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Easy synthesis and ROP of 5-Z-amino- δ -valerolactone: new degradable amino-functionalized (co)polyesters.

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ABSTRACT

Novel 5-Z-amino- δ -valerolactone (5-NHZ-VL) was synthesized with aim to prepare degradable polyesters and copolyesters having amino pendant groups. Following a straightforward and efficient synthetic pathway, 5-NHZ-VL was obtained in only two steps and up to 50 % yield. The monomer was fully characterized by ^1H NMR, ^{13}C NMR, ESI mass spectrometry and HPLC. Various conventional conditions were tested for this lactone ring opening polymerization and led to the novel corresponding poly(5-NHZ-VL) ($M_n = 7000$ g/mol ; PD = 1.2). Following this homopolymerization, 5-NHZ-VL was copolymerized with ϵ -caprolactone to generate a family of copolyesters with an amino-group content ranging from 10 to 80 %. Finally, the polyelectrolyte poly(5-NH $_3^+$ -VL) was recovered by removal of the protecting group under acidic conditions and integrity of the polyester backbone was confirmed by ^1H NMR.

Keywords: lactones; polyelectrolytes; aliphatic polyesters; amino functional polymer; degradable polymers.

INTRODUCTION

Biodegradable aliphatic polyesters have been the subject of a great deal of development work over the past 30 years due to their use in environmental and biomedical applications. However, these polyesters suffer from a lack of functional groups that could broaden the range of their properties, for instance conferring hydrophilicity or chemical reactivity. Considerable effort has therefore been made in recent years to prepare new functionalized polyesters. For example, few years ago, and as first strategy, we described a versatile and rapid method to chemically modify poly(ϵ -caprolactone) (PCL) chains *via* a polycarbanionic intermediate with up to 20 % functionalized units.^{1,2} To obtain higher contents of functional groups, a second strategy is preferred, based on the synthesis and polymerization of previously functionalized lactones.³ However, the chemistry involved in their synthesis often results in poor yields, both due to the number of steps required and the necessary careful purification of the monomers. Also, whether or not polymerization is possible, and the ease with which it can be performed, depends on the size of the lactone ring and the nature of the lactone functionalization. Despite these drawbacks, a large variety of functional lactones has been described ranging from 4-membered β -malolactonate⁴ to 7-membered γ - or α -functionalized ϵ -caprolactone.⁵⁻⁸ Kimura's early work⁹ has most recently been followed by efforts concentrated on lactide-type structures giving access to functional poly(lactide)s with carboxyl,¹⁰ hydroxyl,^{11,12} or even alkyl substituted units.¹³ However, and to the best of our knowledge, although amino-polyesters have great potential in biomedical applications, only two examples of polymerizable amino-functionalized lactones have been reported in the literature. These monomers take the form of a butyrolactone derived from serine **1**,¹⁴⁻¹⁷ and a functional lactide derived from lysine **2** (Scheme 1).¹⁰

Various strategies employed to polymerize these lactones have been reported, but none is fully satisfactory with either i) low yields after the final purification step used to obtain polymerizable monomers, ii) low polymerizability, or iii) marked degradation during the amino group deprotection step.^{10,14-17} In order to overcome some of these drawbacks and increase the diversity of amino-functionalized lactones, we report here a rapid and simple two-step synthesis yielding a novel amino- δ -valerolactone. In a second part, polymerization conditions towards the resulting aliphatic amino-functionalized polyester are discussed. To finish, examples of copolyesters of amino- δ -valerolactone and ϵ -caprolactone are presented with molar ratios of aminated units ranging from 10 % to 80 %.

EXPERIMENTAL

Materials

N-benzyloxycarbonyl-glutamic acid γ -*tert*-butyl ester (ZGlu(OtBu)OH, 99 %), *N*-*N'*-diisopropylethylamine (DIPEA), sodium borohydride powder (NaBH₄, 99 %), sodium bicarbonate (NaHCO₃), magnesium sulfate (MgSO₄), ϵ -caprolactone (ϵ -CL), tin(II) 2-ethylhexanoate (Sn(Oct)₂, \approx 95 %), tin(II) trifluoromethanesulfonate (Sn(OTf)₂, \geq 97.0 %), trifluoroacetic acid (TFA), solution of hydrobromic acid in acetic acid (HBr/AcOH, 33 wt.%), propan-2-ol (*i*-PrOH), ethyl acetate, THF, toluene, DMF, diethyl ether and dichloromethane (DCM) were purchased from Sigma-Aldrich (St-Quentin Fallavier, France). Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) was purchased from Merck (Strasbourg, France). All chemicals and solvents were used without purification with exception of the polymerization solvents, *i*-PrOH and ϵ -CL which were dried over calcium hydride for 24 h at room temperature and distilled under reduced pressure.

Characterizations

Molecular weights of the polymers were determined by size exclusion chromatography (SEC) using Waters Inc. equipment fitted with a 5 μm mixed C PLgel 5 μm MIXED-D (300 \times 7.5 mm) and SHODEX RI 101 refractometric detector. The mobile phase was DMF at 1 mL/min flow. Typically, the polymer (10 mg) was dissolved in DMF (2 mL) and the resulting solution was filtered through a 0.45 μm Millipore filter before injection of 20 μL of filtered solution. M_n and M_w were expressed according to calibration using poly(methyl methacrylate) standards. For water soluble polycations, molecular weights were determined by SEC using a LCC-501 System (Pharmacia Biotech) equipped with a UV-visible detector operated at 214 nm and a column packed with cationic DEAE Sepharose gel. The mobile phase was a 1.6 M NaCl aqueous solution at 0.25 mL/min. M_n and M_w were expressed according to calibration using poly(L-Lysine) standards. Differential scanning calorimetry (DSC) measurements were carried out under nitrogen at a 10 $^\circ\text{C}/\text{min}$ heating rate on a Perkin Elmer Instrument DSC6 Thermal Analyser. ^1H NMR and ^{13}C spectra were recorded using an AMX300 Brucker spectrometer operating at 300 MHz and 75 MHz, respectively. Deuterated dimethyl sulfoxide or chloroform were used as solvent. LC/MS analyses were performed on a Quatromicro (Micromass, Manchester, U.K.) triple-quadrupole mass spectrometer fitted with an electrospray interface and thanks to a Waters Alliance 2690 system (Electrospray : 30 V, 80 $^\circ\text{C}$, 100-200 $\mu\text{L}/\text{min}$; HPLC : Phenomenex Onix Monolith C18 (25 x 4.6 mm, macropore : 2 μm), 3 mL/min, gradient : 100 % (H_2O , 0.1 % HCOOH) to 100 % (ACN, 0.1 % HCOOH), UV detection at $\lambda = 214 \text{ nm}$).

Synthesis of tertibutyl-4-(benzyloxycarbonylamino)-5-hydroxypentanoate (4)

The selective reduction of the main chain carboxylic acid group is based on the formation of an activated ester thanks to the use of BOP as a reagent as previously described in literature.¹⁸ Typically, DIPEA (1.18 ml, 7.1 mmol) and a BOP solution (2.87 g, 6.5 mmol) in 10 ml of THF were slowly added on a stirred suspension of Z-Glu(OtBu)OH **3** (2 g, 6 mmol) in 20 ml of THF at room temperature. After 10 minutes of stirring, NaBH₄ (1.1 g, 30 mmol) was slowly added to the reaction medium which was then stirred for 2 hours at room temperature. The resulting mixture was then diluted in CH₂Cl₂ (150 mL) and carefully washed with a 5 % HCl solution (5×100 mL), followed by NaHCO₃ saturated solution (3×100 mL) and brine (3×100 mL). The organic phase was then dried over MgSO₄ and concentrated under reduced pressure to yield a clear oil. Final purification of compound **4** was obtained by flash column chromatography using in a first step CH₂Cl₂ to elude by-products and in a second step ethyl acetate to recover pure **4** with a 90 % overall yield. ¹H NMR for **4**: (300 MHz; CDCl₃): δ (ppm)= 7.3 (m, 5H, Ph), 5.1 (m, 1H, NH), 5.0 (s, 2H, OCH₂Ph), 3.8-3.7 (m, 1H, CH-NHZ), 3.6-3.5 (m, 2H, CH₂-OH), 2.3-2.2 (m, 2H, CH₂-CH₂-CH), 1.9-1.7 (m, 2H, CH₂-COOtBu), 1.4 (s, 9H, tBu). HPLC for **4**: 1.52 min. Calculated monoisotopic mass for **4** (C₁₇H₂₅NO₅) 323.17 g/mol, ES-MS (70 eV, *m/z*) found for **4**: 324.3 [M+H]⁺, 346.3 [M+Na]⁺

Synthesis of benzyl 6-oxotetrahydro-2H-pyran-3-ylcarbamate (5-Z-amino-δ-valerolactone) (5)

Lactonization of **4** was done *via* the simultaneous removal of the tertibutyl group and cyclization of the resulting intermediate to yield **5**. In a typical experiment, **4** (2 g) was dissolved in a mixture of trifluoroacetic acid (10 mL) and CH₂Cl₂ (10 mL) and stirred for 3 hours at room temperature. After

reaction completion, cold water (80 mL) and CH₂Cl₂ (80 mL) were added. The organic layer was washed with water (5×50 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Column chromatography with AcOEt/Et₂O (5:5), yielded compound **5** (0.85 g, 55 %) as white crystals with a minimum 98 % purity. mp 65°C (from DSC). ¹H NMR for **5**: (300 MHz; DMSO-*d*₆): δ (ppm)= 7.6 (m, 1H, NH), 7.4-7.3 (m, 5H, Ph), 5.05 (s, 2H, OCH₂Ph), 4.3-4.2 (m, 1Ha, CH₂-O), 4.1-4.0 (m, 1Hb, CH₂-O), 3.9-3.8 (m, 1H, CH-NHZ), 2.6-2.4 (m, 2H, CH₂-CO), 2.1-2.0 (m, 1Ha, CH₂-CH₂-CH), 1.8-1.7 (m, 1Hb, CH₂-CH₂-CH). ¹³C NMR for **5**: (75 MHz, DMSO-*d*₆): δ (ppm)= 171 (s, C(O)O), 156.2 (s, NHC(O)O), 137.5 (s, CH₂CCH), 128.8-127.6 (m, CH), 70.6 (s, CH₂O), 65.9 (s, CH₂C(O)ONH), 44.3 (s, CHNH), 27.5 (s, CH₂CHNH), 24.5 (s, CH₂C(O)). HPLC for **5**: 1.23 min. Calculated monoisotopic mass for **5** (C₁₃H₁₅NO₄) 249.10 g/mol, ES-MS (70 eV, *m/z*) found for **5**: 250,2 [M⁺ + H], 499,4 [2M⁺ + H].

Synthesis of poly(5-*Z*-amino-δ-valerolactone) (**6**)

All polymerizations in solution have been carried out using 2 % of either Sn(Oct)₂ (35 % (w/v) THF stock solution) or Sn(OTf)₂ (36 % (w/v) THF stock solution) as a catalyst and dry propan-2-ol (2 % (v/v) THF stock solution) as an initiator. Details of polymerization conditions as well as corresponding results are summarized in Table S1.[†] Typically, a schlenk flask containing a stir bar was fitted with a septum, flame-dried under vacuum, and placed under nitrogen. Monomer and all solutions were added under nitrogen. In a typical procedure (Table S1, 10), **5** (0.3 g, 1.2 mmol) was dissolved in dry NMP (1.5 mL) and heated to 140°C. 28 μL of Sn(OTf)₂ stock solution and 57 μL of propan-2-ol stock solution were added under argon atmosphere. At the desired reaction time the reaction was stopped by adding 3 mL of THF, followed by precipitation of the polymer in cold methanol. Polymer was dried at

room temperature under vacuum after solvent decantation. For bulk polymerizations the same procedure was followed without solvent. In addition, no initiator was used and reaction was carried out in sealed flasks when reduced pressure was used. Monomer conversion was determined by ^1H NMR analysis *via* the signal shift of the methylene protons of the benzyl group from 5.05 ppm to 4.95 ppm in **5** and in poly(5-*Z*-amino- δ -valerolactone), respectively. Molecular weights and polydispersities were determined by SEC: $M_n = 7000$ g/mol, PDI = 1.2 (Table S1, 4). Molecular weights were also calculated using the relative intensities of the signals at 3.40 ppm (m, 1 Ha, $\text{CH}_2\text{-OH}$) and 4.65 ppm (m, 1H, $\text{CH}(\text{NHZ})\text{-CH}_2\text{-OH}$) of the chain end and the intensity of the signal at 1.5-1.6 ppm (m, 2H $\text{CH}_2\text{-CH}_2\text{-CH}$). Final polymerization yield was 81 %. Melting point and glass transition temperature were measured by DSC at 180°C and 45°C, respectively. ^1H NMR : (300 MHz; DMSO-*d*6): δ (ppm)= 7.4-7.3 (m, 5H, Ph), 7.2 (m, 1H, NH), 4.95 (s, 2H, OCH_2Ph), 4.0 (m, 1Ha, $\text{CH}_2\text{-O}$), 3.8 (m, 1Hb, $\text{CH}_2\text{-O}$), 3.6 (m, 1H, CH-NHZ), 2.2 (m, 2H, $\text{CH}_2\text{-CO}$), 1.6 (m, 1Ha, $\text{CH}_2\text{-CH}_2\text{-CH}$), 1.5 (m, 1Hb, $\text{CH}_2\text{-CH}_2\text{-CH}$). ^{13}C NMR : (75 MHz; DMSO-*d*6): δ (ppm)= 26.4 ($\text{CH}_2\text{-CH}_2\text{-CH}$), 30.4 ($\text{CO-CH}_2\text{-CH}_2$), 49.6 (CH-NHZ), 65.8 ($\text{CH}_2\text{-O}$ and OCH_2Ph), 128.1-128.8 (CH of Ph), 137.6 (C of Ph), 156.5 (COCH_2Ph), 172.8 ($\text{CH}_2\text{-CO-CH}_2$).

Synthesis of poly(5- NH_3^+ - δ -valerolactone) (**7**)

Z-amino protected polymer was deprotected following a classical procedure under acidic conditions to yield the corresponding polyester with free ammonium pendant groups. Typically, a solution of hydrobromic acid (0.23 mL, 4.0 mmol) in acetic acid (33 wt.%) was slowly added on a stirred suspension of **6** (0.1g, 0.4 mmol of *Z* group) in dichloromethane (3 mL). Deprotection was carried out at room temperature and was stopped when no more CO_2 bubbling was detected. The reaction medium was precipitated and washed with cold diethyl ether. The obtained polymer was then dissolved in

distilled water and dialyzed against water before freeze-drying to yield the final polymer **7** as white powder (80 % yield). ^1H NMR : (300 MHz; DMSO-*d*6): δ (ppm)= 4.2 (m, 1Ha, $\text{CH}_2\text{-O}$), 4.1 (m, 1Hb, $\text{CH}_2\text{-O}$), 3.5 (m, 1H, CH-NH_3^+), 2.6 (m, 2H, $\text{CH}_2\text{-CO}$), 1.9 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}$). ^{13}C NMR : (75 MHz; DMSO-*d*6): δ (ppm)= 24.8 ($\text{CH}_2\text{-CH}_2\text{-CH}$), 29.8 ($\text{CO-CH}_2\text{-CH}_2$), 49.5 and 52.0 (CH-NH_3^+), 60.8 and 63.5 ($\text{CH}_2\text{-O}$), 172.5 and 174.2 ($\text{CH}_2\text{-CO-CH}_2$).

Synthesis of poly(5-Z-amino- δ -valerolactone-co- ϵ -caprolactone)

In a typical procedure, **5** (99 mg, 0.39 mmol) and ϵ -CL (407 mg, 3.5 mmol) were added in a schlenk flask under nitrogen atmosphere (Table 2, entry 1). Catalyst ($\text{Sn}(\text{Oct})_2$, 0.64 M in THF, 9 μL , $7.8 \cdot 10^{-6}$ mol) and initiator (*i*-PrOH, 2,6 M in THF, 15 μL , $3.9 \cdot 10^{-5}$ mol) were added through the septum. Reaction was carried out for 24 hours at 110°C under nitrogen and atmospheric pressure. At the desired reaction time reaction was stopped by adding 3 mL of THF, followed by precipitation into cold methanol. The obtained polymer was filtrated and dried at room temperature under vacuum. Monomer conversions were determined by ^1H NMR analysis *via* the signal shift of the methylene protons of the benzyl group from 5.05 ppm to 4.95 ppm in **5** and in the copolyesters, respectively, and the shift of the methylene protons from 4.20 ppm to 4.00 ppm in ϵ -CL and in the copolyesters, respectively. Comonomers ratios in the copolyesters were determined by ^1H NMR analysis using the intensities of the signals at 4.95 ppm (s, 2H, OCH_2Ph , **5**) and at 4.00 ppm (t, 2H, $\text{OCH}_2\text{-CH}_2$, ϵ -CL and m, 1Ha, $\text{CH}_2\text{-O}$, **5**).

RESULTS AND DISCUSSION

5-Z-amino- δ -valerolactone synthesis

Synthesis of the novel 5-Z-amino- δ -valerolactone was performed according to a well-known strategy based on the use of α -amino-acids. Functional lactones with hydroxyl, carboxyl or even amino groups were successfully prepared in the past, thanks to this technique. However, in most cases after lactonization, a very careful final purification with several successive column chromatographies is necessary to get a polymerizable monomer. For the few existing examples of amino-protected lactones, typical yields of 60 to 80 % are generally claimed, but these yields correspond to monomers purified by a single column chromatography.^{10,14,16,17} Authors further purify their monomers to get a polymerizable grade but without any mention of the new yields, or when it is the case with yields typically inferior to 10 %.¹⁵ Thus, despite good initial yields, the required high purity of the lactone for an efficient ring opening polymerization generally leads to low final yields. Thanks to a careful choice of the starting α -amino-acid and its protecting groups, we provide here a new amino-functionalized lactone obtained in high purity with up to 50 % yield.

This easy synthesis of **5** was based on the use of a commercially-available glutamic acid derivative, namely N-benzyloxycarbonyl-glutamic acid γ -*t*-butyl ester **3** (ZGlu(OtBu)OH) (Scheme 2). In the first step, the free carboxylic group of **3** was reduced after formation of an activated ester intermediate by following a method described in the literature.^{18,19} In the present work, *N,N'*-diisopropylethylamine/BOP and NaBH₄ were used for activation and reduction, respectively. Flash column chromatography of the step 1 products gave *t*-butyl 4-(benzyloxycarbonylamino)-5-hydroxypentanoate **4** with a 90 % yield.[†] The second step consisted in simultaneous *in situ* deprotection of the carboxylic acid and intramolecular cyclization of **4** in a CH₂Cl₂/TFA (1:1) mixture at room

temperature. The final benzyl 6-oxotetrahydro-2H-pyran-3-yl carbamate **5** (5-NHZ- δ -VL) was purified by column chromatography and recovered as white crystals with a 55 % yield and a high purity (> 98 %). The ^1H NMR spectrum and corresponding signals assignments were consistent with the expected structure of **5** (Figure 1). The structure and the purity were also confirmed by ^{13}C NMR, HPLC and mass spectrometry[†]. The high purity of **5** allowed its spontaneous crystallization together with its polymerization under standard ring-opening polymerization (ROP) conditions without further purification. It is noteworthy that such relative ease in obtaining a pure functionalized lactone is rare and that the overall 50 % yield for the polymerizable lactone confirms the efficiency of the short synthetic route proposed here.

Ring opening polymerization of 5-Z-amino- δ -valerolactone

Homopolymerization of **5** was carried out by ring-opening polymerization. Given previous reports concerning the inherent difficulties of polymerizing amino-functionalized lactones without deprotection/degradation and/or limitation of molecular weights,^{10,14-17} we were interested in testing both polymerization conditions of **5** and subsequent amino group deprotection (Scheme 3). ROP studies were therefore conducted in bulk under conditions conventionally used to obtain high molecular weight PLA, or in solution with toluene, NMP or DMF as solvent. Tin-based catalysts, namely $\text{Sn}(\text{Oct})_2$ and $\text{Sn}(\text{OTf})_2$, were used with *i*-PrOH as initiator (Table 1). For clarity reasons, only the best conditions are listed in Table 1 and other ROP conditions are supplied as supplementary data.[†]

Polymerization was followed by ^1H NMR in $\text{DMSO-}d_6$ using the chemical shifts of the peak corresponding to the methylene protons of the Z protecting group, which were found at 5.05 ppm and 4.95 ppm in **5** and poly(5-NHZ- δ -VL), respectively. Molecular weights were determined by SEC and

calculated using ^1H NMR spectra (Figure 2). It is to note that initiator peaks could not be used for this purpose as they are masked by polymer signals. Instead, the peaks corresponding to the alcohol chain-end were used. These signals were found at 4.65 ppm and 3.40 ppm for $(-\text{CH}(\text{NHZ})-\text{CH}_2-\text{OH})$ and (CH_2-OH) , respectively. These assignments were confirmed by COSY-NMR experiments[†].

First of all it is to note that molecular weight distributions (M_w/M_n) of polyesters were narrow, indicating a fast initiation compared to propagation, and a fast propagation compared to transfer or termination reactions. When conventional $\text{Sn}(\text{Oct})_2$ was used as the catalyst, polymerizations were slow under all the conditions employed with even no polymerization for the lowest temperature of 110°C in toluene or bulk under atmospheric pressure.[†] In an attempt to increase the reaction rate, the temperature was raised to 140°C . Despite this higher temperature, polymerizations were still slow with low conversions after 24h of polymerization.[†] For example, conversions of 20 % in bulk and 12 % in DMF were found with only oligomers ($M_{nSEC} = 1\ 200\text{-}1\ 700$ g/mol) being produced in DMF, possibly due to transfer and/or depolymerization reactions (Figure 3). Longer reaction times and bulk polymerization were the only ROP conditions leading to elevated final conversions and higher molecular weights, up to 7 000 g/mol (PDI = 1.2) (Table 1, Figure 3). It is to note that slightly higher molecular weights were obtained under reduced pressure (7 000 g/mol) compared to atmospheric pressure (5 000 g/mol) as a result of the better removal of potential contaminants.

Although reasonably high and suitable for a variety of applications, this molecular weight obtained with $\text{Sn}(\text{Oct})_2$ was below 20 000 g/mol. Consequently, and to overcome the presumed unfavourable polymerization-depolymerization equilibrium for our lactone, $\text{Sn}(\text{OTf})_2$ was used as it is known to greatly accelerate the lactone polymerization rate even at lower temperature. As expected, $\text{Sn}(\text{OTf})_2$ gave far faster polymerization rate than $\text{Sn}(\text{Oct})_2$ at high temperatures, with 32 % conversion in DMF after 4 h, and up to 75 % conversion in NMP after only 1 hour.[†] However, rapid degradation occurred within the first hours of reaction as confirmed by low M_n and unexpected signals in the NMR spectra,

indicating deprotection of the amino group concomitant with the polymerization. Considering these phenomena, and taking into account the lower temperature required with $\text{Sn}(\text{OTf})_2$, experiments were carried out in NMP at 30°C, and in bulk at 100°C under reduced pressure.[†] These milder conditions resulted in moderate polymerization rates, with for example 58 % monomer conversion obtained after 21 hours at 30°C in NMP, without any degradation of the polymer backbone and no amino group deprotection as confirmed by ^1H NMR. However, despite these more favorable parameters, no improvement in terms of molecular weights was observed for poly(5-NHZ- δ -VL). Limited molecular weights of ca. 2 000 g/mol in solution and up to 5 000 g/mol in bulk were obtained (Figure 3). Again, transfer reactions to the solvents might explain the low molecular weights obtained in DMF and NMP.

To complete our study, poly(5-NHZ- δ -VL) with M_n in the range 3 000 to 7 000 g/mol were analysed by DSC.[†] A strong influence of the molecular weight on the melting temperature (T_m) and glass transition temperature (T_g) was observed. T_m increase from 146 to 180°C and T_g from 27 to 45°C when molecular weights increase from 3 000 to 7 000 g/mol, respectively. In the same time enthalpy of fusion almost doubles passing from 34 to 65 J/g. These very strong variations with molecular weight can be explained by the possibility to form hydrogen bonds between the amido and ester group, which strongly increase the crystallinity of longer polymer chains.

In summary, homopolymerization of **5** led to polymers with molecular weight limited to $M_n = 7000$ g/mol under the investigated conditions. Other conditions, especially other catalytic systems might be of interest to obtain higher molecular weights and this will be studied further in our lab. The main aim of this work is to provide a new class of degradable aminated-polyesters based on the easily obtained 5-NHZ- δ -VL. Indeed, even if molecular weights below 20 000 g/mol are too low for some applications,

for most of the herein targeted biomedical applications, low molecular weights polycations, and above all degradable ones like poly(5-amino- δ -valerolactone), are very attractive. For example, short degradable amino-functionalized polyesters are of interest for transfection of cells and gene delivery due to their ability to complex DNA while being less toxic than high molecular weights and non degradable polycations²⁰⁻²², or to prepare bioconjugates.^{23,24} They also find one of their main applications in the field of amphoteric and/or amphiphilic block copolymers with applications in inter-polyelectrolytes complexes and micelles for drug delivery.²⁵⁻²⁷ All these potential applications could be considered with poly(5-amino- δ -valerolactone) having a molecular weight below 10 000 g/mol. Besides, since copolyesters containing 5-amino- δ -valerolactone units could also be of great interest, we decided to evaluate the feasibility of the copolymerization of **5** with ϵ -CL.

Copolymerization of 5-Z-amino- δ -valerolactone and ϵ -caprolactone

Polymerizations of **5** with ϵ -CL were performed in bulk at 110°C by ROP initiated by *i*-PrOH and catalyzed by Sn(Oct)₂. Copolyesters with molar ratios of aminated units ranging from 10 % to 50 % were prepared by adjusting the initial amounts of **5** and ϵ -CL. This family of copolyesters, with various proportions of amino-group content, is expected to cover a broad range of physico-chemical properties in adequation with some of the above mentioned applications. A degree of polymerization DP = 100 was targeted. Results are shown in Table 2. Experimental molecular weights were determined by SEC. More accurate values would have been provided by ¹H NMR, unfortunately due to the high number of proton signals in the copolyesters, it was not possible to calculate the molecular weight by NMR. The theoretical molecular weight was calculated using Equation (1).

$$\overline{Mn}_{th} = \frac{([5 - NHZ - VL]_0 \times conv_{5-NHZ-VL} \times 249 + [\epsilon - CL]_0 \times conv_{\epsilon-CL} \times 114)}{[i - Pr OH]_0} \quad (1)$$

After 24h, conversions were high for all copolymers with surprisingly higher conversions for **5** than for ϵ -CL. Experimental molar compositions ($F_{5-NHZ-\delta-VL}$) measured by NMR showed a deviation when compared with the theoretical composition ($f_{5-NHZ-\delta-VL}$) calculated by Equation (2), with **5** being preferably incorporated in the copolymer (Table 2, Figure 4). Although no reactivity study has been carried out at that point, this higher incorporation of **5** might allow the presence of small blocks of **5** in the copolymeric structure.

$$f_{5-NHZ-\delta-VL} = \frac{[5 - NHZ - VL]_0}{([5 - NHZ - VL]_0 + [\epsilon - CL]_0)} \quad (2)$$

The composition deviation was accompanied by a molecular weights deviation (Figure 5). It is to note that lower molecular weights, below 5000 g/mol, were obtained for the highest initial **5**/ ϵ -CL ratio, in good agreement with the results found for the homopolymerization of **5**. Hydrodynamic volumes of the copolymers changing with their composition, given molecular weights should be considered with care. However, copolymerization of **5** and ϵ -CL gave access to functional copolyesters with functionalities ranging from 12 % to 83 % and molecular weights up to 8600 g/mol, which might be of interest for further development of biodegradable bioconjugates after recovering of the amino-group.

Amino-group deprotection and poly(5-NH₃⁺- δ -valerolactone) recovery

Poly(5-NHZ- δ -VL) (Table 1, 1) was shortly treated under acidic conditions using a HBr/AcOH mixture on a suspension of the polymer in dichloromethane. The resulting water-soluble poly(5-NH₃⁺- δ -VL) was obtained as a white powder after dialysis and freeze-drying. Quantitative deprotection was confirmed by ¹H NMR with no protecting group being detected in the final poly(5-NH₃⁺- δ -VL) as

shown by the absence of signal at 7.4-7.3 ppm and 4.95 ppm (Figure 6). This was further confirmed by ^{13}C NMR where some peaks are split in doubled peaks.[†] This is attributed to the existence of two configurations of carbon atoms involved in the hydrogen bonds between the ammonium group and carbonyl group of poly(5-NH₃⁺- δ -VL) formed after deprotection. Furthermore, as deprotection was carried out in a strong acidic medium, a major concern was the integrity of the polyester backbone. Reaction time was kept short, typically below 30 minutes, to avoid degradation while insuring the quantitative deprotection of the amino-groups. Degradation was also avoided by using a suspension instead of a solution for the deprotection step. The absence of degradation was checked by ^1H NMR analysis in DMSO, taking into account the methylene protons signals of the alcohol chain end at 3.2 ppm (Figure 6). Polymerization degree was ca. 19 in the starting poly(5-NHZ- δ -VL) (Table 1, 1), which corresponded to $Mn_{\text{NMR}} = 4\,900$ g/mol, and was found equal to 17 in the corresponding poly(5-NH₃⁺- δ -VL), which corresponded to $Mn_{\text{NMR}} = 3\,300$ g/mol. This result confirms the efficiency of the deprotection strategy to remove the protecting groups while conserving the polyester backbone. Finally, SEC analysis of a water-soluble poly(5-NH₃⁺- δ -VL) was carried out using a dedicated low pressure SEC system with NaCl 1.6 M as eluent and cationic DEAE Sepharose gel as stationary phase.[†] Chromatogram showed two characteristic peaks corresponding to the polymer and the bromide counterion as previously described by our group.²⁸ A molecular weight of $Mn_{\text{SEC}} = 1\,100$ g/mol (PDI = 2.3) was calculated using poly(L-Lysine) standards. This value is lower than the one calculated by NMR, however it has to be critically considered taking into account the structural differences of poly(L-Lysine) and poly(5-NH₃⁺- δ -VL), and the possible strong influence of the position of the amino groups towards the backbone on the hydrodynamic radius.

CONCLUSION

A novel amino-functionalized polyester, poly(5-NH₃⁺- δ -VL), was obtained by ROP of the corresponding protected valerolactone. Compared to all functional lactones previously described, the synthesis proposed here, with only two steps and high yields, is remarkably simple and renders the novel 5-NHZ- δ -VL very attractive for future polymerization and copolymerization studies intended to produce fully degradable and functional polyesters. In this purpose, various polymerization conditions were tested. Poly(5-NHZ- δ -VL) with narrow polydispersities and molecular weights in the range 5 000-7 000 g/mol were obtained in bulk. Copolymers of 5-NHZ- δ -VL and ϵ -CL were also prepared to generate a novel family of copolyesters having from 10 % to 80 % of aminated units. Finally, removal of the protecting group under chosen acidic conditions was found to be quantitative and respectful of the polyester backbone. Future work will focus on further improvements in molecular weights and potential applications related to degradable polyelectrolytes including degradation studies.

Acknowledgements

The authors wish to thank the French Ministry of Education and Research for Sebastien Blanquer's fellowship, Sylvie Hunger, Laurent Leclercq and Cédric Paniagua for their help on NMR, low pressure SEC analyses and lactone synthesis, respectively.

†Supporting Information Available: Additional synthetic data and spectral data. This material is available at <http://www3.interscience.wiley.com>

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FIGURE LEGENDS

Scheme 1. Amino-functionalized lactones described in the literature and used for polyester synthesis.

Scheme 2. Synthesis of 5-Z-amino- δ -valerolactone. *Reagents and conditions* a) *i.* DIPEA, BOP, THF, room temperature; *ii.* NaBH₄, 2h, RT, b) TFA/CH₂Cl₂ (1:1), 3h, room temperature.

Scheme 3. Polymerization of 5-Z-amino- δ -valerolactone. *Reagents and conditions* a) ROP, b) DCM/HBr/AcOH, <1h, RT.

Figure 1. ¹H NMR (300 MHz; DMSO-*d*₆) spectrum of 5-Z-amino- δ -valerolactone **5**.

Figure 2. ¹H NMR (300 MHz; DMSO-*d*₆) spectrum of poly(5-Z-amino- δ -valerolactone).

(δ : 2.5 ppm = DMSO-*d*₆, 3.3 ppm = water, C* and D'* chain end)

Figure 3. Molecular weights of final polymers obtained from 5-NHZ- δ -VL with Sn(Oct)₂ or Sn(OTf)₂ as a catalyst and different solvent/temperature/pressure conditions (B for bulk, A for atmospheric pressure and R for reduced pressure 1.10⁻³ bar).

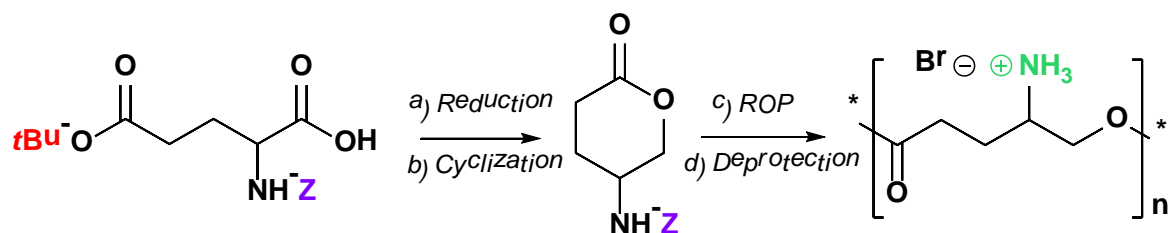
Figure 4. ¹H NMR (300 MHz; DMSO-*d*₆) spectra of the poly(5-NHZ- δ -valerolactone-co- ϵ -caprolactone) (*f*_{5-NHZ- δ -VL} = 10 to 50) and of poly(5-NHZ- δ -valerolactone) (*f*_{5-NHZ- δ -VL} = 100). (Signals at 2.5 and 3.3 ppm correspond to DMSO-*d*₆ and residual water of DMSO-*d*₆, respectively)

Figure 5. SEC chromatograms of poly(5-NHZ- δ -valerolactone-co- ϵ -caprolactone) copolymers. (100 % curve corresponds to the entry 5 of Table S2[†])

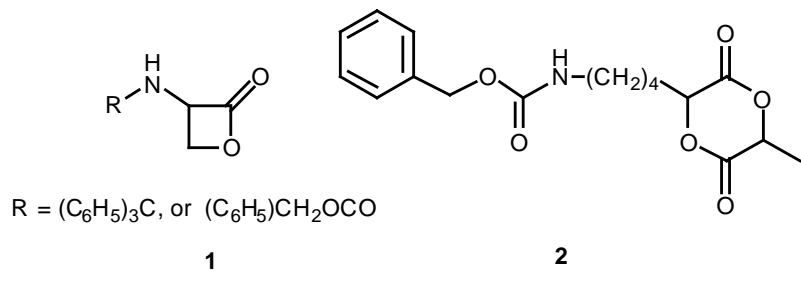
Figure 6. ¹H NMR (300 MHz; DMSO-*d*₆) spectrum of poly(5-NH₃⁺- δ -valerolactone)

(δ : 2.5 ppm = DMSO-*d*₆, 3.2 ppm C* = chain end)

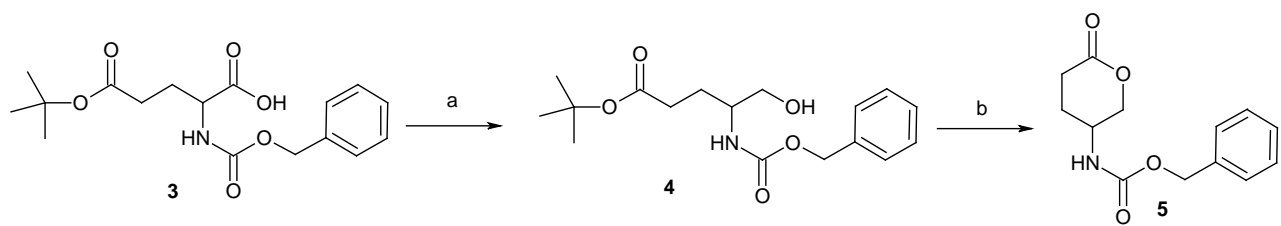
GRAPHICAL ABSTRACT



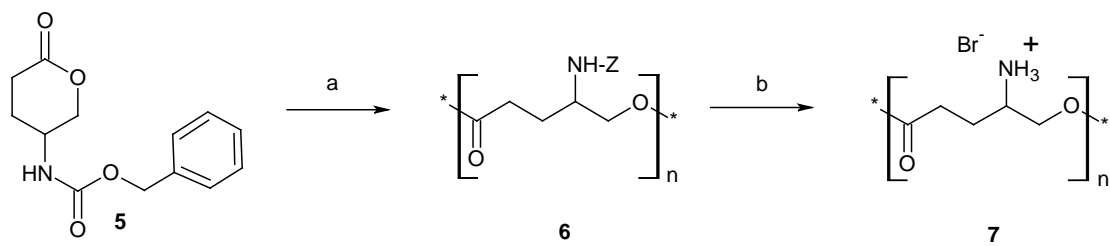
Novel 5-Z-amino- δ -valerolactone (5-NHZ-VL) was easily synthesized in two steps with aim to prepare a family of aliphatic polyesters having amino pendant groups. (5-NHZ-VL) was homopolymerized and copolymerized with ϵ -CL to generate copolyesters with an amino-group content ranging from 10 to 80 %. Finally, the polyelectrolyte poly(5-NH₃⁺-VL) was recovered by removal of the protecting group under acidic conditions and integrity of the polyester backbone was confirmed by ¹H NMR.



Scheme 1



Scheme 2



Scheme 3

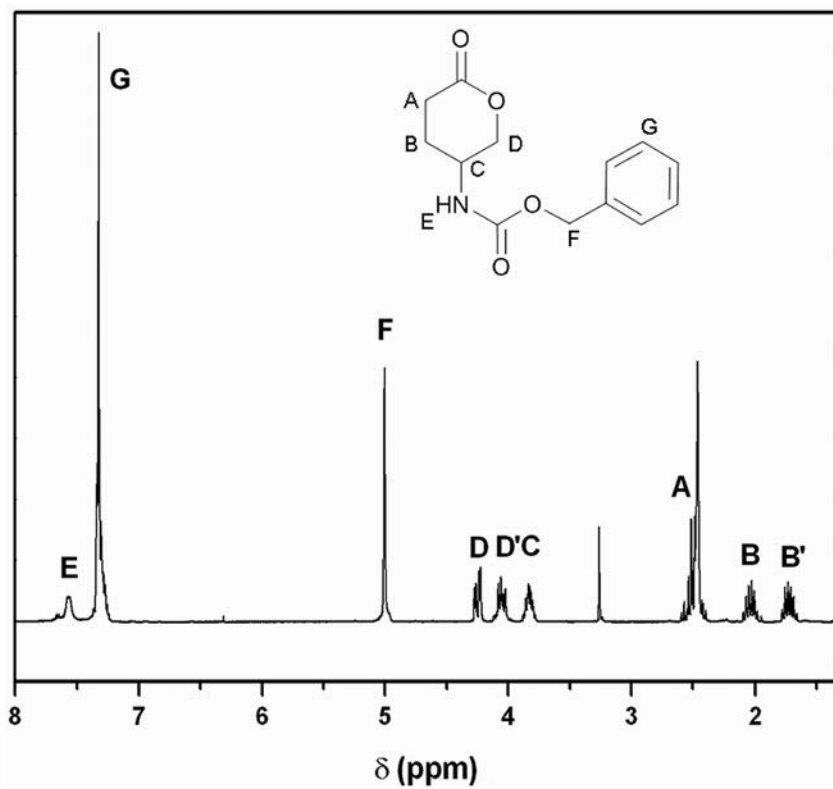


Figure 1

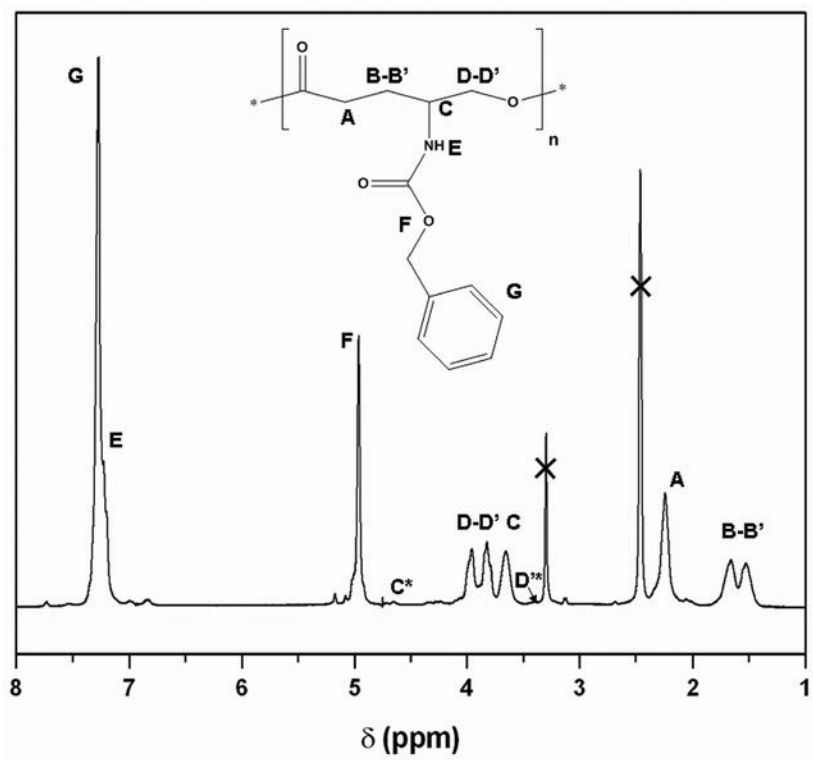


Figure 2

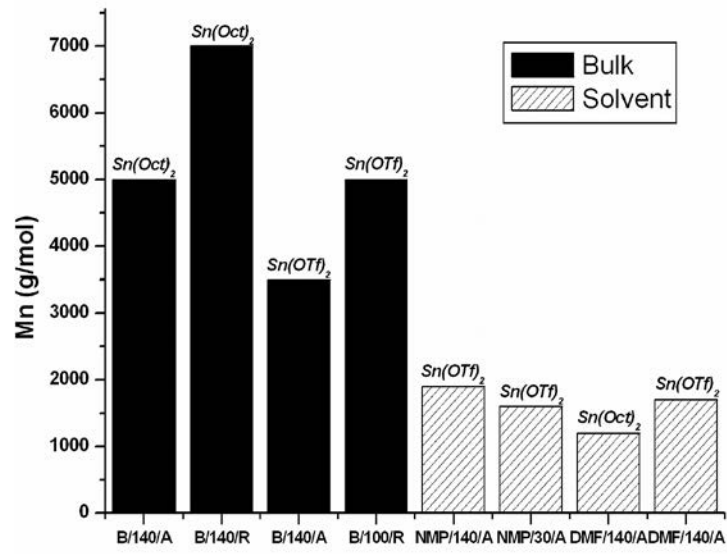


Figure 3

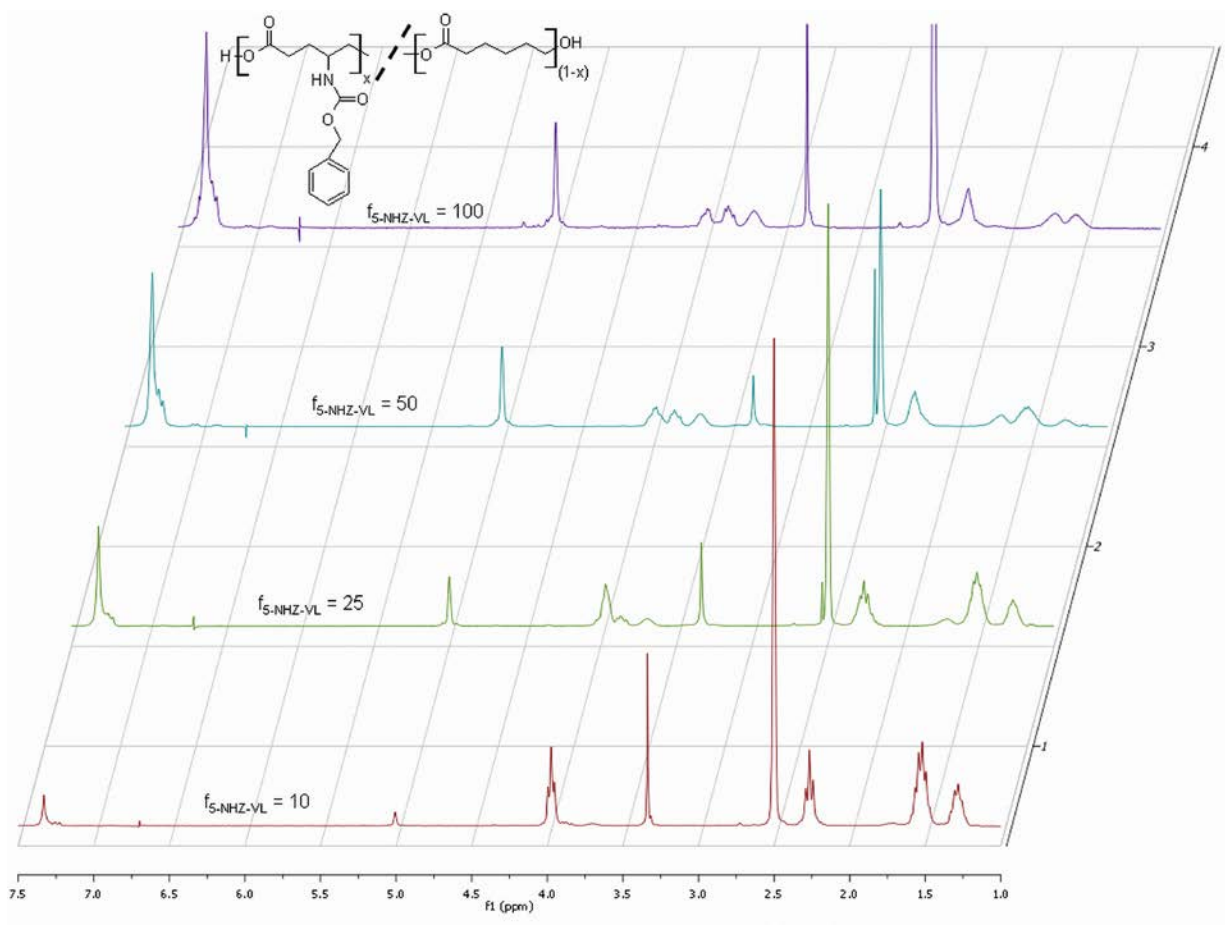


Figure 4

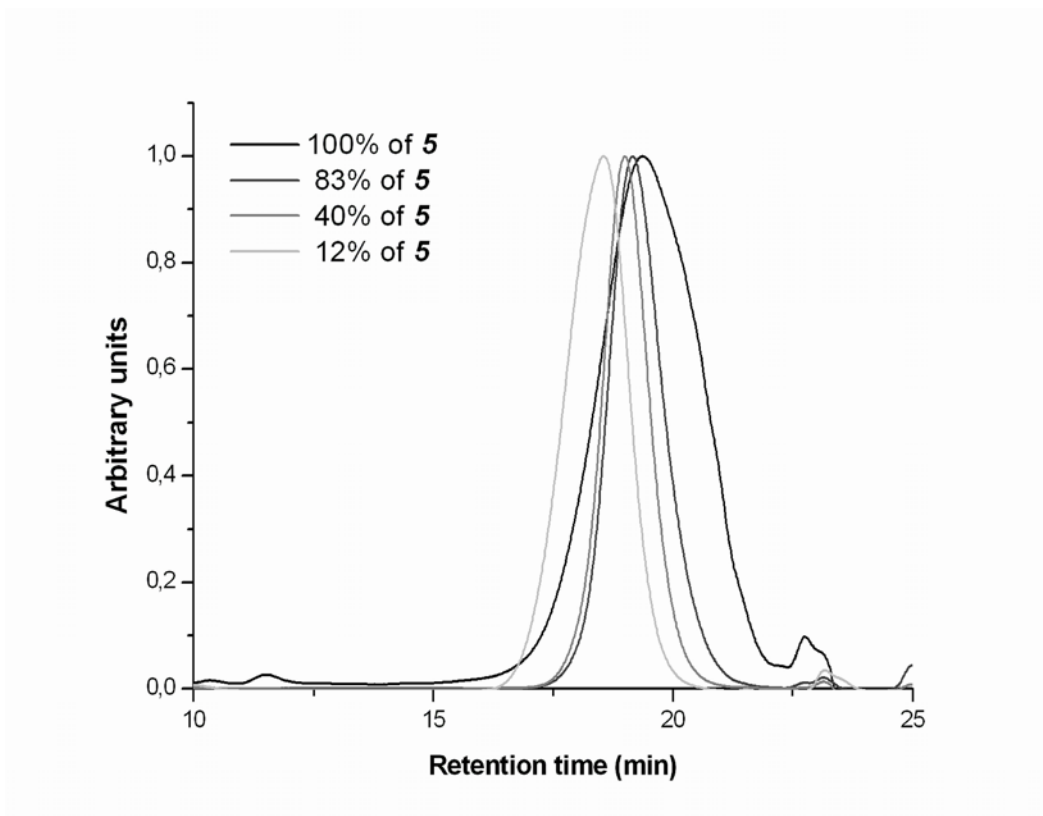


Figure 5

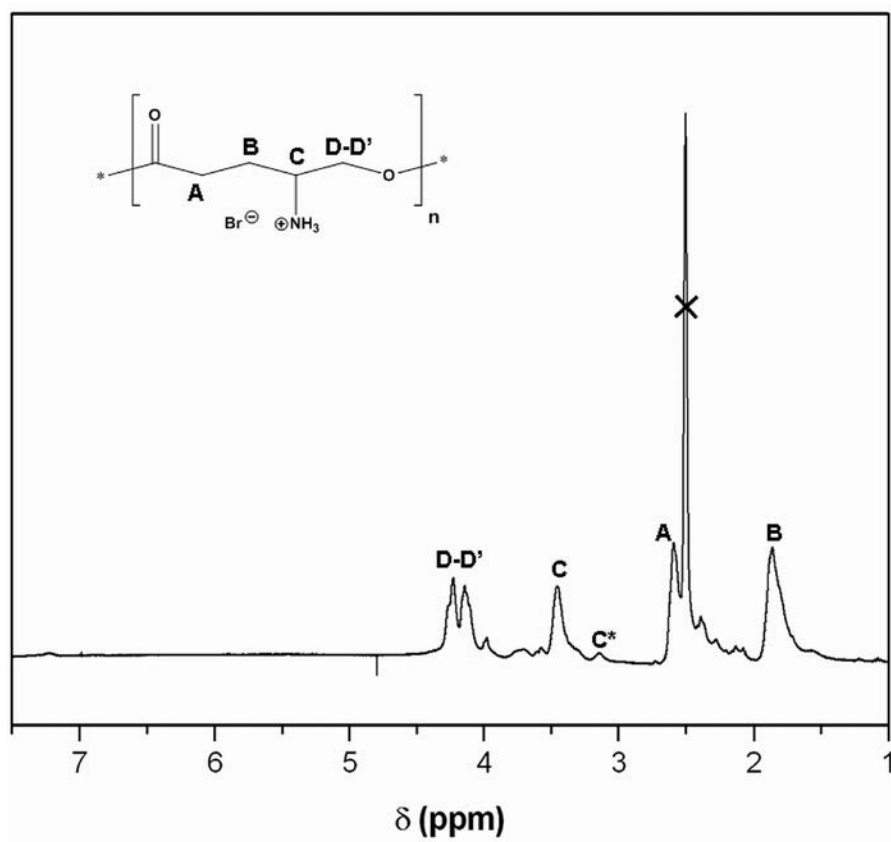


Figure 6

Table 1. Synthesis of poly(5-NHZ- δ -VL) in bulk.

Entry	Catalyst	Temperature (°C)	Pressure (bar)	Reaction time (h)	Conversion (%)	Mn _{NMR} ^a (g/mol)	Mn _{SEC} ^b (g/mol)	Mw/Mn ^b
1	Sn(Oct) ₂	140	1	96	93	4900	5 000	1.2
2	Sn(Oct) ₂	140	1.10 ⁻³	120	91	5600	7 000	1.2
3	Sn(OTf) ₂	100	1.10 ⁻³	120	88	4750	5 000	1.3

a. calculated using ¹H NMR signals at 4.65 ppm and 3.40 ppm

b. SEC in DMF, calibration with PMMA standards

Table 2. Synthesis of poly(5-NHZ- δ -VL-co- ϵ -CL) in bulk (catalyst Sn(Oct)₂, initiator *i*PrOH, 1 bar, 110°C, 24 h).

Entry	$f_{5\text{-NHZ-}\delta\text{-VL}}$ ^a	$F_{5\text{-NHZ-}\delta\text{-VL}}$ ^b	Conversion ^b 5-NHZ- δ -VL (%)	Conversion ^b ϵ -CL (%)	Mn_{th} ^c (g/mol)	Mn_{SEC} ^d (g/mol)	Mw/Mn ^d
1	10	12	95	89	11500	8600	1.2
2	25	40	90	60	10700	5800	1.1
3	50	83	80	70	13950	3300	1.6

a. calculated using Equation (2)

b. calculated using ¹H NMR

c. calculated using Equation (1)

d. SEC in DMF, calibration with PMMA standards

Supporting information

Easy synthesis and ROP of 5-Z-amino- δ -valerolactone: new degradable amino-functionalized (co)polyesters.

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Figure S1. ^1H NMR (300 MHz; CDCl_3) spectrum of tertibutyl-4-(benzyloxycarbonylamino)-5-hydroxypentanoate **4**.

Figure S2. ^1H NMR (300 MHz; $\text{DMSO-}d_6$) spectrum of 5-Z-amino- δ -valerolactone **5**.

Figure S3. ^{13}C NMR (300 MHz; $\text{DMSO-}d_6$) spectrum of 5-Z-amino- δ -valerolactone **5**. (δ : 40 ppm = $\text{DMSO-}d_6$).

Figure S4. HPLC chromatogram of 5-Z-amino- δ -valerolactone **5**.

Figure S5. ESI mass spectrometry spectrum of 5-Z-amino- δ -valerolactone **5**.

Figure S6. DSC thermogram of 5-Z-amino- δ -valerolactone **5**.

Figure S7. ^1H NMR (300 MHz; $\text{DMSO-}d_6$) spectrum of poly(5-Z-amino- δ -valerolactone).

(δ : 2.5 ppm = DMSO , 3.3 ppm = water, C* and D'* chain end)

Figure S8. ^1H NMR (300 MHz; $\text{DMSO-}d_6$) COSY spectrum of poly(5-Z-amino- δ -valerolactone). (δ : 2.5 ppm = DMSO , 3.3 ppm = water, 3.2 ppm and 4.0 ppm = MeOH)

Figure S9. ^{13}C NMR (75 MHz; $\text{DMSO-}d_6$) spectrum of poly(5-Z-amino- δ -valerolactone). (δ : 40 ppm = DMSO)

Figure S10. DSC thermogram of poly(5-Z-amino- δ -valerolactone).

Table S1. Thermal properties of poly(5-Z-amino- δ -valerolactone) as a function of M_n .

Figure S11. Chromatogram of poly(5-Z-amino- δ -valerolactone) (Table S1, entry 4, SEC carried out in DMF, PMMA standards).

Figure S12. ^1H NMR (300 MHz; $\text{DMSO-}d_6$) spectrum of poly(5- NH_3^+ - δ -valerolactone)
(δ : 2.5 ppm = DMSO, 3.2 ppm C^* = chain end)

Figure S13. ^{13}C NMR (75 MHz; $\text{DMSO-}d_6$) spectrum of poly(5- NH_3^+ - δ -valerolactone).
(δ : 40 ppm = $\text{DMSO-}d_6$)

Figure S14. Chromatogram of poly(5- NH_3^+ - δ -valerolactone) (Table S1, entry 4, SEC carried out in NaCl 1.6 M, PLL standards).

Table S2. Conditions used for the ring-opening polymerization of **5**.

Figure S15. Conversion and molecular weight *vs* time for the ROP of **5** using $\text{Sn}(\text{Oct})_2$ as a catalyst.

Figure S16. Conversion and molecular weight *vs* time for the ROP of **5** using $\text{Sn}(\text{OTf})_2$ as a catalyst.

1. Spectral data, chromatograms and thermograms

a) Benzyl 6-oxotetrahydro-2H-pyran-3-ylcarbamate (5-Z-amino- δ -valerolactone) (5):

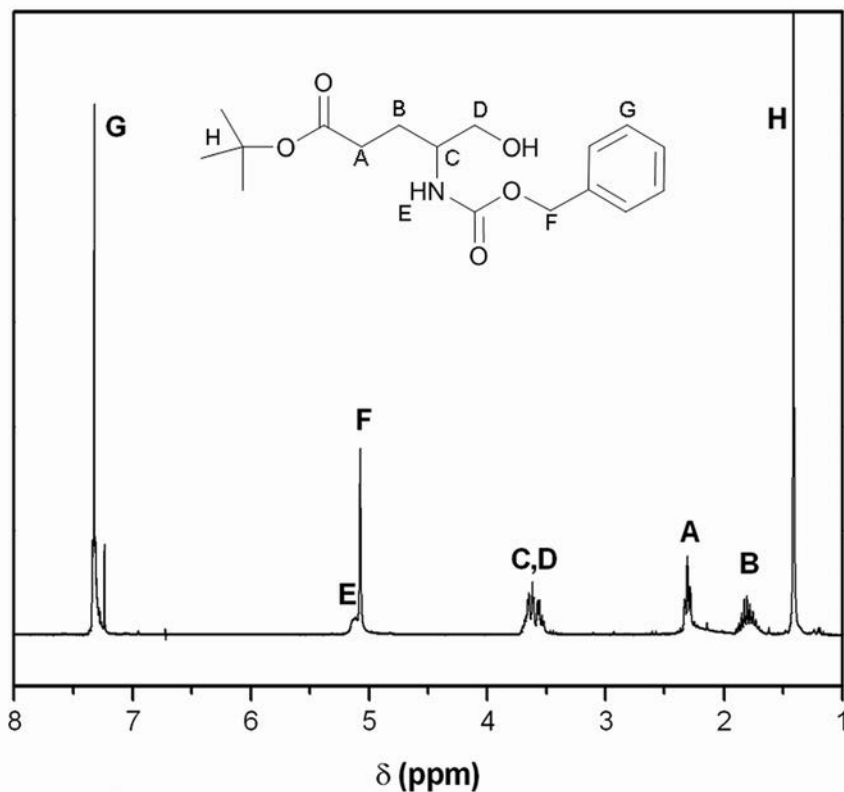


Figure S1. ¹H NMR (300 MHz; CDCl₃) spectrum of tert-butyl-4-(benzyloxycarbonylamino)-5-hydroxypentanoate **4**.

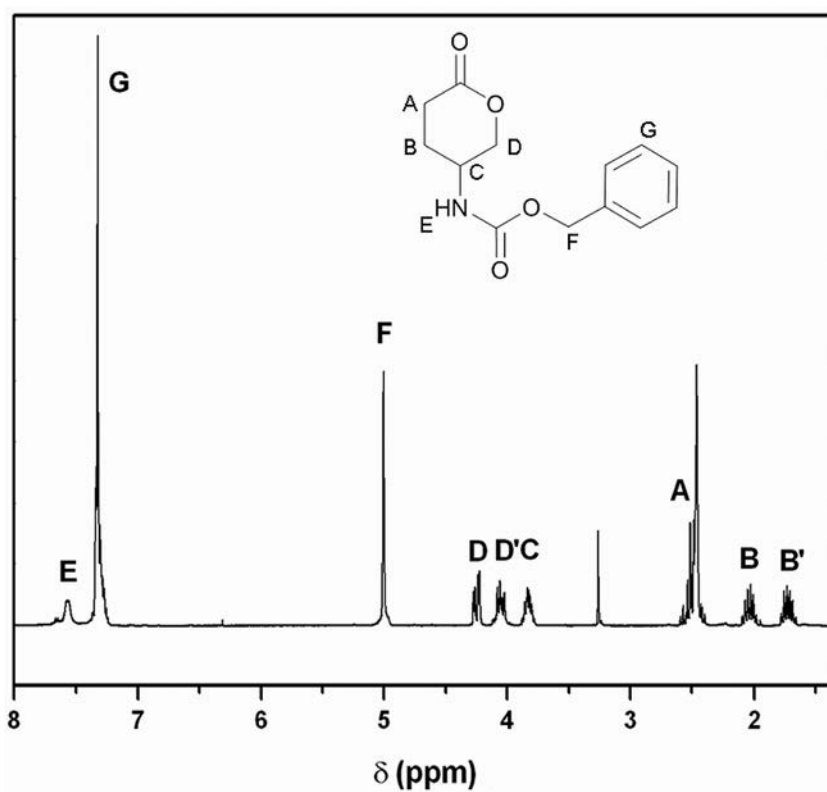


Figure S2. ¹H NMR (300 MHz; DMSO-*d*₆) spectrum of 5-Z-amino- δ -valerolactone **5**.

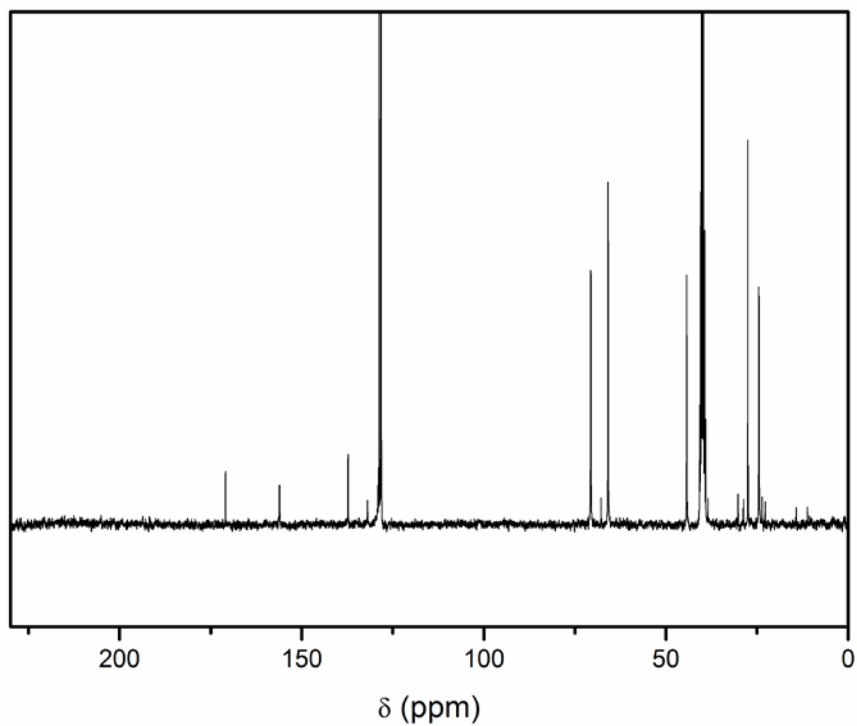


Figure S3. ^{13}C NMR (300 MHz; $\text{DMSO-}d_6$) spectrum of 5-Z-amino- δ -valerolactone **5**. (δ : 40 ppm = $\text{DMSO-}d_6$).

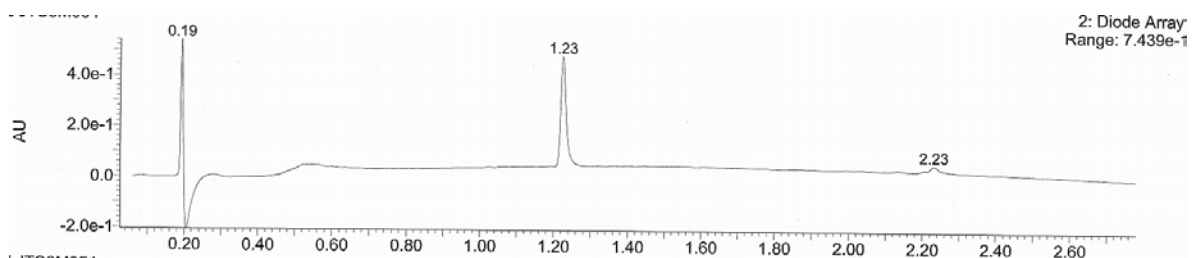


Figure S4. HPLC chromatogram of 5-Z-amino- δ -valerolactone **5**.

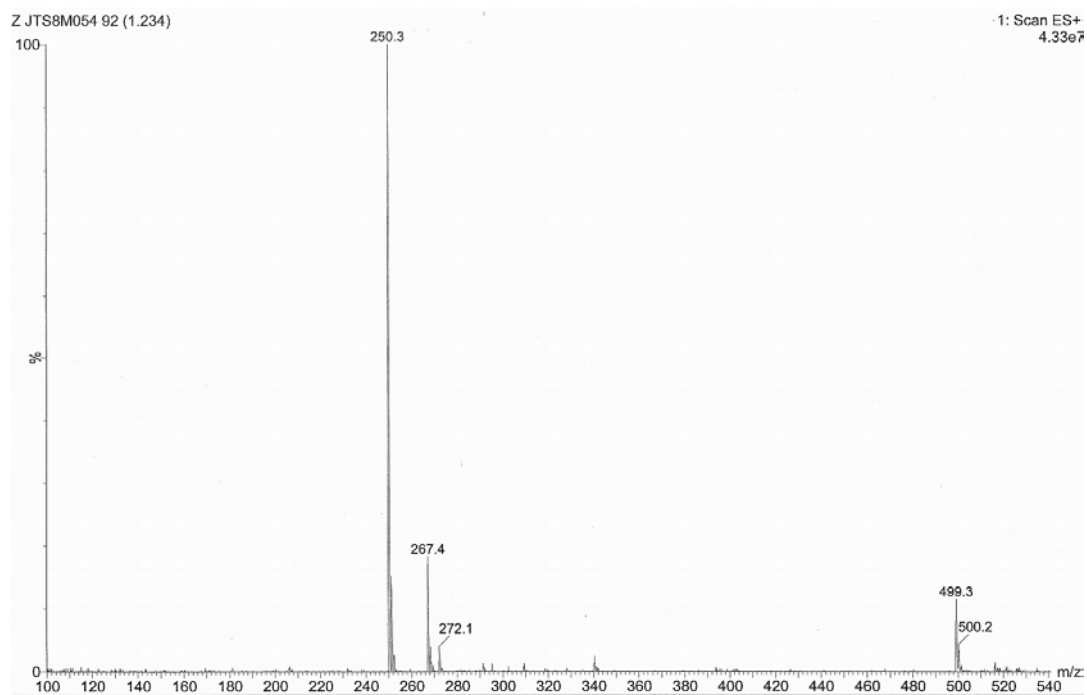


Figure S5. ESI mass spectrometry spectrum of 5-Z-amino- δ -valerolactone **5**.

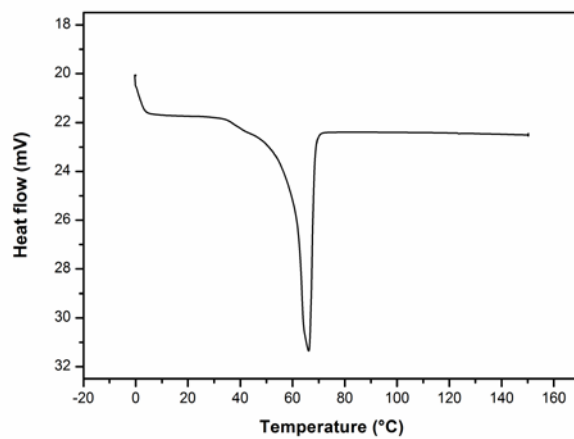


Figure S6. DSC thermogram of 5-Z-amino- δ -valerolactone **5**.

b) Poly(5-Z-amino- δ -valerolactone) (6):

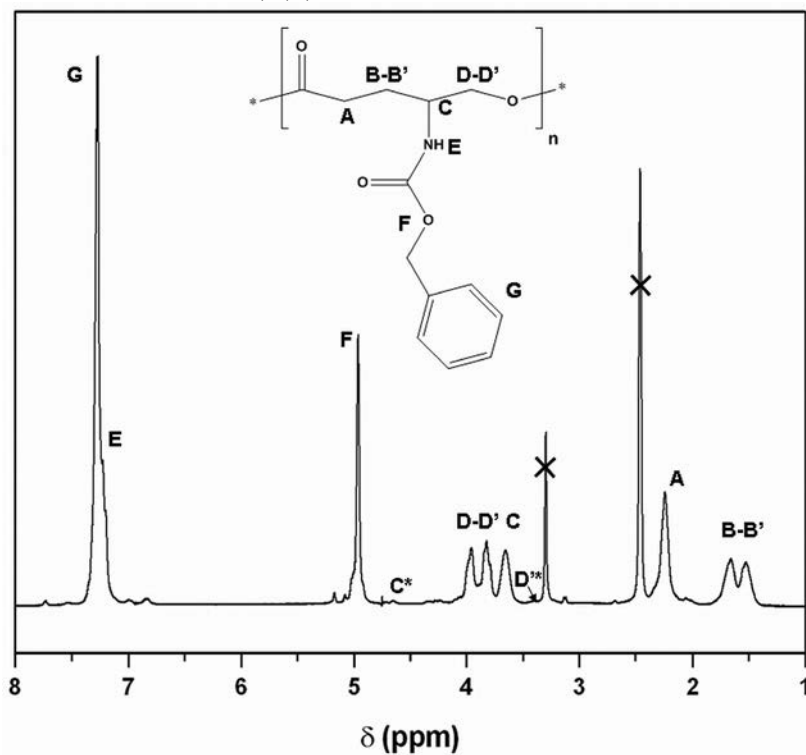


Figure S7. ¹H NMR (300 MHz; DMSO-*d*₆) spectrum of poly(5-Z-amino- δ -valerolactone). (δ : 2.5 ppm = DMSO, 3.3 ppm = water, C* and D* chain end)

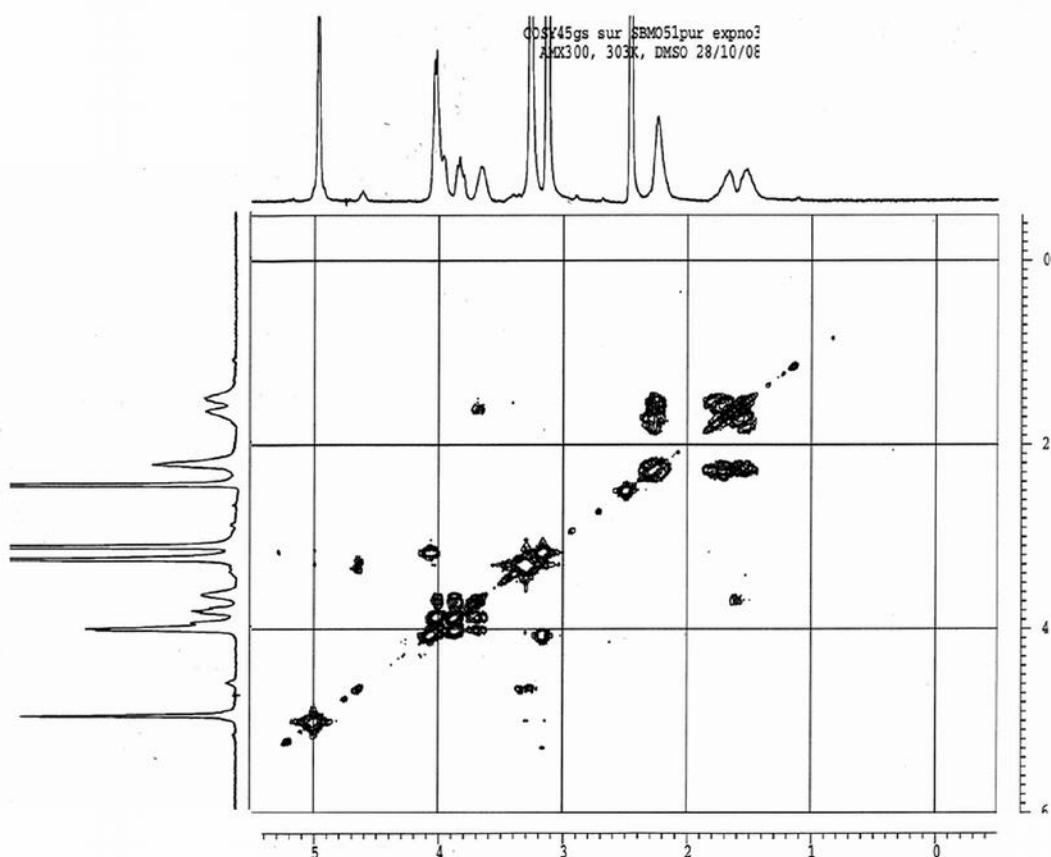


Figure S8. ¹H NMR (300 MHz; DMSO-*d*₆) COSY spectrum of poly(5-Z-amino- δ -valerolactone). (δ : 2.5 ppm = DMSO, 3.3 ppm = water, 3.2 ppm and 4.0 ppm = MeOH)

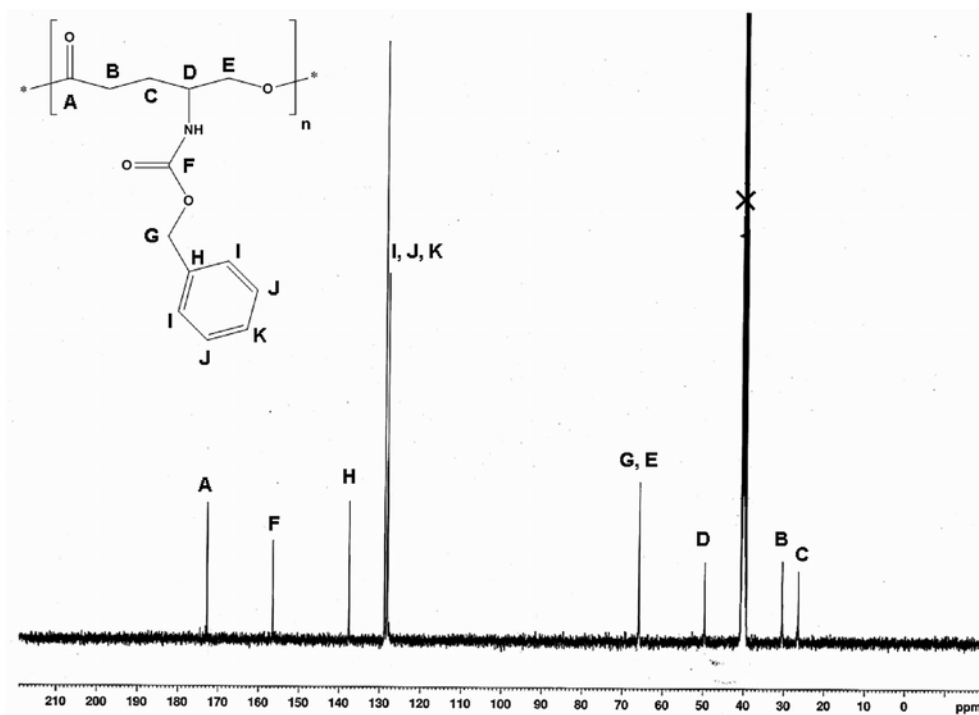


Figure S9. ^{13}C NMR (75 MHz; $\text{DMSO-}d_6$) spectrum of poly(5-Z-amino- δ -valerolactone). (δ : 40 ppm = DMSO)

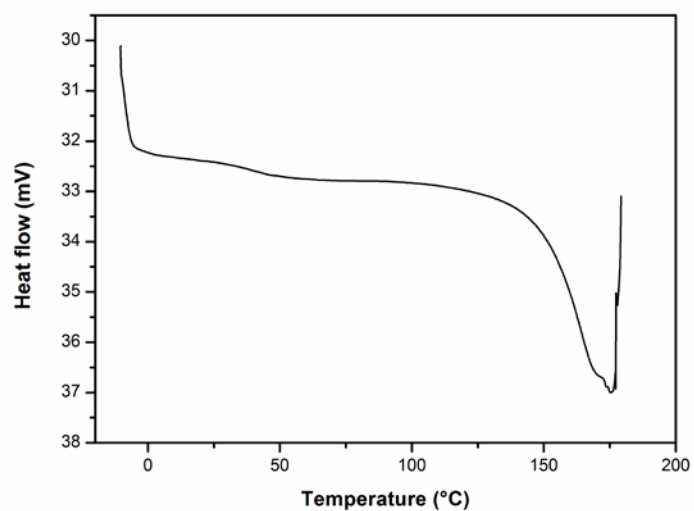


Figure S10. DSC thermogram of poly(5-Z-amino- δ -valerolactone).

Table S1. Thermal properties of poly(5-Z-amino- δ -valerolactone) as a function of Mn.

Mn (g/mol)	T _g (°C)	Heat capacity (J/g.°C)	T _m (°C)	ΔH_m (J/g)
3000	26,7	0,119	146	34
5000	37,3	0,229	176	46
7000	44,7	0,279	180	65

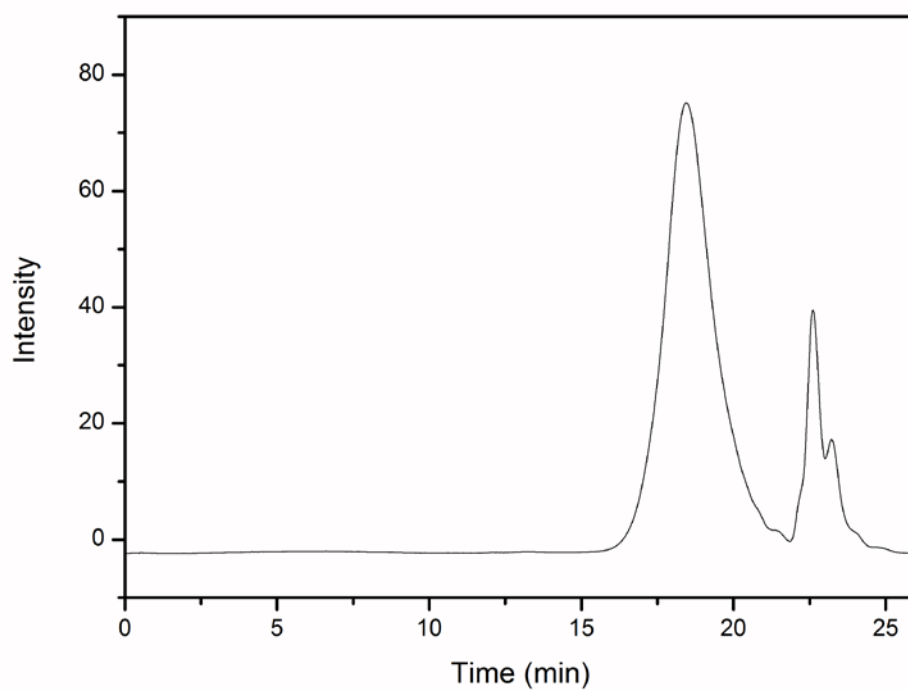


Figure S11. Chromatogram of poly(5-Z-amino- δ -valerolactone) (Table S1, entry 4, SEC carried out in DMF, PMMA standards).

c) Poly(5-NH₃⁺- δ -valerolactone) (7):

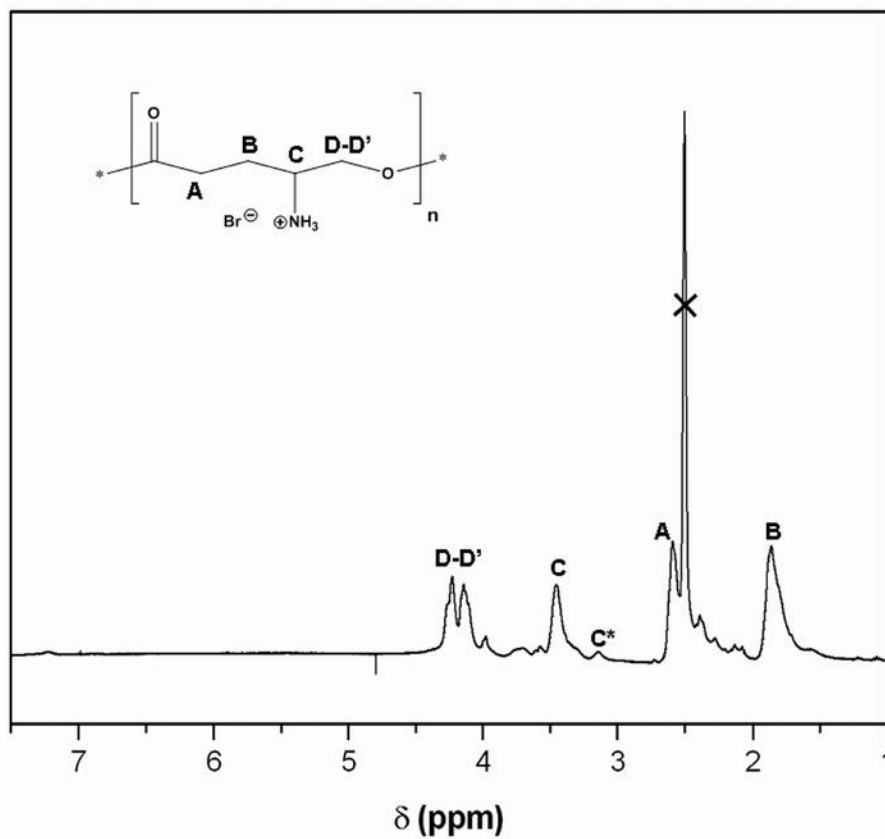


Figure S12. ¹H NMR (300 MHz; DMSO-*d*₆) spectrum of poly(5-NH₃⁺- δ -valerolactone) (δ : 2.5 ppm = DMSO, 3.2 ppm C* = chain end)

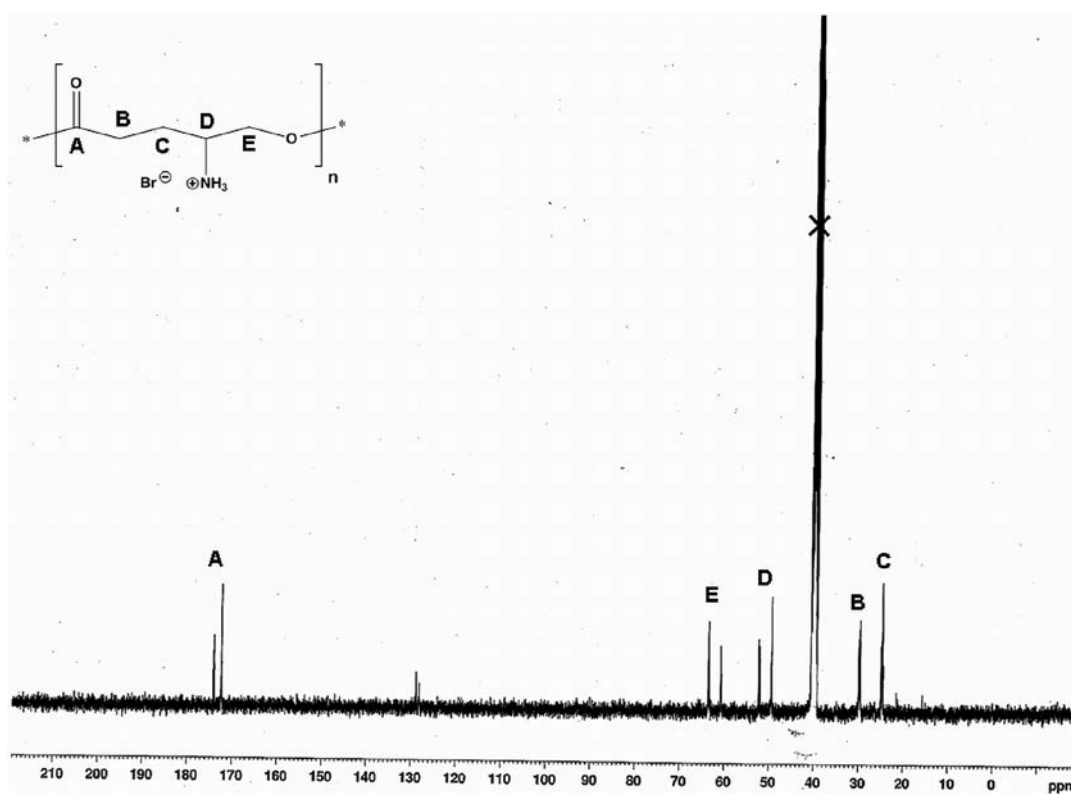


Figure S13. ¹³C NMR (75 MHz; DMSO-*d*₆) spectrum of poly(5-NH₃⁺-δ-valerolactone). (δ : 40 ppm = DMSO-*d*₆)

All peaks are split in doubled peaks with exception of B and C. This is attributed to the existence of two configurations for the carbons (A, D and E) involved in hydrogen bonds between the ammonium group and carbonyl group.

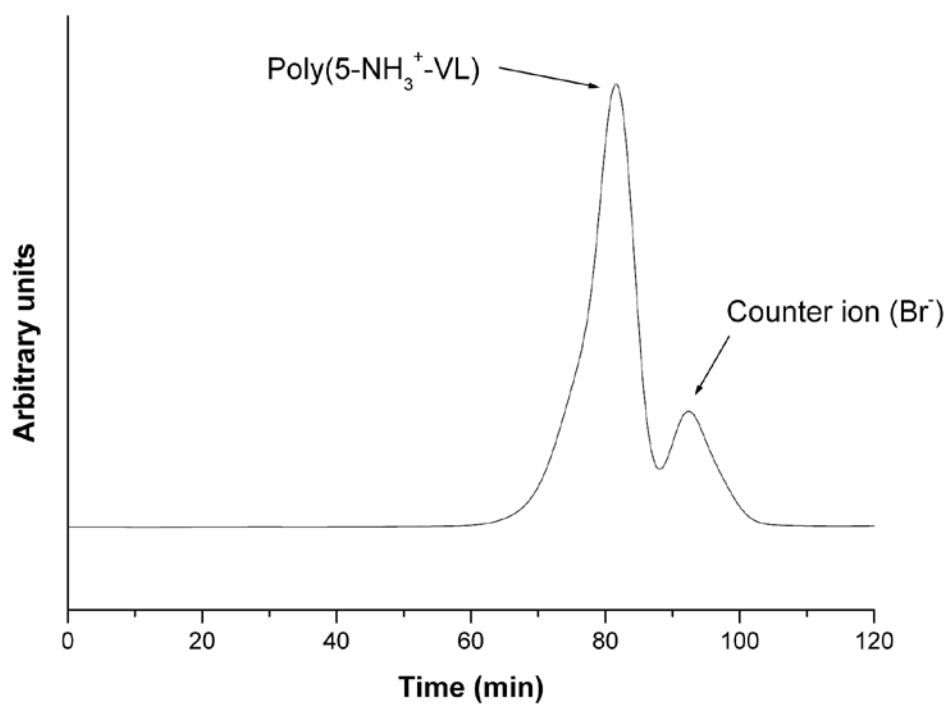


Figure S14. Chromatogram of poly(5-NH₃⁺- δ -valerolactone) (Table S1, entry 4, SEC carried out in NaCl 1.6 M, PLL standards).

Due to ion exchanges with the column, part of the initial counter-ions are no longer paired with the ammonium groups, which explains that they are visible in the chromatogram.²⁸

2. Homopolymerization of benzyl 6-oxotetrahydro-2H-pyran-3-ylcarbamate (5-NHZ-VL).

Table S2. Conditions used for the ring-opening polymerization of **5**.

Entry	Solvent	Catalyst	Temperature (°C)	Pressure (bar)	Reaction time (h)	Conversion (%)	Mn (g/mol)	PDI
1	toluene	Sn(Oct) ₂	110	1	24	0	/	/
2	none	Sn(Oct) ₂	110	1	24	0	/	/
3	none	Sn(Oct) ₂	140	1	96	93	5 000	1.2
4	none	Sn(Oct) ₂	140	1.10 ⁻³	120	91	7 000	1.2
5	none	Sn(Oct) ₂	120	1.10 ⁻³	96	80	3600	1.5
6	DMF	Sn(Oct) ₂	140	1	53	50	1 200	1.5
7	none	Sn(OTf) ₂	140	1	53	55	3 500	1.1
8	none	Sn(OTf) ₂	100	1.10 ⁻³	120	88	5 000	1.3
9	DMF	Sn(OTf) ₂	140	1	4	32	1 700	1.2
10	NMP	Sn(OTf) ₂	140	1	1	75	1 900	1.1
11	NMP	Sn(OTf) ₂	30	1	21	58	1 600	1.1

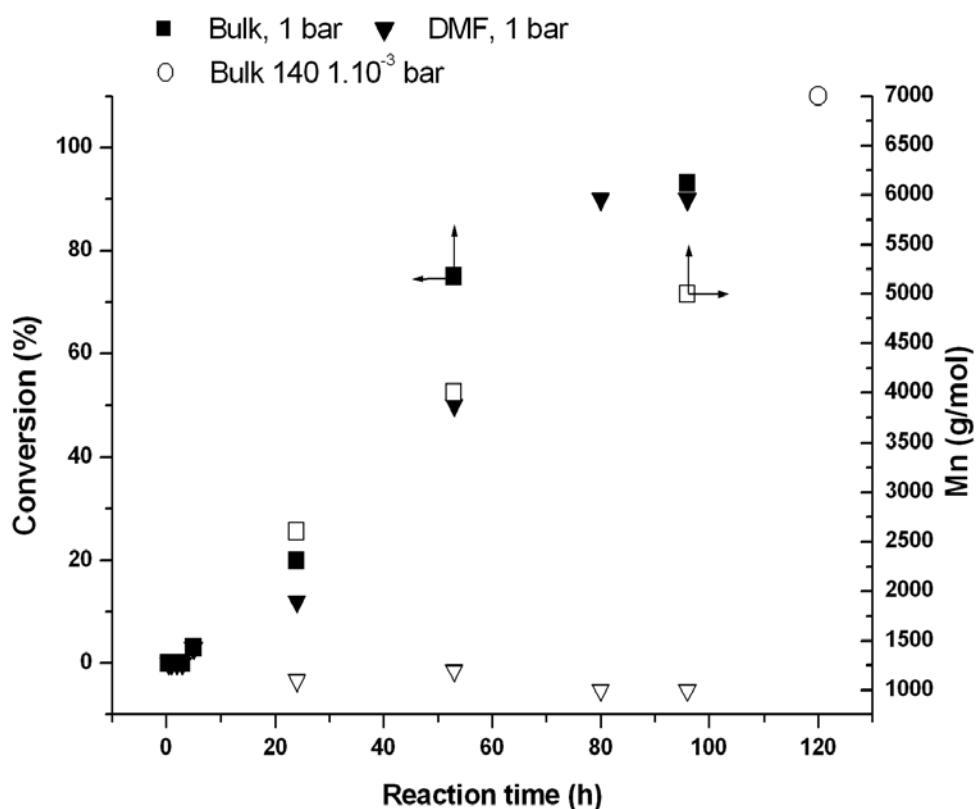


Figure S15. Conversion and molecular weight vs time for the ROP of **5** using Sn(Oct)₂ as a catalyst.

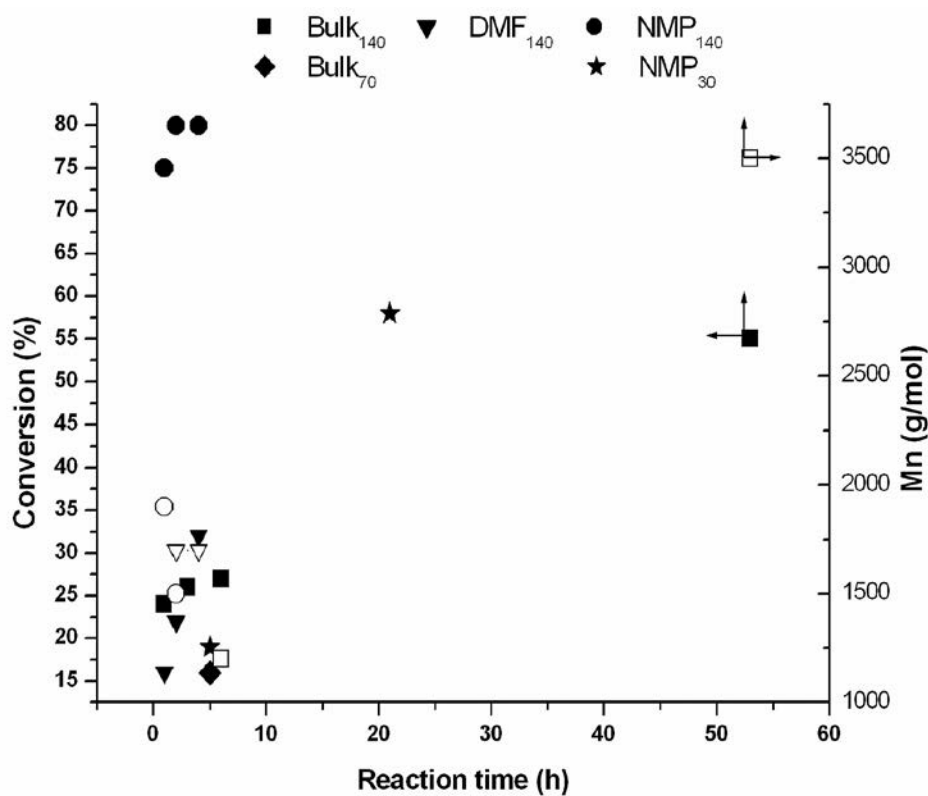


Figure S16. Conversion and molecular weight vs time for the ROP of **5** using Sn(OTf)₂ as a catalyst.