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Ring-opened 4-hydroxy-δ-valerolactone subunit as a key structural fragment of polyesters that degrade without acid formation

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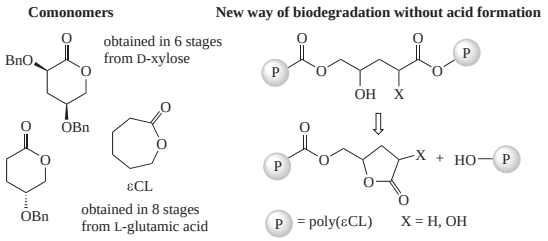
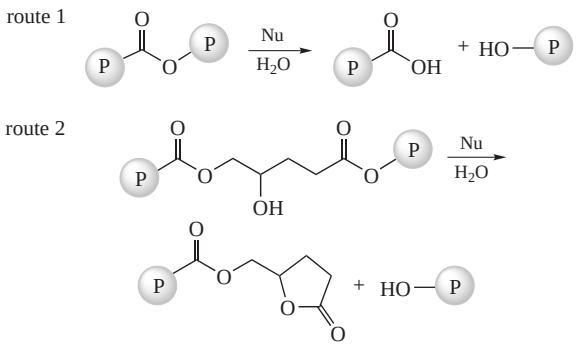
Random copolymers of ε-caprolactone with *O*-benzyl-protected 4-hydroxy- or 2,4-dihydroxy-δ-valerolactone after hydrogenation form γ-hydroxy functionalized polyesters that degrade *via* the cyclization to γ-butyrolactone fragments without carboxylic acid formation.



The control of the degradation rate and the release of degradation products are essential aspects in the design of synthetic polymers for biomedical use. Adjusting the degradation rate is necessary to tailor material for a specific application.[1–4] Despite the absence of toxicity, degradation products from aliphatic polyesters may cause an inflammatory response at the implantation site due to the formation of acids that generally have a negligible effect on the surrounding tissue.[5–7] In addition, a pH decrease induced by a large amount of acidic degradation products might cause a toxic response if the degradation occurs at an anatomical site with limited body fluid flow.[8,9] Acidic degradation products may also influence the stability and hydrolysis rate of pH-sensitive drugs used for drug delivery applications.[10] The design of polymers that degrage without acid formation represents a significant way for the development of biomedical materials with enhanced biocompatibility.[11,12]

Polylactones represent an important group of biopolymers. Their hydrophilicity and biodegradability are controlled by monomer type,[1,6,13,14] as well as by introducing poly(ethylene glycol)[15,16] or poly(ethylene phosphate)[17–19] blocks. However, traditional hydrolytic biodegradation of the polyester backbone leads to the formation of cardoxylic acid fragments (Scheme 1, route 1).

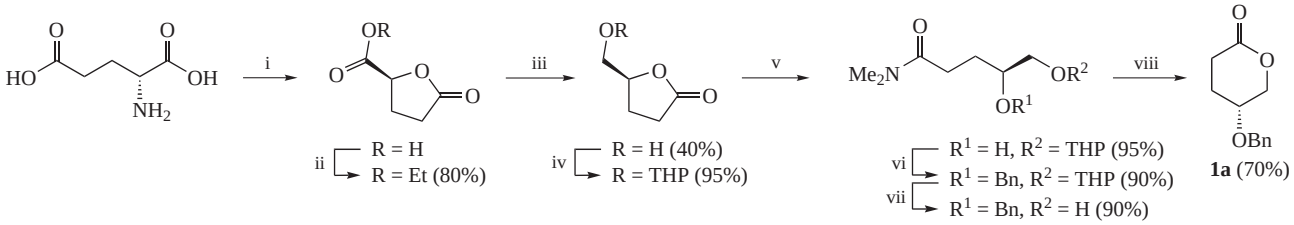


Scheme 1

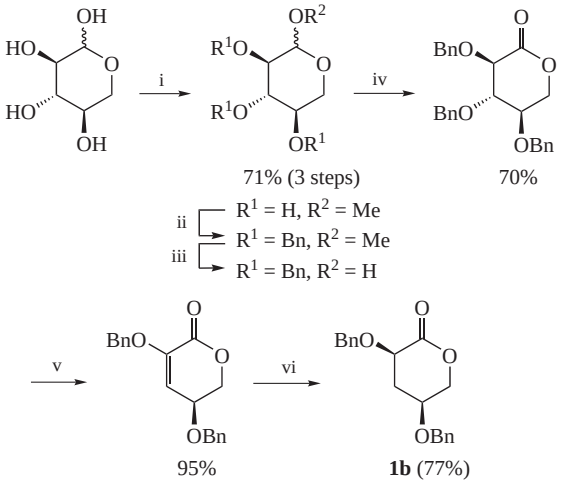
Ring-opening polymerization (ROP) of cyclic esters is mainly used in the synthesis of polyesters. Ring-opening with a formation of polyester polymer chain is energetically favorable for strained β-propiolactone, and for lactones with six-membered (δ-valerolactone), seven-membered (ε-caprolactone, εCL) and extended cycles; five-membered γ-butyrolactone (γBL) is thermodynamically stable.[20] Recently we demonstrated the tendency of organic compounds containing the $HO(CH_2)_3C(O)$ fragment to form γBL cycle in the presence of efficient ROP catalysts such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[21]

We hypothesized that the high stability of γBL can be effectively used in the design of polyesters, which are able to decompose by non-traditional reaction mechanism with a formation of γBL cycles (see Scheme 1, route 2) thus retaining the medium acidity. To test this assumption, we synthesized cyclic esters, 4-benzyloxy-δ-valerolactones **1a**,**b** from available starting compounds, L-glutamic acid and D-xylose, respectively (Schemes 2 and 3, detailed description of experiments is given in Online Supplementary Materials). Then, we performed the copolymerization of lactones **1a**,**b** with εCL, prepared the deprotected copolymers containing OH groups, and proved the feasibility of the route 2 (see Scheme 1) for the degradation of polyesters. Note that the application of benzyl protective groups for ROP monomers was demonstrated earlier through the example of 3-benzyloxytrimethylene carbonate.[22,23]

Lactones **1a**,**b** were enantiopure. As shown previously,[24] diazotization at the first stage of the synthesis of **1a** is stereospecific, the configuration of asymmetric carbon atom at subsequent stages remains unchanged. The first stages of the synthesis of **1b** also do not affect the configuration of the chiral centers of the molecule. We should also note the high stereoselectivity of hydrogenation at the last stage of the synthesis of **1b** (more than 90% by NMR, see Online Supplementary Materials). The



Scheme 2 *Reagents and conditions*: i, $NaNO_2$, H_2SO_4; ii, EtOH, TsOH; iii, $NaBH_2$, EtOH; iv, THP, CH_2Cl_2; v, Me_2NH, H_2O; vi, BnBr, NaH, THF; vii, TsOH, MeOH; viii, TsOH, C_6H_6, reflux.

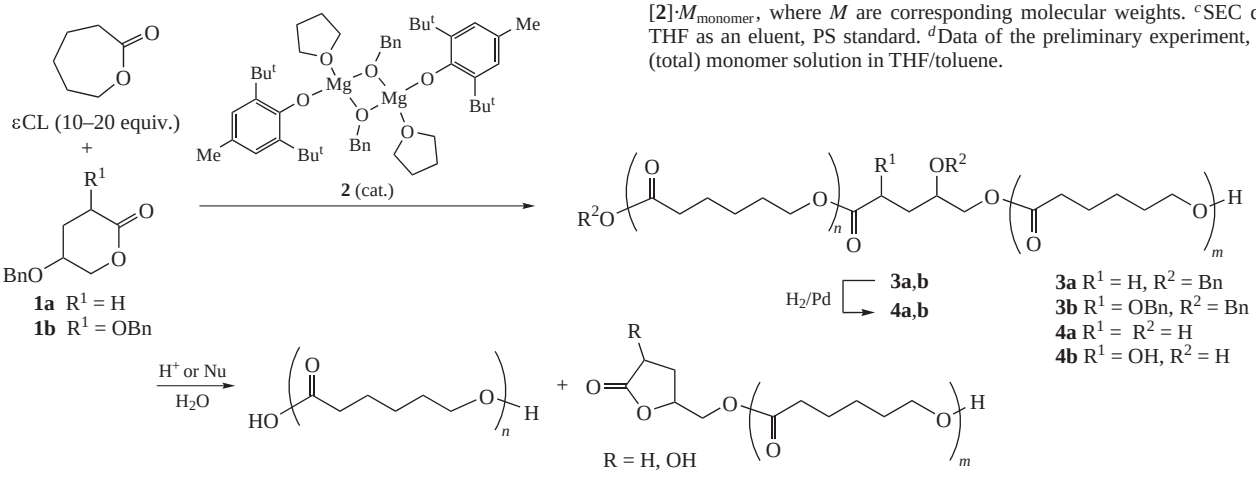


Scheme 3 *Reagents and conditions*: i, $SOCl_2$, MeOH, reflux; ii, NaH, BnBr, THF, DMF; iii, H_2SO_4, H_2O, 1,4-dioxane, AcOH, reflux; iv; I_2, K_2CO_3, CH_2Cl_2; v, TBD, 130 °C; vi, H_2, PtO_2, AcOEt.

molecular structure of **1b** was confirmed by X-ray diffraction analysis (Figure 1).†

In copolymerization of **1a**,**b** with εCL (Scheme 4) we used single-component catalyst $[(BHT)Mg(\mu\text{-}OBn)(THF)]_2$ **2** that demonstrated high activity in polymerization of lactones.[25–27] Reactions were carried out in toluene/THF. Polymer characteristics are given in Table 1.

Narrow molecular weight distribution curves (SEC) and sufficient agreement between M_n^{NMR} and M_n^{SEC} values confirm the 'living' character of copolymerization. Copolymers **3a**,**b** (see Scheme 4) were hydrogenated to eliminate benzyl protective



Scheme 4

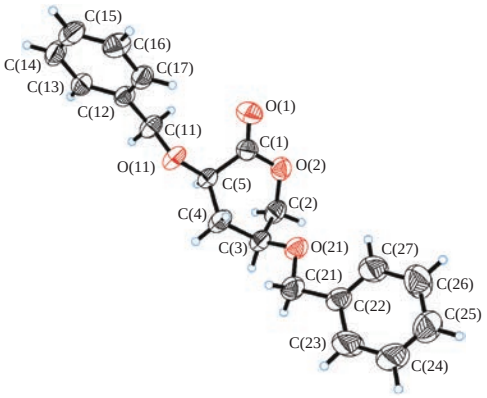


Figure 1 Molecular structure of 2,4-dibenzyloxy-δ-valerolactone **1b** (50% thermal ellipsoid probability). Selected bond lengths (Å): C(1)–O(1) 1.192(2), C(1)–O(2) 1.349(2), C(1)–C(5) 1.512(2), C(2)–O(2) 1.442(2), C(2)–C(3) 1.503(2), C(3)–C(4) 1.533(2), C(4)–C(5) 1.5200(19).

Table 1 Synthesis and characteristics of the products of copolymerization of εCL with monomers **1a**,**b** and corresponding products of hydrogenation.[a]

Run	Monomer (equiv.)	εCL (equiv.)	*t*/h	Conversion (%)	Copolymers **3a**,**b**				Copolymers **4a**,**b**	
					M_n^{th} [b]	M_n^{NMR}	M_n^{SEC} [c]	$Đ_M$ [c]	M_n^{SEC} [c]	$Đ_M$ [c]
1[d]	**1a** (5)	45	6	99	6280	7500	9100	1.43	8600	1.55
2	**1a** (5)	95	1	96	11980	14800	18200	1.58	15500	1.64
3	**1b** (5)	95	1	92	12510	24100	23600	1.52	17900	1.61
4	**1a** (10)	90	1	98	12440	20900	28500	1.64	16100	1.70
5	**1b** (10)	90	1	95	13500	22500	26500	1.56	18000	1.68

[a] Reaction conditions: 0 °C, 2 M (total) monomer solutions in THF/toluene. [b] Calculated by formula $M_n^{th} = M_{BnOH} + [\varepsilon CL]/[\mathbf{2}]\cdot M_{\varepsilon CL} + [\text{monomer}]/[\mathbf{2}]\cdot M_{monomer}$, where *M* are corresponding molecular weights. [c] SEC data, THF as an eluent, PS standard. [d] Data of the preliminary experiment, 1 M (total) monomer solution in THF/toluene.

† *Crystallographic data for* **1b**: $C_{19}H_{20}O_4$, M = 312.35, monoclinic, space group $P2_1$, a = 11.153(4), b = 5.579(2), c = 13.192(3) Å, β = 92.63(2)°, V = 820.0(5) Å^3, Z = 2, d_{calc} = 1.265 g cm^{-3}, $F(000)$ = 332, λ(CuKα) = = 1.54178 Å, T = 295 K, 3.35° ⩽ θ ⩽ 75.03°, 6462 reflections measured, 3351 independent reflections (R_{int} = 0.020), R_1 = 0.0401 for 3186 reflections with $I > 2\sigma(I)$; wR_2 = 0.1100 for all data; GOF = 1.050, largest diff. electron density, peak/hole: 0.166/–0.164 e Å^{-3}.

CCDC 1845789 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

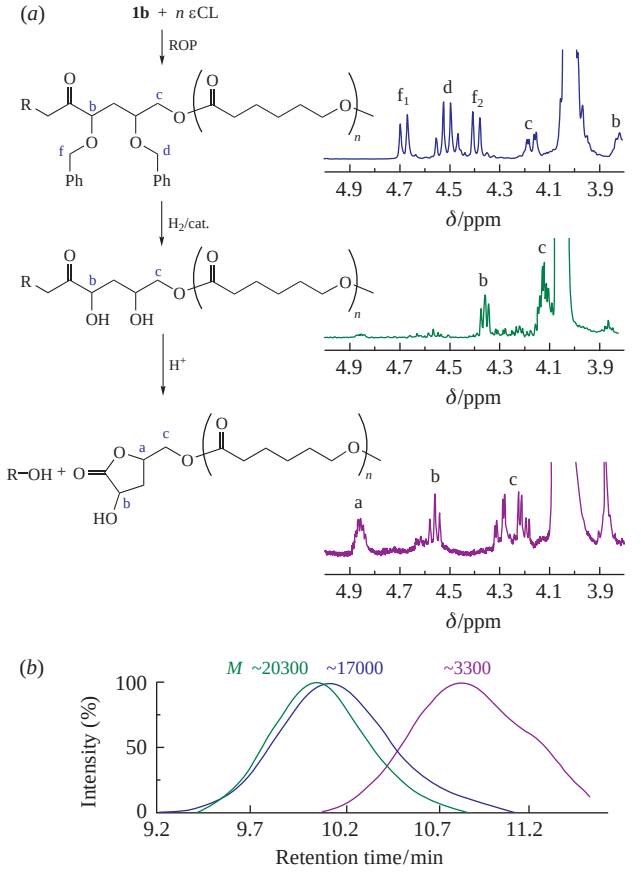


Figure 2 (*a*) The scheme of the synthesis and degradation of polymer **4b** and the corresponding fragments of ^{1}H NMR spectra and (*b*) SEC traces.

group. The characteristics of obtained hydroxy functionalized copolymers **4a**,**b**‡ are also given in Table 1.

We studied the reactivity of hydroxy polyesters **4a**,**b** toward acidic ($MeSO_3H$) and nucleophilic (TBD) reagents that are soluble in organic media ($CDCl_3$). NMR monitoring of the reaction mixtures showed that the fragmentation with a formation of γ-BL cycles is the main degradation route for both of them. SEC analysis of the destruction products demonstrated that the length of the fragments correlate with comonomer ratio in the starting copolymer: thus, copolymer **4b** (see Table 1, run 3) degraded with a formation of oligomers containing ~20 monomer subunits [Figure 2(*c*), SEC data]. Characteristic fragments of the ^{1}H NMR spectra of copolymer **4b** and corresponding hydrogenation and scission products are also provided in Figure 2.

Our results indicate that polyester macromolecule with 4-hydroxyalkylcarbonyl fragment exhibits the tendency to form γ-butyrolactone end groups under the impact of both acidic and basic reagents. These preliminary results allow us to anticipate the prospects of introducing HO–$(CH_2)_4$–C=O fragments into the polymer chain to create biomedical materials which would not reveal an acidic inflammatory response in tissues. The study of biodegradation of such polymers is the subject of a separate long-term research which is currently being performed in our laboratory.

‡ For details of synthetic experiments and NMR spectra of copolymers, see Online Supplementary Materials.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.11.022.

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