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The synthesis and copolymerization of 4-hydroxybenzylglycolide: experimental and theoretical aspects

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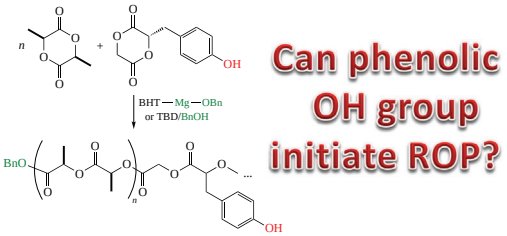
Based on tyrosine, 4-hydroxybenzylglycolide was synthesized. Its study in ring-opening copolymerization with lactides in view of the ability of the phenolic hydroxy group to initiate polymerization was performed experimentally and with DFT modeling.



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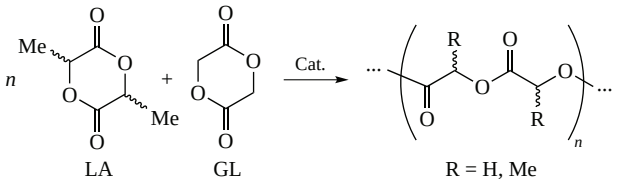
Both polylactide (PLA) and copolymers of lactide (LA) with glycolide (GL) represent biodegradable and biocompatible polymers with high-level mechanical characteristics and controlled biodegradability.[1–7] Poly(lactoglycolide) (PLGA) based materials and articles have promising prospects for drug delivery, controlled drug release, tissue engineering, bone surgery, and other biomedical applications.[8–12] Meanwhile, PLGAs alone have limited ability to binding with biomedically significant molecules, additional grafting or functionalization is needed.[13–16] Because ring-opening polymerization (ROP) is the most efficient method of PLGA synthesis (Scheme 1),[17–19] the evident and prospective approach to chemically active PLGAs implies the use of comonomers containing reactive functional groups. Considering high reactivity of GL and LA in ROP, the appropriate comonomers should be the substituted glycolides. However, to date only rare publications report the synthesis and employment of functionalized glycolides in coROP with lactides.[20–22]

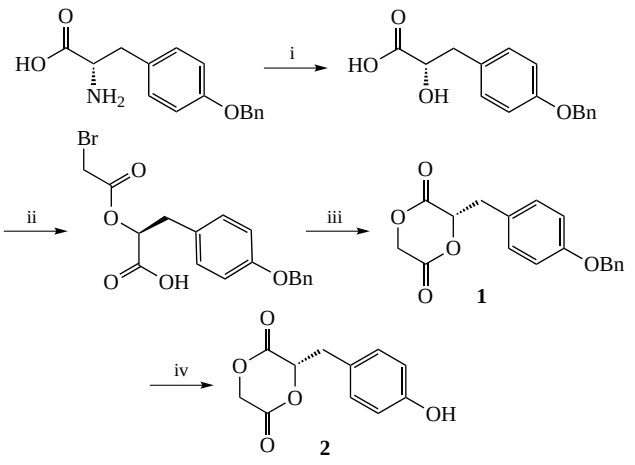
In our previous study,[23] we have established an efficient synthetic approach to substituted glycolides including glycolide **1** that represents the tyrosine derivative containing 4-benzyloxybenzyl fragment (Scheme 2). Considering that benzyl group can be easily eliminated by catalytic hydrogenolysis,[24] we synthesized new compound, 4-hydroxybenzyl-substituted glycolide **2**, and examined compounds **1** and **2** as prospective comonomers in the synhesis of biodegradable PLGAs capable of the further chemical modifications (for experimental details, see Online Supplementary Materials). Note that the synthesis of compound **2** was previously reported in the patent,[25] however the compound was then described incorrectly without any spectral data.



Scheme 1

We have chosen two catalysts for copolymerization experiments, namely, heteroleptic 2,6-di-*tert*-butyl-4-phenoxy magnesium complex $[(BHT)Mg(\mu\text{-}OBn)(THF)]_2$ (BHT–Mg),[26] and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[27] Compound BHT–Mg was a single-component catalyst, TBD was used in combination with BnOH.

First, we carried out BHT–Mg catalyzed copolymerization of benzylated derivative **1** with (*S*)-LA which led to copolymer containing comonomers in given ratio (see Online Supplementary Materials, Figure S5), the calculated value of M_n matched the SEC



Scheme 2 *Reagents and conditions*: i, $NaNO_2/H_2SO_4$, 0–5 °C, 60%; ii, $BrCH_2C(O)Br$, Py, CH_2Cl_2; iii, DIPEA, MeCN, 60 °C, 78%; iv, H_2, Pd/C, 96%.

Table 1 Copolymerization experiments with glycolides.[a]

Entry	Mon1	Mon2	Catalyst	Initiator	Mon1/Mon2/ Catalyst/Initiator ratio	Reaction T/°C	Reaction time/h	Conversion, Mon1/Mon2 (%)	$M_n^{th} \times 10^3$ (see[b])	$M_n^{NMR} \times 10^3$ (see[c])	$M_n^{SEC} \times 10^3$ (see[d])	$Đ_M^3$
1	**1**	(*S*)-LA	BHT–Mg	–	10 : 90 : 1 : –	20	20	>99/>99	16.2	–	16.6	1.99
2	**2**	(*S*)-LA	BHT–Mg	–	20 : 180 : 1 : –	40	10	23/0	1.1	–	n.d.[e]	n.d.
3	**2**	(*S*)-LA	TBD	BnOH	20 : 180 : 1 : 1	20	20	47/0	2.2	–	n.d.	n.d.
4	**2**	*rac*-LA	BHT–Mg	–	3 : 27 : 1 : –	20	10	67/31	1.7	–	5.4	1.32
5	**2**	*rac*-LA	BHT–Mg	–	9 : 81 : 1 : –	75	3	>99/94	12.4	24.4	29.3	1.41
6	**2**	*rac*-LA	TBD	BnOH	3 : 27 : 1 : 1	20	1	>99/>99	4.7	5.8	2.78	1.98
7	**2**	*rac*-LA	TBD	BnOH	5 : 45 : 1 : 1	20	2	>99/>99	7.7	8.1	23.8	1.40

[a] Substituted glycolide **1** or **2** (2 mmol, 1 equiv.) and lactide (2.595 g, 18 mmol, 9 equiv.) were dissolved in THF (up to 9 ml solution). In the separate vial, the solution of TBD and BnOH or BHT–Mg of the total volume of 1 ml was prepared. The vial containing comonomer solution was placed into thermostated bath, and the solution of the catalyst was added (resulting concentration of comonomers was 2 M). After required period of time, the polymerization was stopped by adding a 5-fold excess of AcOH. The reaction mixture was evaporated, kept in vacuum for THF removing, and was analyzed by ^{1}H NMR for the determination of the comonomer conversion. [b] Calculated by the formula $M_n^{th} = [Mon1]_0/[I]_0 conv_{Mon1} + [Mon2]_0/[I]_0 conv_{Mon2} + MW_I$, where $[Mon1]_0$, $[Mon2]_0$, $[I]_0$ – initial concentrations of monomers and initiator, MW_I – molecular weight of BnOH, $conv_{Mon1}$, $conv_{Mon2}$ – monomers conversion determined by ^{1}H NMR. [c] Calculated from the ratio of the integrals of the signals of copolymer and the signal of C_6H_5 fragment of the initiator. [d] SEC data, multiplying by the correction factor 0.58 (for PLA). [e] Not determined.

data (Table 1, entry 1). We have initially presupposed to carry out the further hydrogenation of this copolymer targeting for 4-hydroxybenzyl-functionalized copolymer. The experiment on hydrogenolysis was conducted under the conditions that were used in the synthesis of **2**. However, even after 3 days we did not detected the formation of the 4-hydroxybenzyl-substituted copolymer.

Based on the assumption of low reactivity of phenolic hydroxy group as an initiator of ROP,[23] we studied copolymerization of phenolic derivative **2** with (*S*)-LA catalyzed by BHT–Mg and TBD/BnOH (see Table 1, entries 2 and 3, respectively). In both cases, we detected the formation of low MW homopolymers of **2** as (*S*)-LA was unreactive. In view of the higher reactivity of *rac*-lactide (*rac*-LA) in comparison with (*S*)-LA in BHT–Mg catalyzed polymerization, we continued the experiments with *rac*-LA. Even at lower comonomer/BHT–Mg ratios, after 10 h of the reaction at room temperature, the conversions of **2** and *rac*-LA amounted to 67 and 31%, respectively (entry 4). In the experiment at elevated temperature (75 °C, entry 5), high conversions were achieved for both comonomers. The analysis of the ^{1}H NMR spectra of the precipitated copolymer (see entry 5) has shown low content of BnO fragments, the values of M_n^{NMR} and M_n^{SEC} having been more than double the value of M_n^{th}. We assume that such difference can be attributed to partial deactivation of the catalyst *via* the proton transfer from more acidic phenolic group of **2** to benzyloxy group of BHT–Mg with a formation of less active bis(aryloxy) magnesium species.

In our next experiments on **2**/*rac*-LA copolymerization, TBD/BnOH has proved to be more active catalyst in comparison with BHT–Mg (see Table 1, entries 6 and 7, respectively). At relative low comonomer/catalyst ratio (30 : 1), the full conversions of **2** and *rac*-LA were detected at room temperature within an hour. When reaction time was increased, we obtained copolymer with M_n^{SEC} = 23.8 kDa triple those of the expected M_n^{th} = 7.7 kDa (entry 7). The analysis of ^{1}H NMR spectrum of this copolymer had shown the presence of two groups of the C_6H_4O signals, which could be attributed to C_6H_4OH and $C_6H_4OC(O)$ fragments (see Online Supplementary Materials, Figure S6). In this way, in the presence of TBD phenolic OH group was capable of the ROP initiation.

To evaluate the possibility of the initiation of TBD-catalyzed ROP by phenolic hydroxy group, we made comparative quantum chemical modeling for BnOH and PhOH initiators of (*S*)-LA polymerization using PRIRODA[28,29] software at PBE/3ζ[30] level of the density functional theory (DFT). As shown previously, TBD–ROH complexes represent the ground states for TBD/ROH catalyzed ROP.[27] Our calculations demonstrated that the formation of such complex by PhOH is preferable in comparison with BnOH, the difference in free energies was ~0.6 kcal mol^{-1}. Therefore, phenolic hydroxy group of **2** is capable of bonding with TBD, which may lead to slow down polymerization.

The reaction profiles of the initiation of TBD-catalyzed (*S*)-LA ROP by BnOH and PhOH are presented in Figure 1.

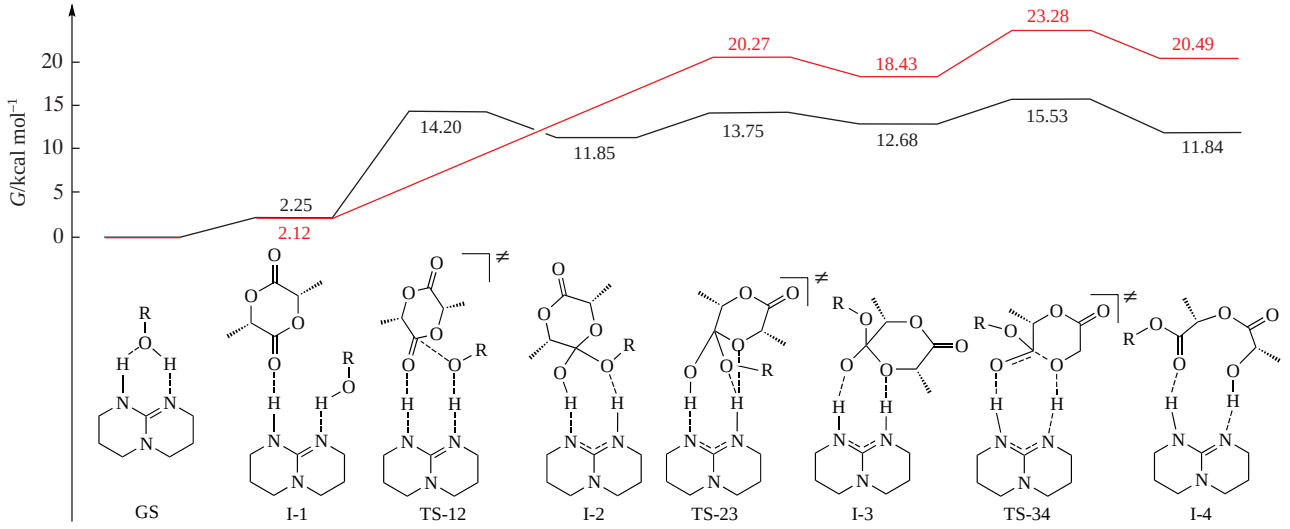


Figure 1 Calculated free energy profiles (kcal mol^{-1}) of the initiation of TBD-catalyzed (*S*)-LA ROP by BnOH (black line) and PhOH (red line).

These profiles show that the calculated difference in free activation energies for BnOH and PhOH initiated ROP of (*S*)-LA is about 8 kcal mol^{-1} (TS-34, relative to GS). One can assume that in the presence of large excess of (*S*)-LA the polymerization is going on, however the lowering the concentration of (*S*)-LA during polymerization and slowing down ROP give rise to coordination of phenolic OH group, followed by slow ROP or transesterification with a formation of branched copolymers.

In this way, using new comonomer, 4-hydroxybenzyl-substituted glycolide **2**, we successfully obtained PLGAs functionalized with phenolic groups. However, the control on the degree of polymerization was complicated by the ability of phenolic hydroxy group to initiate ROP of lactide. Note that such ability in the absence of alkoxy initiators has been demonstrated previously for catalytic systems comprising phenol and tertiary amine.[31,32] The results of our preliminary study clearly indicate the need for the use of the protective groups for phenolic hydroxy group, and the research in this direction is currently underway in our laboratory.

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Online Supplementary Materials

Supplementary data associated with this article (experimental details, NMR spectra of **1**, **2** and copolymers obtained, DFT calculations data) can be found online at doi: 10.1016/j.mencom.2021.09.036.

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