Hydrolytic and enzymatic degradation studies of aliphatic 10-undecenoic acid-based polyesters

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Abstract

The hydrolytic and enzymatic degradations of aliphatic polyesters: poly (10,11-epoxyundecanoic acid) (PEAU) bearing hydroxyl groups along the main chain and poly(11-hydroxyundecanoate)diol (PHU), were studied and compared to that of commercial poly(ε-caprolactone)diol (PCL). Changes taking place after polyester degradation in sample weight, molecular weight (Mn), chemical constitution, thermal properties, crystallinity and morphology were monitored by size exclusion chromatography (SEC), ^{1}H nuclear magnetic resonance (NMR) spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), X-Ray diffraction (XRD) and environmental scanning electron and atomic force microscopies (ESEM and AFM). A significant decrease of PEUA Mn in both hydrolytic and enzymatic degradation was detected versus PHU and PCL, and related to its hydrophilic character, by the presence of hydroxyl pendant groups, and the superior amorphous character. An accelerated degradation in acidic media, monitored by SEC and ^{1}H

NMR spectroscopy to study in detail all residual material of three polyesters, showed the complete degradation only in the case of PEUA and PCL.

INTRODUCTION

For the last 60 years, synthetic polymeric materials have grown progressively basically due to their low cost, their reproducibility, and their resistence to physical aging and biological attacks. However, the resistance of synthetic polymers to the degrading action of living systems is becoming increasingly problematic in several domains where they are used for a limited period of time before becoming wastes. This is the case in surgery, in pharmacology, in agriculture, and in the environment as well.

Nowadays the open and the patent literature propose a large number of polymers whose main chains can be degraded usefully. Among these degradable polymers, aliphatic polyesters are receiving special attention because they are all more or less sensitive to hydrolytic and enzymatic degradation [1-3]. Aliphatic polyesters containing flexible ester bonds appear to be the most promising because of their excellent biocompability and variable degradability and are the most representative examples of environmentally relevant polymeric materials [4-7].

Many aliphatic polyesters biodegrade via a two-step process. First, polymer backbone bonds must be enzymatically or otherwise hydrolized to produce oligomers, which are subsequently broken down and further, in soil return water, carbon dioxide, and hummus [8]. Generally, polyester degradation rate is impacted by the structure of the polymer backbone, including the electrophilicity of the carbonyl atoms and the presence or absence of bulky substituents. Among the critical

factors that affect the degradation rate of polyesters, one is the distance between ester groups in the polymer which determine the polymer character, e.g. hydrophobicity and crystallinity. Molecular weight and crystallinity have been shown to have the largest impact in polyester degradation due to a hindrance in water being able to difuse into the matrix.

Moreover, the presence of hydrophilic (hydroxyl and carboxyl) end groups also promotes the polyester degradation. It is well known the effect of autocatalysis by the acid ended chain fragments, which leads to a dramatic increase of the rate of degradation as degradation advances [9]. It is established that carboxyl end groups formed by chain cleavage catalyze degradation and that amorphous regions are preferently degraded [5,10,11].

The introduction of functional groups into commonly used polyesters such as PLA and PCL provides polymers with tuneable degradation behaviour by suppression of crystallinity and enhanced hydrophilicity that also favours cell adhesion to the surfaces important for tissue engineering purposes [12]. Further, increased hydrophilicity results in a greater water absorbing capacity of the polymers, thereby increasing the degradation rate and probably preventing a pH drop inside the degrading matrices and hence preventing incomplete release of degraded fragment or encapsulated compounds [13].

Aliphatic polyesters degrade either by bulk erosion or surface erosion [14-16]. Polymer hydrolytic degradation is produced by scission of chemical bonds in the polymer backbone, by water uptake, to form oligomers and finally monomers. In the first step, water molecules attack the water-labile bonds by either direct access to the

polymer surface or by imbibition into the polymer matrix followed by bond hydrolysis. This nucleophilic attack by water can be catalysed by acids, bases or enzymes [17].

In this paper we study the hydrolytic and enzymatic degradation of two aliphatic polyesters synthesized from castor oil-derived 10-undecenoic acid: poly(10,11-epoxyundecanoic acid) which contains primary and secondary hydroxyl pendant functions along the main chain and poly(11-hydroxyundecanoate)diol, and compared with commercial poly(ε-caprolactone)diol. Changes taking place in sample weight, molecular weight, chemical constitution, thermal properties, crystallinity and surface morphology of the polyesters were evaluated and related to the polymer structure and degradation conditions.

2. Experimental

2.1. Materials

The following chemicals were obtained from the sources indicated and used as received: 1,6-hexanediol (99%), 10-undecenoic acid (98%) (UA), methyl 10-undecenoate (96%), poly(ε-caprolactone)diol (PCL) M_n 2.000 Da, titanium (IV) isopropoxide (97%), methanesulfonic acid (99.5%), tetrabutylphosphonium bromide (98%) (TBPB), hydrogen peroxide (30%), boron trifluoride diethyl etherate (99%) *Candida Antarctica* immobilized on acrylic resin (5.000 U/g) (CALB), lipase from porcine pancreas (100-500 U/g, pH 8.0, 37 °C) and phosphate buffered saline pH 7.4 (at 25 °C) from Sigma Aldrich. Anhydrous magnesium sulfate and tetramethylsilane (TMS) from Scharlau; citric acid buffer solution pH 2.0 (20 °C) from Fluka, sodium

azide and sodium borohydride from Probus; chloroform-D ($CDCl_3$) from euriso-top; toluene, tetrahydrofuran (THF), dimethylformamide (DMF), diethyl ether, dichloromethane (DCM) and methanol (MeOH) from Scharlau. Analytical grade solvents were purified and dried by standard methods. 4 Å powdered molecular sieves were activated 24 h at 220 °C and cooled under vacuum prior use. Flash column chromatography was carried out using neutral silica-gel 60 F254 (from Panreac) and hexane-ethyl acetate as eluent.

2.2. Synthesis of monomers

2.2.1. Synthesis of methyl 11-hydroxyundecanoate. (SI.1)

Methyl 11-hydroxyundecanoate was prepared in 72 % yield by hydroboration of methyl 10-undecenoate following a reported procedure [18].

2.2.2. Synthesis of 10,11-epoxyundecanoic acid (EUA). (SI.1)

10,11-epoxyundecanoic acid was prepared by enzymatic oxidation of 10-undecenoic acid using CALB and 30% H_2O_2 as previously described. [19]

2.3. Synthesis of polyesters

2.3.1. Polymerization of EUA: PEUA. (SI.2)

PEUA was synthesized using TBPB as catalyst in toluene as previously described [19] obtaining a hydroxypolyester with Mn 3650 Da, by ^{19}F NMR, and Mn 8400 Da, *Đ* 3.9 by SEC.

2.3.2. Preparation of poly(11-hydroxyundecanoate) (PHU) by polymerization of methyl 11-hydroxyundecanoate initiated by 1,6-hexanediol. (SI.2)

In a 50 mL schlenk flask 5.4 g (0.025 mol) of methyl 11-hydroxyundecanoate and 0.25 g (0.0021 mol; molar ratio 12:1) of 1,6-hexanediol were melted with stirring under argon atmosphere at 130 °C. Over the resulting homogeneous clear mixture, 0.07 mL (0.00025 mol, 1% molar) of titanium tetraisopropoxide was added and the temperature raised to 190 °C with the application of vacuum (2 mmHg). After 4h the mixture was cooled and the resulting solid white mass was dissolved in 25 mL of THF and precipitated twice over 1000 mL of cold diethylether. The resulting white solid was collected by filtration, rinsed with diethyl ether, and dried under vacuum. (Yield: 92%, Mn: 3520 Da, by ^{1}H NMR, and 3900 Da, *Đ* 2.0 by SEC.

^{1}H NMR ($CDCl_3$, δ, ppm): 4.86 (m, 2H, CH_2-O<u>H</u> (end group), 4.05 (t, 8H, COO-C<u>H</u>$_2$-CH_2), 3.64 (t, 4H, HO-C<u>H</u>$_2$) (end group), 2.29 (t, 4H, C<u>H</u>$_2$-COO), 1.61 (m, 20H, -COO-CH_2-C<u>H</u>$_2$; HO-CH_2-C<u>H</u>$_2$; C<u>H</u>$_2$-CH_2-COO), 1.28 (m, 56H, -(C<u>H</u>$_2$)$_n$-).

^{13}C NMR ($CDCl_3$, δ ppm): 175.1 (s) (<u>C</u>OO), 64.4 (t) (<u>C</u>H_2-OOC), 63.0 (t) (<u>C</u>H_2-OH), 34.4 (t) (<u>C</u>H_2-COO), 29.4-25.0 (t) $(CH_2)_n$.

2.3.3. Purification of PCL

Commercial PCL-diol was solved in THF and precipitated twice in cold methanol yielding a white solid that was filtered and dried under vacuum. (Yield: 88%, Mn: 2580 Da, by ^{1}H NMR, and 3600 Da, *Đ* 1.9 by SEC.

2.4. Polymer solubility

In a 25 mL vial, 0.25 g of finely grounded polymer and 2 mL of each solvent was mixed and stirred, for 2 h at room temperature.

2.5. Water uptake

In a closed chamber, accurately weighted disk samples were kept in a constant humidity environment (saturated solution of $Na_2CO_3.10H_2O$) at 37 or 45 °C for 48 h. Next, samples were weighted and the water uptake was determined by difference, and was expressed as weight increase percentage. An average of three measurements was taken.

2.6. Degradation procedures

Sample disks (12.0 mm x ~0.40 mm; surface area to volume ratio equal to 0.1 cm^{-1}) weighting about 50 mg, were prepared by compression moulding (4 ton) using a manual hydraulic press 15-ton sample pressing (SPECAC) equipped with a water cooled heater. Finely grounded samples were introduced into the preheated (40 °C) mould and after 3 h pressed under vacuum and kept at room temperature for 1h. Disks were demoulded under cool N_2 and dried under vacuum to constant weight (m_0). After incubation in the selected media for the scheduled period of time, three samples of each polymer were rinsed thoroughly with distilled water and weighted immediately after wiping the surface with a filter paper to absorb the surface water to obtain the wet weight (m_w). Next, the samples were vacuum-dried for 48 h and weighted again to obtain the dry weight (m_d). Finally, samples were grounded and analyzed by ^{1}H NMR spectroscopy, SEC, DSC, TGA, XRD, ESEM and AFM.

2.6.1. Hydrolytic degradation

For hydrolytic degradation, samples were immersed in Falcom tubes containing about 24 ml of citric acid buffer (pH 2.0) and kept sterile by adding 0.03% (w/v) of NaN_3. Incubation took place at 45 °C. Samples were removed at specific intervals, cleaned and dried under vacuum to constant weight.

Weight loss was determined by Eq. (1).

$$WL\% = [(m_0 - m_d)/m_0] \times 100 \qquad \text{Equation (1)}$$

where m_0 is the initial mass, m_t is the final mass after drying at a predetermined time. An average of three measurements was taken.

2.6.2. In vitro enzymatic degradation

In vitro enzymatic degradation tests were carried out in a similar way using a phosphate buffer (pH 7.2) containing lipase from porcine pancreas (20 mg). Buffered enzyme solution were replaced every 72 h to maintain enzyme activity. Incubation took place at 37 °C. Samples were removed at specific intervals, cleaned and dried under vacuum to constant weight. Weight loss was determined by Equation(1).

2.6.3. Accelerated degradation

500 mg of powdered polymer were mixed with methanesulfonic acid water solution (1M, 20 mL) and the mixture was heated under reflux. After 24 hours the solution was neutralized with Na_2CO_3 saturated solution and the organic products

were extracted with DCM, concentrated under vacuum and analyzed by SEC and ^{1}H NMR.

2.6.4. PEUA accelerated degradation: kinetic study

180 mg of PEUA were mixed with methanesulfonic acid water solution (0.5M, 8 mL), and heated under reflux. At prefixed times, aliquots of solutions were taken, cooled down, neutralized with Na_2CO_3 saturated solution and the organic products extracted with DCM. The solvent was removed under vacuum and products analyzed by SEC and ^{1}H NMR.

2.7. Instrumentation and analysis

^{1}H (400 MHz) and ^{13}C (100.5 MHz) NMR spectra were recorded using a Varian Gemini 400 spectrometer. Spectra were recorded at room temperature using 10-15 mg (^{1}H NMR) or 30-40 mg (^{13}C NMR) of sample in $CDCl_3$ as solvent and TMS as internal standard. In ^{13}C NMR the central peak of deuterated solvent was taken as reference and the chemical shift given in ppm from TMS using the appropriate shift conversion.

ESI-TOF measurements were carried out using an Agilent 1200 liquid chromatography coupled to 6210 Time of Flight (TOF) mass spectrometer from Agilent Technologies (Waldbronn, Germany) with an ESI interface.

Calorimetric studies were carried out on a Mettler DSC3+ thermal analyzer using N_2 as a purge gas (100 ml/min). Calibration was made using an indium standard (heat flow calibration) and an indium-lead-zinc standard (temperature calibration). Samples

of 5-7 mg were sealed in aluminium pans. A three-step procedure was applied at scanning rate of 10 °C/min: first, heating up to 30-40 °C above the melting temperature of the polymer and holding for 5 min, to erase the thermal history; second, cooling down to -80 °C and holding for 5 min; finally, a second heating from -80 °C to the same temperature at the first heating. The second heating scans were used to characterize the crystallinity and melting behaviour. The crystallinity was calculated according to the equation (2).

χ_c (%) = ΔH_m / ΔH_m^0 x 100 Equation (2)

where the melting enthalpy (ΔH_m) is the value of the second heating run and ΔH_m^0 is the melting enthalpy reported for a 100% pure crystalline polyester. The average value of three measurements were given.

Thermal stability studies were carried out on a Mettler TGA/SDTA851e/LF/1100 with N_2 as purge gas in the 30-800 °C temperature range at scan rates of 10 °C /min.

Contact angle measurements were determined at 25 °C using deionized water on polymer surfaces prepared by casting over glass slides. The water drop method (3µL) was used on an OCA 15EC contact angle setup (Neutek Instruments).

Size exclusion chromatography (SEC) analysis in THF was carried out with an Agilent 1200 series system equipped with three serial columns (PLgel 3µm MIXED-E, PLgel 5µm MIXED-D and PLgel 20m MIXED-A from Polymer Laboratories) and an Agilent 1100 series refractive-index detector working at room temperature at a flow

rate of 1.0 mL/min. Calibration curves for SEC analysis were obtained with polystyrene standards.

Environmental scanning electron microscopy (ESEM) images were obtained with a FEI QUANTA 600 instrument using low vacuum and an accelerating potential of 20 KV.

Atomic force microscopy (AFM) images were taken in acoustic mode with Agilent 5500 instrument.

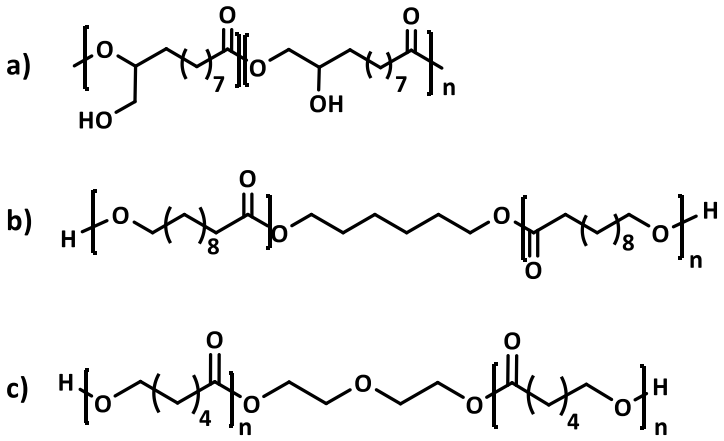
XRD (X-ray diffraction) measurements were made using a Siemens D5000 diffractometer (Bragg-Brentano parafocusing geometry and vertical θ-θ goniometer) fitted with a curved graphite diffracted-beam monochromator, incident and diffracted-beam Soller slits, a 0.06º receiving slit and scintillation counter as a detector. The angular 2θ diffraction range was between 15 and 30º. The data were collected with an angular step of 0.03º at 6 s per step and sample rotation. A low background Si (510) wafer was used as sample holder. $Cu_{k\alpha}$ radiation (λ= 1.5418 Å) was obtained from a copper X-ray tube operated at 40 kV and 30 mA. Each diffractogram was fitted as a sum of several pseudo-Voigt functions representing the crystalline and the amorphous part with the software TOPAS 6.0 (Bruker, TOPAS V6. Bruker AXS, Karlsruhe, Germany). The percentage of crystallinity was then calculated as the area ratio between the peaks associated to the crystalline part and the amorphous part.

3. Results and discussion

3.1. Polyesters synthesis and characterization

Linear poly(10,11-epoxyundecanoic acid) (PEUA) was synthesized through carboxylic ring opening polymerization of 10,11-epoxyundecanoic acid catalyzed by TBPB with high yield (87%) [19]. Poly(11-hydroxyundecanoate)diol (PHU) was synthesized by transesterification reaction initiated by 1,6-hexanediol and catalysed by titanium tetraisopropoxide, with high yield (92%). These two polymers are obtained from 10-undecenoic acid-derived monomers and thus using non-edible castor oil as starting renewable material. PEUA is a copolymer arising from the attack of carboxylic acid either to the less or to the more substituted carbons in the oxirane ring. Therefore, two different units with primary and secondary hydroxyl pendant groups along the main chain are present in about 30:70 ratio according to ^{1}H NMR measurements [19]. PHU is a telechelic polyester containing hydroxyl end groups. Poly(ε-caprolactone)diol (PCL) diethylenglycol initiated was obtained by purification of the commercial product and used to compare the degradation behaviour of the two 10-undecenoic acid-derived renewable polyesters with a commercial versatile and widely used polymer with similar structure.

Structure of the three polymers is represented in Scheme 1 and the main features in connection with the degradation study carried out in this work are listed in Table 1 and Table 2.



Scheme 1. Structure of polymers a) PEUA, b) PHU and c) PCL.

Table 1. Molecular weight, thermal properties and XRD of initial polymers

	NMR	SEC		DSC 1st heating			DSC 2ond heating			TGA		XRD
	M_n[(a)] (kDa)	M_n[(b)] (kDa)	Đ[(b)]	Tg[(c)] (°C)	T_m[(d)] (°C)	ΔH_m[(d)] (KJ/mol)	T_m[(e)] (°C)	ΔH_m[(e)] (KJ/mol)	χ_c[(f)] (%)	$T_{5\%}$[(g)] (°C)	T_{max}[(h)] (°C)	χ_c[(i)] (%)
PEUA	3.65	8.40	3.4	-12	92.1±0.6 100.1±0.5	17.5±0.6	43.2±0.2	7.1±0.3	--	342	386 432	54.2
PHU	3.52	3.90	2.0	--	73.8.±0.3	27.7±0.4	72.9±0.3	22.4±0.4	56.7	327	425	66.3
PCL	2.58	3.60	1.9	--	58.0±0.6	11.7±0.3	52.0±0.4	9.8±0.2	54.7	217	413	62.0

(a) Number average molecular weight determined by NMR; (b) Number average molecular weight and polydispersity index determined by SEC in THF relative to PS standards; (c) Glass-transition temperature (T_g) taken as the inflection point of the first heating DSC curves recorded at 10 °C·min^{-1}; (d) Melting temperatures (T_m) and enthalpies (ΔH_m) determined by DSC on the first heating scan at heating rates of 10 °C·min^{-1}; (e) Melting temperatures (T_m) and enthalpies (ΔH_m) determined by DSC on the second heating scan at heating rates of 10 °C·min^{-1}; (f) Fractional crystallinity estimated by DSC using ΔH^0_m described in literature; (g) Temperature at which 5% weight loss was observed by TGA; (h) Temperature for maximum degradation rate from TGA; (i) Fractional crystallinity estimated by XRD from the amorphous and crystalline pattern areas.

The absolute molecular weights were determined by NMR measurements. Mn of PEUA was calculated by ^{19}F NMR of the corresponding trifluoroacetyl derivative as previously reported. [19] In the case of PHU and PCL, Mn was calculated by ^{1}H NMR spectroscopy by comparison of the intensities of signals corresponding to the α–methylene to ester group in the main chain at 2.3 ppm, and CH_2OH end groups at ca. 3.6 ppm in both cases. (Figures SI.2.a and SI.7.a). As can be seen, PEUA and PHU

have similar Mn whereas Mn of commercial PCL is something lower. Mn of the three polyesters was also determined by SEC which was the technique used to follow the hydrolytic and enzymatic degradation. The resulting values are higher, especially in the case of PEUA. This can be attributed to differences in the hydrodinamic volume with the PS standards. Moreover, as PEUA contains hydroxyl pendant groups it should be expected to have a more expanded coil in good solvents such as THF.

According to DSC scans, all polyesters PEUA, PHU and PCL are semicrystalline. Relatively small decreases in melting temperature and melting enthalpy between the first and second scan are observed for PHU and PCL indicating a strong tendency of the chains to reorganize and crystallize. Moreover, melting temperatures of PHU and PCL are lower than those reported for the pure crystalline samples [20], which confirms its semicrystalline character. In regard to commercial PCL, it is reported that melting temperature occurs in the range of 59-64 °C depending upon the crystallite size [21]. PEUA shows a different behaviour having much higher melting temperature and melting enthalpy in the first scan, which is consistent with literature [22]. From the observed melting temperatures of pristine polyesters, it was established that 45 °C had to be the maximum incubation temperature to maintain the shape and integrity of all samples.

After erasing the thermal history, the fractional crystallinity (χ_c) of PHU and PCL based on their enthalpy of fusion in the second heating scan could be estimated [23], as the heat of fusion for the 100% crystalline samples is reported (PHU 39.5 KJ/mol and PCL 17.9 KJ/mol) [20]. According this estimation, PHU has slightly higher crystallinity degree than PCL and XRD measurements confirms the same result. The

complete linear structure of both polymers favours aliphatic chain packing and fast reorganization. In the case of PEUA there is no reference for the pure crystalline sample. However, according to XRD data it seems to be less crystalline than PHU and PCL, which is concordant to its random copolymer structure and the presence of hydroxyl pendant groups**.**

TGA curves for the three polyesters have approximately the same shape with the only difference that the hydroxypolyester, PEUA, shows and additional decomposition process and a slight lower thermal stability [19]. Aliphatic polyesters without reactive pendant groups usually have a single step degradation. Under the given experimental conditions, no measurable amount of volatile compounds (moisture, unreacted monomers, and small molar mass product of reaction) is detected below 270 °C. From the measured TGA curves of three polyester samples, temperatures obtained for mass losses of 5% and maximum rate temperatures for main decomposition processes were calculated and collected in Table 1.

Hydrophilic/hydrophobic behaviour of these polyesters (Table 2) was determined measuring their solubility, water uptake and contact angle.

Table 2. Solubility, water uptake and contact angle of PEUA, PHU and PCL.

	Solubility[(a)]				**Water uptake[(b)]**		**Contact angle**
Polym	**DMSO**	**DMF**	**THF**	**$CHCl_3$**	**37 °C**	**45 °C**	**Θ_{water} (°)**
PEUA	+	+	+	+	1.5±0.1	1.86±0.0	79.1±1.4
PHU	-	+	+	+	0±0.0	0.23±0.0	83.4±1.3
PCL	-	+	+	+	2.2±0.2	5.25±0.2	66.2±2.6

(a) (-) insoluble, (+) soluble; (b) expressed as weight increase percentage.

Solubility properties were assessed in an assortment of representative polar, protic and aprotic solvents. As expected by their predominant polymethylene moieties, all polyesters were insoluble in water and ethanol but soluble in medium to high polarity aprotic solvents. The hydrogen bonding interactions between hydroxyl groups in PEUA and the highly polarized S=O groups could explain its different solubility in DMSO.

Polymer water uptake was measured at 37 °C and 45 °C, temperatures at which hydrolytic and enzymatic degradation were performed. It can be observed increasing values according to their expected hydrophilic character, PCL > PEUA > PHU taking into account their relative ester density and the presence of additional hydroxyl groups in PEUA. The same behavior was observed through water contact angle measurements (Figure SI. 4) confirming the hydrophilicity order.

3.2. Hydrolytic and enzymatic degradation

The study is focused on two main elements: composition of the polymer matrix during the hydrolysis (weight loss and molecular weight decrease) and composition of the degradation products.

The variation in sample weight and M_n for PEUA, PHU and PCL upon incubation in aqueous buffers at pH 2.0 and 45 °C and at pH 7.4 with porcine pancreas lipase and 37 °C, respectively, is depicted in Figure 1 and Figure 2.

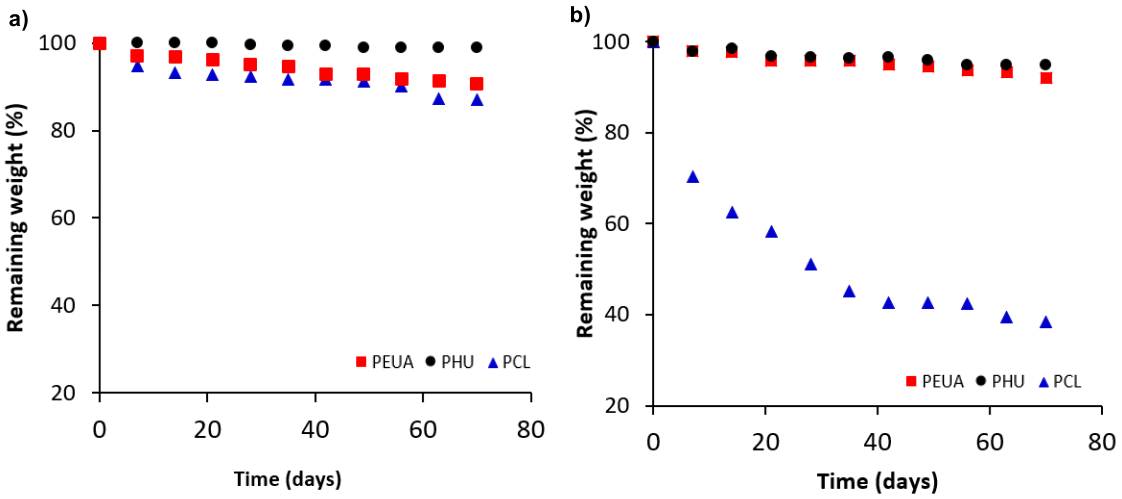


Figure 1. Remaining weight of polymers by measure of weight loss versus time: a) at pH 2.0 at 45 °C; b) at pH 7.4 at 37 °C with porcine pancreas lipase.

The weight losses undergone by PCL and PEUA were about 7% and 5%, respectively, after 10 weeks of incubation at pH 2.0 at 45 °C, thus showing the release of soluble oligomers produced by degradation. By contrast, the invariance observed for PHU in both weight loss and Mn is indicative of none degradation. When incubated under enzymatic conditions, after 10 weeks, scarce variance was observed in remaining weights in PEUA and PHU, therefore none of them underwent significant degradation. However, the weight loss for PCL was about 60% but the fact that there was no significant change in molecular weight (Figure 2 b), indicates clearly a surface erosion mechanism for polymer degradation as confirmed by the observed sample size reduction [14,24].

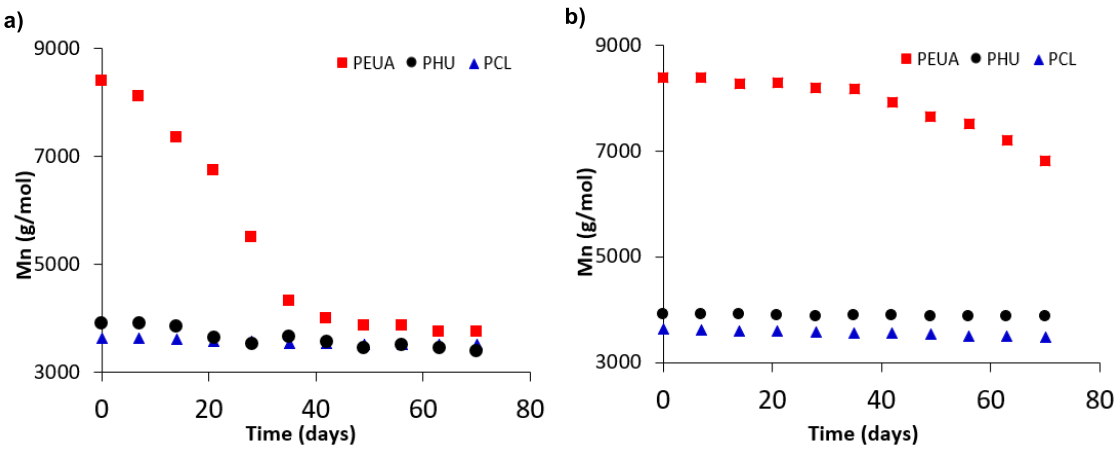


Figure 2. Degradation of polymers by SEC determination; a) Molecular weight at pH 2.0 at 45 °C; b) Molecular weight at pH 7.4 at 37 °C with porcine pancreas lipase.

In the case of PEUA, a significant decrease of Mn was observed for at pH 2.0 at 45 °C. The initial M_n was 8400 Da with Đ 3.4 and the final Mn 3700 Da with Đ 2.6, however, weight loss is very low (up to 5%). This seems to indicate that, even in small extent, hydrolytic degradation proceeds through a bulk erosion mechanism. In enzymatic degradation, Mn also decrease but in a minor extension and without significant changes in Đ. This is consistent with the difficulty of enzymes to penetrate polymer systems and only to diffuse into poorly ordered amorphous regions [25,26].

By comparison to PHU behaviour in both hydrolytic and enzymatic media it can be inferred that the pendant hydroxyl group and the superior amorphous character in PEUA play a significant role in the degradation mechanism by increasing hydrophilicity, water uptake and swelling of the amorphous domains, facilitating the ester cleavage and the decrease of molecular weight. This behaviour is especially remarkable in acidic medium where the formation of shorter chains modify crystallinity (*vide infra).*

3.2.1. Thermal analysis

To evaluate thermal changes during hydrolytic an enzymatic degradation, second heating DSC traces of the three polyesters after 10 weeks of incubation at pH 2.0 at 45 ^{o}C and at pH 7.4 at 37 ^{o}C with porcine pancreas lipase were carried out, and compared with those of the pristine polymers (in Table 2). DSC scans are shown in Figure 3 a) and measured melting temperatures, melting enthalpies and estimated fractional crystallinities (χ_c) are collected in Table 3.

Table 3 Melting temperatures, melting enthalpies and crystallinity degrees estimated by DSC and XRS of polyesters after 10 weeks of incubation at pH 2.0 at 45 ^{o}C and at pH 7.4 at 37 ^{o}C with porcine pancreas lipase.

	pH 2.0 (45 °C)				**pH 7.4 (37 °C) lipase**			
Polym.	$T_m^{(a)}$ (°C)	$\Delta H_m^{(a)}$ (KJ/mol)	$\chi_c^{(b)}$ (%)	$\chi_c^{(c)}$ (%)	$T_m^{(a)}$ (°C)	$\Delta H_m^{(a)}$ (KJ/mol)	$\chi_c^{(b)}$ (%)	$\chi_c^{(c)}$ (%)
PEUA	29.2±0.2	6.2±0.3	--	54.4	52.5±0.2	7.7±0.3	--	57.9
PHU	72.9±0.2	21.7±0.2	54.9	65.1	73.2±0.2	21.4±0.3	54.2	67.0
PCL	49.3±0.4	9.5±0.2	53.0	66.6	50.9±0.2	9.8±0.2	54.7	66.4

(a) Melting temperatures and melting enthalpies measured by DSC at heating/cooling rates of 10 °C min^{-1}; (e) Fractional crystallinity estimated by DSC using ΔH^0_m described in literature; (c) Fractional crystallinity estimated by XRD from the amorphous and crystalline pattern areas.

Several factors can provoke crystallinity changes during polymer degradation [14]. One is the generation of crystallizable oligomers and monomers. The other stems from the behaviour of semicrystalline polymers during erosion. It was well recognized that degradation is much faster in amorphous domains that in crystalline ones, mostly because water penetration is easier within a disordered network of polymer chains [5,27,28]. Moreover, when introducing the samples in the incubation media, water uptake lowered the glass transition temperature, increasing mobility of the

chains making it possible for them to reorganize and crystallize [24]. In our case, from DSC traces different behaviour for the three polyesters is observed. For PCL, both melting enthalpy and melting temperature remain almost unaffected after incubation in both hydrolytic and enzymatic media. This confirms that surface erosion is the predominant degradation mechanism producing a layer-by-layer ester cleavage and solubilisation. This mechanism is especially remarkable under enzymatic conditions where about 60 % of the initial weigh is lost after 10 weeks. For PHU, also no significant changes in melting enthalpy and melting temperature are observed what is consistent with a scarce degradation observed. It must be pointed out that PHU, due to the linear aliphatic chain structure, possess the highest crystalline and hydrophobic character of the three samples studied, and shortage of amorphous domains to promote a fast degradation mechanism.

PEUA due to the presence of hydroxyl groups and the two different sequence monomeric units possess a lower ability to crystallize as it is shown by their relative lower melting enthalpy values (Tables 1 and 3). On incubation after 10 weeks at pH 2.0, a decrease in both melting temperature and melting enthalpy is observed as result of the formation of smaller crystals from shorter chains resulting after the bulky degradation process [29]. This behaviour is consistent with the significant molecular weight decrease produced in the degradation in this medium (Figure 2a). On the contrary, on incubation after 10 weeks at pH 7.4 in enzymatic media, a moderate increase in both melting temperature and melting enthalpy is observed, suggesting a crystallinity increase. In this case, the observed decrease of molecular weight is much lower (Figure 2b) and the increase of crystallinity could be related to

the increased mobility and rearrangement of polymer chains promoted by water swelling during incubation.

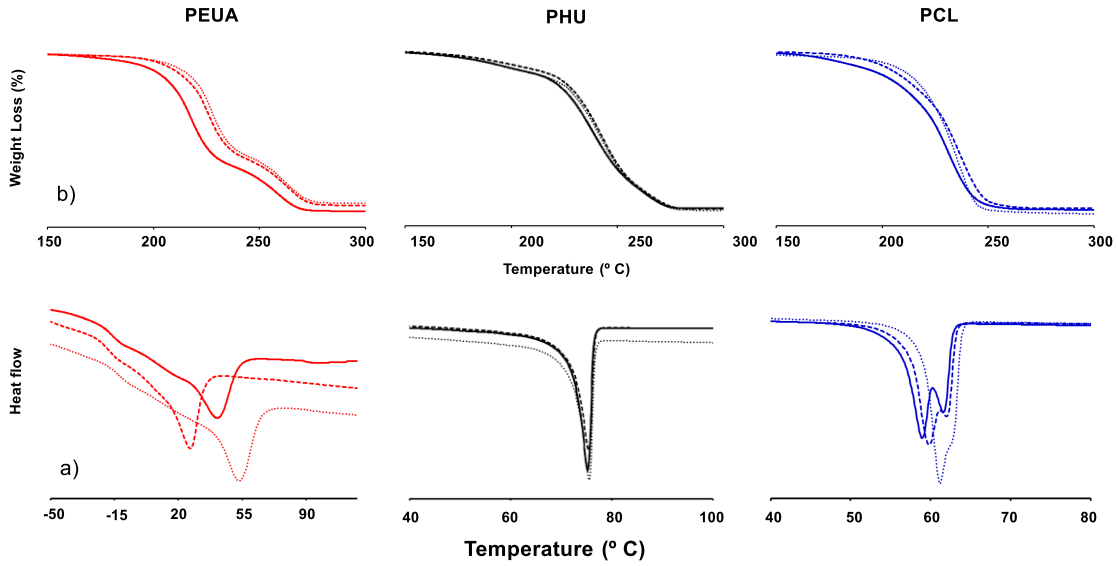


Figure 3. Second heating DSC (a) and TGA plots (b) of initial polyesters (——), polyesters after 10 weeks incubation at pH 2.0 at 45 °C (----) and polyester after 10 weeks incubation at pH 7.4 at 37 °C with porcine pancreas lipase (·····).

Thermal stability changes were studied by TGA (Figure 3 b). Curves of initial and incubated samples for each polymer, show the same degradation profile. For PHU no significant changes are observed according to the negligible degradation and no variation in the crystallinity degree. For PCL and PEUA a slight increase in thermal stability is observed, which can be related with the reduction of the low molecular weight fractions by degradation/solubilization after incubation.

3.2.1. XRD analysis

Although crystallinity can be roughly estimated by DSC, X ray measurements afford a more accurate crystallinity measurement and crystalline arrangement determination. XRD patterns of pristine and incubated samples of PEUA, PHU and

PCL are shown in Figure 4. Moreover, fractional crystallinity (χ_c) determined from the amorphous and crystalline pattern areas are collected in Tables 1 and 3.

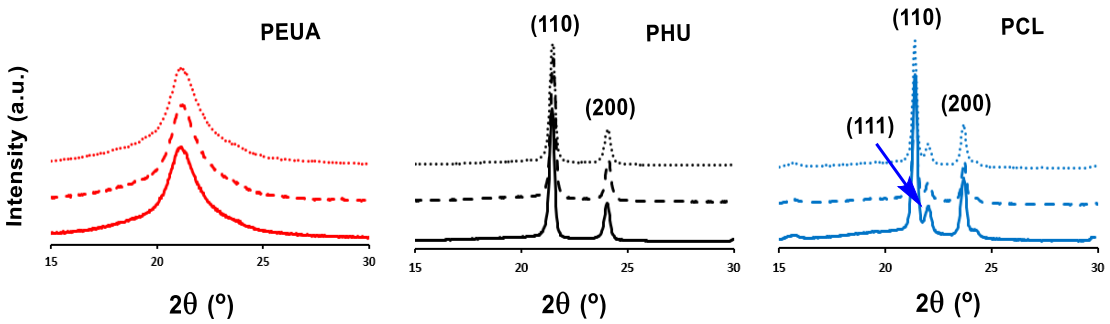


Figure 4. XRD patterns of initial polyesters (—), polyesters after 10 weeks incubation at pH 2.0 at 45 ^{o}C (- - -) and polyester after 10 weeks incubation at pH 7.4 at 37 ^{o}C with porcine pancreas lipase (·····).

XRD patterns for PHU and PCL coincide with the previously described in literature [30,31] and confirm the high crystalline character of both polymers. Calculated fractional crystallinities are systematically higher (χ_c = 62-67%) than those estimated by DSC (χ_c = 54-57%) and confirm the lower crystallinity of PEUA, also indicated by the significant broad dispersion pattern shown in Figure 4. In the case of PEUA, χ_c values before and after incubation at pH 2.0 at 45 ^{o}C are similar, although by DSC lower melting enthalpy and melting temperature are observed. Under incubation at pH 7.4 at 37 ^{o}C and lipase, a slight increase in crystallinity is observed which is in agreement with DSC results. In the case of PCL, despite the fact that by DSC no increase in melting enthalpy was observed, XRD pattern suggest a slight enrichment in crystallinity that could be related with the preferential degradation of the amorphous domains in the surface erosion.

3.2.2. Morphological observations

Surface morphology changes of PEUA, PHU and PCL after hydrolytic and enzymatic degradation were observed by ESEM. PHU and PCL micrographs are shown in Figures SI.5. PHU ESEM micrographs (Figure SI.5.a), b) and c) revealed that no changes in morphology had taken place upon incubation. For PCL (Figure SI.5.d), e) and f) images are consistent with a degradation mechanism by superficial erosion. Initially, the surface appears fairly flat, and surface morphology is induced by the mold used for compression molding. After incubation 10 weeks, a homogeneus and porous structure indicating hydrolytic attack at the amorphous phase at the surface is observed. This erosion seems to be more prominent under enzymatic degradation conditions. This result is in agreement with the superior weight loss observed in Fig 1 b).

ESEM micrographs of PEUA are shown in Figure 5.

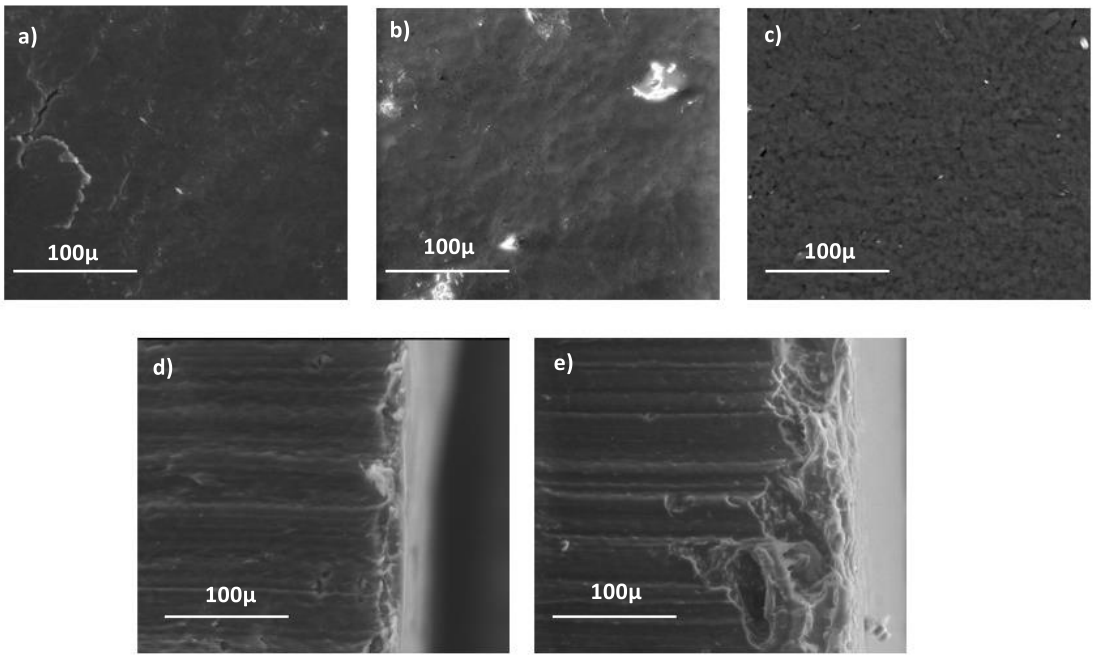


Figure 5. ESEM micrographs of a) initial PEUA; b) PEUA after incubation at pH 2.0 at 45 ^{o}C; c) PEUA after incubation at pH 7.4 at 37 ^{o}C with porcine pancreas lipase; d) vertical section of initial PEUA and e) vertical section of PEUA after incubation at pH 2.0 at 45 ^{o}C.

For PEAU surface, ESEM micrographs show that the initial flat surface is transformed in a porous structure indicating hydrolytic attack at the amorphous domains occurs both in acid and enzymatic media. This erosion mechanism can be visualized more clearly in the cut vertical edge (Figure 5 d and e) of samples degraded in acid media. The stretch marks induced by the cutting blade become deeper and in addition, some eroding regions can be observed in the surface.

To provide a better understanding of microstructural changes in PEUA morphology after incubation at pH 2.0 and 45 ^{o}C, we use atomic force microscopy (AFM) that provide high-resolution, three dimensional imaging of material surface [32]. The three-dimensional topographic images and the corresponding two-dimensional images of initial PEUA and after incubation of 10 weeks are displayed in Figure 6. As can be seen after incubation in these conditions a significant surface erosion with deep valleys and pores is observed.

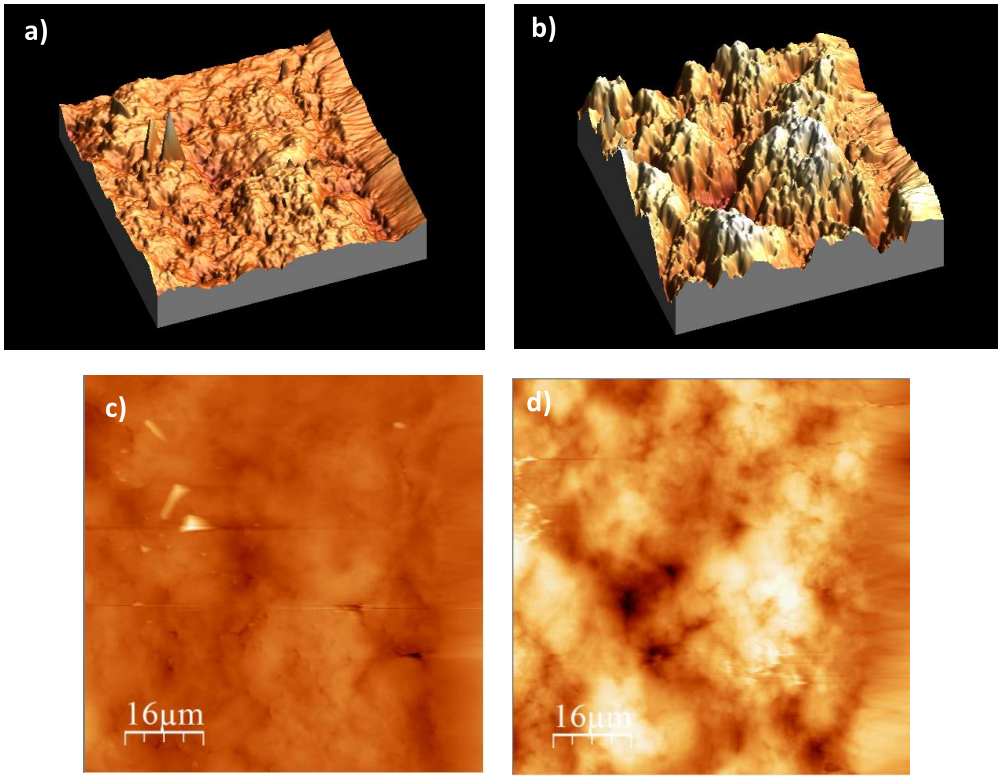


Figure 6. AFM images three-dimensional representation (top): a) initial PEUA; b) PEUA after incubation at pH 2.0 at 45 ^{o}C and two-dimensional representation (bottom): c) initial PEUA; d) PEUA after incubation at pH 2.0 at 45 ^{o}C.

The processes involved in the erosion of a degradable polyester are complex. Water enters the polymer bulk, which might be accompanied by swelling. The intrusion of water triggers the chemical polymer degradation, leading to the creation of oligomers and monomers. Progressive degradation changes the microstructure of the bulk through the formation of pores [14].

3.2.3. Degradation study by ^{1}H NMR

In order to deep insight the degradation of polyester chain at the molecular level a NMR study was carried out. ^{1}H NMR spectra of the residual material resulting after 10 weeks of incubation at pH 2.0 at 45 ^{o}C, and at pH 7.4 at 37 ^{o}C and lipase have been recorded. Residual material of PHU and PCL spectra showed only negligible differences with their initial spectra (Figures SI.6 b) and c) and SI.7 b) and c) respectively, confirming no significant variations in the chemical constitution. By contrast, some structural changes in residual material are observed after both hydrolytic and enzymatic degradation of PEUA (Figure 7 b) and c), due to the progressive chain cleavage. These changes are in agreement to the decrease of Mn observed by SEC (Figure 2).

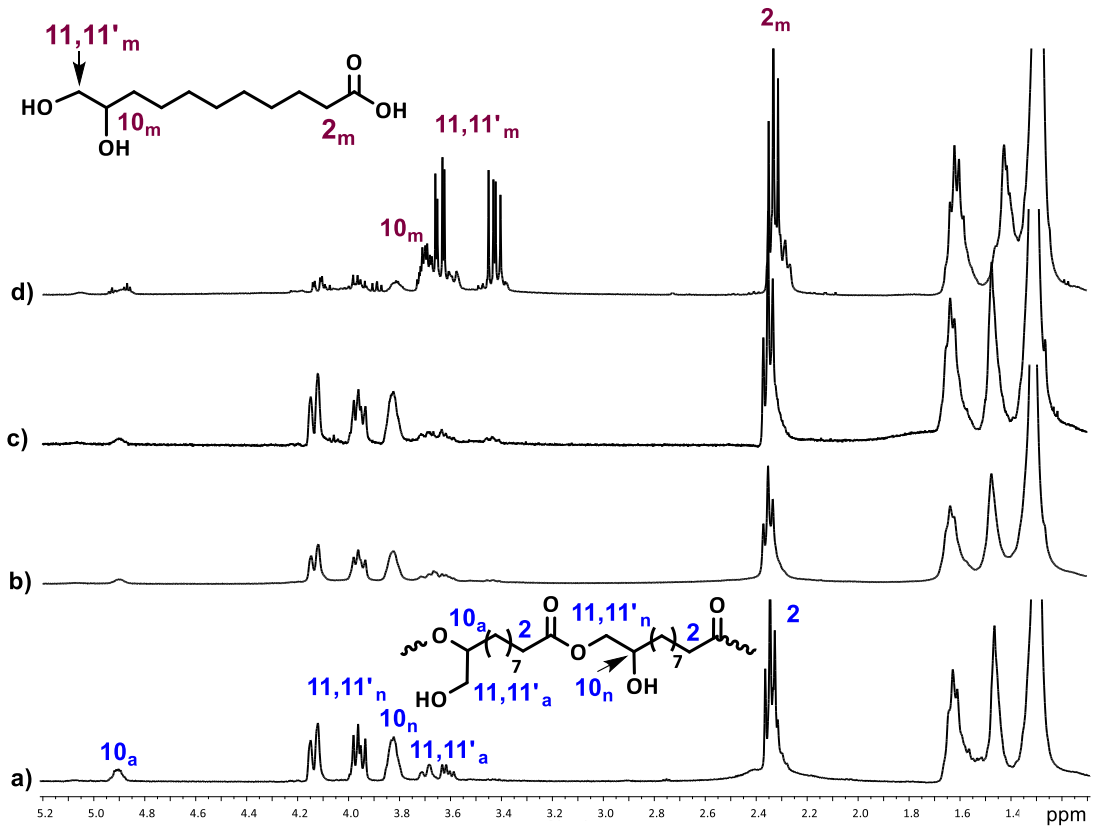


Figure 7. ^{1}H NMR spectra of PEUA: a) initial sample; b) after incubation at pH 2.0 at 45 ^{o}C; after incubation at pH 7.4 at 37 ^{o}C; d) after accelerated hydrolytic degradation with methanesulfonic 1M at 100 ^{o}C.

3.3. Accelerated hydrolytic degradation

To study in detail all residual material of three polyesters, accelerated degradation tests with methanesulfonic acid 1M for 1 day at 100 ^{o}C were performed. Accelerated degradation methods allow obtaining degradation results in a shorter period of time [33,34].

^{1}H NMR spectrum of residual material after accelerated degradation of PEUA (Figure 7 d) shows a great extent of polymer degradation giving mostly 10,11-dihydroxy undecanoic acid (DHUA) and oligomers as bear out by SEC curves (Figure 8 a).

^{1}H NMR spectrum of residual material after accelerated degradation of PHU (Figure SI.6 d) shows an increase of hydroxyl end group signals (at 3.64 ppm) and the

appearance of a new signal (at 2.35 ppm) corresponding to the carboxyl end group signals, confirming the partial cleavage of ester groups, leading to a polymer with lower molecular weight. (Figure 8 b).

^{1}H NMR spectrum of residual material after accelerated degradation of PCL (Figure SI.7 d) reveals a great extent of polymer degradation giving mainly 6-hydroxy-hexanoic acid, confirming the almost complete degradation of PCL. (Figure 8 c).

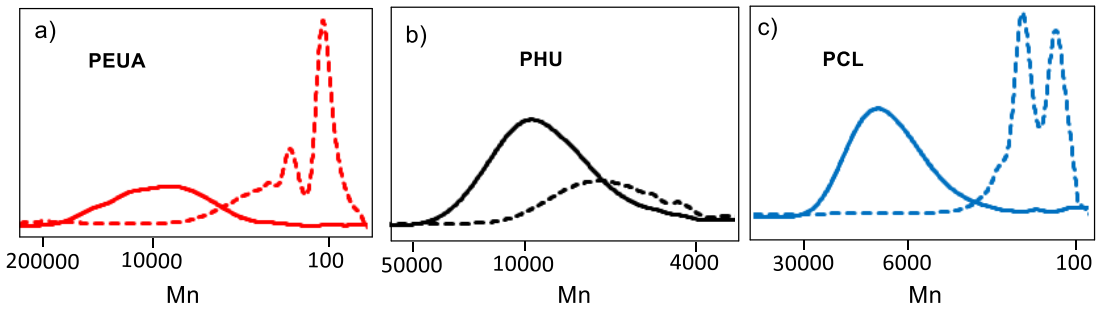


Figure 8. SEC traces for hydrolytic accelerated degradation with methanesulfonic acid at 100 ^{o}C. a) PEUA; b) PHU; c) PCL. Initial sample (continue line) and after degradation (dashed line).

To study in detail the structural changes undertaken by PEUA during accelerated hydrolytic degradation a kinetic study was carried out by ^{1} NMR spectroscopy (Figures 9 and 10). In Figure 9a) is shown the weight percentage decrease of PEUA and the increase of DHUA versus time. As can be seen, although degradation occurs through intermediate oligomeric species, there is a complementary relationship between PEUA degradation and DHUA formation (Figure 10, 5h).

As commented above, on the structure of PEUA there are two kind of repetitive units with pendant secondary or primary alcohols arising from the attack of the carboxylic acid either to the less (leading to a normal unit) or the more substituted carbon (leading to an abnormal unit) of oxirane ring on the starting 10,11-

epoxyundecanoic acid. According to ^{1}H NMR microstructural determination these normal/abnormal units are present in a 72:28 molar ratio in the starting polymer (Figure 9b and 10, 0h). During degradation studies we observed a change in the comonomer composition due to the different hydrolysis rates of primary and secondary esters (Figure 9b). Thus, as observed in the first degradation stages, selective primary ester (normal unit) degradation is predominant and consequently its relative content in the copolymer decreases. Moreover, a significant percentage of branched units was detected from 1 h (Figure 9b and 10, 2h and 3h). The characteristic NMR signals of these branched units in PEUA have been previously assigned and reported [19]. The formation of these units are related with transesterification reactions throughout process. These transesterification reactions have been previously reported for PEUA and similar polyesters [19,35]. Thus, progressive degradation of PEUA lead not only to a decrease in molecular weight but also to a change in its microstructure that goes from linear to branched oligomers.

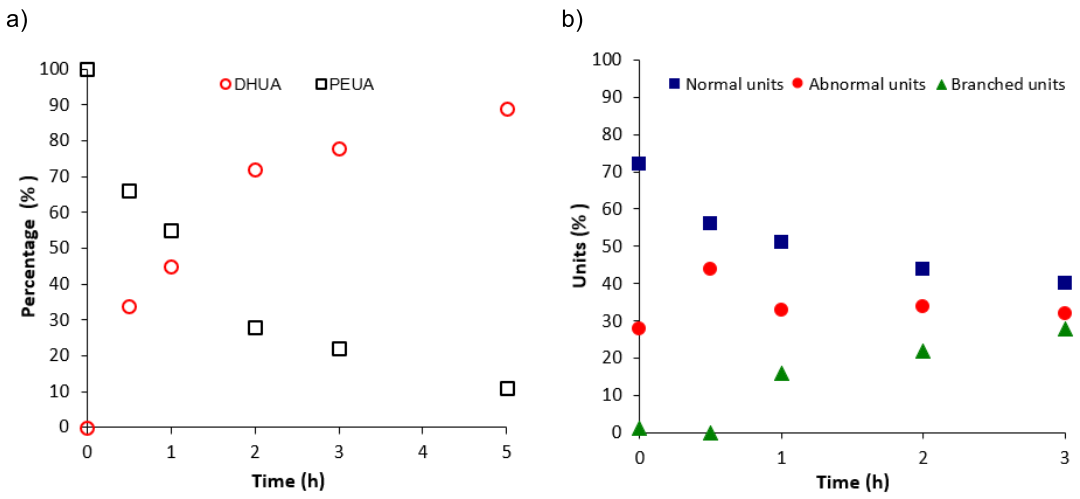


Figure 9. Accelerated hydrolytic degradation kinetic of PEUA with 0.5M of methanesulfonic acid at 100 ^{o}C. a) Weight percentage of PEUA and PHU determined by ^{1}H NMR spectroscopy; b) Percentage of normal, abnormal and branched units in PEUA determined by ^{1}H NMR spectroscopy.

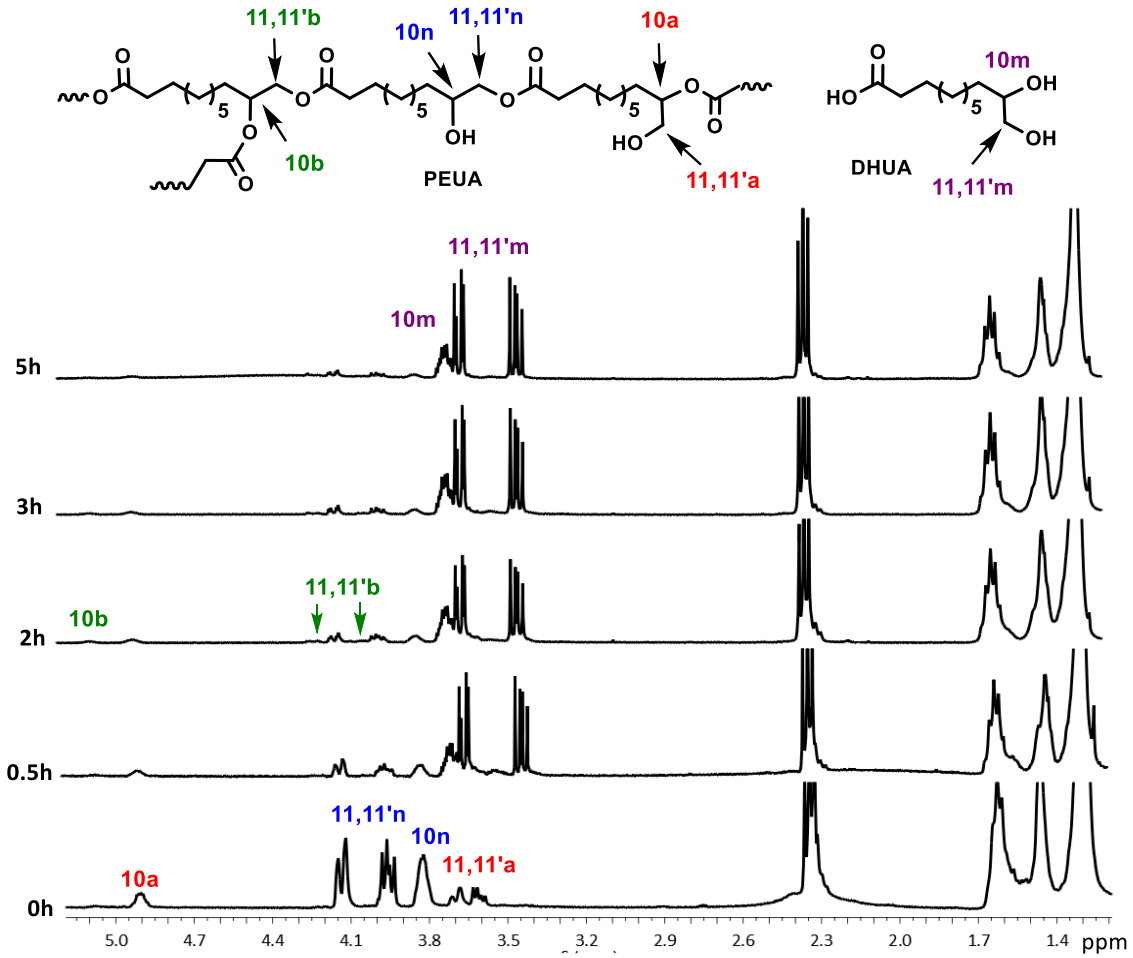


Figure 10. ^{1}H NMR spectra of PEUA accelerated hydrolytic degradation with 0.5M of methanesulfonic acid at 100 ^{o}C versus time. Assigned signals correspond to normal (10n, 11,11'n), abnormal (10a, 11,11'a), branched (10b, 11,11'b) units and DHUA monomer (10m, 11,11'm).

4. Conclusions

PEUA with hydroxy pendant groups and PHU, both derived from 10-undecenoic acid were synthesized with high yield. The hydrolytic and enzymatic degradations of PEUA and PHU were studied and compared with that of the commercial PCL. PEUA, PHU and PCL were characterized by ^{1}H RMN, SEC, DSC, TGA, XRD and hydrophilic/hydrophobic character. PHU showed the highest hydrophobicity and crystallinity, so that scarce hydrolytic degradation was detected. In contrast, in PEUA a Mn decrease by both hydrolytic and enzymatic degradations was observed

demonstrating that in this polyester the presence of hydrophilic pending group together with the superior amorphous character are determinant when comparing degradation of polyesters with the same chain length (C_{11}) and similar Mn. Significant weight loss (60 %) was only observed for PCL under enzymatic conditions. This different behaviour seems to indicate that PCL degrades through a surface erosion mechanism while PEUA do it through bulk erosion mechanism. Even after accelerated degradation in stronger conditions, PHU undergoes slight degradation whereas that PEUA and PCL suffer a significant degradation to produce low molecular weight products.

Acknowledgments

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Hydrolytic and enzymatic degradation studies of aliphatic 10-undecenoic acid-based polyesters

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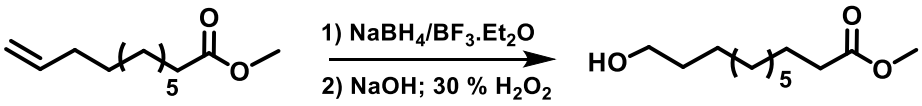
Supporting information

SI.1. Monomer synthesis

Synthesis of methyl-11-hydroxyundecanoate [i]

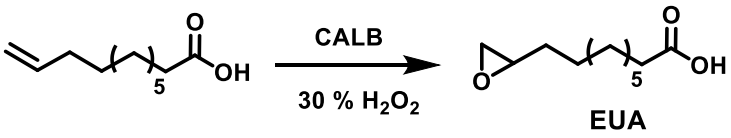


Scheme SI.1. Methyl 11-hydroxyundecanoate synthesis.

In a 250 mL round bottomed flask under argon, 2.46 g (65 mmol) of sodium borohydride were suspended in anhydrous THF (120 mL) and 47.2 mL (210 mmol) of methyl 10-undecenoate were added with stirring. The mixture was cooled on a ice-bath and 9.9 mL (80 mmol) of freshly distilled boron trifluoride diethyletherate were added drop wise during 1h. The ice-bath was removed and mixture stirred for two additional hours and cooled again with a new ice-bath. Next, 21 mL of 3M NaOH and 21 mL of 30% H_2O_2 were added in this order in small portions during 1h and the mixture kept at room temperature overnight. After neutralization with a concentrated NaH_2PO_4 solution, the organic layer was extracted several times with diethyl ether. After solvent evaporation, the resulting yellow oil was distilled under vacuum (120-125 °C, 0.8 mmHg) to afford 31.7 g of colourless oil (yield 69 %).

($CDCl_3$/TMS, δ ppm): 3.68 (s, 3H, $COOCH_3$); 3.63 (t, 2H, CH_2OH); 2.32 (t, 2H, CH_2COO); 1.71-1.50 (m, 4H, $C\underline{H}_2CH_2COO$ and $C\underline{H}_2CH_2OH$); 1.40-1.20 (m, 12H, $(CH_2)_6$). ^{13}C NMR ($CDCl_3$, δ ppm): 174.2 (COO); 63.2 (CH_2OH); 51.4 (CH_3); 33.8 ($\underline{C}H_2COO$); 32.1 ($\underline{C}H_2CH_2OH$); 29.7-29.0 $(CH_2)_5$); 25.6 and 25.0 ($\underline{C}H_2CH_2COO$ and $\underline{C}H_2CH_2OH$).

Synthesis of 10,11-epoxyundecanoic acid (EUA [ii].



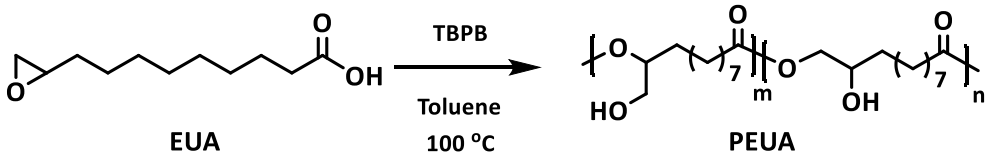
Scheme SI.2. EUA synthesis.

In a 250 mL two necked round bottomed flask, 15.0 g (80.5 mmol) of 10-undecenoic acid in 90 mL of toluene, 6.6 mL (130 mmol) of 30% hydrogen peroxide and 3.0 g (10% w/w) of CALB were vigorously stirred at 40˚C for 24 h. Enzyme was filtered off and the resulting solution diluted in toluene, washed several times with water, dried over anhydrous magnesium sulfate, concentrated and dried under vacuum. The product was obtained as a white solid (yield 98%) with melting point of 49-52 ˚C (lit. [iii] 50˚C).

ESI-TOF, exact mass m/z 200.1414 [M+H] (Theoretical mass: 200.1412). ^{1}H-NMR ($CDCl_3$/TMS, δ ppm): 2.91 (m, 1H, $(CH_2)_2$-C<u>H</u>-O, in oxirane ring), 2.75 (dd, 1H, J_{cis} = 5.2 Hz, CH-C<u>H_2</u>-O), 2.47 (dd, 1H, J_{trans} = 2.4 Hz, CH-C<u>H_2</u>-O), 2.33 (t, 2H, C<u>H_2</u>COOH), 1.64-1.32 (m, 12H, C<u>H_2</u>).^{13}C NMR ($CDCl_3$, δ ppm): 180.72 (COOH), 139.26 (CH_2-<u>C</u>H-O), 114.29 (CH-<u>C</u>H_2O), 34.25-25.78 $(CH_2)_7$.

SI.2. Polyester synthesis

Synthesis of PEUA [ii]



Scheme SI.3. Polymerization of EUA.

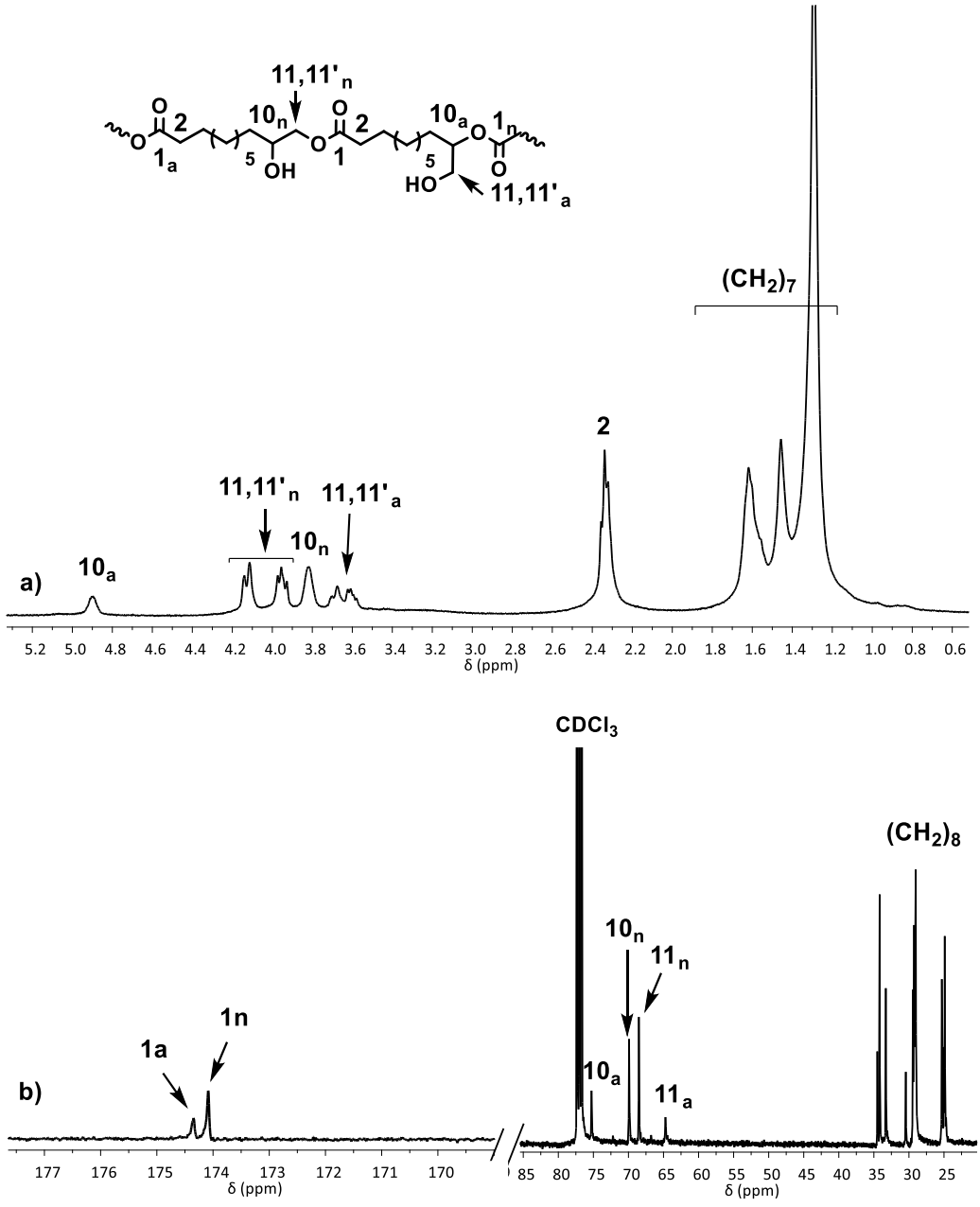
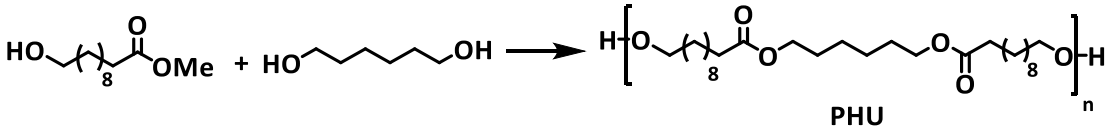


Figure SI.1. a) ^{1}H NMR and b) ^{13}C NMR spectra of PEUA.

Synthesis of PHU



Scheme SI.4. Polymerization of methyl 11-hydroxyundecanoate initiated by 1,6-hexanediol.

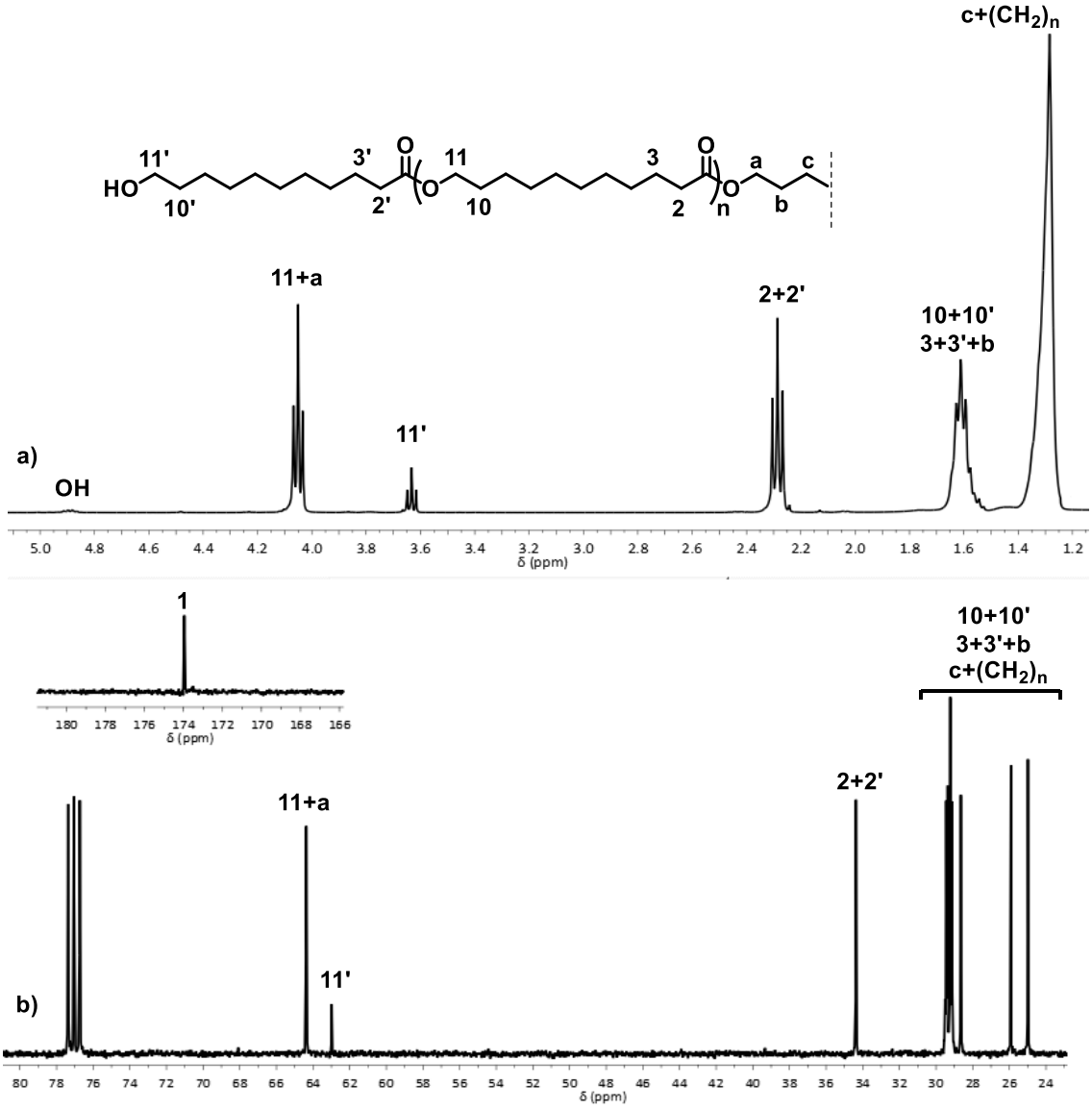


Figure SI.2. a) ^{1}H NMR and b) ^{13}CNMR spectra of PHU.

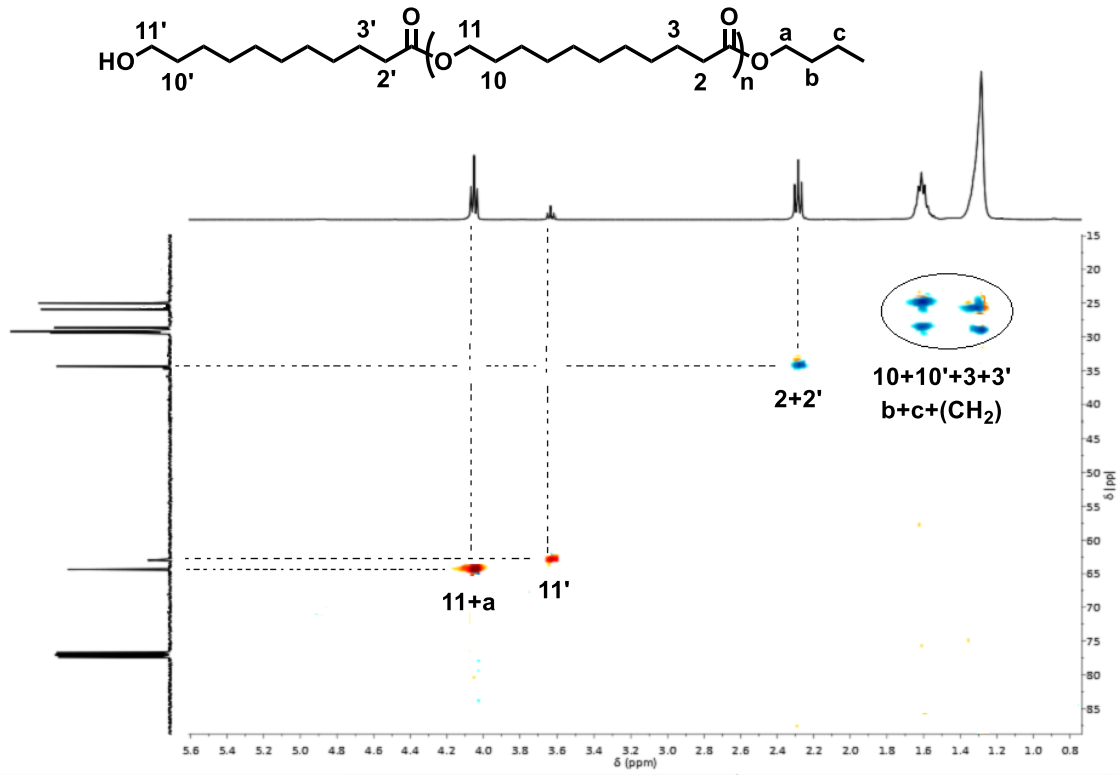


Figure SI.3. Heteronuclear single quantum correlation (HSQC) spectra of PHU

SI.3. Water contact angle

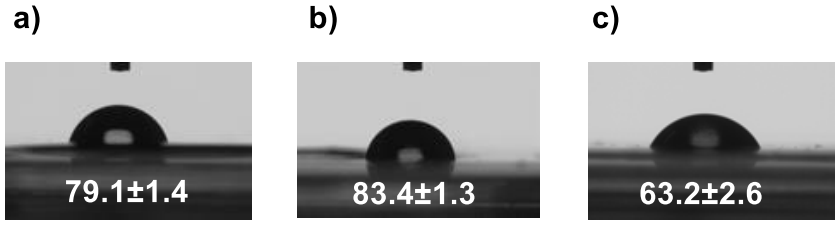


Figure SI.4. Water contact angle images of starting polymers a) PEAU, b) PHU and c) PCL.

SI.4. Hydrolytic and enzymatic degradation

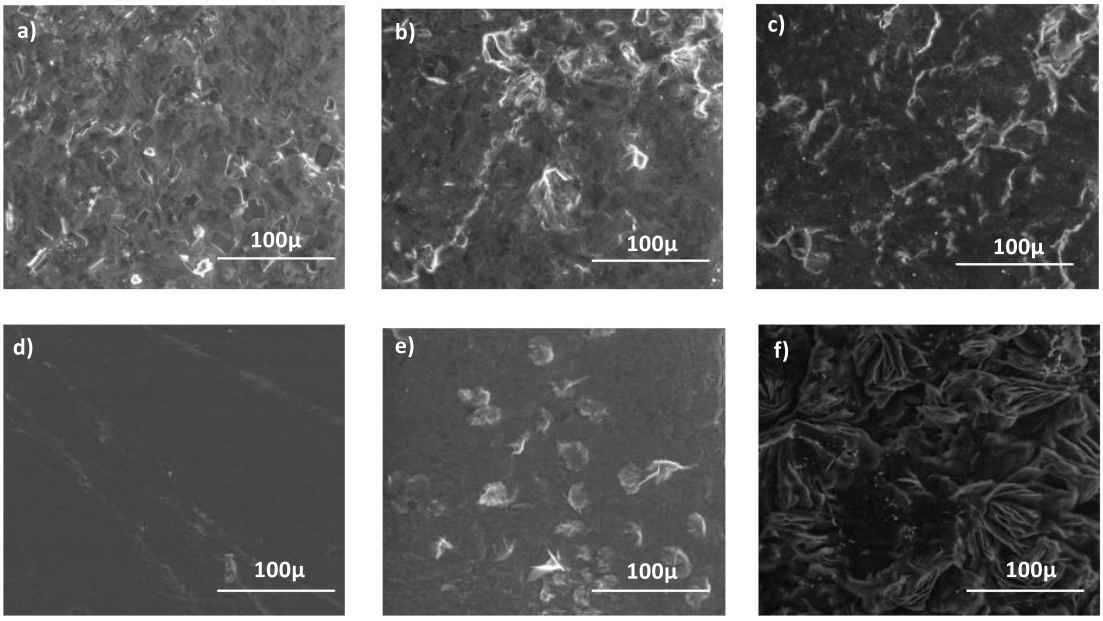


Figure SI.5. ESEM micrographs of a) initial PHU; b) PHU after incubation at pH 2.0 at 45 °C; c) PHU after incubation at pH 7.4 at 37 °C, d) initial PCL; e) PCL after incubation at pH 2.0 at 45 °C and f) PCL after incubation at pH 7.4 at 37 °C with porcine pancreas lipase

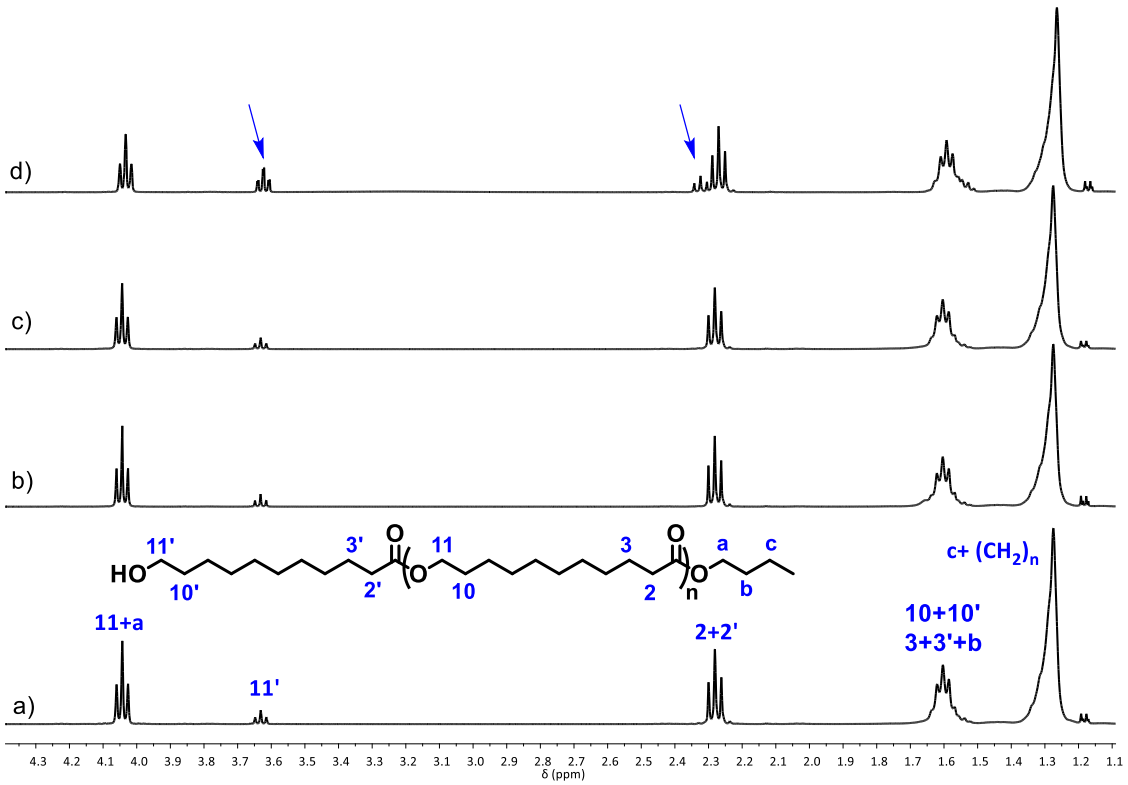


Figure SI.6. ^{1}H NMR spectra of PHU a) initial sample; b) after incubation at pH 2.0 at 45 °C; after incubation at pH 7.4 at 37 °C with porcine pancreas lipase; d) after accelerated hydrolytic degradation with methanesulfonic acid at 100 °C.

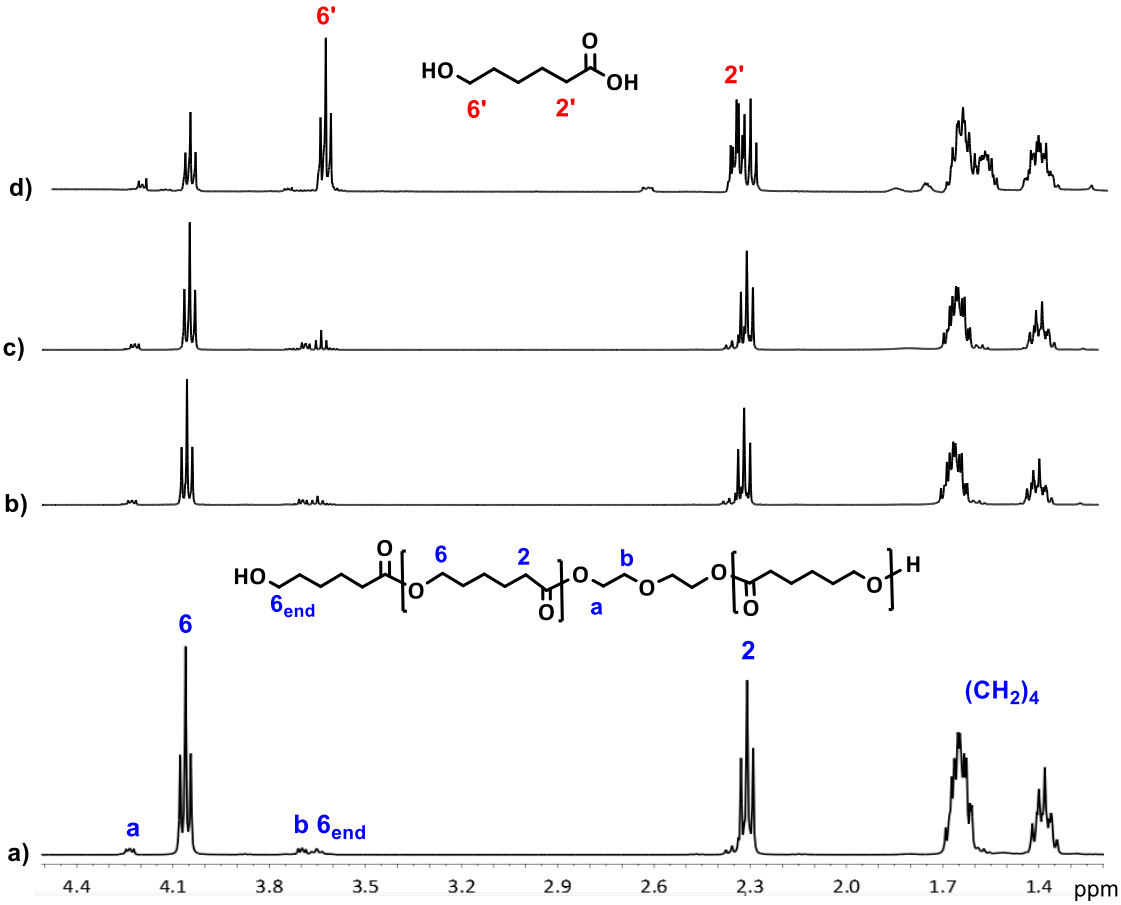


Figure SI.7. ^{1}H NMR spectra of PCL a) initial sample; b) after incubation at pH 2.0 at 45 ^{o}C; after incubation at pH 7.4 at 37 ^{o}C with porcine pancreas lipase; d) after accelerated hydrolytic degradation with methanesulfonic acid at 100 ^{o}C.

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