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Synthesis and Characterization of L-alanine based Poly(ester-amide)s

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Abstract

Novel biomaterials L-alanine based poly(ester-amide)s (PEAs) differing in the amide/ester ratio have been directly synthesized by direct melt copolycondensation of Adipic acid, L-alanine and various aliphatic and heterocyclic diols. PEAs were systematically characterized with intrinsic viscosity, FTIR, ^{1}H-NMR, ^{13}C-NMR, DSC and SEC measurements. The resulting copolymers are amorphous and present increasing glass transition temperatures at increasing L-Alanine contents. L-Alanine-PEAs proved to be materials having high molecular weights that could reach 41800 g/mol.

Keywords: Adipic acid/ L-alanine/ melt polycondensation/ microstructure/ NMR/ Poly(ester-amide).

1. Introduction

In the past few decades, poly(ester-amide)s (PEAs) based on natural amino acids have attracted much attention in terms of their special and distinctive characteristics, they combine the interesting properties of conventional PEAs with those resulting from the presence of the amino acids (1). These polymers possess good thermal stability and good mechanical and processing properties like tensile strength and modulus, due to the strong hydrogen-bonding interactions established between amid groups. The use of amino acids in PEAs synthesis can be also justified by many reasons; in addition to their abundant availability from natural resources, they confers to their derivatives potential susceptibility to biodegradation under certain enzymatic catalyzed conditions, in the opposite of their counterparts based on other types of monomers like diamines (2).

In this context, biocompatibles amino acids based PEAs find a wide range of medical applications (3), like drug delivery systems; indeed microsphers or electrospun nanofibers based on PEAs could perform good controlled drug release (4,5). In tissue engineering, it has been proved that amino acid based PEAs could be used as cardiovascular biomaterials, they were able to support the attachment, spreading and proliferation of smooth muscle cells of the human coronary artery, which make them good candidates for vascular tissue engineering scaffolds (6-8). Drug charged hydrogels can be also elaborated by photopolymerization of amino acids based PEA and the appropriate drug (9,10).

Different synthesis methodologies of PEAs from amino acids were reported in literature. Ring opening polymerization of morpholine-2,5-dione derivatives which are cyclic dimers resulting from α-hydroxyacids and α-aminoacids, is a very old technique. It can be elaborated in the presence of metallic or enzymatic catalysis (11-14). The ring opening polymerization of ε-caprolactone with different amino acids was reported recently and leads to PEAs with high molecular weights and high Young's modulus and tensile strength (15-18).

These polymers can be also obtained by solution polycondensation of an amino acid with a diol and a dicarboxylic acid, this method followed by Chu et coll (19-26) is advantageous because it is carried out in mild operating conditions and accomplished in high yields and molecular weights, but in return, it requires very high monomers purity and extensive polymer purification to eliminate solvent and toxic by-products

generated. Puiggali et coll synthesized regular PEAs by interfacial or thermal polycondensation. Interfacial polycondensation consist on the preparation of di-p-toluenesulfonic acid salts by Fischer esterification between amino acids like L-alanine (27-31), Glycine (30-33), β-alanine (34) or L-phenylalanine (35), and diols, in the presence of p-TSA, and its reaction with diacyl chlorides. The thermal polycondensation involves the reaction of a diol with a diester-terminated diamide, previously obtained from the condensation of a diacyl chloride with an amino acid methyl ester (36-40).

Melt direct polymerization is a very advantageous method for industrial use because it is carried on in one step, it avoids the prior preparation of the intermediates mentioned previously for other synthesis routes, and because no post-treatment of resulting polymers is necessary. Our group performed the melt polycondensation of β-alanine and gycolic acid (41); random amorphous PEAs were obtained with high thermal stability and high glass transition temperatures. We reported in a previous work the synthesis of β-alanine based PEAs, amorphous PEAs were obtained (42). In order to improve the glass transition temperatures and the solubility of resulting polymers, we study the substitution of β-alanine by L-alanine. In fact, L-alanine based polymers have particular properties; methyl side groups increases glass transition temperatures, they also improves the solubility in organic solvents such as chloroform, in this way it is possible to obtain microspheres that can be used as drug delivery systems (31). Moreover, polymers based on L-alanine show better enzymatic degradation than their counterparts based on other types of monomers like glycine (30).

To the best of our knowledge, L-alanine was never used in direct melt polycondensation, we proposed in the present paper to synthesize novel PEAs by direct melt polycondensation between L-alanine, adipic acid and different aliphatic or heterocyclic diols and to study the effect of amide percentage on microstructure and thermal properties of resulting copolymers.

2. Experimental Part

2.1 Materials

L-Alanine (L) (purchased from Aldrich), Adipic acid (A) (purchased from Acros Organics), Ethylene glycol (E); 1,3-Propanediol (P); 1,4-Butanediol (D); 1,6-Hexanediol (H); Isosorbide (I) (purchased from Aldrich),Tetrabutoxytitanium ($Ti(BuO)_4$) (purchased from Aldrich) were high purity compounds used as received without further purification.

2.2 Synthesis of PALD copolymers: PALE, PALP, PALB, PALH and PALI

A series of poly(ester-amide)s were synthesized according to scheme 1 and table 1. A reactor equipped with a magnetic stirrer was charged with L-Alanine (L) (1 mol), Adipic acid (A) (1 mol), and an excess of a diol (3 mol) (Ethylene glycol (E); 1,3-Propanediol (P); 1,4-Butanediol (B); 1,6-Hexanediol (H) or Isosorbide (I)). Tetrabutoxytitanium (0.3 wt %) was added as a catalyst for the condensation reaction. The reactor was heated in an oil bath at 210 °C in order to melt the mixture under nitrogen atmosphere and to help eliminate water and the excess of diol. After one hour, the temperature was raised to 220 °C for 4h. After cooling the reactor to room temperature, vacuum was applied (0.01 mmHg) while the temperature was raised progressively to 190°C for 2h, and then to 220 °C for 6h. The resulting polymers were analyzed without further purification.

2.3 Synthesis of PALB-x/y copolymers

The Poly(ester-amide)s are denoted PALB-x/y, where x/y represents the Amide/ester ratio and varied from 50/50 to 10/90 (table 1). A typical PALB-50/50 copolymer was prepared as follows: A mixture of Adipic acid (1mol), L-alanine (2 mol) and 1,4-Butanediol (2 mol) was heated at 210 °C for 2 h under nitrogen atmosphere in a reactor fitted with a magnetic stirrer. Tetrabutoxytitanium (0.3 % mol) was carefully added. The reactor was then heated to 220 °C and kept at this temperature under vacuum (0.01 mmHg) for 4 h. The resulting product was analyzed without further purification. L-alanine has a very high melting temperature (295°C), we could not exceed 50% of initial amide percentage because of the difficulty of the solubility of amino acid (L-Ala) in reaction medium.

2.4 Characterization

Infrared absorption spectra were recorded with a Perkin-Elmer spectrum 100 spectrometer in the 4000-700 cm^{-1} range. NMR spectra of polymers were registered from deuterated chloroform. Chemical shifts were referenced to the peak of residual $CHCl_3$ at 7.26 ppm. A Bruker AC-300 spectrometer operating at 300 MHz and a Bruker AC 400spectrometer operating at 400 MHz were used for ^{1}H and ^{13}C-NMR investigations respectively.

Molecular weight (M_n and M_w) and molar mass dispersity ($Đ_M$) of all copolyemers were determined using size exclusion chromatography (SEC) analyses performed on a Shimadzu LC-20AD liquid chromatography equipped with two Varian PL gel 5 µm MIXED-C columns (column, injection and refractometer temperature: 30°C; injection volume: 100 µL) and a refractive index detector (Shimadzu RID-10A). THF was used as the eluent at a flow rate of 1.0 mL/min. The molecular characteristics were determined relative to linear polystyrene calibration standards. All polymers were dissolved in THF (10 mg mL^{-1}).

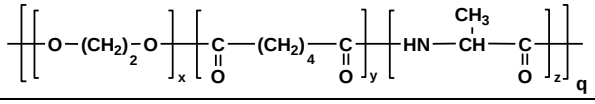
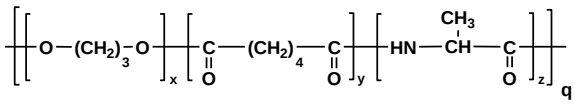
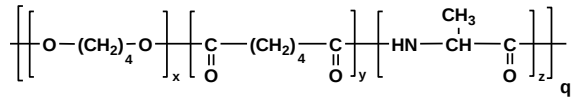
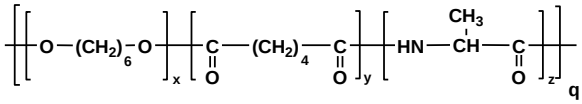
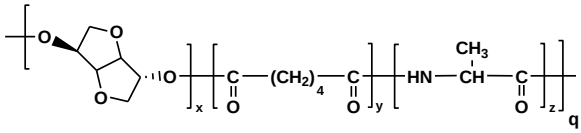
Thermal analyses were performed by differential scanning calorimetry (DSC) using a TA Instrument DSC calorimeter Q 2000.The samples (10 mg) were subjected to two successive temperature ramps under nitrogen from-70 °C to 180 °Cat a rate of 20°C/min.

Thermogravimetric analyses were performed with a TA Instrument TGA Q500. Between 3 and 8 mg of sample were placed in a platinum crucible and subjected to a temperature ramp from 20°C to 800 °C with a rate of 10 ° C / min under nitrogen flow.

Intrinsic viscosity [η_{int}] measurements were performed by using an Ubbelohde viscometer at 25°C in chloroform. All copolymers were dissolved at room temperature in order to prepare solutions of 1.5 g/dl concentration.

Intrinsic viscosity was calculated using the Solomon–Ciuta equation (43, 44). $[\eta_{int}] = [2((t/t_0) - \ln(t/t_0) - 1)]^{1/2} / C$. Where C is the concentration of the solution; t, the flow time of solution and t_0 is the flow time of pure solvent.

Table1.Chemical formulas of different synthesis Poly(ester-amide)s (PALD)

Copolymer	Chemical formula
PALE	
PALP	
PALB	
PALH	
PALI	

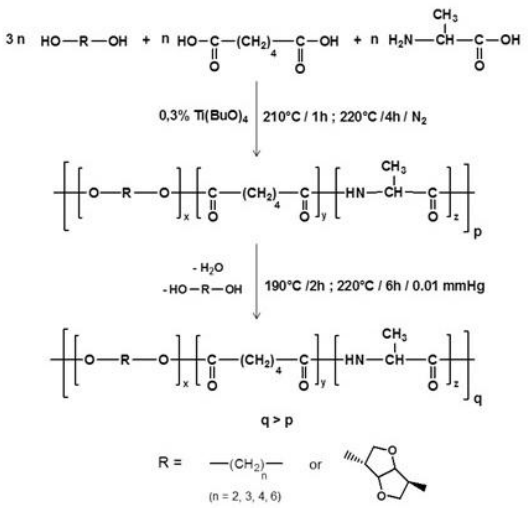
3. Results and discussion

Various Poly(ester-amide)s copolymers denoted PALD were synthesized from Adipic acid (A), L-alanine (L) and different diols (D) by direct melt copolycondensation according to Scheme 1. The mixture of monomers was first heated to perform the formation of a dicarboxy-terminated amide dimers from L-alanine and adipic acid, then the esterification of generated dimers by the appropriate diol. Titanium butoxide catalyst is added to activate the carbonyl of the dicarboxylic acid and facilitate its attack by amino or hydroxyl functions. The resulting oligomer mixture was then reacted under vacuum to yield high molar mass copolymers.

3.1 Influence of the nature of dihydroxy monomer unit

Five poly(ester-amide)s synthesized from adipic acid, L-alanine and ethylene glycol, 1,3-Propanediol, 1,4-Butanediol, 1,6-Hexanediol and Isosorbide respectively were selected for this study. The major difference between these PEAs is the length of the dihydroxy monomer unit.

The ^{1}H-NMR, ^{13}C-NMR and FTIR spectroscopic data of resulting PEAs were in total agreement with their anticipated chemical constitution.



Scheme1. Synthesis of PALD copolymers

FTIR spectra of PALD copolymers exhibit the expected features. A typical infrared spectrum of PALE is shown in Figure 1, with absorptions corresponding to amide NH (amide A), amide carbonyl (amide I) and amide C-N (amide II) at 3315, 1642 and 1550 cm^{-1} respectively, to aliphatic CH at 2922 cm^{-1}, ester carbonyl at 1739cm^{-1},and C-O simple bond at 1154 cm^{-1}.

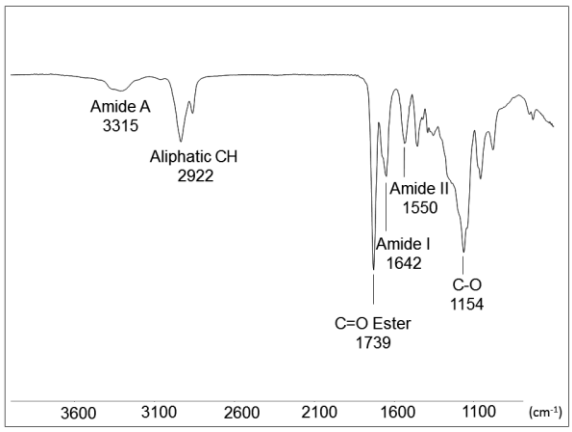


Figure 1. Infrared spectrum of PALE copolymer

Typical ^{1}H-NMR spectrum of PALE copolymer is shown in Figure 2. We show the presence of L-L dyads of poly(L-alanine) sequence (1^{LL} and 2^{LL} at 4.57 and 1.40 respectively), the presence of E-A dyads of poly(ethylene adipate) sequence (3^{AE}, 4^{AE} and 5^{EA} at 2.35, 1.66 and 4.26 respectively). We observe also the presence of the mixed ester-amide E-L and A-L dyads (5^{EL} and 3^{AL} at 4.29 and 2.23 respectively). The proton resonances of the -CH- and -CH$_3$ of L-alanine units are not affected by the nature of neighboring units, and are observed overlapped at 4.57 (1^{LL} = 1^{LE} = 1^{LA} = 1^{L}) and 1.40 (2^{LL} = 2^{LB} = 2^{LA} = 2^{L}). (See Table 3 for dyads structures and atom numbering).

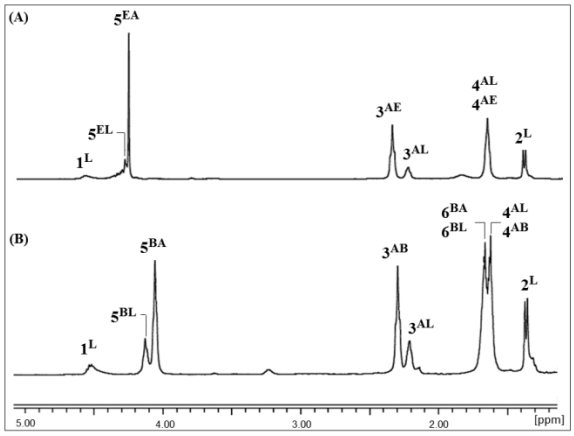


Figure 2.^{1}H-NMR spectra of a PALE (A) and PALB-50/50 (B) copolymers (300 MHz, $CDCl_3$, ref δ ($CHCl_3$) = 7.26 ppm)

The experimental proton chemical shifts of all PALD copolymers are listed in table 3 and 4. In addition to the signals present in PALE spectrum, another signal that appears at 1.96 ppm is observed when we use propane-diol corresponding to the methylene (6^{P}) in β position relative to the hydroxyl group, this signal denoted 6^{B} in PALB spectrum appears less deshielded (at 1.69 ppm) when we use butane-diol. In ^{1}H-NMR spectrum PALH, the aliphatic sequence of the diol becomes longer and therefore the signal 6^{H} appears at 1.59 ppm, preceded by another signal (7^{H}) at 1.47 ppm attributed to the methylene in γ position relative to the hydroxyl group.

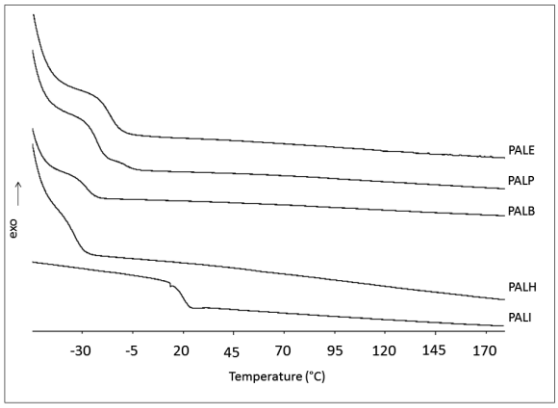


Figure3. DSC curves of PALD poly(ester amide)s

Table2. Dyads present in copolymers (adipic acid (A), L-alanine (L) and diol (D))and the corresponding atom numbering.

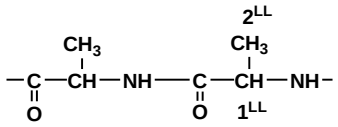
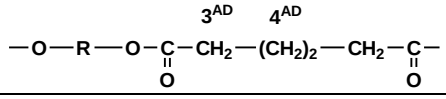
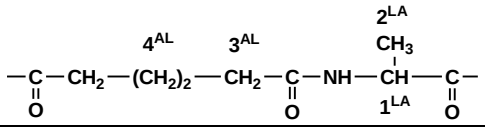
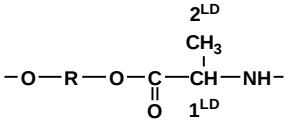
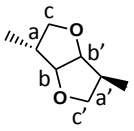
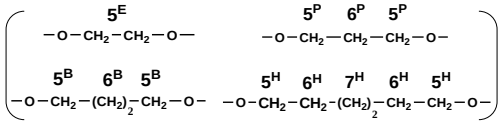
L-L	
D-A	
A-L	
D-L	
R =  **or** —$(CH_2)_n$— : (n = 2, 3, 4, 6) 	

Table 3. Chemical shifts and assignments of the ^{1}H-NMR spectra of PALE, PALP, PALB and PALH based on adipic acid (A), L-alanine (L) and diols (D); ethylene glycol(E), propanediol (P), butanediol (B) and hexanediol (H)

	Proton	1^L	2^L	3^{AL}	3^{AD}	4^{AD} 4^{AL}	5^{DA}	5^{DL}	6^{DA} 6^{DL}	7^{DA} 7^{DL}
δ (ppm)	PALE	4.57	1.40	2.23	2.35	1.66	4.26	4.29	*	*
	PALP	4.57	1.40	2.23	2.32	1.65	4.14	4.21	1.96	*
	PALB	4.57	1.40	2.23	2.32	1.65	4.08	4.16	1.69	*
	PALH	4.57	1.38	2.23	2.32	1.65	4.05	4.13	1.59	1.47

Table 4. Chemical shifts and assignments of the ^{1}H-NMR spectra of PALI, based on Adipic acid (A), L-alanine (L) and Isosorbide (I)

	Proton	1^L	2^L	3^{AL}	3^{AI}	4^{AI} 4^{AL}	a, a’	b	b’	c	c’
δ (ppm)	PALI	4.65	1.40	2.22	2.38	1.65	5.17	4.82	4.44	3.93	3.90

Monomer composition can be evaluated from ^{1}H-NMR spectra taking into account the area of signals corresponding to -***CH$_2$***-CO protons of adipic acid units (3^{AD} and 3^{AL}), -***CH***- protons of L-alanine units (1^L) and -***CH$_2$***-O protons of diol units (5^{DA} and 5^{DL}).

In this way, diol (*f*D), adipic acid (*f*A) and L-alanine (*f*L) molar fractions were calculated according to the equations 1, 2 and 3 respectively:

$$F(D) = \frac{\frac{I(5DA+5DL)}{4}}{\left[\left(\frac{I(5DA+5DL)}{4}\right)+\left(\frac{I(3AD+3AL)}{4}\right)+\left(\frac{I(1L)}{1}\right)\right]} \quad (1)$$

$$F(A) = \frac{\frac{I(3AD+3AL)}{4}}{\left[\left(\frac{I(5DA+5DL)}{4}\right)+\left(\frac{I(3AD+3AL)}{4}\right)+\left(\frac{I(1L)}{1}\right)\right]} \quad (2)$$

$$F(L) = \frac{\frac{I(1L)}{1}}{\left[\left(\frac{I(5DA+5DL)}{4}\right)+\left(\frac{I(3AD+3AL)}{4}\right)+\left(\frac{I(1L)}{1}\right)\right]} \quad (3)$$

The experimental ester bond molar content (EB) in the resulting polymer can be calculated according to the equation 4:

$$EB(\%) = 100 \times \frac{2f(D)}{(2f(D)+f(L))} \quad (4)$$

The initial Amide/ester ratio of PALE, PALP, PALB and PALH polymers is 25/75, experimental determination of this ratio from the intensities of resonances of NMR spectra shows that these polymers possess very close experimental ester bond percentage (77.5%) and final monomer composition (38.3% of diol, 39.3% of Adipic acid and 22.2% of L-Alanine). In the same way for PALI, in which the final ester bond percentage is 72.9%, and it contains 35.3% of Isosorbide, 38.3% of Adipic acid and 26.2% of L-Alanine.

Differential scanning calorimetry and thermogravimetric data of these PEAs are summarized in table 5. The polymers are obtained in a totally amorphous state. It should be noted that the transition temperature (T_g) decreases when the aliphatic diol sequence becomes longer. This result is expected since the aliphatic chain length in the polymer structure provides some flexibility which facilitates segmental rotations thus leads to human falls in (Tg) values.

While, the presence of cyclic units in the polymer PALI gives it some rigidity which is manifested by an increase in its glass transition temperature (20°C). DSC curves of these polymers are shown in figure 3. All PEAs are thermally stable and exhibit 5% mass loss temperatures ($T_{d,5\%}$) that can reach 320°C.

The intrinsic viscosities of all Poly(ester amide)s are evaluated in chloroform at 25°C, the results shown in table 5 indicate that these samples possess good intrinsic viscosities, that can reach 0.5 dl/g for PALP.

Table 5 presents also the values of M_w and $Đ_M$ of different copolymers. All polymers possess important molar masses (for PALB, M_w can reach 22680 g/mol) in the exception of PALI copolymer. The moderate molecular weight and intrinsic viscosity of this sample can be explicated by the difficulty of eliminating the excess of Isosorbide during the reaction, which has a high boiling temperature.

Table 5. Size exclusion chromatography (SEC), Intrinsic viscosity [η_{int}] and thermal analyses (DSC, TGA), of PALD polymers: Mass-average molar mass (M_w), molar-mass dispersity ($Đ_M$), glass transition temperature (T_g) and 5% mass loss temperature ($T_{d,5\%}$).

Polymer	M_w* (g/mol)	$Đ_M$*	[η_{int}]** (dl/g)	T_g (°C)	$T_{d,5\%}$ (°C)
PALE	19080	2.0	0.36	-16	304
PALP	19450	2.1	0.50	-22	309
PALB	22680	2.4	0.40	-27	320
PALH	15580	2.2	0.22	-34	234
PALI	2780	1.8	0.09	20	224

3.2 Influence of Amide/Ester ratio

PALB-x/y poly(ester-amide)s were synthesized by changing the amide ester ratio of initial monomers, this variety in their composition has a notable effect on spectroscopic data, thermal properties, viscosity and SEC measurement of resulting polymers.

In FTIR spectra of PALB-50/50 to 10/90 copolymers, we observe the characteristic absorption bands corresponding to amide NH (a), amide I (d), and amide II (e) at 3300, 1648, and 1532 cm^{-1}, to aliphatic CH (b) at 1941 cm^{-1}, ester carbonyl (c) and at 1727, and C–O simple bond (f) at 1164 cm^{-1}. Their relative intensities vary in the expected way when the amide/ester ratio changes. For instance, decreasing L-alanine content clearly leads to a decrease of the amide I absorption which appears at 1648 cm^{-1}(peak (d)).(Fig 4).

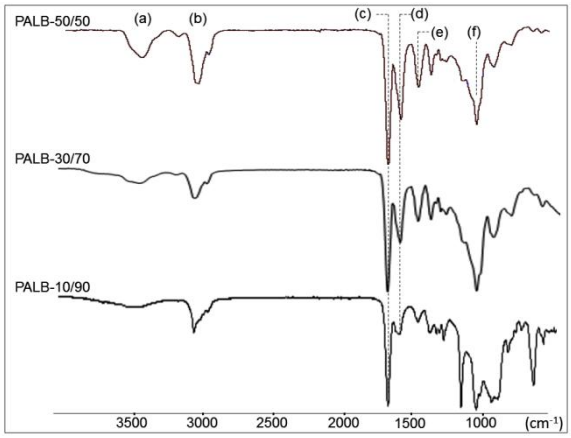


Figure 4. Infrared spectra of PALB-50/50, 30/70 and 10/90. See text for comments on absorptions (a)-(f)

All proton NMR spectra exhibit the expected signals relative to the different dyads mentioned in table 2, a typical spectrum of PALB-50/50 is shown in Fig.2-B. The resonances were assigned with the help of 2D $^{1}H/^{1}H$ (cosy 45) spectrum of PALB-50/50 shown in Fig. 5. In addition to 1^{LL} and 2^{LL} signals respectively at 4.56 and 1.40 ppm relative to amides sequences, and 3^{AB} and 5^{BA} signals respectively at 2.32 and 4.08 ppm relative to ester sequences, we observe also the expected signals related to mixed ester-amide dyads synonym of the good progress of the interchange reaction. The formation of these sequences is confirmed by the presence of 5^{BL} and 4^{AL} signals at 4.15 and 2.23 ppm respectively.

As mentioned above, the proton resonances of the -CH- and -CH_3 of L-alanine units are not affected by the nature of neighboring units (($1^{LL} = 1^{LB} = 1^{LA} = 1^{L}$, observed at 4.56 ppm and $2^{LL} = 2^{LB} = 2^{LA} = 2^{L}$, observed at 1.40 ppm)).

Monomer composition and ester bond percentage were calculated as previously from ^{1}H-NMR spectra following the equations 1, 2, 3 and 4. The summarized data in Table 6 show a good agreement between the final composition of PALB-x/y copolymers and the monomers feed ratio, with the exception of polymers PALB-50/50 and 40/60 having the higher L-Alanine fraction. In fact, they exhibit a slight increase in the final ester ratio, this is caused by the sublimation of L-alanine during the reaction.

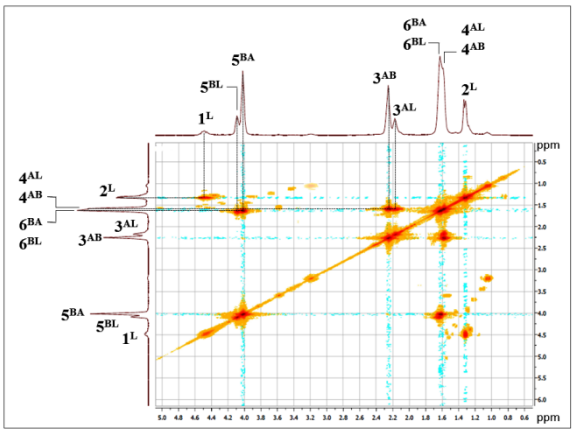


Figure 5. 2D ^{1}H-^{1}H COSY NMR spectrum of PALB-50/50 copolymer (300 MHz, $CDCl_3$, ref δ ($CHCl_3$) = 7.26 ppm)

Table 6. Composition of PALB-x/y copolymers

	Composition			
Polymer	*f* B (%)	*f* A (%)	*f* L (%)	EB (%)
PALB-50/50	33.3	36.3	30.3	68.7
PALB-40/60	34.3	35.3	30.3	69.3
PALB-30/70	37.3	38.3	24.2	75.5
PALB-20/80	40.4	42.4	17.1	82.4
PALB-10/90	43.8	45.9	10.2	89.5

Fig. 6 shows the ^{13}C-NMR spectrum of a representative polymer (PALB-50/50). Great complexity can be found, since multiple peaks are observed for each kind of carbon due to their sensitivity to the different neighbors, suggesting a non-block distribution of monomers.

Chemical shifts, and assignments related to the most significant carbons; -***CO***, -***CH***$_2$-O, -***CH***(CH$_3$)-NH, -***CH***$_2$-CO, -***CH***$_2$-CH$_2$O, -***CH***$_2$-CH$_2$CO and -***CH***$_3$, are reported in table 7.

Signals near 65 ppm (attributed to the *CH*$_2$-*O*- carbon atom of a butanediol unit) appear split due to neighboring group effects. Four observed signals are attributed to four different sequences B-L-L, B-L-A, B-A-B and B-A-L. Note that these signals are split, since differences appear after only five or seven atoms for B-L and B-A dyads respectively.

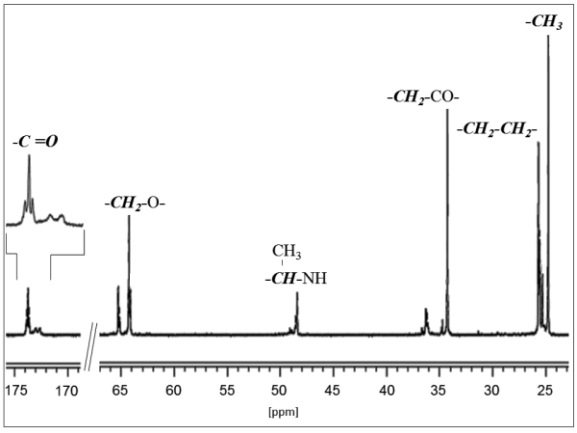


Figure 6. ^{13}C-NMR spectrum of PALB-50/50 showing zones associated to the -*CO*, -*CH*$_2$O -, -*CH*(CH$_3$)-NH, -*CH*$_2$CO, -*CH*$_2$*CH*$_2$- and -*CH*carbons with their chemical shifts (ppm) (300 MHz, $CDCl_3$, ref δ ($CDCl_3$) = 77.16 ppm)

The methylene adjacent to the CO group (Adipic unit) appears split into four signals. These signals are associated to the triads B-A-B, L-A-B, B-A-L or L-A-L, since chemical differences are found after only four atoms in the direction of the preceding monomer and one atom in the direction of the following monomer. As a general trend, sequences with ester groups move downfield with respect to similar ones constituted by amide groups. This fact, together with the displacements deduced from the reference polymers, allows the assignment given in table 7 to be proposed.

Much more complicated is the assignment of signals corresponding to the methylene adjacent to other methylene groups that appears near 25 ppm and that can belong either to a butanediol or an adipic unit. The observed signals are associated to seven possible triads taking into account the influence of adjacent units on the chemical shift value of the observed signal.

It should be noted that the resonances corresponding on L-Alanine methyl groups are not affected by the nature of neighboring units and appear at 24.77 ppm, while -CH- carbons are manifested by two signals at 48.41 and 48.59 ppm depending on the nature of the adjacent unit.

Table 7.Chemical shifts, and assignments of the ^{13}C-NMR spectrum of PALB-50/50

	Sequence	***δ* (ppm)**
L-B	–CO–NH–CH(CH_3)***CO***–O–	173.85
B-A-B	–O–CO(CH_2)$_4$***CO***–O–	173.72
L-A-B	–NH–CO(CH_2)$_4$***CO***–O–	173.60
L-L-L	–CO–NH–CH(CH_3)***CO***–NH–CH(CH_3)CO–	173.00
A-L	–CO(CH_2)$_4$***CO***–NH–CH(CH_3)CO–	172.61
B-L-L	–***CH*$_2$**O–CO–CH(CH_3)–NH–CO–CH(CH_3)NH–	65.28
B-L-A	–***CH*$_2$**O–CO–CH(CH_3)–NH–CO(CH_2)$_4$CO–	65.15
B-A-B	–***CH*$_2$**O–CO(CH_2)$_4$CO–O–	64.27
B-A-L	–***CH*$_2$**O–CO(CH_2)$_4$CO–NH–	64.14
B-L-L	–O–CO–***CH***(CH_3)–NH–CO–CH(CH_3)NH–	48.59
B-L-A	–O–CO–***CH***(CH_3)–NH–CO(CH_2)$_4$CO–	48.59
L-L-L	–NH–CO–***CH***(CH_3)–NH–CO–CH(CH_3)NH–	48.41
L-L-A	–NH–CO–***CH***(CH_3)–NH–CO(CH_2)$_4$CO–	48.41
B-A-B	–O–CO(CH_2)$_3$***CH*$_2$**CO–O–	36.30
L-A-B	–NH–CO(CH_2)$_3$***CH*$_2$**CO–O–	36.14
B-A-L	–O–CO(CH_2)$_3$***CH*$_2$**CO–NH–	34.74
L-A-L	–NH–CO(CH_2)$_3$***CH*$_2$**CO–NH–	34.26
A-B-L	–CO–OCH$_2$CH$_2$***CH*$_2$**CH$_2$O–COCH(CH_3)NH–	25.70
L-B-A	–NHCH(CH_3)CO–OCH$_2$CH$_2$***CH*$_2$**CH$_2$O–CO–	25.70
A-B-A	–CO–OCH$_2$***CH*$_2$*CH*$_2$**CH$_2$O–CO–	25.70
B-A-B	–O–COCH$_2$***CH*$_2$*CH*$_2$**CH$_2$CO–O–	25.58
L-A-B	–NH–COCH$_2$CH$_2$***CH*$_2$**CH$_2$CO–O–	25.58
B-A-L	–CH$_2$O–COCH$_2$CH$_2$***CH*$_2$**CH$_2$CO–NH–	25.33
L-A-L	–NH–COCH$_2$***CH*$_2$*CH*$_2$**CH$_2$CO–NH–	25.33
B-L-A	–O–COCH(***CH*$_3$**)NH–CO(CH_2)$_4$CO–	24.77
B-L-L	–O–COCH(***CH*$_3$**)NH–COCH(CH_3)-NH–	24.77
L-L-A	–NH–COCH(***CH*$_3$**)NH–CO(CH_2)$_4$CO–	24.77
L-L-L	–NH–COCH(***CH*$_3$**)NH–COCH(CH_3)NH–	24.77

(*) carbon attributed

As expected, the DSC results of PALB-x/y copolymers show a clear relationship of the T_g values with the Amide/ester ratio. Indeed, increasing the fraction of L-alanine in the polymer composition improves its glass transition temperature, due to the formation of intermolecular hydrogen bonds. These polymers are thermally stable and exhibit 5% mass loss temperatures ($T_{d,5\%}$) above 280°C (Table 8). They are totally amorphous, in the exception of PALB-10/90 which possesses a semi-crystalline structure with a melting temperature in the order of 28°C. This is clearly due to its very high ester ratio.

Very important intrinsic viscosities and molecular weights were obtained for PALB-x/y polymers (Table 8), however we noticed that the increase in L-alanine molar fraction in the initial mixture leads to a molar mass decrease of polymers. A similar negative effect of amino-acids on molar mass has been reported for the synthesis of glycine or β-alanine based PEAs and was interpreted by a partial catalyst deactivation due to interactions between titanium and amine and/or amide groups present during the reaction (15, 16).

Table 8. Size exclusion chromatography (SEC), Intrinsic viscosity [η_{int}] and thermal analyses (DSC, TGA), and of PALB-x/y polymers: Mass-average molar mass (M_w), molar-mass dispersity ($Đ_M$), glass transition temperature (T_g), melting point (T_m), melting enthalpy (ΔH_m) and 5% mass loss temperature ($T_{d,5\%}$).

Polymer	M_w* (g/mol)	$Đ_M$*	$[\eta_{int}]$** (dl/g)	T_g (°C)	T_m (°C)	ΔH_m (J/g)	$T_{d,5\%}$ (°C)
PALB-50/50	6430	2.7	0.16	-10	-	-	284
PALB-40/60	9170	2.2	0.24	-14	-	-	281
PALB-30/70	11220	1.9	0.75	-14	-	-	311
PALB-20/80	32380	2.0	0.88	-27	-	-	320
PALB-10/90	41800	2.7	1.06	-42	28	2.6	330

*Determined by SEC using polystyrene standards.
**1.5 dl/g of polymer in $CHCl_3$ at 25°C.

Conclusion

In this work we have studied the synthesis and characterization of a series of poly(ester-amide)s derived from L-Alanine, adipic acid and five different diols. The Infrared and NMR results are fully consistent with their anticipated chemical structures. Final monomer composition of all PEAs was evaluated from 1H-NMR spectra, the resulting data show a good agreement between the final composition and the monomer feed ratio. All resulting polymers are thermally stable to temperatures that could reach 330°C. We noticed the influence of the nature of used diol on the glass transition temperature values (Tg) of PALD polymers, indeed this temperature decreases when the aliphatic sequence of the diol is longer. The use of a diol having a heterocyclic structure (isosorbide) increases the Tg value, and hence improve the thermal properties of the resulting polymer. The impact of Amide/ester ratio on thermal properties was studied through PALB-x/y polymers. As expected, the increase in amino acid content leads to an increase in the glass transition temperature. These polymers possess very high inherent viscosities that could reach 1.06 dl/g for PALB-10/90, and therefore very important molecular weights (Mw=41800g/mol).

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