Journal of Applied Polymer Science

# Quasi-alternating polyesteramides from ε-caprolactone and α-amino acids

**Abdoulkader Ali Mohamed,[1,2*] Slim Salhi,[1] Souhir Abid,[1] Rachid El Gharbi,[1] Alain Fradet[2]**

Université De Sfax, Faculté Des Sciences, Laboratoire De Chimie Appliquée H.C.G.P, 3038 Sfax, Tunisie

Sorbonne Universités, UPMC Univ Paris 06, CNRS, UMR 8232, Institut Parisien De Chimie Moléculaire (IPCM), Chimie Des Polymères, 4 Place Jussieu. F-75005, Paris, France

*Present address: Université de Djibouti, Djanaleh BP 1904, Djibouti

Correspondence to: A. Fradet (E-mail: alain.fradet@upmc.fr)

**ABSTRACT:** Glycine-ε-caprolactone-based and α-alanine-ε-caprolactone-based polyesteramides with a strong tendency to form alternating sequences (degree of randomness = 1.64 and 1.31) were synthesized by melt polycondensation of intermediate hydroxy- and ethyl ester-terminated amides. These intermediates were synthesized by the reaction of equimolar amounts of ε-caprolactone and glycine or L-α-alanine ethyl esters in mild conditions. The structure and microstructure of these polyesteramides are discussed on the basis of an in-depth nuclear magnetic resonance study. Both polyesteramides are semi-crystalline, but the glycine-based one presents the highest melting enthalpy. This polyesteramide also exhibits higher Young's modulus and stress at break than its α- and β-alanine counterparts. © 2016 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 44220.

**KEYWORDS:** α-amino acids; biopolymers and renewable polymers; polyesteramides; polyesters

Received 15 April 2016; accepted 17 July 2016

**DOI: 10.1002/app.44220**

## INTRODUCTION

In recent years, the preparation of biobased and biodegradable polymeric materials for biomedical- or environmental applications has attracted a lot of attention.[1,2] Much effort has been devoted to biodegradable aliphatic polyesters, such as polylactide,[3,4] poly-ε-caprolactone,[5] poly(glycolic acid),[6] and their copolymers,[7] for biomedical as well as environmental applications. However, many applications require materials with a wider and tunable range of properties, for example, hydrophobicity/hydrophilicity to improve affinity with various types of drugs or tissues[8,9] or flexibility/stiffness to improve thermal properties and mechanical strength.[10] Introducing amino acid monomer units in aliphatic polyester chains is a way of broadening the range of properties and applications of biodegradable polymers. The resulting amino acid-based polyesteramides present both interesting mechanical properties, due to intermolecular hydrogen bonding between amide groups, and degradability, due to the presence of hydrolyzable ester groups.[11,12]

Various approaches have been employed to synthesize amino acid-based polyesteramides exhibiting block,[13] random,[14,15] or alternating[16] structures. Block amino acid-based polyesteramides are prepared by the ring-opening polymerization of ε-caprolactone initiated by amine-terminated peptides or by the ring opening polymerization of α-amino acid N-carboxyanhydrides (NCAs) initiated by amine-terminated polylactide or poly(ε-caprolactone).[17–20] Random polyesteramides can be prepared by simple procedures that do not require the use of solvents or expensive monomers like NCAs. Some studies have reported the synthesis of random amino acid-based polyesteramides by the direct reaction of amino acids with cyclic esters[21–25] or by the direct bulk polycondensation of amino acids and α-hydroxyacids.[26,27]

On the other hand alternating amino acid-based polyesteramides can be synthesized by reacting diol or diacid derivatives with intermediate compounds, such as diamine-terminated diesters, prepared from α-amino acids and diols[16,28–34] or diester-terminated diamides, prepared from α-amino acid derivatives and dicarboxylic acids.[28,35] For instance, diamine-terminated diesters were first synthesized by 1/2 mol/mol solution reaction of a diol with an α-amino acid in the presence of p-toluenesulfonic acid and alternating amino acid-based polyesteramides were then obtained either by interfacial polycondensation of these diesters with a diacid chloride[29] or by solution polycondensation with an activated p-nitrophenyl dicarboxylate.[32] In these conditions interchange reactions cannot take place and, therefore, polyesteramide randomization is avoided. Another method of synthesizing alternating amino acid-based polyesteramides is the bulk ring opening polymerization of morpholine-2,5-diones. The resulting polyesteramides, called

polydepsipeptides, are composed of alternating α-amino acid and α-hydroxy acid monomer units.[36–38] They are reported to be non-toxic and biodegradable *in vivo* and are interesting materials for biomedical applications such as medical implants or controlled drug release systems.[39–41] Since such cyclic compounds cannot be easily synthesized from larger monomers, the method is limited to the preparation of amino acid-based polyesteramides from α-amino acids and α-hydroxy acids.

In a previous work, we reported the synthesis of "quasi-alternating" polyesteramides by simple bulk polycondensation between the hydroxy- and ethyl ester-terminated dimer of β-alanine and ε-caprolactone.[24] Since hydroxy-amide and ethyl ester-amide interchange reactions are much slower than ethyl ester-hydroxy polycondensation, randomization was avoided during the bulk polycondensation step and a quasi-alternating amino acid-based polyesteramides was obtained.

To our best knowledge, no study has yet been reported on the bulk synthesis of alternating polyesteramides based on α-amino acids and lactones. The aim of the present work is to study the synthesis and properties of polyesteramides exhibiting a high content of alternating sequences and prepared by the bulk copolymerization of dimers of ε-caprolactone and glycine or L-α-alanine.

## EXPERIMENTAL

### Materials

ε-caprolactone (CL, 97%), glycine ethyl ester hydrochloride (G-COOEt, HCl, 99%), L-α-alanine ethyl ester hydrochloride (α-AlaCOOEt, HCl, 99%), 1,5,7- triazabicyclo [4.4.0]dec-5-ene (TBD, 98%), tetrabutoxytitanium ($Ti(OBu)_4$, 97%), sodium hydrogenocarbonate ($NaHCO_3$, >99%), and trifluoroacetic anhydride (TFA, ≥99%) were purchased from Sigma-Aldrich and used as received.

### Synthesis of Amino Acid-Based Polyesteramides

The glycine-based- and L-α-alanine-based polyesteramides are denoted PCG and PCA, respectively. PCG and PCA were synthesized by reacting equimolar amount of ε-caprolactone and glycine or L-α-alanine ethyl ester hydrochloride. For instance, PCG was prepared as follows: CL (33.80 g, 0.296 mol), G-COOEt, HCl (41.33 g, 0.296 mol), sodium hydrogenocarbonate (24.87 g, 0.296 mol), and TBD catalyst (1 wt % with respect to the total amount of reactants) were heated at 120 °C for 1 h under nitrogen in a 200 mL reactor fitted with a mechanical stirrer, a nitrogen inlet, a distillation side arm and a vacuum line. After cooling to room temperature, the reaction product was solubilized in dichloromethane (200 mL) and sodium chloride was eliminated by filtration. The organic solution was then washed twice by water (50 mL) to eliminate TBD and inorganic residues. The organic layer was dried over sodium sulfate, filtered and dried under vacuum, yielding 50.33 g (67%) of intermediate dimer (DCG). Fifty grams of this compound was then heated at 200 °C for 1 h under nitrogen in the presence of tetrabutoxytitanium (0.2 wt %,), then at 200 °C under vacuum (0.1 mbar) for 4 h. The resulting product (quantitative yield) was analyzed without further purification.

### NMR Characterizations

$^1$H NMR spectra were recorded on Bruker Avance 200 or 500 spectrometers at 200 or 500 MHz. $^{13}$C NMR spectra were recorded on the Avance 500 spectrometer at 125 MHz, using a 5 mm inverse probe. Two-dimensional (2D) $^{13}$C-$^1$H HSQC correlation spectra were recorded on the Avance 500 spectrometer through a phase sensitive gradient enhanced 2D HSQC using echo-antiecho experiment (HSQCETGP sequence). The 2D $^{13}$C-$^1$H long-distance correlation HMBC spectra were recorded via heteronuclear zero and double quantum coherence (HMBCGPLPNDQF sequence). The samples were dissolved in $CDCl_3$/TFA solutions (2/1 vol/vol). Chemical shifts were referenced to residual $CHCl_3$ peak (7.26 ppm, $^1$H) and to the central peak of $CDCl_3$ (77.16 ppm, $^{13}$C).

### Thermal Properties

Differential Scanning Calorimetry (DSC) analyses were carried out under nitrogen on a TA Instruments DSC Q2000 system. The samples (15 mg) were heated from −80 to 200 °C, then cooled to −80 °C and finally heated to 200 °C (cooling and heating rates: 10 °C/min). Melting and glass transition temperatures ($T_m$ and $T_g$) were measured from the second heating curves.

Thermogravimetric analyses (TGA) were carried out on a TA instruments Q50 system at 10 °C/min under nitrogen atmosphere from room temperature to 800 °C.

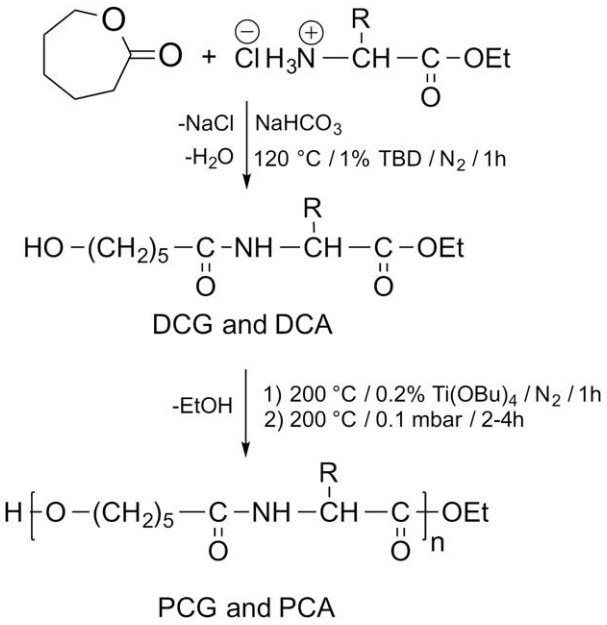
Size exclusion chromatography (SEC) analyses were performed at 60 °C on a column set consisting of two PSS GRAM 1000 Å columns (8 × 300 mm; separation limits: 1–1000 kg/mol) and one PSS GRAM 30 Å (8 × 300 mm; separation limits: 0.1–10 kg/mol) connected to a Viscotek VE5111 injector, VE7510 pump and TDA 305 triple detector. DMF (containing 1 g/L LiBr,) was used as eluent (0.8 mL/min). About 100 µL of filtrated polymer solutions in DMF (5 mg/mL) were injected. The chromatograms were processed using the OmniSEC software and PMMA standards (Polymer Laboratories) were used for the calibration.

### Tensile Properties

Tensile tests were performed at room temperature according to ISO 527-2 using 5A-type dumbbell tensile specimens and a T2000 mechanical testing machine (Alpha Technologies) operating at 50 mm/min. The specimens were molded on a Thermo-Haake Minijet II injection molder set at 200 °C with a mold temperature of 75 °C.

## RESULTS AND DISCUSSION

In order to obtain polyesteramides based on ε-caprolactone (CL) and glycine or α-alanine, 50/50 mol/mol mixtures of CL and amino-acid ethyl ester hydrochloride were first reacted with $NaHCO_3$ to deprotonate the hydrochloride, in the presence of TBD to promote the ring opening of CL by the free amine of the amino-acid ethyl ester (Scheme 1). The formation of long PCL and poly(amino-acid) sequences is disfavored in these conditions. The reaction was carried out at moderate temperature (120 °C) to avoid amine-ester interchanges and favor the formation of dimers (DCG and DCA). These compounds were reacted in the presence of tetrabutoxytitanium at high




**Scheme 1.** Synthesis of DCG (R = H) and DCA (R = $CH_3$) dimers and of PCG (R = H) and PCA (R = $CH_3$) copolymers.

temperature (200 °C) under vacuum to yield the corresponding polyesteramides (Scheme 1).

The polycondensation step involves hydroxy-ester interchanges with ethanol elimination. Hydroxy-amide and ethyl ester-amide interchanges, which would lead to polyesteramide randomization, are disfavored in these conditions.[42] The polyesteramides obtained from glycine and L-α-alanine are denoted as PCG and PCA, respectively. The SEC results indicate that high-molar-mass polymers were obtained, with a molar-mass dispersity ($M_w/M_n$) close to what can be expected for condensation polymers (Table I).

**NMR Characterization**

In order to determine the microstructure and degree of randomization of PCG and PCA, an in-depth knowledge of their $^1$H- and $^{13}$C-NMR spectra is required. Since there is not yet any literature data on such polyesteramides, the various NMR peaks were assigned with the help of 2D NMR $^{13}$C-$^1$H HSQC and HMBC experiments.

**NMR Characterization of Glycine-Based Intermediate Dimer DCG and Polyesteramide PCG.** The $^1$H-NMR spectrum of DCG (Figure 1) shows the expected resonances of mixed ester-amide dyads (GC and CG) and only small signals corresponding to CC (5cc) dyad (see Table II for dyad and triad structures and

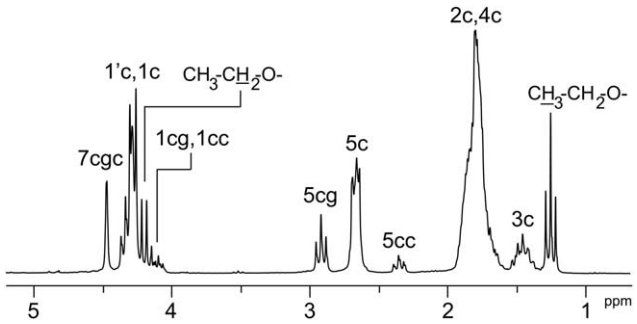



**Figure 1.** $^1$H-NMR spectrum of DCG (200 MHz, $CDCl_3$/TFA 2/1 vol/vol, ref δ($CHCl_3$) = 7.26 ppm).

atom numbering). The signals at 4.10 and 2.35 ppm (1cc and 5cc), are relative to CC dyads present in CCC, CCG, and GCC triads. The mixed ester-amide dyads give two signals: (i) 7cgc at 4.47 ppm, which corresponds to the methylene of glycine units (Gly) connected to CL units in CGC triads and (ii) 5cg at 2.91 ppm, which correspond to the methylene of CL units connected to Gly units in GCG and CCG triads. Two types of end-groups appear in the spectrum: (i) Glycine ethoxy end-groups at 1.25 ppm (methyl resonance) and at 4.20 ppm (methylene resonance) and (ii) CL hydroxymethyl end-groups at 4.34 ppm (methylene 1′c). The signal at 2.66 ppm (5c) corresponds to unreacted CL that could not be eliminated during the purification step due to the close solubility of dimer and CL in water and common organic solvents. On the other hand unreacted amino acid was eliminated during the reaction step, leading to CL/amino acid ratio different from the theoretical one.

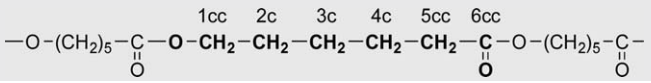
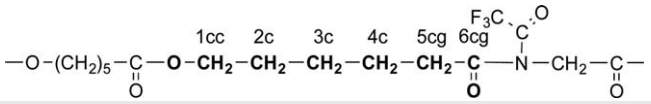
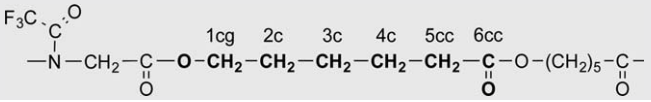
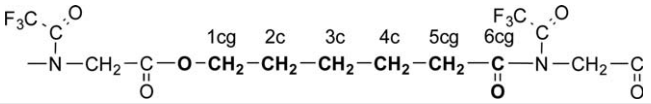
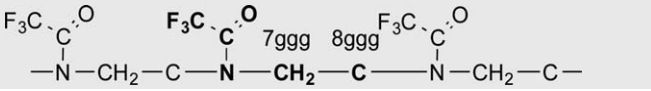
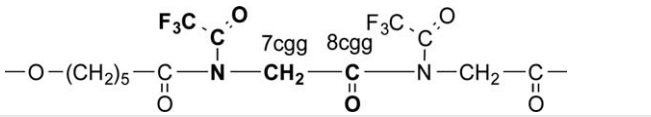
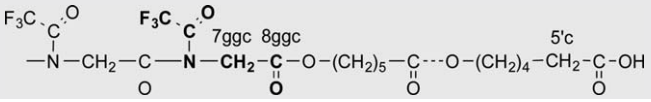
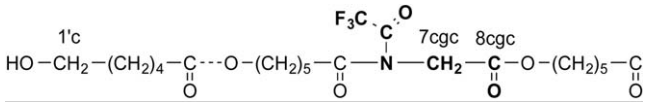
In the spectrum of final PCG (Figure 2), additional small peaks appearing at 4.84 and 4.61 ppm (7ggg, 7cgg, and 7ggc, respectively) correspond to GG dyads of polyglycine in GGG, CGG, and GGC triads, showing that randomization of alternating sequences took place to a small extent during the polycondensation reaction. The peaks corresponding to ethoxy end-groups become very small and the peak of free CL disappear in final PCG. On the other hand, the intensity of 5cc signal increases, showing that unreacted CL present in the intermediate was converted to PCL sequences during the polymerization step of reaction (Table III).

While the ring-opening reaction of highly strained β-lactones may occur both by alkyl-oxygen and acyl-oxygen cleavage in the presence of nucleophiles,[43] it is reported that larger ring, medium strained lactones, such as ε-caprolactone, only react via an acyl-oxygen scission mechanism leading to the formation of alkoxides as growing species, alkyl-oxygen scissions being extremely

**Table I.** Size Exclusion Chromatography (SEC) and Thermal Analyses (DSC, TGA) of PCG and PCA: Mass-Average Molar Masses ($M_w$), Molar-Mass Dispersity ($Đ_M$), Glass Transition Temperature ($T_g$), Melting Point ($T_m$), Crystallization Temperature ($T_c$), Melting Enthalpy ($\Delta H_m$), and 5% Mass Loss Temperature ($T_{d,5\%}$)

| Polymer | $\overline{M_w}$ (g/mol) | $Đ_M$ | $T_g$ (°C) | $T_m$ (°C) | $T_c$ (°C) | $\Delta H_m$ (J/g) | $T_{d,5\%}$ (°C) |
|---|---|---|---|---|---|---|---|
| PCG | 48,800 | 2.48 | −42 | 41 | 19 | 18 | 284 |
| PCA | 78,400 | 2.21 | −3 | 53 | — | 8 | 304 |

**Table II.** DCG Trifluoroacetylated Triads and Corresponding Atom Numbering (C = CL Units and G = Gly Units)

| Triads | Structures and atom numbering |
|---|---|
| CCC |  |
| CCG |  |
| GCC |  |
| GCG |  |
| GGG |  |
| CGG |  |
| GGC |  |
| CGC |  |

unlikely.[44–48] In the present case, however, the formation of a small amount of CL carboxy end-groups (5′c) shows that a side reaction involving alkyl-oxygen scissions takes place. This is confirmed by the presence of two peaks, one at 3.49 ppm (1c*), assigned to a methylene of CL unit in α position to a secondary NH, and another one at 4.34 ppm (7g*), corresponding to a methylene of Gly unit in α position to a secondary NH. These peaks result from the reaction of glycine amine groups with a methylene in α position to the alkyl oxygen of ε-caprolactone (alkyl-oxygen scission), according to Scheme 2.

The $^{13}$C-NMR spectrum of PCG (Figure 3) confirms the conclusions drawn from the $^{1}$H NMR study. The three resonances at 160–180 ppm reflect the presence of: (i) ester carbonyls of CC dyads (6cc) in CCC and GCC triads, (ii) amide carbonyls of CG dyads (6cg) in CCG and GCG triads and (iii) ester carbonyl (8cgc) in CGC triad. The signals of amide carbonyls of GGG and CGG triads corresponding to polyglycine sequences are not detected in the spectrum showing that alternating sequences predominates in PCG.

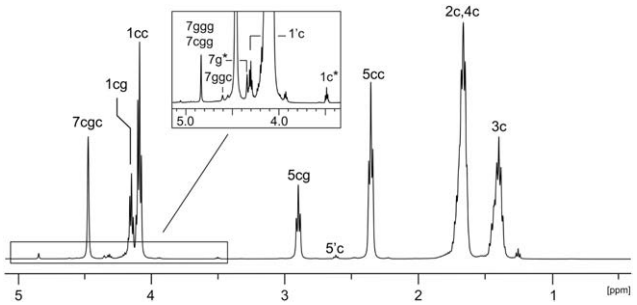
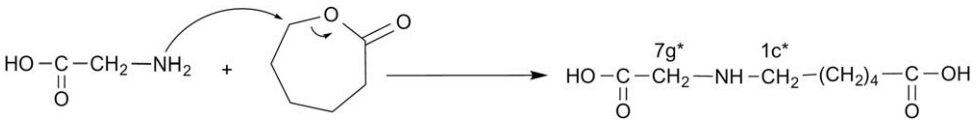



**Figure 2.** $^{1}$H-NMR spectrum of PCG [500 MHz, $CDCl_3$/TFA 2/1 vol/vol, ref δ($CHCl_3$) = 7.26 ppm].

In the 30–70 ppm range, the methylene carbons of CC dyads, 1cc and 5cc, are detected at 65.29 and 34.41 ppm, respectively. The signals of CL units adjacent to Gly units (1cg and 5cg) appear at 66.28 and 38.66 ppm, respectively. On the other hand, the chemical shift of the methylene of Gly units (7g) is not influenced by the nature of the other units linked to this group.

**Table III.** Molar Fractions of CL Units in the intermediate Dimers (DCG and DCA) and the Final Polymers (PCG and PCA) Obtained by integration of Corresponding Signals in the $^{1}$H-NMR Spectra

| Compound | Free CL | CC | CG or CA |
|---|---|---|---|
| DCG | 0.700 | 0.082 | 0.218 |
| PCG | 0 | 0.715 | 0.285 |
| DCA | 0.556 | 0.085 | 0.359 |
| PCA | 0 | 0.356 | 0.644 |




**Scheme 2.** Alkyl-oxygen scission of ϵ-CL by glycine.

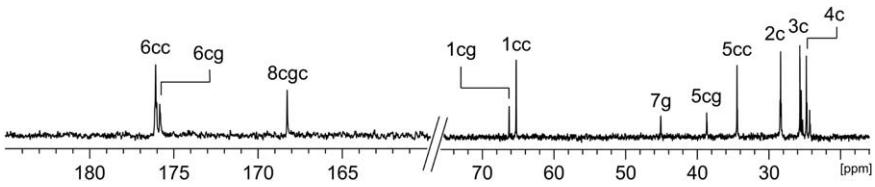



**Figure 3.** $^{13}$C-NMR spectrum of PCG [125 MHz, $CDCl_3$/TFA 2/1/vol/vol, ref δ($CDCl_3$) = 77.16 ppm].

**NMR Characterization of α-Alanine-Based Intermediate Dimer DCA and Polyesteramide PCA.** In the $^1$H-NMR spectrum of DCA (Figure 4, Table IV), the two signals 1ca and 5ca, respectively, at 4.19 and 2.81 ppm, shows the presence of ester-amide dyads (CA). The very small signal 5cc at 2.39 ppm corresponds to CC dyads. In opposition to what observed above for glycine units, the $^1$H-NMR chemical shift of α-Ala unit methylene (7a) at 4.55 ppm, is not influenced by the nature of neighboring groups (7aaa = 7caa = 7aac = 7cac = 7a). The signal at 2.68 ppm (5c) corresponds to unreacted CL, as already discussed above in the case of DCG. Two types of end-groups appear in the spectrum: (i) α-alanine ethoxy end-groups at 1.24 ppm (methyl resonance) and at 4.21 ppm (methylene resonance) and (ii) CL hydroxymethyl end-groups at 4.35 ppm (methylene 1′c).

In the spectrum of final PCA (Figure 5), the presence of mixed ester-amide dyads is reflected by the signal at 4.16 ppm corresponding to the methylene 1ca of CL units in CL-OCO-Ala dyads and by two broad signals at 2.74 and 2.80 ppm assigned to the methylene 5ca of CL units in CL-CONH-Ala dyads. The presence of two broad signals for methylene 5ca could reflect the racemization of L-α-Ala units during the reaction. It should also be underlined that, contrary to what observed above for glycine, the resonances of secondary amine methylenes and of carboxymethyl end-groups are not detected in the spectrum, showing in this case the absence of alkyl-oxygen scissions. Like in the case of the reaction with glycine, the peaks corresponding to ethoxy end-groups become very small in final PCA and the peak of free CL disappears. The intensity of 5cc and 5ca signals, corresponding respectively to ester-ester and ester-amide sequences, increases in final PCA as compared with DCA dimer (Table III). It seems, therefore, that unreacted CL present in intermediate DCA was converted to CL-CL and CL-Ala sequences during the polymerization step of reaction.

As expected, the $^{13}$C-NMR spectrum of PCA (Figure 6) exhibits three resonances in the carbonyl region (160–180 ppm): Ester carbonyls of CC dyads (6cc, 177.3 ppm), amide carbonyls of CA dyads (6ca, 176.5 ppm) and (iii) ester carbonyls of mixed CAC triad (8cac, 170.9 ppm). The signals of the amide carbonyl corresponding to poly(α-alanine) sequences (8aaa and 8caa) are not detected in the spectrum, showing that alternating sequences also predominate in PCA. In the 30–70 ppm range, the signals of CC dyads (1cc and 5cc, 65.8 and 34.5 ppm) and of CA dyads (1ca and 5ca, 66.7 and 38.5 ppm) are easily assigned. As already observed for glycine, the $^{13}$C-NMR chemical shift of α-Ala methylene (7a, 54.83 ppm) is not influenced by the nature of the other units linked to this group.

**Microstructure.** The experimental CL/amino acid molar composition of the two amino acid-based polyesteramides was determined by integration of the corresponding $^1$H-NMR peaks: 5cc, 5cg, and 7g for PCG and 5cc, 5ca, and 7a for PCA (Table V).

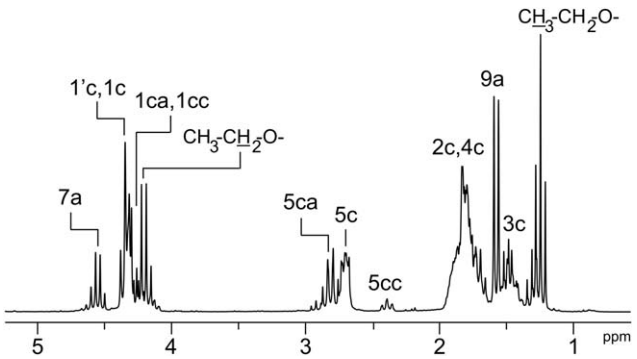



**Figure 4.** $^1$H-NMR spectrum of DCA [200 MHz, $CDCl_3$/TFA 2/1 vol/vol, ref δ($CHCl_3$) = 7.26 ppm].

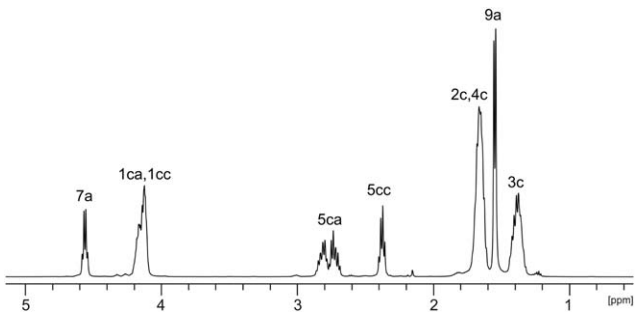
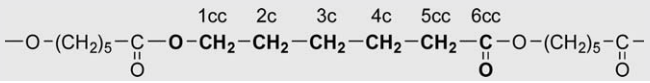
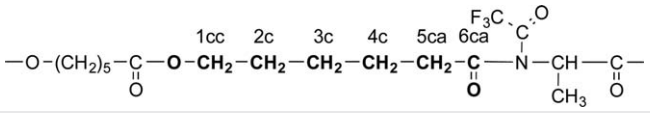
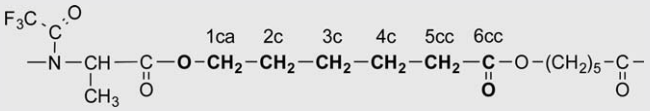
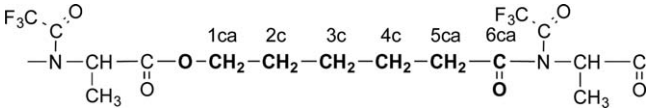
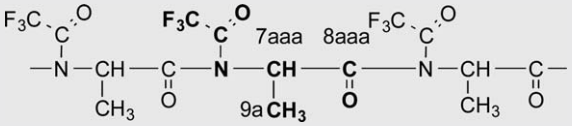
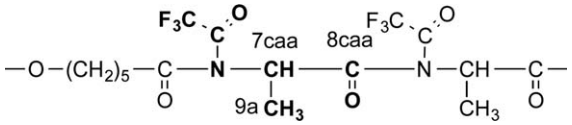
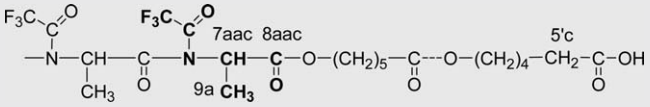
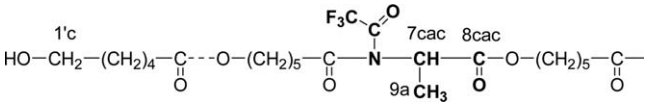



**Figure 5.** $^1$H-NMR spectrum of PCA [500 MHz, $CDCl_3$/TFA 2/1 vol/vol, ref δ($CHCl_3$) = 7.26 ppm].

**Table IV.** DCA Trifluoroacetylated Triads and Corresponding Atom Numbering (C = CL Unit and A = α-Ala Unit)

| Triads | Structures and atom numbering |
|---|---|
| CCC |  |
| CCA |  |
| ACC |  |
| ACA |  |
| AAA |  |
| CAA |  |
| AAC |  |
| CAC |  |

$$\text{For PCG: CL/Gly} = (I_{5cc}+I_{5cg})/(I_{7g}) = 77/23$$

$$\text{For PCA: CL/α-Ala} = (I_{5cc}+I_{5ca})/(I_{7a}) = 60/40$$

The degree of randomness, $R$, reflects the extent of randomization in copolymers and is a key parameter for determining their microstructure. $R = 0$ for mixtures of homopolymers, $R = 1$ for random copolymers and $R = 2$ for perfectly alternating copolymers. In the present case, $R$ can be defined as the probability of finding hetero-type CG or CA dyads ($P_{cg}$ or $P_{ca}$) divided by the product of the probabilities of finding the corresponding C and G or A groups in polyesteramide chains ($P_c$ and $P_g$ or $P_a$): $R = P_{cg}/(P_c \cdot P_g)$ for PCG and $R = P_{ca}/(P_c \cdot P_a)$ for PCA. $P_{cg}$, $P_c$, $P_g$, $P_{ca}$, and $P_a$ were determined by the integrations ($I$) of the corresponding $^1$H NMR resonances:

$$P_{cg} = I_{5cg}/(I_{5cg}+I_{5cc}+I_{7g}),\ P_c = (I_{5cg}+I_{5cc})/(I_{5cg}+I_{5cc}+I_{7g}),$$
$$P_g = (I_{7g})/(I_{5cg}+I_{5cc}+I_{7g}).$$

$$P_{ca} = I_{5ca}/(I_{5ca}+I_{5cc}+I_{7a}),\ P_c = (I_{5ca}+I_{5cc})/(I_{5ca}+I_{5cc}+I_{7a}),$$
$$P_a = (I_{7a})/(I_{5ca}+I_{5cc}+I_{7a}).$$

The number-average sequence lengths, $L_c$ and $L_g$ or $L_a$, defined as the number of units of a given type (C, G, or A) divided by the number of sequences of this type, that is, the number of hetero-type dyads (GC and CG), are given by:

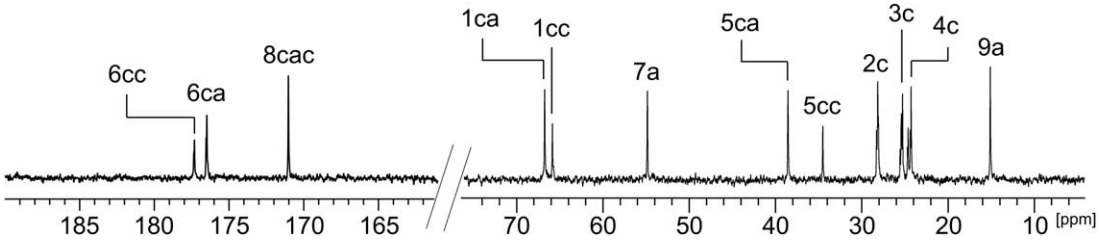



**Figure 6.** $^{13}$C-NMR spectrum of PCA [125 MHz, $CDCl_3$/TFA 2/1/vol/vol, ref δ($CDCl_3$) = 77.16 ppm].

**Table V.** Experimental Molar Composition, Degree of Randomness ($R$), and Number-Average Sequence Length ($L_c$, $L_g$, $L_a$) for PCG and PCA, Based on $^1$H NMR Data

| Polymer | CL/amino acid experimental | $R$ | $L_c$ | $L_g$, $L_a$ |
|---|---|---|---|---|
| PCG | 77/23 | 1.31 | 3.12 | 1.01 |
| PCA | 60/40 | 1.64 | 1.56 | 1.00 |

$$L_g = I_{7g}/I_{5cg} \quad \text{and} \quad L_c = (I_{5cg} + I_{5cc})/I_{5cg} \quad \text{for PCG}$$

$$L_a = I_{7a}/I_{5ca} \quad \text{and} \quad L_c = (I_{5ca} + I_{5cc})/I_{5ca} \quad \text{for PCA}$$

As shown in Table V, PCA has a strong tendency to alternate, with $R = 1.64$ (2.0 for a perfectly alternating copolymer) and number-average sequence lengths close to 1. On the other hand, PCG presents a lower tendency to alternation. The higher $L_c$ number-average CL sequence length in PCG is due to the higher CL unit content.

The two polyesteramides (Table I) exhibit very different glass transition temperature ($T_g$) (−3 °C for PCA and −42 °C for PCG). The short and rigid lateral substituent (methyl group) present in PCA and not in PCG decreases the mobility of PCA macromolecular chains and leads to a higher $T_g$ value. The two amino acid-based polyesteramides have similar melting temperatures but PCG presents a crystallization peak at 19 °C in opposition to PCA. The lower melting enthalpy observed for PCA is probably due to the partial thermal racemization of the amino acid units during the synthesis.[49,50]

Tensile tests were carried out on injection-molded specimens of PCG (Table VI and Figure 7). The results were compared with the previously synthesized random and quasi-alternating polyesteramides, synthesized from equimolar amounts of CL and β-alanine.[24] PCA was too fragile to allow the preparation of tensile specimens, likely due to its low degree of crystallinity. For the comparison of tensile properties of polyesteramides, four parameters should be taken into consideration: microstructure, molar mass, amino acid unit concentration, and number of methylene groups in the amino acid unit. Although PCG has a lower concentration in amino acid units than its alternating β-alanine counterpart,[24] its higher molar mass and the lower number of methylene groups of glycine with respect to β-alanine leads to notably higher Young's modulus and stress at break for PCG. The difference is even greater between PCG and the less organized random CL-β-alanine polyesteramide (Table VI, Figure 7).

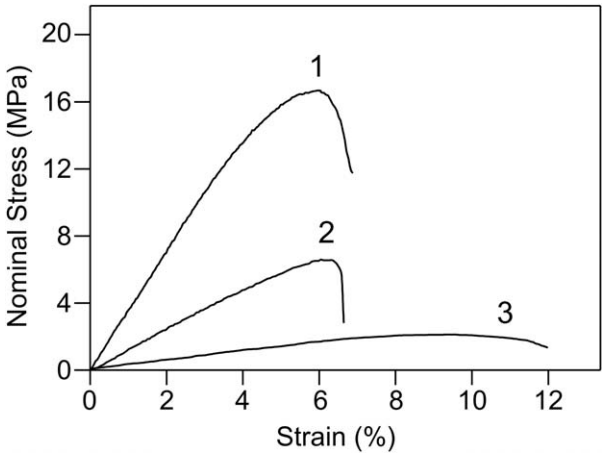



**Figure 7.** Tensile curves of 1: PCG, 2: quasi-alternating CL-β-alanine polyesteramide (PEA2-50/50[24]) and 3: random CL-β-alanine polyesteramide (PEA1-50/50[24]).

## CONCLUSIONS

Two high-molar-mass polyesteramides (PCG and PCA) with a strong tendency to form alternating sequences were synthesized by reacting ε-caprolactone with glycine or L-α-alanine ethyl ester hydrochlorides in a two-step bulk reaction keeping the extent of interchange reactions to a low level. Their structures were fully characterized by $^1$H and $^{13}$C NMR. In spite of a lower content in amide units, the glycine-based polyesteramide exhibit a higher melting enthalpy than the L-α-alanine-based one, probably due to the racemization of L-α-alanine units during the synthesis. The glycine-based polyesteramide exhibits also notably higher Young's modulus and tensile strength than its previously described quasi-alternating- and random β-alanine counterparts.

## ACKNOWLEDGMENTS

The Présidence and the Ministère de l'Enseignement Supérieur et de la Recherche de la République de Djibouti are gratefully acknowledged for AAM's doctoral fellowship.

## REFERENCES

1. Lutz, J. F.; Andrieu, J.; Üzgün, S.; Rudolph, C.; Agarwal, S. *Macromolecules* **2007**, *40*, 8540.
2. Green, J. J.; Zhou, B. Y.; Mitalipova, M. M.; Beard, C.; Langer, R.; Jaenisch, R.; Anderson, D. G. *Nano Lett.* **2008**, *8*, 3126.

**Table VI.** Results of Tensile Tests for Quasi-Alternating Polyesteramide of CL and Glycine (PCG) and for Random and Quasi-Alternating Polyesteramides of CL and β-Alanine (PEA1-50/50 and PEA2-50/50, Respectively[24])

| Amino acid-based polyesteramides | $\overline{M_n}$ (g/mol) | CL/amino acid experimental | $E$ (MPa) | $R_m$ (MPa) | $\sigma_r$ (MPa) | $\epsilon_r$ (%) |
|---|---|---|---|---|---|---|
| PCG | 19700 | 77/23 | 385 | 16.6 | 11.7 | 6.9 |
| PEA1-50/50[24] | 12400 | 51/49 | 31 | 2.1 | 1.3 | 12.0 |
| PEA2-50/50[24] | 9300 | 55/44 | 135 | 6.7 | 6.0 | 6.5 |

3. Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181.
4. Albertsson, A. C.; Varma, I. K. *Biomacromolecules* **2003**, *4*, 1466.
5. Qian, Z.; Li, S.; He, Y.; Zhang, H.; Liu, X. *Biomaterials* **2004**, *25*, 1975.
6. Wang, N.; Wu, X. S.; Li, C.; Feng, M. F. *J. Biomater. Sci. Polym. Ed.* **2000**, *11*, 301.
7. MacDonald, J. P.; Parker, M. P.; Greenland, B. W.; Hermida-Merino, D.; Hamley, I. W.; Shaver, M. P. *Polym. Chem.* **2015**, *6*, 1445.
8. Vert, M. *Biomacromolecules* **2005**, *6*, 538.
9. Higgins, S. P.; Solan, A. K.; Niklason, L. E. *J. Biomed. Mater. Res. A* **2003**, *67A*, 295.
10. Tang, Y. R. *J. Chem. Proc. Eng.* **2014**, *1*, 1.
11. Rodriguez-Galan, A.; Franco, L.; Puiggali, J. *Polymers* **2010**, *3*, 65.
12. Sun, H.; Meng, F.; Dias, A. A.; Hendriks, M.; Feijen, J.; Zhong, Z. *Biomacromolecules* **2011**, *12*, 1937.
13. Cakir, S.; Kierkels, R.; Koning, C. *J. Polym. Sci. Part A: Polym. Chem.* **2011**, *49*, 2823.
14. Chromcová, D.; Baslerová, L.; Roda, J.; Brožek, J. *Eur. Polym. J.* **2008**, *44*, 1733.
15. Deshayes, G.; Delcourt, C.; Verbruggen, I.; Trouillet-Fonti, L.; Touraud, F.; Fleury, E.; Degée, P.; Destarac, M.; Willem, R.; Dubois, P. *Macromol. Chem. Phys.* **2009**, *210*, 1033.
16. Song, H.; Chu, C. C. *J. Appl. Polym. Sci.* **2012**, *124*, 3840.
17. Fan, Y.; Chen, G.; Tanaka, J.; Tateishi, T. *Biomacromolecules* **2005**, *6*, 3051.
18. Motala-Timol, S.; Jhurry, D.; Zhou, J.; Bhaw-Luximon, A.; Mohun, G.; Ritter, H. *Macromolecules* **2008**, *41*, 5571.
19. Kricheldorf, H. R.; Hauser, K. *Biomacromolecules* **2001**, *2*, 1110.
20. Hrkach, J. S.; Ou, J.; Lotan, N.; Langer, R. *Macromolecules* **1995**, *28*, 4736.
21. Qian, Z.; Li, S.; He, Y.; Li, C.; Liu, X. *Polym. Degrad. Stab.* **2003**, *81*, 279.
22. He, Y.; Du, Y. R.; Liu, X. B. *Adv. Mater. Res.* **2011**, *287–290*, 1538.
23. Qian, Z.; Li, S.; He, Y.; Zhang, H.; Liu, X. *Colloid Polym. Sci.* **2004**, *282*, 1083.
24. Ali-Mohamed, A.; Salhi, S.; Abid, S.; El Gharbi, R.; Fradet, A. *Eur. Polym. J.* **2014**, *53*, 160.
25. Ali-Mohamed, A.; Salhi, S.; Abid, S.; Gharbi, R.; Fradet, A. *J. Appl. Polym. Sci.* **2014**, *131*, DOI: 10.1002/app.40573.
26. Wang, Z.; Hou, X.; Mao, Z.; Ye, R.; Mo, Y.; Finlow, D. E. *Iran. Polym. J.* **2008**, *17*, 791.
27. Lu, D.; Ren, Z.; Zhou, T.; Wang, S.; Lei, Z. *J. Appl. Polym. Sci.* **2008**, *107*, 3638.
28. Asín, L.; Armelin, E.; Montané, J.; Rodríguez-Galán, A.; Puiggalí, J. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 4283.
29. Paredes, N.; Rodriguez-Galán, A.; Puiggalí, J.; Peraire, C. *J. Appl. Polym. Sci.* **1998**, *69*, 1537.
30. Wu, J.; Mutschler, M. A.; Chu, C. C. *J. Mater. Sci. Mater. Med.* **2011**, *22*, 469.
31. Deng, M.; Wu, J.; Reinhart-King, C. A.; Chu, C. C. *Acta Biomater.* **2011**, *7*, 1504.
32. Katsarava, R.; Beridze, V.; Arabuli, N.; Kharadze, D.; Chu, C. C.; Won, C. Y. *J. Polym. Sci. Part A: Polym. Chem.* **1999**, *37*, 391.
33. Pang, X.; Wu, J.; Reinhart-King, C.; Chu, C. C. *J. Polym. Sci. Part A: Polym. Chem.* **2010**, *48*, 3758.
34. Montané, J.; Armelin, E.; Asín, L.; Rodríguez-Galán, A.; Puiggalí, J. *J. Appl. Polym. Sci.* **2002**, *85*, 1815.
35. Casas, M. T.; Gestí, S.; Puiggalí, J. *Cryst. Growth Des.* **2005**, *5*, 1099.
36. Feng, Y.; Klee, D.; Keul, H.; Höcker, H. *Macromol. Chem. Phys.* **2000**, *201*, 2670.
37. Kricheldorf, H. R.; Hauser, K. *Macromol. Chem. Phys.* **2001**, *202*, 1219.
38. Feng, Y.; Guo, J. *Int. J. Mol. Sci.* **2009**, *10*, 589.
39. Wang, D.; Feng, X. D. *Macromolecules* **1997**, *30*, 5688.
40. Ouchi, T.; Seike, H.; Nozaki, T.; Ohya, Y. *J. Polym. Sci. Part A: Polym. Chem* **1998**, *36*, 1283.
41. Franz, N.; Klok, H. A. *Macromol. Chem. Phys.* **2010**, *211*, 809.
42. Xue, C.; Luo, F. T. *J. Chin. Chem. Soc.* **2004**, *51*, 359.
43. Hofman, A.; Słomkowski, S.; Penczek, S. *Makromol. Chem.* **1984**, *185*, 91.
44. Duda, A.; Biela, T.; Kowalski, A.; Libiszowski, J. *Polimery* **2005**, *50*, 501.
45. Jedliński, Z.; Wałach, W.; Kurcok, P.; Adamus, G. *Makromol. Chem.* **1991**, *192*, 2051.
46. Sipos, L.; Zsuga, M.; Kelen, T. *Polym. Bull.* **1992**, *27*, 495.
47. Dubois, P.; Degee, P.; Jerome, R.; Teyssie, P. *Macromolecules* **1992**, *25*, 2614.
48. Liu, J.; Liu, L. *Macromolecules* **2004**, *37*, 2674.
49. Heinrich, M. R.; Rohlfing, D. L.; Bugna, E. *Arch. Biochem. Biophys.* **1969**, *130*, 441.
50. Palla, G.; Marchelli, R.; Dossena, A.; Casnati, G. *J. Chromatogr. A* **1989**, *475*, 45.