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New insights into the hydrolytic degradation of poly(lactic acid): participation of the alcohol terminus

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Abstract

The hydrolytic degradation of monodisperse lactic acid oligomers was studied in vitro to gain insight into the degradation of oligolactic acid grafted to dextran, which we use for the preparation of hydrogels based on physical interactions, or the degradation of PLA/PLGA. The decrease in the amount of oligomer and the formation of degradation products was monitored by HPLC and MS. The amount of lactic acid oligomer decreased according to pseudo-first-order kinetics and was dependent on the dielectric constant of the medium and the pH. The OH end group was found to play a crucial role in the hydrolytic degradation; when the OH was blocked no significant degradation was observed. At acidic pH, hydrolysis was shown to proceed by chain-end scission whereas in alkaline medium, lactoyl lactate was split off. The possible consequences of these findings for the degradation of PLA matrices are discussed.

Keywords: Lactic acid oligomers; Poly(lactic acid); Hydrolysis

1. Introduction

Biodegradable polyesters, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers (PLGA) are under investigation for biomedical (e.g. orthopedic fixture materials [1], degradable sutures [2], absorbable fibres [2]) and pharmaceutical applications (e.g. controlled-release devices [3]). Degradation of these materials occurs by uptake of water followed by hydrolysis of ester bonds. Different factors affect the hydrolysis kinetics of these polymers. The pH is an important factor in the hydrolysis of these polyesters, because hydrolysis is catalyzed by both acid and base [4]. The presence of a crystalline phase, the T_g of the amorphous phase as well as the hydrophobicity also affect the degradation rate [5–8]. The latter point is illustrated by the observation that the degradation rate increases upon copolymerization of lactic acid with glycolic acid, which decreases the hydrophobicity of the polymer [9]. The effect of molecular architecture on the in vitro degradation properties has also been investigated [10]. The initial degradation rate of star-block copolymers of PLA–PEO was slower compared to the linear copolymers of PLA–PEO. Furthermore, it was shown that PLGA with a free carboxyl group at the polymer terminus (uncapped PLGA) degrades faster than PLGA with a hydrophobic alkyl ester linkage at the polymer terminus (capped PLGA) [11]. This illustrates the influence of the PLGA end group. Other factors that strongly affect the degradation are the molecular weight [12–14] and the enantiomeric composition of the polymer [15]. Different molecular weights or enantiomeric composition yields matrices with varying morphology, ranging from amorphous materials to materials with various degrees of crystallinity. The degradation rate is also dependent on the film thickness, as reported by Lu et al. [16]. The degradation kinetics is furthermore affected by additives, such as metal salts [17], monomer [18,19], basic compounds e.g. coral [20,21], acid drugs [18,22], superoxide ion [23], and catalysts such as $SnOct_2$ and zinc metal [24–27].

The hydrolytic degradation of massive, amorphous poly(DL-lactic acid) devices was shown to proceed heterogeneously and to go faster inside than at the surface, because in the interior there is a larger contribution of auto-catalysis

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[1,28–30]. Initially, hydrolysis of the ester bonds proceeds homogeneously through the matrix. During degradation, two factors are of importance. First, degradation causes an increase in the number of carboxylic acid chain ends which are known to auto-catalyze ester hydrolysis. Second, only oligomers, which are soluble in the surrounding aqueous medium, can escape from the matrix. As aging goes on, soluble oligomers, which are close to the surface can leach out before they fully degrade, whereas those which are located in the core of the matrix remain entrapped. This yields a low pH in the core which, in turn, results in an accelerated degradation.

The degradation of semi-crystalline PLLA matrices proceeds even more complicated. It was reported by Fischer et al. that the hydrolytic degradation occurs in two stages [31]. In the first stage, water diffuses into the amorphous regions resulting in random hydrolytic scission of ester bonds. The degree of crystallinity can even increase as degradation proceeds [31]. The second stage starts when most of the amorphous regions have been degraded. The hydrolytic attack then progresses from the edge towards the center of crystalline domains. A retardation in degradation has been observed during the degradation of intrinsically amorphous poly(DL-LA) by the formation of a crystalline phase of an oligomeric stereocomplex as intermediate. This intermediate stereocomplex is highly resistant to hydrolysis [28].

According to Shih [32], base-catalyzed hydrolysis of PLA proceeds by a random scission mechanism whereas in acid-catalyzed hydrolysis of PLA, chain-end scission is faster. Belbella et al. [33] came to the opposite conclusion: a sequential cleavage from the chain end in alkaline medium and random scission at acidic pH values. It was not specified which end group (COOH or OH) of the PLA chain was involved.

The use of polydisperse PLA hampers the study of the effect of the end groups on the degradation process. In the degradation studies with polydisperse PLA, weight loss and corresponding molecular weight distribution of PLA as a function of time were monitored, providing a proposed mechanism for hydrolysis [34]. The formation of low molecular weight degradation products, such as lactic acid and lactoyl lactate, were monitored by capillary zone electrophoresis (CZE) [35], HPLC [36–38], and time-of-flight secondary ion mass spectrometry (MS) [39].

In previous papers, we reported on the preparation of monodisperse lactic acid oligomers and their use in degradable hydrogels by grafting them onto dextran [40,41]. In this way, hydrogels are formed in which crosslinking is established by physical interaction between lactic acid oligomers of opposite chirality. To gain insight into the degradation of these hydrogels, we first carried out a systematic study on the degradation of the oligomers. In the present study we used monodisperse lactic acid oligomers to monitor the hydrolytic degradation. The starting lactic acid oligomer and all degradation products were simultaneously monitored in time by HPLC and MS. This gives more insight into the kinetics and mechanism of degradation of the lactic acid oligomers. The results obtained are also of interest to get a better understanding of the degradation of PLLA and PLGA matrices.

2. Experimental

2.1. Materials

L-lactide ((3S-*cis*)-3,6-dimethyl-1,4-dioxane-2,5-dione, >99.5%) and D-lactide ((3R-*cis*)-3,6-dimethyl-1,4-dioxane-2,5-dione, >99.5%) were obtained from Purac Biochem BV (Gorinchem, The Netherlands) and used without further treatment. The following compounds were used as received: 2-(2-methoxyethoxy)-ethanol (MEE, Aldrich-Chemie, Steinheim, Germany), stannous octoate (tin (II) bis-(2-ethylhexanoate), 95%, Sigma Chemical Co., St. Louis, MO), acetonitrile (ACN, HPLC-S Gradient grade, Biosolve LTD, Valkenswaard, The Netherlands), succinic anhydride (99 + %, Janssen Chimica, Geel, Belgium). Before use, L-lactic acid (85–90%, Janssen Chimica, Geel, Belgium) was treated with NaOH (10 M, for 5 min) to hydrolyze possible dimers, trimers and oligomers. Tetrahydrofuran (THF, Biosolve LTD, Valkenswaard, The Netherlands) was distilled from $LiAlH_4$ immediately before use. Triethylamine (TEA, 99%) was obtained from Acros (Geel, Belgium).

2.2. Synthesis of monodisperse lactic acid oligomer

Polydisperse lactic acid oligomers were synthesized according to De Jong et al. by ring opening polymerization of lactide [40]. 2-(2-Methoxyethoxy)ethanol (MEE) and stannous octoate were used as initiator and catalyst, respectively. The monodisperse lactic acid oligomers were obtained by fractionation of polydisperse lactic acid oligomers with preparative HPLC, as previously described [40]. The end products contained less than 40 ppm tin according to atomic absorption spectrometric (AAS) analysis.

2.3. Synthesis of oligo(lactic acid)succinic acid mono-ester (lact-SA)

Monodisperse lactic acid oligomer (DP 7, 30 mg, 0.048 mmol) was dissolved in THF (3 ml). Succinic anhydride (4.8 mg, 0.048 mmol, 1 eq.) and triethylamine (TEA, 7 μl, 0.053 mmol, 1.1 eq.) were added and the reaction mixture was stirred for 72 h at 40°C. The THF and the TEA were removed in vacuum.

^{1}H NMR ($CDCl_3$): δ 5.14–5.06 (overlapping q, 7 H, C*H*–CH_3), 4.26 (m, 2H, CH_2–O–CO), 3.67 (m, 2H, CH_3–O–CH_2), 3.57 (m, 2H, CH_2–O), 3.50 (m, 2H, CH_2–O), 3.33 (s, 3H, CH_3–O), 2.63 (m, 4H, O–CO–$(CH_2)_2$–COOH), 1.55 (overlapping d, 18H, CH–CH_3), 1.38 (d, 3H, CH_3–CH–O–CO–$(CH_2)_2$–COOH).

MS (ESI): most intense peak at m/z 747.3 ($(M + Na)^+$ of lact-SA, DP 7), small peak at m/z 646.8 ($(M + Na)^+$ of lactic acid oligomer, DP7, without SA end group).

2.4. Standard degradation study

The degradation experiments were carried out in 10 ml glass bottles, placed in a thermostated water-bath at 37°C. The pH was measured before and after degradation at the temperature of the experiment. For the standard degradation experiments 1.5 ml of stock solution of lactic acid oligomer DP 7 in acetonitrile (ACN, 2 mg/ml) was diluted to a final concentration of 1 mg/ml with the appropriate buffer (100 mM, the ionic strength (μ) adjusted to 0.3 with sodium chloride), in such a way that ACN:buffer was 50:50 (v/v); the buffer concentrations need to be at least 100 mM to keep the pH at a fixed value. Samples of 300 μl were drawn at regular time intervals and adjusted to pH 4 with hydrochloric acid (1 M) (or acetate buffer (pH 4, 1 M) when pH was 1–2) to inhibit further degradation. The samples were stored at 4°C prior to analysis. For each degradation curve, at least six points were used in a time frame corresponding with 1–3 half-lives. For the lactic acid oligomer with DP 8 and lact-SA oligomer the degradation conditions were the same as for the standard degradation study.

2.5. Log k_{obs}–pH profile

Buffers used were perchloric acid at pH 0, hydrochloric acid at pH 1–2, acetate at pH 3–6, phosphate at pH 7–9, borate at pH 9.5, and carbonate at pH 10. Buffer concentrations were 100 mM and ACN:buffer = 50:50 (w/w). The reaction rate constant k_{obs} at a certain pH was calculated from the slope of the plot of the natural logarithm of the residual lactic acid oligomer DP 7 vs. time. The mean value and standard deviation for k_{obs} (pH 9.2) were found to be $2.4(\pm 0.04) \times 10^{-4}$ s^{-1} and $2.7(\pm 0.26) \times 10^{-4}$ s^{-1} for the intraday and interday variation, respectively, ($n = 5$). This corresponds to a typical intraday variation of less than 5% and an interday variation in the order of 5–10%.

2.6. pH measurements

The pH measurements were done at the temperature of the experiment with a Metrohm 632 pH-meter (Methrohm Ltd, Herisau, Switzerland), equipped with a combination glass pH electrode. The pH of the solution of lactic acid oligomer in ACN:buffer was measured and used as the pH at which degradation took place.

2.7. Degradation in media with different dielectric constants

A stock solution of lactic acid oligomer (DP 7) in ACN (100 mg/ml) was diluted to a concentration of 1 mg/ml with phosphate buffer (pH 8, 100 mM). Acetonitrile to buffer ratios of 25:75, 50:50 and 75:25 (v/v) were used. To study the degradation in aqueous solution without ACN, the lactic acid oligomer was mixed with buffer. All other degradation conditions were identical to the standard degradation study. The addition of ACN shifts the pH of the buffer. Therefore, the experimental k_{obs} values in various ACN:buffer ratios were used to calculate the k_{obs} at pH 7.0 assuming that the order in OH^- is 1.

2.8. Influence of stannous octoate

A stock solution of $SnOct_2$ in ACN (34 mg/ml) was prepared. An appropriate amount of this solution was added to lactic acid oligomer (DP 7) solution in acetonitrile/phosphate buffer (pH 8, 100 mM). The final concentration of oligomer was 1 mg/ml and the ACN:buffer ratio was 50:50 (v/v). Ratios of 2 and 4 mol of $SnOct_2$ per mol oligomer were used.

2.9. Reversed-phase high performance liquid chromatography (RP-HPLC)

HPLC analysis was carried out on a Waters system (Waters Associates Inc., Milford, MA, USA) consisting of a pump Model 600, an autoinjector Model 717, and a variable wavelength absorbance detector Model 996. The injection volume was 100 μl, the flow was set at 1.0 ml/min, and the detection wavelength was 210 nm. An analytical column, LiChrospher 100 RP-18 (5 μm, 125 × 4 mm i.d.) with an RP-18 guard column (4 × 4 mm) (Merck) was used. A gradient was run from 100% A (water/acetonitrile 95:5 (w/w)) to 100% B (acetonitrile/water 95:5 (w/w)) in 40 min. Calibration curves were generated for each series of lactic acid oligomer (DP 7) solutions in acetonitrile/acetate buffer pH 4 (100 mM), 50:50 (v/v) in the appropriate concentration range. Peak areas were determined and calibration curves were made with MILLENNIUM32 VERSION 3.05 software (1998 Waters Corporation).

2.10. Mass spectrometry

Mass spectrometric analysis (positive ion mode) was carried out with a Shimadzu QP 8000 LC-MS. The probe voltage was +4.5 kV with a detector voltage of 1.5 kV. The CDL voltage was set at −55 V, and the CDL temperature was 230°C. A deflector voltage of 50 V was used. The nebulizing gas (N_2) had a flow of 4.5 l/min. The LC-MS measurements were made with a HPLC system consisting of a pump model LC-10ADVP, an autoinjector SIL-10ADVP and a UV–VIS detector model SPD-10AVP. The column used was adsorbosphere XL C8 (90 Å, 5 μm, 150 × 2.1 mm). The flow was 200 μl/min. A gradient was run from 100% A (0.1% TFA/H_2O) to 100% B (0.085% TFA in ACN:H_2O 95:5 (w/w)) in 30 min and UV detection at 220 nm. Instrumental control was performed with a CLASS 8000LCMS software package. Mass spectra (negative ion mode) were recorded on a Fisons VG Platform II single quadrupole mass spectrometer (Micromass, Manchester, UK), equipped with an electrospray ion source operated at atmospheric pressure. The same instrument was used for RP-HPLC-MS. The instrument was calibrated with NaI

over the range *m/z* 100–1000. Nitrogen was used as the nebulizer gas (12 l/h) and as curtain gas (400 l/h). The capillary voltage was −3.8 kV, the cone voltage was 30 V, and the source temperature 80°C (MS) or 120°C (LC-MS). The scan time was 2 s, and the interscan time 0.1 s. Spectra (*m/z* 100–1000) were recorded with a Digital PC (DECpc 466D2LP) and MICROMASS MASSLYNX software (Manchester, UK). All masses quoted are nominal masses.

2.11. NMR spectroscopy

^{1}H NMR spectra were recorded on a Varian G-300 (300 MHz) spectrometer (Varian, NMR Instruments, Palo Alto, CA). Chemical shifts are given in ppm, relative to $CHCl_3$ at 7.26 ppm.

3. Results and discussion

3.1. Degradation of oligomers: qualitative observations

The degradation studies of the monodisperse lactic acid oligomers were carried out in water/acetonitrile at different pH values and at 37°C. Acetonitrile is used to obtain a good solubility of the oligomers. The degradation of lactic acid oligomer results in an oligomer fragment with hydroxyl and MEE as the end groups and in a fragment with COOH and OH end groups. With the HPLC method used, only the fragments with the MEE-group were identified because, under the conditions used, the free acids eluted in/or near the void volume. Fig. 1A shows the chromatograms of the degradation sample at different time points of the study at pH 8. During degradation, the lactic acid oligomer DP 7 was first converted into oligomer DP 5 which, in turn, is converted into oligomer DP 3. This indicates that hydrolysis occurred in such a way that a dimer (lactoyl lactate) was cleaved from the OH terminus of the oligomer. The identification of the HPLC peaks was done by LC-MS in the positive ion mode with which, as for HPLC, only the fragments with the MEE end group were detected. We, therefore, also analyzed the degradation samples with MS in the negative ion mode, which also allows the detection of the fragments with the COOH end group. With this technique, the presence of both lactoyl lactate (M^- adduct, *m/z* 161) and lactic acid (M^- adduct, *m/z* 89) were indeed observed. The latter product is most likely to have formed by hydrolysis of lactoyl lactate (see Section 3.5, Fig. 5A). The preferential cleavage of the lactoyl lactate from the OH end of the oligomer at alkaline pH was also observed during the degradation of an oligomer with DP 8: first lactic acid oligomer DP 6 was detected as a degradation product followed by oligomer DP 4 (result not shown). For the degradation of lactic acid oligomer DP 8 the same degradation rate (k_{obs}, see Section 3.2.) was observed as for oligomer DP 7 under the same degradation conditions.

Interestingly, when lactic acid oligomer with DP 7 was degraded at pH 2, HPLC showed that at this low pH lactic

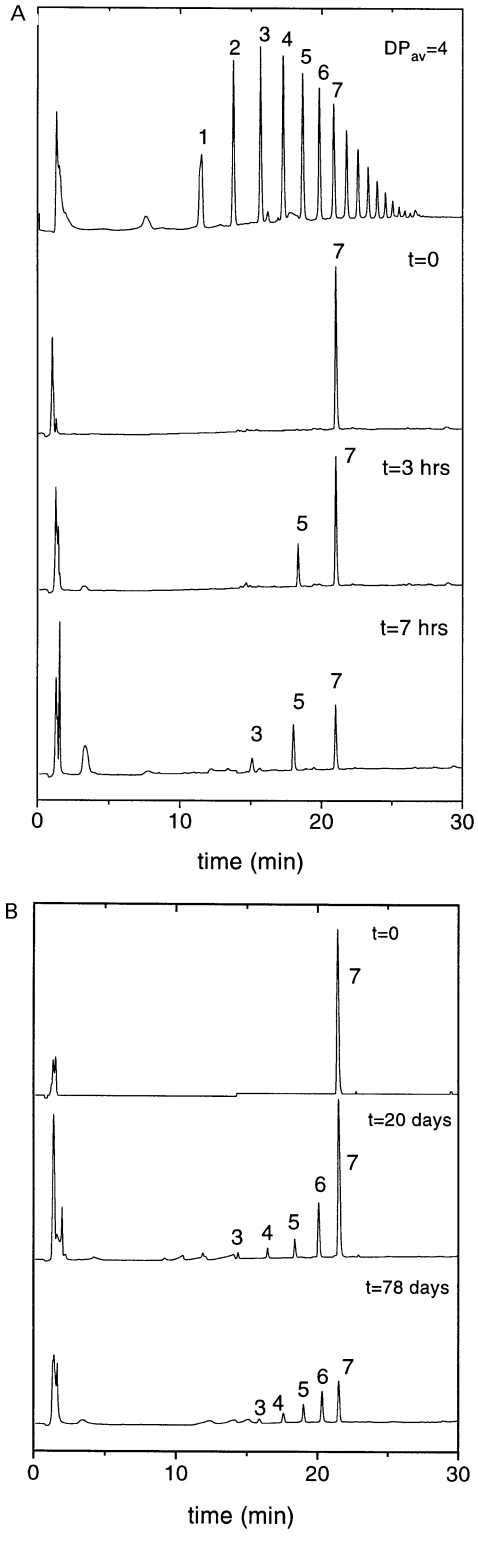

Fig. 1. HPLC chromatograms (obtained with a RP18 column) of polydisperse lactic acid oligomer DP_{av} 4 (A) and the degradation samples of monodisperse lactic acid oligomer DP 7 at different time points at pH 8 at $t = 0$, 3 and 7 h (A) and at pH 2 at $t = 0$, 20, and 78 days (B). The numbers at the peaks represent the degrees of polymerization of the corresponding lactic acid oligomers.

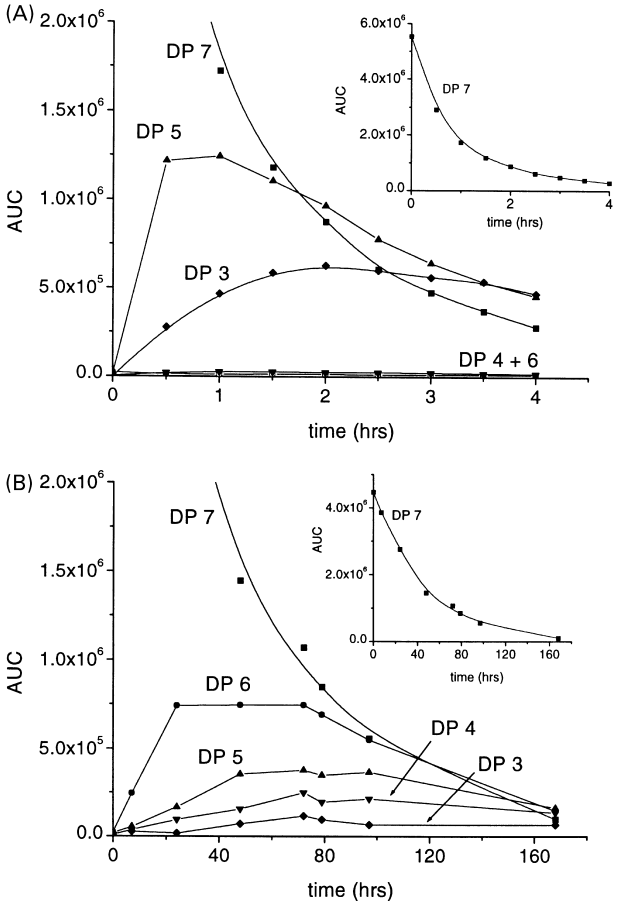

Fig. 2. Degradation profile of lactic acid oligomer DP 7 at (A) pH 8 and (B) pH 2. (AUC = area under curve.) The starting material was contaminated with a little amount of DP 6, which was converted to DP 4, etc.

acid was preferentially cleaved from the OH terminus of the oligomer (Fig. 1B). Mass spectrometric analysis confirmed this observation (results not shown).

3.2. Log k_{obs}–pH profile

In Fig. 2, the decrease in lactic acid oligomer DP 7 and the amounts of oligomers with lower DP are plotted against time for pH 8 (Fig. 2A) and for pH 2 (Fig. 2B). The degradation was studied in media with various pH values (0.2–11.2). The concentration of lactic acid oligomer DP 7 decreased according to pseudo-first-order kinetics for the studied pH range. The pH dependence of k_{obs} for lactic acid oligomer DP 7 is shown in Fig. 3. k_{obs} is described by the general rate constant equation (Eq. (1))

$$k_{obs} = k_0 + k_H[H^+] + k_{OH}[OH^-], \quad (1)$$

where k_0 is the first-order rate constant for degradation in water only, and k_H and k_{OH} are the second-order rate constants for degradation catalyzed by protons and hydroxyl ions, respectively. The log k_{obs}–pH profile in Fig. 3 shows that the hydrolysis is specifically hydroxyl-catalyzed above pH 5, since the slope in this part of the curve approaches +1.

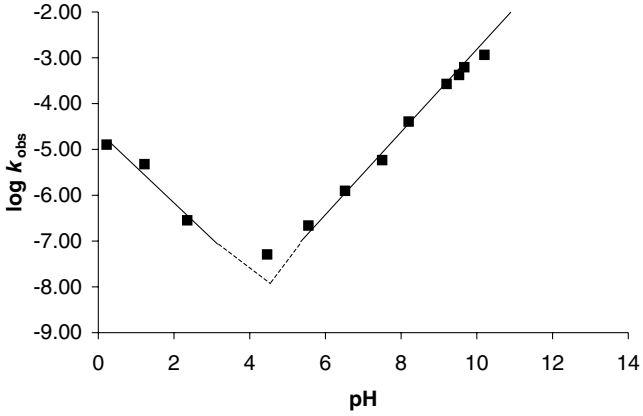

Fig. 3. Log k_{obs}–pH profile of lactic acid oligomer DP 7. Degradation conditions: pH range 0.2–11.2, $\mu = 0.3$, $T = 37°C$, buffer concentration = 100 mM, ratio ACN:buffer = 50:50 (k_{obs} in s^{-1}).

Specific proton catalysis occurs at pH values below the minimum in the profile around 4 (the slope approaches −1).

3.3. Effect of dielectric constant

The influence of the dielectric constant (ϵ) was studied by performing the degradation studies with different ACN: buffer (pH 7, 100 mM) ratios. It was shown that higher k_{obs} values were observed at a higher dielectric constant of the medium ranging from $\epsilon = 47.7$ to 68.3 (Fig. 4). Already in the late 1960s, it was reported that in some solvents, such as dioxane and *t*-butanol, the hydrolysis rate of polyesters decreases continuously with decreasing dielectric constant [42]. The explanation is that the organic solvent molecules stabilize the ground state more than the transition state, which results in lower activity of the ester towards hydrolysis [42,43].

The ACN:buffer ratio did not have any influence on the hydrolysis pattern. At pH 7, a lactoyl lactate was preferentially cleaved from the lactic acid oligomer in all cases whereas one lactate group was split off preferentially in a buffer pH 1. It can, therefore, be concluded that the presence of acetonitrile only affects the degradation kinetics.

In case of a linear relationship between the degradation rate and ϵ, the highest k_{obs} was expected in water as shown in Fig. 4 by the open symbol. However, the degradation rate was lower than expected (Fig. 4, closed symbol). The explanation for this phenomenon may be the low water solubility of the oligomer DP 7 (5 μg/ml in aqueous buffer pH 4 (100 mM), the concentration of the degradation sample is 1 mg/ml). Therefore, the hydrophobic oligomer will not be completely dissolved in the absence of acetonitrile, and dissolution of the oligomer is, under these conditions, the rate determining step. Degradation in solution is more rapid than when the oligomer is dispersed.

3.4. Influence stannous octoate

Degradation of PLA without stannous octoate ($SnOct_2$)

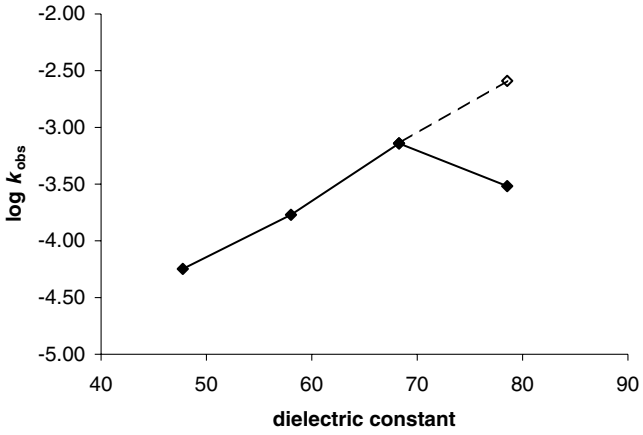

Fig. 4. Influence of the dielectric constant (ϵ) on the k_{obs} (pH 7, 37°C). The open symbol represents the expected k_{obs} at the highest ϵ by extrapolation. The dielectric constant was calculated according to the formula $\epsilon = (\epsilon_{acetonitrile} \times ACN(\%) + \epsilon_{water} \times H_2O(\%))/100$, with $\epsilon_{acetonitrile} = 37.5$ and $\epsilon_{water} = 78.54$.

has not been investigated yet, since this catalyst is not completely removed by normal purification methods such as precipitation. However, contributions of residual $SnOct_2$ to the degradation of PLA has been suggested [11,17,27]. Since the contamination of the oligomers with $SnOct_2$ was low (<40 ppm), the oligomers allow a good evaluation of the possible influence of $SnOct_2$ on their degradation. In the presence of $SnOct_2$ (2 or 4 equiv. per mol of lactic acid oligomer DP 7, ratio ACN:buffer 50:50, pH 7, 37°C) the same degradation pattern was observed as without catalyst. Furthermore, the catalyst did not contribute to the degradation rate, since approximately the same k_{obs} was observed with or without $SnOct_2$.

3.5. Mechanism of hydrolysis

Possible mechanisms for the observed degradation profiles and patterns of the oligolactates are given in Fig. 5. In neutral or alkaline medium the observed degradation may be explained by intramolecular transesterification, also called back-biting [44]. Nucleophilic attack of the hydroxyl end group on the second carbonyl group leads to the formation of a stable six-membered ring as an intermediate. This reaction is base-catalyzed, since a base can interact with the hydroxyl end group, thereby increasing the nucleophilicity of the oxygen atom (Fig. 5A). According to this mechanism, lactic acid oligomer DP 5 and lactide are formed during degradation. Although lactide was not detected in the degradation samples, this does not prove that the mechanism is false: the half-life time of the lactide is less than 1 min under the degradation conditions. Therefore, even if lactide is formed it will not be observed. As evidence for the participation of the end group in the degradation, the hydroxyl end group of lactic acid oligomer was modified by reaction with succinic anhydride to yield lactic acid oligomer with a carboxylic acid end group. The degradation samples at pH 7 were analyzed with MS and compared with the mass spectra of the degradation sample of unmodified lactic acid oligomers at the same time points. In the studied time frame of 15 days, no significant degradation of the lact-SA was observed, whereas the unmodified lactic acid oligomer was almost completely degraded (results not shown). This indicates the importance of the hydroxyl end group of the lactic acid oligomer for hydrolytic degradation in alkaline medium.

The preferential cleavage of the ester bond at the terminal hydroxyl end of the oligomer at low pH can be explained as follows: the degradation is initiated by protonation of the OH end group, followed by formation of an intramolecular hydrogen bridge. Of all possible intermediate structures, the five-membered ring is the most stable one (Fig. 5B). The electrophilicity of the carbonyl group increased by hydrogen bridge formation and attack of a water molecule at that site is therefore preferred. Lactic acid will be split off leaving lactic acid oligomer with a DP of one less than the starting compound.

This study shows that, under both acidic and basic conditions, the different ester groups in lactic acid oligomers do not have the same susceptibility for hydrolysis. This means that the hydrolysis of these oligomers does not proceed randomly as suggested for PLA (and related polymers such as PLGA) but that, starting from the terminal hydroxyl group of the oligomer, the first and the second ester bond are preferentially cleaved under acidic and basic conditions, respectively. We explained the preferential hydrolysis by the assistance of the terminal hydroxyl group. The possible involvement of this OH-group in the hydrolysis of PLA has not been suggested before. When our findings are translated to the degradation of bioerodable systems (implants, microspheres) based on P(D)LLA and PLGA, the following remarks can be made. First, due to the low concentration of the OH-end group in the initial degradation phase of these systems, it is not unlikely that initially the hydrolysis occurs randomly in the polymer chain. However, when the degradation proceeds, the number of end groups increases, whereby the OH-end group-catalyzed hydrolysis, as suggested here, might have an increasing contribution to the overall degradation occurring in bioerodable systems. Second, it has been demonstrated that within the PLLA and PLGA matrices the pH decreases with increasing degradation [45,46]. This is ascribed to the increasing number of COOH groups as well as to the accumulation of water soluble, low molecular weight degradation products inside these matrices. Fig. 3 demonstrates that when degradation starts at physiological pH, the degradation rate should decrease with time due to a decreasing pH generated in the matrix. This would mean that the degradation will almost stop when, inside the matrix a pH 3–4 is reached. On the other hand, with increasing degradation of the matrix, its hydrophilicity increases, which will be associated with an increase in the dielectric constant in the matrix. A higher dielectric constant, in turn, results in a faster degradation (Fig. 4).

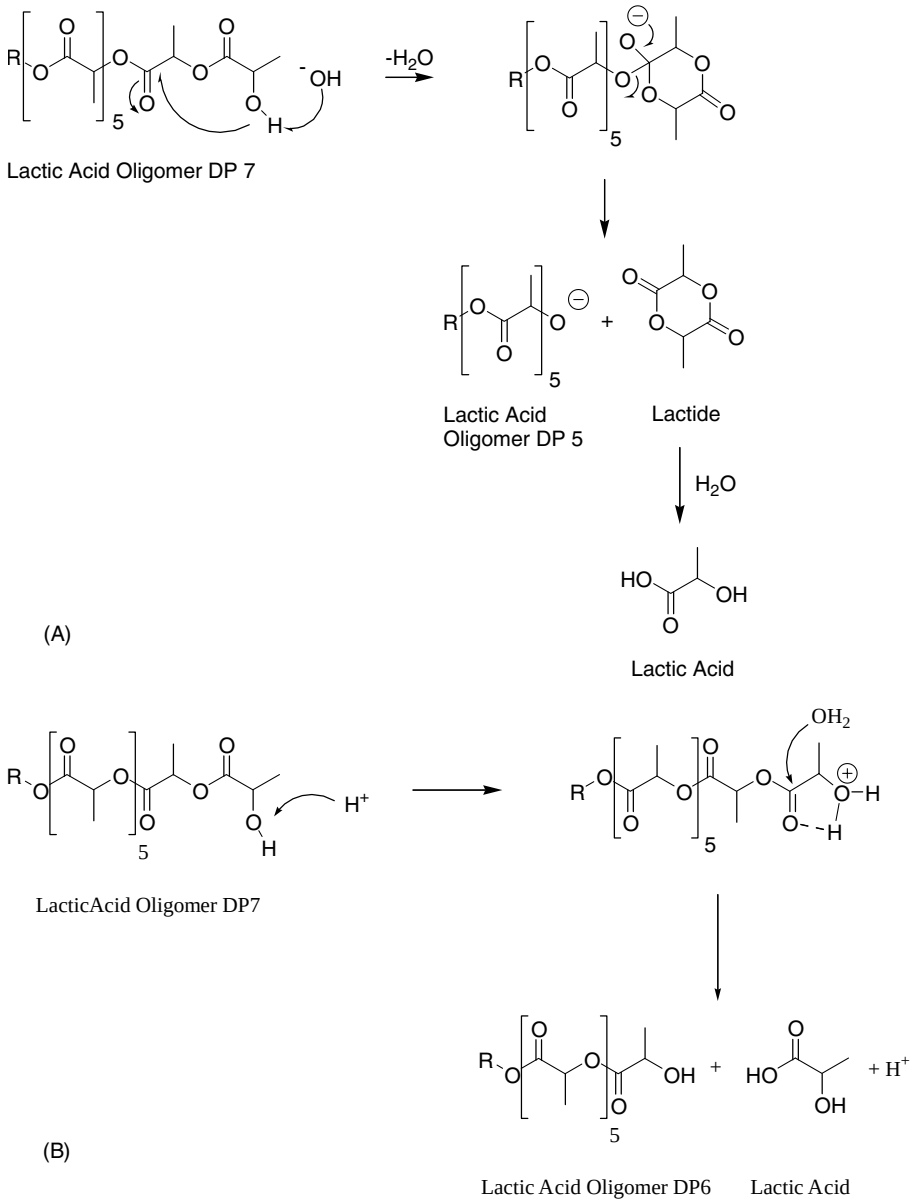

Fig. 5. Suggestions for mechanism of hydrolysis in: (A) alkaline environment and (B) acidic environment. (R is the 2-(2-methoxyethoxy)ethanol (MEE) end group).

Obviously, the fact that PLLA and PLGA matrices fully degrade when placed in an aqueous environment suggests that the increase in hydrophilicity contributes more to the overall degradation process than the decrease in pH.

4. Conclusions

The decrease in the amount of oligomer DP 7 and the formation of the degradation products as a function of pH were monitored by HPLC and MS. In this way, insight into the degradation mechanism and kinetics of PLA were obtained. It was shown that the hydrolysis mechanism at acidic pH proceeds via chain-end scission and that in alkaline medium lactic acid dimer was formed via an intramolecular cyclization reaction. The OH end group of the lactic acid oligomer was found to play a crucial role in the degradation in both alkaline and acidic medium. Protection of this hydroxyl group results in a substantial retarded degradation. The obtained results can be used to get an insight into the degradation of oligolactic acid grafted to dextran, which we use for the preparation of hydrogels based on physical interactions [41], as well as the degradation of PLA and PLGA.

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