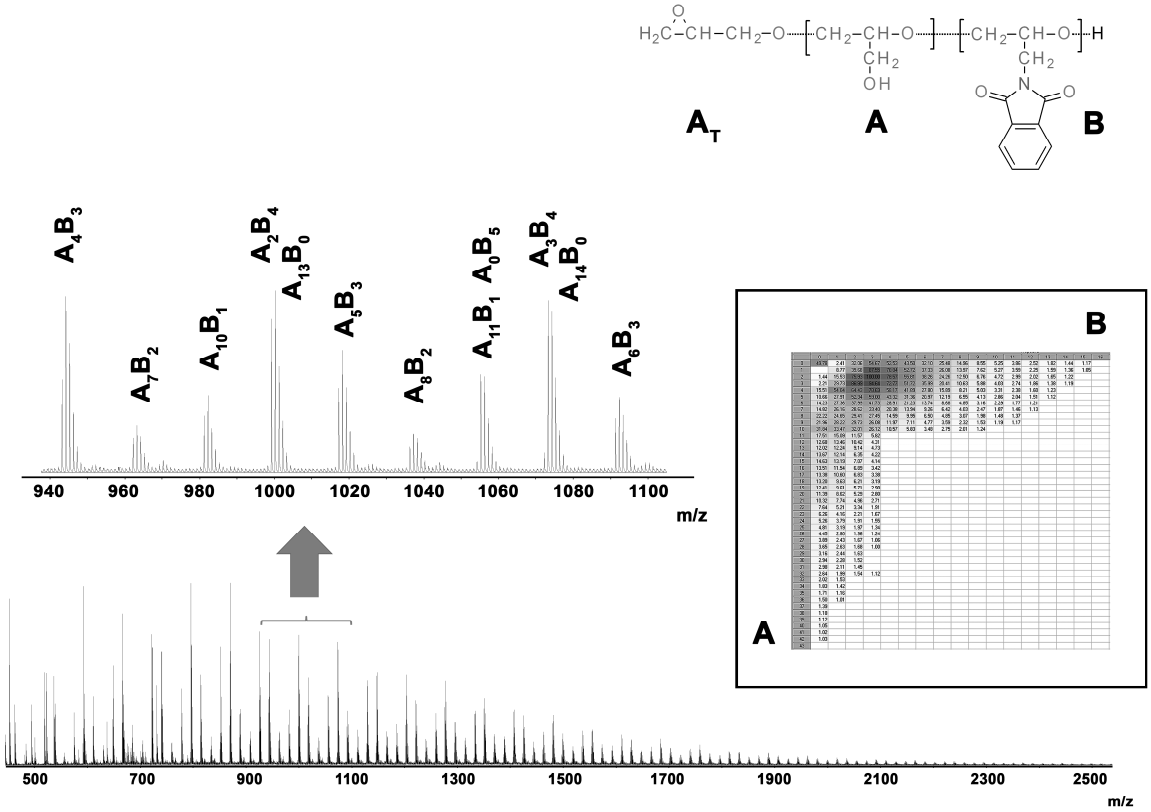
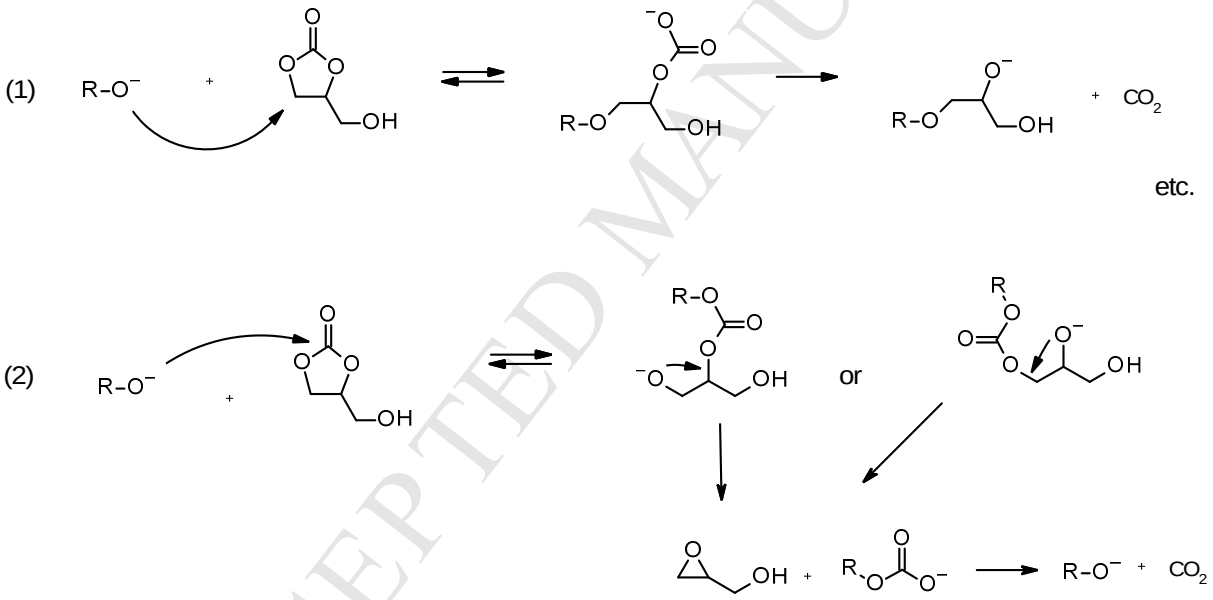


Figure 9. MALDI-TOF (DCTB, K^+) spectrum of polyglycerol obtained from glycerol carbonate (**3**) and N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide (**2**) used in the molar ratio 1:2.

Its spectrum is shown in Fig.9. All the signals in the spectrum can be assigned to a combination of masses of repeating units produced from glycerol carbonate and phthalimide monomer **2** and the mass of potassium cation. The core molecule (residual mass 74.08 m/z) was glycidol of the same molar mass as the repeating unit **A**. As shown in the monomer distribution plot in the inset of Fig. 9, the molar masses of majority of macromolecules

corresponded to approx. 10 glycerol (**A**) or phthalimide (**B**) repeating units where the numbers of **A** and **B** units are on the comparable levels. One would expect higher unit **A** content. However, the aromatic structures absorb the laser light and undergo excitation more easily than aliphatic ones. Therefore the population of signals corresponding to aromatic structures is higher than expected. For comparison reasons a sample MALDI-TOF spectrum of a HBPG-3 polymer containing initiator molecule (TMP) is available in supplementary materials (Figure 8s).

As stated above, the glycidol molecule was found at the core of hyperbranched structure. In fact, it was produced in the reaction mixture and could act as an initiator or an intermediate leading to hyperbranched polymer. Thus, the growth of the polymer could be achieved according to the reaction (1) (Scheme 4) or by anionic polymerization of glycidol. The formation of glycidol in the reaction mixture is explained in Scheme 4.



Scheme 4. Polymerization with decarboxylation of glycerol carbonate (**3**) (reaction 1) and formation of glycidol under reaction conditions (reaction 2).

The formation of glycidol from glycerol carbonate under reaction conditions was also confirmed by ^{1}H NMR spectroscopy. The reaction mixture containing glycerol carbonate and potassium carbonate was heated at reduced pressure allowing the volatile molecules to distill off the mixture. The distillate was collected and investigated. As shown in Fig. 10 it consisted of glycerol carbonate and glycidol in the molar ratio 1 to 1.5 (60 % mol. of glycidol).

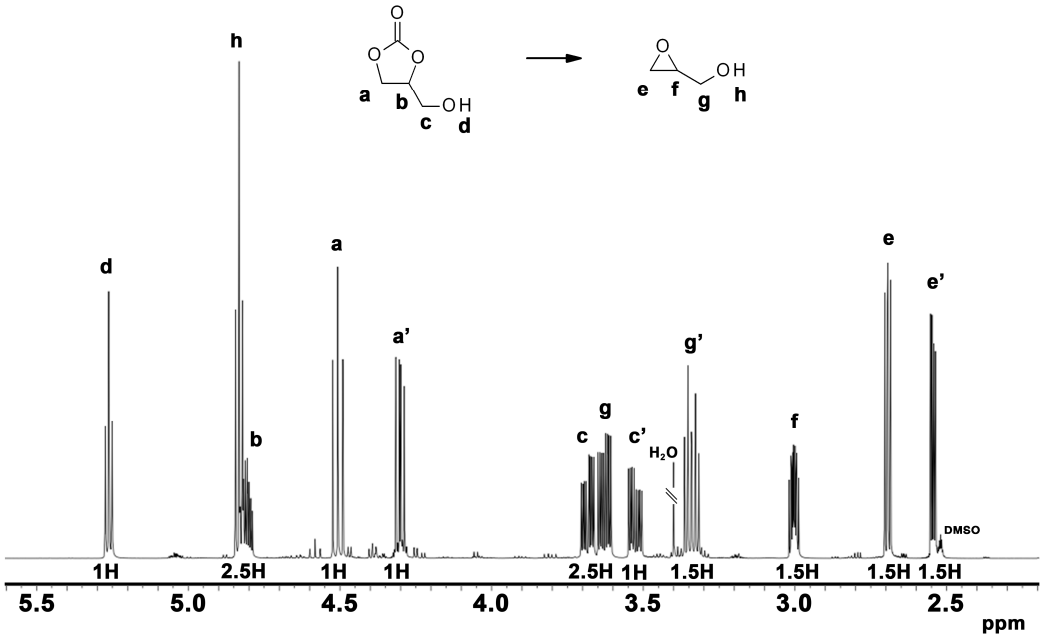


Figure 10. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of a distillate obtained from the mixture of glycerol carbonate and K_2CO_3.

3.4 Hydrazinolysis of glycerol carbonate - N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide copolymers

The final aminated polyglycerols (A-HBPGs) were obtained in the reaction of synthesized in the first step copolymers with 65% aqueous hydrazine hydrate performed in ethanol for 20 h at reflux. This method produced a precipitate of phthalhydrazide along with the primary amine groups in the polymer. The precipitate was removed by filtering acidified methanol solution of the polymers. Then the solution was alkalized (pH = 10) by addition of Na_2CO_3 and evaporated to dryness. Inorganic salts were removed from the polymers by multiple precipitation from the methanol/ethanol mixtures. Attempts to purify the polymers by dialysis were not effective due to low yields of this process.

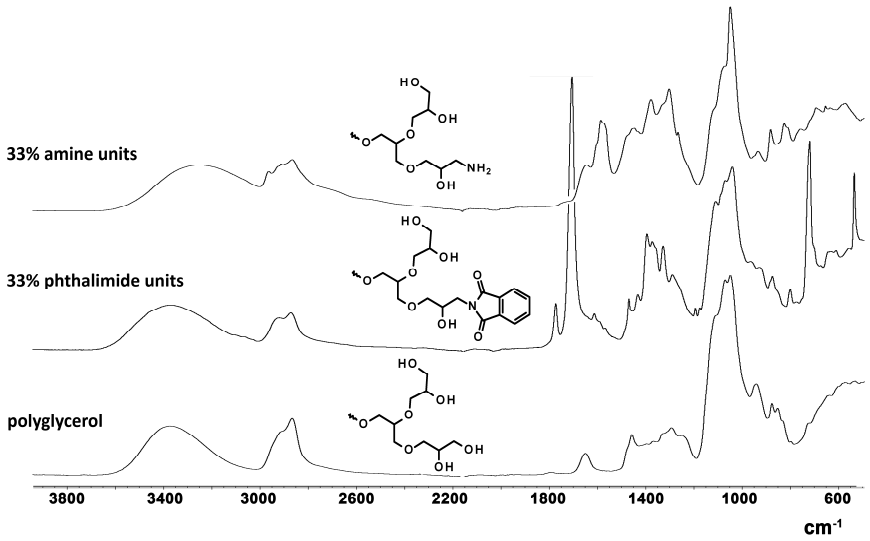


Figure 11. FT-IR (ATR) spectra of polyglycerol **HBPG-0** and copolymers **HBPG-8** (containing phthalimide residues) and **A-HBPG-8** (deprotected one) based on mixture containing 34% mol of **2**.

The procedure of removal of phthalimide residues described above was effective which was confirmed by spectral data. Fig. 11 shows a set of three FTIR spectra of reference polymer **HBPG-0**, copolymer **HBPG-8** based on a mixture of glycerol carbonate and 33%$_{mol}$ of **2** and its deprotected counterpart **A-HBPG-8**. The removal of aromatic rings was accompanied by disappearance of characteristic imide carbonyl absorption band at 1705 cm^{-1}, aromatic ring CH bending vibrations band at 724 cm^{-1} and 530 cm^{-1} O=C-N out of plane rocking vibration band.

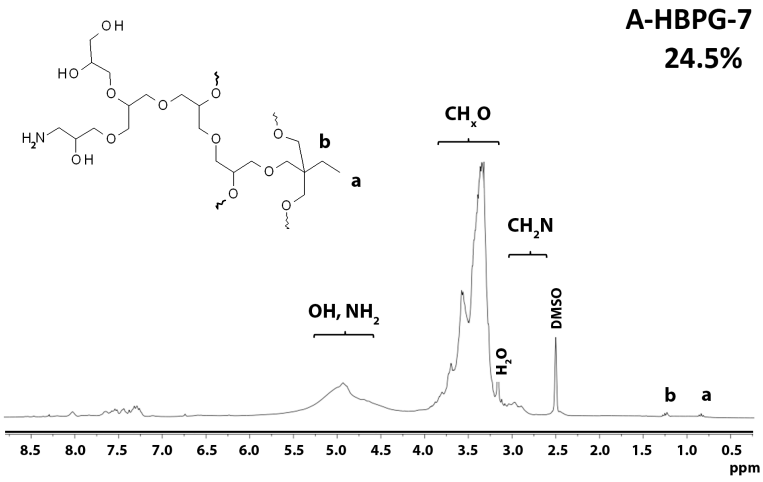


Figure 12. ^{1}H NMR (400MHz, DMSO-d$_6$) spectrum of deprotected **A-HBPG-7** polymer containing 24.5% of amine containing repeating units.

Similarly, the ^{1}H NMR spectrum shown in Fig. 12 showed disappearance of aromatic protons. Because the spectrum does not give a definitive proof of amine group presence in the structure, the polymer was reacted with acetic anhydride. Such modification revealed presence of two amide proton signals at 5.14 i 5.04 ppm in the ^{1}H NMR spectrum. Moreover, the ^{13}C NMR spectrum of **A-HBPG-8** showed presence of $\underline{C}H_2NH_2$ aliphatic carbon signal at 48.7 ppm. The spectra are given in supplementary materials (Figures 2s and 3s).

The MALDI-TOF spectrum (Fig. 13) of deprotected polyglycerol obtained from glycerol carbonate (**3**) and N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide (**2**) in the molar ratio 1:2 also confirmed successful removal of phthalimide moieties.

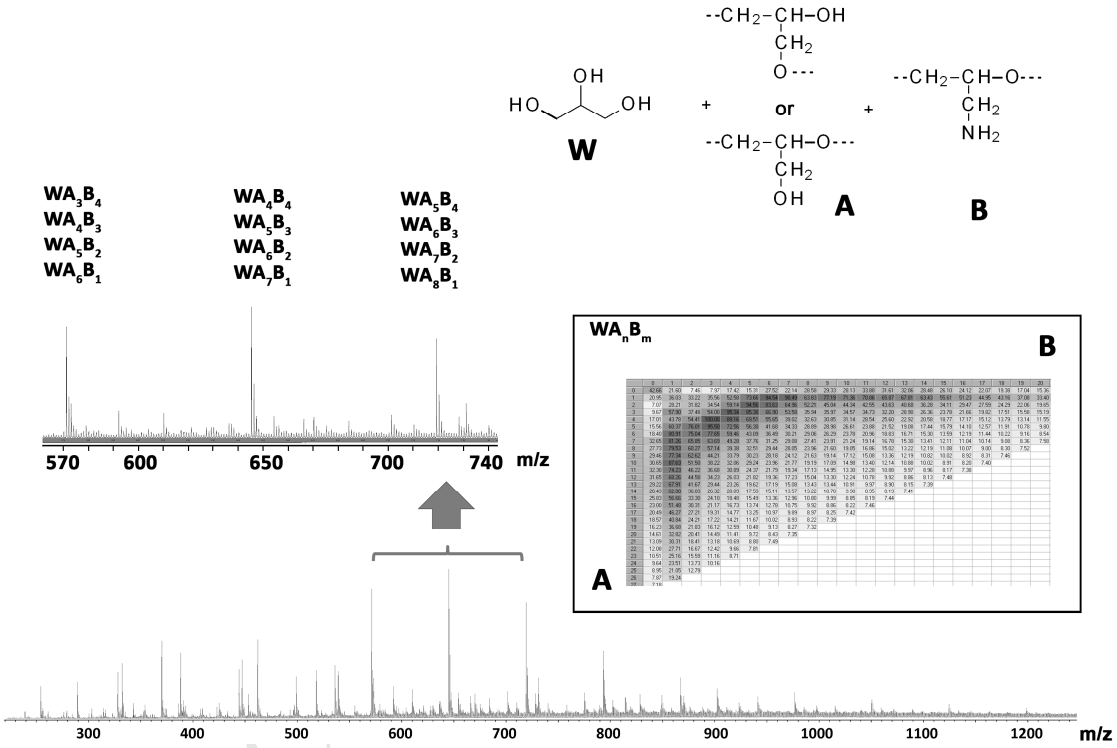


Figure 13. MALDI-TOF (DCTB, K^{+}) spectrum of polyglycerol obtained from glycerol carbonate (**3**) and N-[(2-oxo-1,3-dioxolan-4-yl)methyl]phthalimide (**2**) in the molar ratio 1:2 with deprotected amine groups.

The spectrum contains several series of signals that are overlapping. They all can be assigned to one core molecule: glycerol (residual mass 92.09 m/z). This type of core molecule results from a glycidol one that was hydrolized under hydrazinolysis reaction conditions. Each series of signals can be assigned to molecules containing one molecule of glycerol and multiple units containing hydroxyl (derived from glycerol carbonate) and amine (derived from

phthalimide monomer **2**) (A and B in Fig. 13) repeating units. The molar mass difference between those two types of repeating units is equal 1, therefore the peaks are grouped in sets and overlaping. The small signals seen close to the baseline were identified as molecules containing one or two phthalimide groups. This is in agreement with NMR data, since small quantity of the phthalimide residues are also seen in Fig. 14 at approx. 7.5 ppm.

The distribution plot present in tn Fig. 13 shows that both A and B units are evenly distributed in copolymer macromolecules.

Typically, GPC is used for the analysis of the molar masses of polymeric materials. In case of hyperbranched polymers the NMR calculated results are more precise. For comparison purposes acetylated samples of copolymers of **2** and glycerol carbonate in a molar ratio 1 to 2 were measured by GPC using polystyrene standards. The sample containing phthalimide residues showed molar mass M_w=1560 g/mol and dispersity D=2.13, while the deprotected, amine containing polymer 790 g/mol and dispersity D=2.13. A sample GPC curve is available in supplementary materials (Figure 4s).

Finally, we confirmed the presence of nitrogen in the deprotected polymer samples by elemental analysis. The results showed slightly lower content of nitrogen than expected. The sample **A-HBPG-7** showed 6.53% of N (7.43% theoret.) while the **A-HBPG-8** 7.47% N (8.32% theoret.). This confirmed that described synthetic procedure was correct.

4. Conclusions

Hyperbranched aliphatic polyethers with hydroxyl and amine end groups were produced from glycerol carbonate (4-hydroxymethyl-1,3-dioxolan-2-one) and cyclic carbonate bearing phthalimide moiety. Anionic polymerization of cyclic carbonate monomers, which proceeds with simultaneous decarboxylation, was performed using a simple catalyst - potassium carbonate and trimethylolpropane (TMP) or glycerol carbonate as an initiator. The polymerization conditions were optimized. The polymers were characterized by means of NMR, FTIR, MALDI-TOF, GPC and elemental analysis.

It was shown that during the process of polymerization an intermediate - glycidol is formed and acts as initiator or monomer. The easy production and purification of phthalimide - cyclic carbonate monomer enables multigram synthesis of amine functionalized polyglycerols that will be investigated as biomolecules carriers, antibacterial agents, carbon dioxide scavengers or modifiers of mechanical properties of epoxy resins and polyurethanes.

5. Acknowledgments

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Highlights

Hyperbranched aliphatic polyethers with hydroxyl and amine end groups were produced from glycerol carbonate.

It was shown that during the process of polymerization an intermediate - glycidol is formed and acts as initiator or monomer.

The easy production and purification of phthalimide - cyclic carbonate monomer enables multigram synthesis of amine functionalized polyglycerols.