Kinetics of the Ring-Opening Polymerization of 6-, 7-, 9-, 12-, 13-, 16-, and 17-Membered Lactones. Comparison of Chemical and Enzymatic Polymerizations

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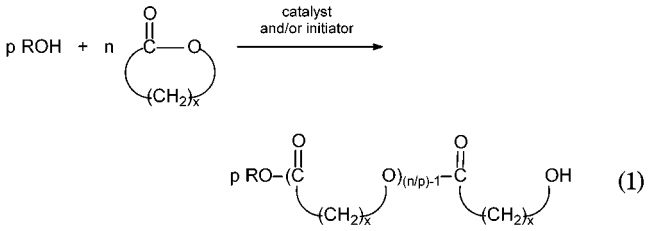
ABSTRACT: The kinetics of bulk polymerization of 6-, 7-, 9-, 12-, 13-, 16-, and 17-membered lactones initiated with a zinc 2-ethylhexanoate/butyl alcohol system at 100 °C was studied and compared with that of lipase-catalyzed polymerization. Instantaneous concentrations of the lactone monomers were determined on the basis of the relative intensities of signals in the ^{1}H NMR spectra (500 MHz, $CDCl_3$ as a solvent, room temperature) from the ω-methylene protons ($-(CH_2)_{x-1}C\mathbf{H}_2OC(O)-$) (where $x = 4$, 5, 7, 10, 11, 14, and 15) in the lactone monomer and the polyester repeating units, respectively. Linearity of the semilogarithmic kinetic dependencies ($\ln([\text{lactone}]_0/[\text{lactone}])$ vs time), revealed a first order of propagation in monomer for all of the polymerizations studied. This kinetic behavior, pointing to the constant concentration of the involved active centers and thus to the practical elimination of termination side reaction, allowed the relative polymerization rates to be determined. The following order of polymerization rates has been obtained: 2500:330:21:0.9:1.0:0.9:1.0 for the 6-, 7-, 9-, 12-, 13-, 16-, and 17-membered lactones, respectively. The order of rates of the enzymatic polymerization, determined earlier in an independent paper, shows an inverted dependence on the ring size, namely 0.10:0.13:0.19:0.74:1.0 for the 7-, 12-, 13-, 16-, and 17-membered lactones, respectively. The resulting difference in the orders of lactone reactivities in chemical and enzymatic polymerizations is explained in terms of a difference in factors controlling polymerization rates in both processes. The ring strain, which decreases with increasing lactone size, is partially released in the transition state of the elementary reaction of the polyester chain growth, which eventually leads to faster propagation for more strained monomers in chemical polymerizations. In enzymatic polymerizations, the rate-determining step involves formation of the lactone−lipase complex. The latter reaction is promoted by the hydrophobicity of the lactone monomer, which is higher for the larger lactone rings.

Introduction

Poly(aliphatic ester)s have recently become important class of polymers of both the specialty biomedical polymers and the large-scale production commodity thermoplastics.[1−7] These applications are mainly related to their biocompatibility and ability to "spontaneously" degrade in the natural environment, after the required time of exploitation. The most widely used method for the controlled synthesis of poly(aliphatic ester)s is a ring-opening polymerization of the respective cyclic monomers, such as lactones, glycolide, lactides, or cyclic aliphatic carbonates.[8−14] Moreover, polymerization of these monomers provides convenient model systems for studies of the mechanisms of the ring opening chemical[8−10,15−18] and enzymatical[11−14,19−30] polymerizations.

For example, polymerization of lactones conducted in the presence of compounds containing hydroxyl group (H_2O, alcohols or hydroxyacids (ROH)) (eq 1) can be controlled with respect to the polymerization degree of the resulting polyester simply by adjusting the starting concentrations lactone to ROH ratio (i.e., $DP_n = ([\text{lactone}]_0 - [\text{lactone}])/[\text{ROH}]_0$). The catalysts and/or initiators include covalent metal alkoxides and carboxylates.



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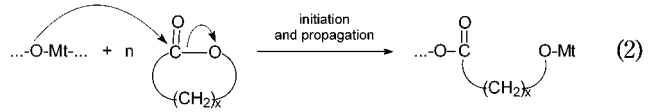
Termination and transfer side reactions can be practically or at least considerably eliminated.[8−10] Whether the alkoxide or the carboxylate initiator is used, the resulting active center is of the macroalkoxide structure (see, for example, refs 15−18). The elementary chain growth reactions proceed via nucleophilic attack of the alkoxide species at the carbon of the monomer carbonyl, followed by scission of the acyl−oxygen bond and reformation of the alkoxide species (eq 2). In polymerizations of cyclic esters promoted by enzymes, the best



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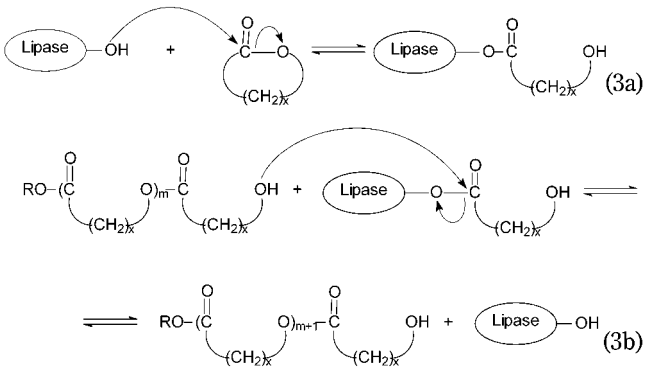
results have been obtained for the lipase-catalyzed processes (see refs 11−14 and references therein). In this case, the polyester chain growth process most probably involves, ring-opening of the monomer by nucleophilic attack of the serine residue of lipase, followed by hydrolysis of the acyl−enzyme intermediate or its esterification with low molar mass alcohol or hydroxy-terminated polyester chain (eq 3).[19,20] This



work compares the kinetics of chemical polymerization of lactones of medium and large ring sizes with the pertinent results obtained in enzymatic polymerization studies.[20−24]

More systematic kinetic studies were reported only for anionic[31−33] or pseudoanionic (covalent) polymerization of ϵ-caprolactone,[34−38] allowing determination of the absolute rate constants for ion pairs, free ions, and covalent species. We were able to find only two papers reporting the kinetics of chemically initiated polymerization of macrolides.[39,40] Therefore, we have performed the comparative kinetic measurements for the 6-, 7-, 9-, 12-, 13, 16, and 17-membered lactones (cf. eq 1: $x = 4$, 5, 7, 10, 11, 14, and 15, respectively).

Experimental Section

Materials. δ-Valerolactone (tech.), ϵ-caprolactone (99%), and 12-dodecanolide (98%), were purchased from Aldrich. 11-Undecanolide (99%), 15-pentadecanolide (99%), and 16-hexadecanolide (99%) were purchased from Wako Pure Chemical Industries Ltd., Japan. 8-Octanolide was prepared by reacting cyclooctanone with *m*-chloroperbenzoic acid as described in ref 41). Crude monomers were dried over freshly activated molecular sieves 4A and purified by vacuum distillation before use. Zinc octoate (2-ethylhexanoate) (95%), from ABCR, Karlsruhe, Germany, was purified by vacuum distillation (10^{-3} mbar, 180 °C). Butyl alcohol (99%), from Aldrich, was dried with Na metal and distilled before use. Deuterated chloroform (99.5% isotopic purity), from Dr. Glaser AG, Basel, Switzerland and methylene chloride (99%), from POCh, Gliwice, Poland, were purified by distillation over calcium hydride.

Polymerization Procedure. A general polymerization procedure follows the example described below. 16-Hexanolide (3.125 g, 13 mmol), zinc octoate (0.386 g, 1.1 mmol), and butyl alcohol (0.082 g, 1.1 mmol) were poured into a 50 mL round-bottom flask. Substrates were homogenized at temperature above melting point of 16-hexanolide (≈38 °C), and the resulting reaction mixture has been put into a thermostat at 100 °C. Samples of the monomer/polymer mixtures (0.1 g) were withdrawn after a predetermined polymerization times, depending on the monomer reactivity (cf. Figure 1), cooled to room temperature, and dissolved in $CDCl_3$ (∼ 10 wt %), and their ^{1}H NMR spectra were recorded. All operations were carried out under argon atmosphere.

NMR Measurements. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker DRX 500 spectrometer operating at 500 MHz. Chloroform was used as an internal standard ($\delta = 7.26$ ppm).

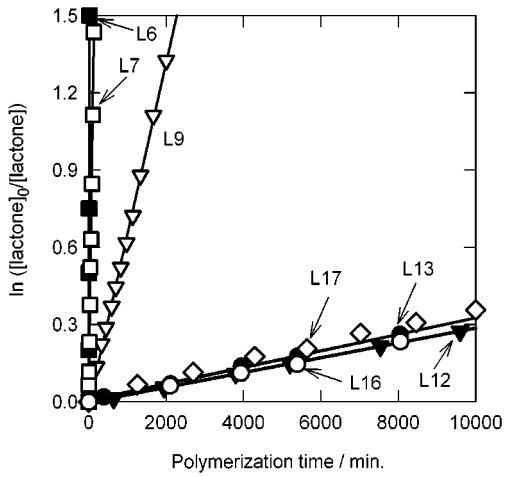


Figure 1. Kinetics of the bulk polymerization of δ-valerolactone (■, L6), ϵ-caprolactone (□, L7), 8-octanolide (▽, L9), 11-undecanolide (▼), 12-dodecanolide (●, L13), 15-pentadecanolide (○, L16), and 16-hexanolide (◇, L17) initiated with zinc octoate/butyl alcohol equimolar mixture. Polymerization conditions: $[Zn(Oct)]_0 = [BuOH]_0 = 0.28$ mol·L^{-1}, 100 °C; starting concentrations of lactones ($[lactone]_0$) are given in Table 1.

Molar Mass Measurements. Number-average molar masses (M_n) and polydispersity indexes (M_w/M_n) of the resulting polylactones were determined from size exclusion chromatography (SEC) of the crude polymerization mixtures, applying calibration on poly(ϵ-caprolactone) standards prepared in the Center of Molecular and Macromolecular Studies, Lodz, Poland. SEC measurements were performed with a LKB 2150 HPLC pump, set of TSK Gel columns (G 2000 H_{XL} and 6000 H_{XL}; pore sizes 2.5×10^2 and 10^6 Å, respectively) and a Wyatt Optilab 903 interferometric refractometer (Wyatt Technology Corp., Santa Barbara, CA) as detector. CH_2Cl_2 was used as the eluent at 20 °C with a flow rate of 0.8 mL min^{-1}.

Results and Discussion

We have carried out a series of kinetic measurements for polymerization of lactones of various ring sizes, namely δ-valerolactone (L6), ϵ-caprolactone (L7), 8-octanolide (L9), 11-undecanolide (L12), 12-dodecanolide (L13), 15-pentadecanolide (L16), and 16-hexanolide (L17), initiated by an equimolar mixture of zinc octoate ($Zn(Oct)_2$) and butyl alcohol (BuOH). To ensure operable polymerization times for all of the monomers and to obtain liquid, homogeneous reaction mixtures the polymerizations were studied in bulk at 100 °C. Starting concentrations of monomers and co-initiators are given in Table 1. Instantaneous monomer concentrations were determined from the relative intensities of signals in the ^{1}H NMR spectra (500 MHz, $CDCl_3$ solvent, room temperature) coming from the ω-methylene protons $-(CH_2)_{x-1}CH_2OC(O)-$ in monomer and in repeating units of the resulting polyester. In the spectra recorded in $CDCl_3$ these two signals were well-resolved, separate triplets (see pertinent chemical shifts reported in Table 1).

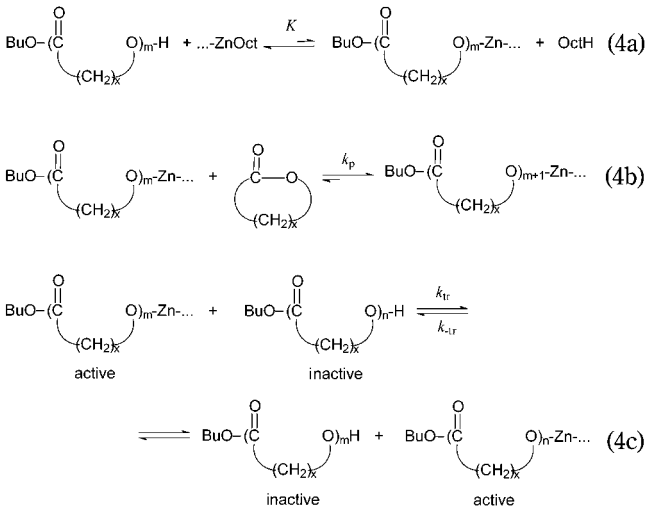
We have shown recently that polymerization in the lactone/$Zn(Oct)_2$/BuOH system proceeds in a controlled manner, both with respect to molar masses and to the end groups of the resulting polylactone and does not require application of a high vacuum technique to obtain reproducible results.[42] Moreover, side reactions leading to formation of the octoate ester end groups are kinetically depressed in comparison with the process conducted with the tin(II) octoate ($Sn(Oct)_2$)/BuOH system.[43]

Table 1. Comparison of Rates of Polymerization Determined for Lactones of Various Ring Sizes in Processes Initiated with Zinc Octoate/Butyl Alcohol[a] and with Lipase *Pseudomonas fluorescens*/Octyl Alcohol[b] Systems

lactone	$[lactone]_0$/ mol·L^{-1}	chemical shifts $-CH_2O(O)-$ δ in ppm ($CDCl_3$, room temp) monomer	polymer	relative rate of polymerization this work	enzymatic polymerization	$\Delta H_p°$/ kJ·mol^{-1}	$\Delta S_p°$/ J·mol^{-1}·K^{-1}	dipole moment[f]/ C·m
δ-valerolactone (L6)	9.7	4.31	4.04	2500		−9.9[c]	−13	4.22
ϵ-caprolactone (L7)	8.3	4.25	4.07	330	0.10	−13.9[d]	−10.4	4.45
8-octanolide (L9)	5.8	4.30	4.06	21				
11-undecanolide (L12)	4.8	4.19	4.04	0.9	0.13			1.86
12-dodecanolide (L13)	4.5	4.16	4.05	1.0	0.19			1.86
15-pentadecanolide (L16)	3.5	4.13	4.05	0.9	0.74	3[e]	23	1.86
16-hexadecanolide (L17)	3.2	4.11	4.04	1.0	1.00			
butyl caproate			4.06	-				1.75

[a] $[Zn(Oct)]_0 = [BuOH]_0 = 0.28$ mol·L^{-1}, bulk polymerization carried out at 100 °C. [b] Conditions: $[lactone]_0 = 0.3$ mol·L^{-1}, $[octyl\ alcohol]_0 = 0.03$ mol·L^{-1}, 200 mg of lipase, total volume 10 mL, isopropyl ether as a solvent, and 60 °C; relative polymerization rates were calculated from ratios of the Michaelis−Menten kinetic parameters (V_{max}/K_m).[24] [c] Data from ref 45, monomer and polymer liquid, 77 °C. [d] Data from ref 46, monomer and polymer: liquid, 77 °C. [e] Data from ref 47, monomer and polymer liquid, 100 °C. [f] Data from ref 13.

Therefore, lactone polymerization initiated by the $Zn(Oct)_2$/BuOH system can be described schematically by a scheme in which the actual active species (zinc alkoxides) are formed in a fast establishing equilibrium (eq 4a), and then the polymer chain growth proceeds exclusively on the zinc−oxygen alkoxide bond (eq 4b). (Macro)alcohol-(macro)alkoxide exchange (chain transfer to alcohol)[15−18] proceeds simultaneously (eq 4c). (Oct



and Bu stand for $C_4H_9(C_2H_5)CHC(O)O$ and C_4H_9 groups; K denotes equilibrium constant of carboxylate-alkoxide ligands exchange, k_p the rate constant of propagation, and k_{tr} and k_{-tr} the rate constants of chain transfer to (macro)alcohol (m, $n = 0, 1, 2, 3, ...$)). Transestrifications (both inter- and intramolecular)[44] are omitted in eq 4, parts a−c, because these side reactions do not affect the kinetics of propagation.

Figure 1 shows the results of the kinetic measurements using semilogarithmic coordinates. The linearity of these plots suggests that equilibrium 4a is established fast (relative to propagation), initiation is also fast, termination is practically eliminated, and equilibrium monomer concentrations can be neglected, at least for the degrees of monomers consumption studied.

The slopes of the kinetic plots given in Figure 1 thus correspond to the $k_p[P_n*]$ product (where $[P_n*]$ denotes concentration of the propagating species):

$$\ln([lactone]_0/[lactone]) = k_p[P_n*]t \qquad (5)$$

($[lactone]_0$, [lactone], and t denote starting and instantaneous lactone concentrations, and polymerization time, respectively).

Since the butyl alcohol and the macroalcohol formed are much more nucleophilic than cyclic esters, differences in the starting concentrations of the individual lactones ($[lactone]_0$) should not influence the position of equilibrium 4a. The linearity of the first-order kinetic plots supports this assumption. Consequently, $[P_n*]$ is practically identical for all of the monomers studied, under similar conditions. There is also another problem related to differences in $[lactone]_0$ in bulk polymerization of various lactones. Namely, these differences could affect the pertinent k_p values because of, for example, various polarities of the polymerization media and/or the importance of monomer-active centers complexation phenomena. The instantaneous concentration of lactone and thus the polarity of the polymerization medium change as the polymerization progresses—particularly in the case of L6 and L7. Again, taking into account a linearity of the kinetic plots in Figure 1, up to high degrees of monomer consumption, this objection can be rejected. Indeed, to the best of our knowledge, there is no data in the literature reporting k_p change with $[lactone]_0$ in the pseudoanionic polymerization of these monomers.

Thus, the ratios of the products $k_p[P_n*]$, determined from the slopes of the kinetic plots, give the corresponding ratios of k_p's. These ratios are given in Table 1 in the column of relative rates of polymerization. Because active species operating in polymerization of various lactones are practically identical, viz. ...$-C(O)(CH_2)_{x-1}$-CH_2O-Zn-..., the order of k_p's is equivalent to the order of lactone reactivities.

Comparison of the lactone ring sizes with the relative polymerization rates shows that the larger the lactone ring the lower its reactivity. However, the reactivities of L12, L13, L16, and L17 are essentially within experimental error.

Thermodynamic polymerizability is usually discussed in terms of the enthalpy ($\Delta H_p°$) and entropy ($\Delta S_p°$) of the propagation−depropagation equilibria, allowing prediction of the position of the monomer−polymer equilibrium under the given polymerization conditions. The thermodynamic parameters are not available for some lactones studied in this work. However, the thermodynamic data can be supplemented by the dipole moment values (Table 1), which are larger for medium

size lactones due to their larger ring-strain, in comparison with those for macrolides and the acyclic acid ester (butyl caproate). Thus, we conclude from the existing data that a liquid-state polymerization of smaller ring lactones is driven by the negative change of enthalpy (because $\Delta H_p° < 0$, $\Delta S_p° < 0$, and $|\Delta H_p°| > -T\Delta S_p°$). The polymerization of larger rings eventually becomes driven by a positive change in entropy ($\Delta H_p° > 0$, $\Delta S_p° > 0$, and $\Delta H_p° < |-T\Delta S_p°|$).

The negative enthalpy of polymerization of a cyclic monomer results mostly from its ring strain. One of the characteristic features of the studied monomers, pointing to the decreasing ring-strain with the lactone size, is the almost continuous decrease of the chemical shift of the ω-methylene protons: $(CH_2)_{x-1}C\mathbf{H_2}OC(O)$ from $\delta = 4.31$ ppm for L6 to $\delta = 4.11$ ppm for L17, approaching the values of $\delta \approx 4.07-4.04$ for nonstrained linear polyesters and low molar mass linear ester (Table 1).

This strain should be partially released the transition state of the elementary reaction of the polyester chain growth this strain is partially released, and the resulting enthalpy of activation ($\Delta H_p^{\ddagger}$) lower for strained monomers in comparison with the nonstrained ones. This is probably, main reason the reactivity of lactones decreases with increasing size and eventually reaches a constant value for larger rings. Other factors, such as electrophilicity of the monomer acyl atom or steric hindrance, hampering the approach of the active species to the lactone ester group, probably play a minor role (cf. however entries for δ-valerolactone and ϵ-caprolactone in Table 1).

Results obtained previously in enzymatic polymerization (Table 1) suggest that the reactivity of lactones in this process is no longer controlled by their ring strain. A striking feature of enzymatic polymerization is related to relatively high polymerization rates of macrolides. These nonstrained monomers polymerize with comparable or even higher rates than δ-valerolactone and ϵ-caprolactone.[20−24] Such particular behavior can be explained assuming that formation of the enzyme-activated monomer (EM, acyl−enzyme intermediate), via an enzyme−lactone complex (eq 3a), is the rate-determining step of enzymatic polymerization. Then the elementary act of propagation proceeds via fast nucleophilic attack of the hydroxyl group at the polyester chain-end on EM ("activated monomer mechanism").[12,19,20] The rate of the complex formation depends on the ease of monomer recognition by the lipase. In living cells, the lipase is inherently used as an enzyme for hydrolysis of the glycerol fatty acid ester.[48] Macrolides are close to the latter species in their hydrophobic nature and in molecular shape and therefore are more readily recognized by lipase than the smaller ring lactones, such as ϵ-caprolactone. Consequently, the ring-opening reactivity orders of lactones of various ring sizes are completely different in chemical and enzymatic polymerizations.

Despite fundamental differences and kinetics of chemical and enzymatic polymerization of lactones, the two processes seem to proceed similarly, at least from the material chain growth viewpoint. The M_n's calculated assuming that every molecule of an alcohol starts growth of exactly one polylactone chain agree with the M_n's determined by means of size exclusion chromatography (SEC) with poly(ϵ-caprolactone) standards (Table 2). This confirms the validity of our earlier, but not explicitly expressed, assumption that chain transfer reactions represented by equilibrium 4c are fast compared to propagation.The M_w/M_n values in Table 2 are characteristic of a Flory−Schulz distribution and most probably result from segmental exchange (intermolecular transestrification), especially at higher temperatures (100 °C in the present work).[44] Fortunately, this side reaction affects neither the number of the polylactone chains nor the concentration of the actually growing macromolecules.

Table 2. Control of Number Average Molar Masses (M_n) of Polylactones Formed in Bulk Polymerization of Lactones of Various Ring Sizes Initiated with Zinc Octoate/butyl Alcohol System[a]

lactone	$[\text{lactone}]_0$/mol·L^{-1}	α[b]	M_n(calcd)[c]	M_n(SEC)[d]	M_w/M_n[d]
L6	9.7	≈1	3543	3400	1.98
L7	8.3	≈1	3458	3350	1.97
L9	5.8	0.74	2253	2100	2.02
L12	4.8	0.50	1654	1550	1.99
L13	4.5	0.55	1827	1700	1.98
L16	3.5	0.48	1516	1350	1.95
L17	3.2	0.51	1557	1400	1.94

[a] Polymerization conditions are given in Table 1. [b] α denotes degree of lactone consumption as determined from ^{1}H NMR spectra of the polymerization mixtures. [c] M_n(calcd) denotes the number-average molar mass of the resulting polylactone calculated from feed composition and α; $M_n(\text{calcd}) = \alpha M_L[\text{lactone}]_0/[\text{BuOH}]_0 + 74.12$, where M_L stands for a given lactone molar mass (M_L = 100.12, 114.14, 142.16, 184.28, 198.31, 240.39, and 254.42 for L6, L7, L9, L12, L13, L16, and L17, respectively), and 74.12 is the molar mass of butyl alcohol. [d] Determined by SEC using poly(ϵ-caprolactone) standards.

In enzymatic polymerization compounds bearing hydroxyl groups (H_2O, alcohols or α-hydroxy-ω-carboxylic acids (ROH)) act as both of initiators and chain transfer agents, starting and then continuing polylactone chain growth (eq 3b); in principle, the molar mass of the resulting polylactone can be controlled by the $[\text{lactone}]_0/[\text{ROH}]_0$ ratio. By adjustment of this ratio, polylactones with M_n in the wide range 10^3-10^5 have been prepared;[29,49,50] however, the efficiency of initiation and chain transfer in enzymatic polymerization is still a problem since polydispersity indexes (M_w/M_n), reported for example in refs 20, 23, and 24, are well above 2—the value expected for a thermodynamically equlibrated system.

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