Synthesis and Characterization of Poly(ε-caprolactone)-Containing Amino Acid-Based Poly(ether ester amide)s

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ABSTRACT: A new family of biodegradable amino acid-based poly(ether ester amide)s (AA-PEEAs) consisting of three building blocks [poly(ε-caprolactone) (PCL), L-phenylalanine (Phe), and aliphatic acid dichloride] were synthesized by a solution polycondensation. Using DMA as the solvent, these PCL-containing Phe-PEEA polymers were obtained with fair to very good yields with weight average molecular weight (M_w) ranging from 6.9 kg/mol to 31.0 kg/mol, depending on the original molecular weight of PCL. The chemical structures of the PCL-containing Phe-PEEA polymers were confirmed by IR and NMR spectra. These PCL-containing Phe-PEEAs had lower T_g than most of the oligoethylene glycol (OEG) based AA-PEEAs due to the more molecular flexibility of the PCL block in the backbones, but had higher T_g than non-amino acid based PEEA. The solubility of the PCL-containing Phe-PEEA polymers in a wide range of common organic solvents, such as THF and chloroform, was significantly improved when comparing with aliphatic diol based poly(ester amide)s and OEG based AA-PEEAs. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 125: 812–819, 2012

Key words: amino acids; poly(ether ester amide); polycaprolactone; biodegradable polymers; unsaturated biodegradable polymers; polycondensation

INTRODUCTION

Synthetic biodegradable (or bioabsorbable) and biocompatible polymers with controllable absorption lifetimes have become increasingly important due to their wide range of applications in biomedical and tissue engineering.[1–5] Amino acid based poly(ester amide)s (AA-PEAs) are one of the most promising synthetic biodegradable polymers that derived from amino acids and non-amino acid building blocks. The integration of polyester and polyamide moieties into a single entity like AA-PEAs could provide researchers with tremendous opportunities of tuning the properties of the resulting AA-PEA polymers to meet a desirable profile in terms of biodegradability, chemical, mechanical, physical, thermal, and biological properties.[6–15]

In our laboratory, amino acid derived PEAs having saturated (SPEA)[16,17] and unsaturated (UPEA) backbones,[9] copolymers of SPEA and UPEA (USPEA),[18] and functional AA-PEAs[6–8,13–15] have been designed, successfully synthesized, and characterized. Most of those published AA-PEAs have three building blocks: amino acids, aliphatic diols, and diacids. Recently, oligoethylene glycol (OEG) like diethylene glycol and tetraethylene glycol were also introduced into the AA-PEA macromolecular backbone as the replacement for aliphatic diols.[11,19] These new AA-PEA family, poly(ether ester amide) (AA-PEEA), have ether bonds incorporated in addition to the ester and amide linkages common to all AA-PEAs. As a result, the hydrophilicity, solubility, and biodegradability of these OEG-based PEEAs were found to be enhanced when compared to the AA-PEA polymers and copolymers designed and synthesized from conventional aliphatic diols.

In this study, a low molecular weight aliphatic polyester, poly(ε-caprolactone) (PCL), was used to replace the conventional aliphatic diols for the design and synthesis of a new family amino acid-based PEAs that could provide not only more flexible backbone chains but also hydrolytic degradation capability due to the presence of the PCL segment. PCL is a well-known FDA approved synthetic absorbable aliphatic polyester with known biocompatibility and absorption property; PCL is one of the most frequently used absorbable biomaterials in drug delivery and surgical implants due to its biocompatibility, low T_g, and high permeability.[20] By incorporating PCL block into the AA-PEA backbone chain, the PCL-containing AA-PEAs obtained would have controllable PCL block with ether bond, which can be used to balance the rigidity of the polymer backbone thus to improve the thermal properties of the AA-PEEA polymers.

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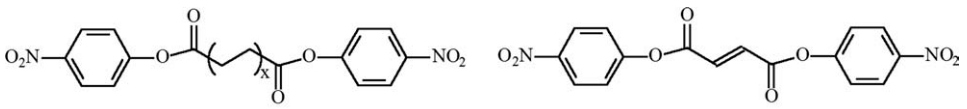


Ia: di-*p*-**N**itrophenyl **A**dipate (**NA**), x=2
Ib: di-*p*-**N**itrophenyl **S**ebacate (**NS**), x=4

Ic: di-*p*-**N**itrophenyl **F**umarate (**NF**)

Scheme 1 Di-*p*-nitrophenyl esters of dicarboxylic acids as monomer I.

In this report, a series of saturated and unsaturated PCL-containing L-phenylalanine-PEEAs (PCL-Phe-PEEA) were synthesized by a solution polycondensation of unsaturated or saturated diester monomers and saturated PCL-based Phe diamine salts. The chemical structures of these PCL-Phe-PEEAs were confirmed by FTIR and NMR spectra. The molecular weight, molecular weight distribution (MWD), thermal property, and solubility of the resulting PCL-Phe-PEEA polymers were examined as well.

EXPERIMENTAL

Materials

L-Phenylalanine (L-Phe), *p*-toluenesulfonic acid monohydrate (TosOH·H_2O), sebacoyl chloride, adipoyl chloride, fumaryl chloride (Alfa Aesar, Ward Hill, MA), polycaprolactone diol, (PCL-diol, M_n = 530 or 1250 g/mol, Aldrich), and *p*-nitrophenol (J. T. Baker, Phillipsburg, NJ) were used without further purification. Triethylamine from Fisher Scientific (Fairlawn, NJ) was dried by refluxing with calcium hydride, and then distilled. *N,N*-Dimethylforamide (DMF) from Aldrich Chemical Company (Milwaukee, WI) was dried over calcium hydride and distilled. Other solvents like benzene, trifluoroethanol (TFE), tetrahydrofuran (THF), ethyl acetate, acetone, acetonitrile, *N,N*-dimethylacetamide (DMA), and dimethyl sulfoxide (DMSO) were purchased from VWR Scientific (West Chester, PA) and were purified by standard methods before use.

Synthesis of monomers and polymers

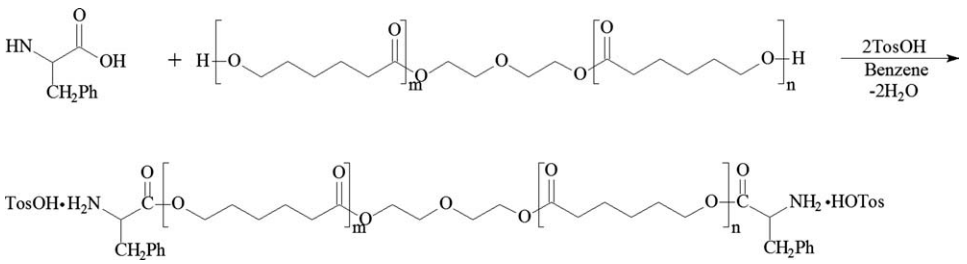
The synthesis of PCL-based PEEAs involved the following three basic steps: (1) synthesis of three di-*p*-nitrophenyl esters of dicarboxylic acids (**I**), one of which was unsaturated and the other two were saturated; (2) synthesis of two di-*p*-toluenesulfonic acid salts of *bis*-L-Phe esters (**II**) from PCL-diols; and (3) solution polycondensation of the monomers, (**I**) and (**II**), obtained in steps (1) and (2).

Synthesis of di-p-nitrophenyl esters of dicarboxylic acids (I)

Three di-*p*-nitrophenyl esters of dicarboxylic acids (**Ia**, **Ib,** and **Ic**, Scheme 1) were prepared by reacting the corresponding dicarboxylic acyl chlorides with *p*-nitrophenol as described previously.[9]

Synthesis of di-p-toluenesulfonic acid salts of *bis*-L-Phe esters (II)

Di-*p*-toluenesulfonic acid salts of *bis*-L-Phe esters were prepared by the modified procedures of our previous published study[9] as shown in Scheme 2. Instead of using toluene as the solvent in our prior study,[9] benzene was used because the high boiling point of toluene may cause the decomposition of the reactants. Typically, L-Phe (0.176 mol), *p*-toluenesulfonic acid monohydrate (0.176 mol), and PCL-diols (0.08 mol) in 300 mL of benzene were placed in a flask equipped with a Dean-Stark apparatus, a $CaCl_2$ drying tube, and a magnetic stirrer. The solid-liquid reaction mixture was heated (c.a. 100°C) to reflux for 16 h until 6.1 mL (0.34 mol) of water evolved. The reaction mixture was then cooled to room temperature. After the solvent was removed by rotate evaporation, the mixture was dried *in vacuo* overnight and finally purified by recrystallization from 2-propanol for three times.



Scheme 2 Synthesis of di-*p*-toluenesulfonic acid salts of *bis*-L-phenylalanine polycaprolactone ester (Phe-PCL) as monomer II. PCL-diol, M_n = 530 or 1250 g/mol.

TABLE I
Monomer Combinations for PCL-Containing AA-PEEAs

		Monomer II	
		Phe-PCL530	Phe-PCL1250
Monomer I	NF	FP-PCL530	FP-PCL1250
	NA	AP-PCL530	AP-PCL1250
	NS	SP-PCL530	SP-PCL1250

Phe-PCL530 and Phe-PCL1250

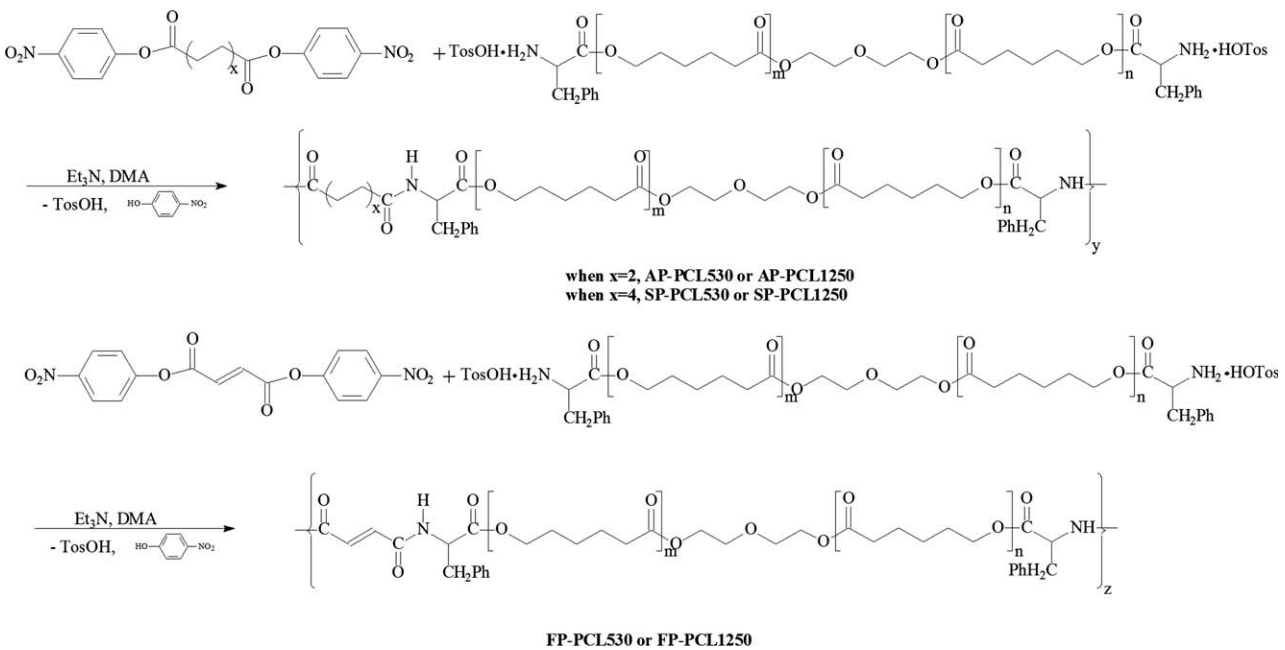
Recrystallized from 2-propanol

mp: 34°C (Phe-PCL530); 44°C (Phe-PCL1250). IR (cm^{-1}): 1737 [—C(O)—], 1177 (—O—), 1127 (—CH_2—O—CH_2—). ^{1}H NMR (DMSO-d_6, ppm, δ): 1.16 (—O—C_2H_4—**C**H_2—C_2H_4—), 1.29 (—O—CH_2—**C**H_2—C_3H_6—), 1.53 [—O—C_3H_6—**C**H_2—CH_2—], 2.27, [—O—C_4H_8—**C**H_2—C(O)—], 2.29 (H_3C—Ph—SO_3—), 3.05, 3.10 (PhCH_2—), 3.60 [—(O)C—O—CH_2—CH_2—O—], 3.98 [—O—**C**H_2—C_4H_8—C(O)—], 4.11 [$^+H_3$N—C**H**(CH_2Ph)—], 4.31 [—(O)C—O—CH_2—CH_2—O—], 7.10–7.44 (—CH_2—**Ph**), 7.46, 7.48 (H_3C—**Ph**—SO_3—), 8.37 [$^+$**H**$_3$N—CH(CH_2Ph)—]. ^{13}C NMR (DMSO-d_6, ppm, δ): 20.72 (H_3**C**—Ph—SO_3—), 24.05 [—O—C_3H_6—**C**H_2—CH_2—], 24.86 (—O—C_2H_4—**C**H_2—C_2H_4—), 27.77 (—O—CH_2—**C**H_2—C_3H_6—), 33.31 [—O—C_4H_8—**C**H_2—C(O)—], 36.11 (Ph**C**H_2—), 53.18 [$^+H_3$N—**C**H(CH_2Ph)—], 63.44 [—O—**C**H_2—C_4H_8—C(O)—], 65.31 [—(O)C—O—**C**H_2—CH_2—O—], 68.17 [—(O)C—O—CH_2—CH_2—O—], 125.45, 127.17, 128.50, 137.76, (**Ph**CH_2—), 128.05, 129.28, 134.57, 145.32 (H_3C—**Ph**—), 169.04 [—CH—**C**(O)—], 172.67 (—C_5H_{10}—**C**(O)—O—].

Solution polycondensation of monomers I and II

PEEAs based on PCL—OH (linked by ether bond) were prepared by the solution polycondensation of di-*p*-toluenesulfonic acid diester salt (Phe-PCL530 or Phe-PCL1250) with one di-*p*-nitrophenyl ester (NA, NS, or NF). The combinations tried in this study and their name designations are summarized in Table I and shown in Scheme 3. In Table I, the designations of AA-PEEAs starting with F like FP-PCL530 or FP-PCL1250 were unsaturated AA-PEEAs with C=C double bonds in the diamide segment and the rest AA-PEEA designations were saturated.

An example of the synthesis of AP-PCL530 via a solution polycondensation is given below to illustrate the details of the synthesis procedures. Ten millimoles (1.42 mL) triethylamine was added dropwise to the mixture of monomers NA (**Ia** 4.0 mmol) and Phe-PCL530 (**IIa** 4.0 mmol) in 3 mL of dry DMA, and the solution was heated to 60°C with stirring until a complete dissolution of monomers. The reaction vial was then kept at 70°C for 48 h without stirring. The resulting viscous solutions were precipitated by different solvents, depending on fumaryl based polymer or nonfumaryl based polymer. For the fumaryl-based AA-PEEA polymer (FP-PCL530 and FP-PCL1250), the viscous solution was poured into chilled ethyl acetate to precipitate the product. The polymers were then filtered and extracted by ethyl acetate in a Soxhlet apparatus for 48 h, and finally dried *in vacuo* for 48 h. For the rest AA-PEEA polymers (nonfumarate-based), chilled ethyl ether was used as the precipitation solvent and then polymer was washed by ethyl ether twice,



Scheme 3 Synthesis of saturated and unsaturated polycaprolactone and L-phenylalanine-based poly(ether ester amide)s.

filtered, and finally dried *in vacuo* for 48 h before a further study.

AP-PCL530/AP-PCL1250

IR (cm^{-1}), 1738 [—**C(O)**—O—], 1643, 1532 [—**C(O)**—NH—], 1126 (—CH_2—O—CH_2—), 3306 [—C(O)—**NH**—]. ^{1}H NMR (DMSO-d_6, ppm, δ): 1.29 [—NH—(O)C—CH_2—C**H**$_2$—], 1.46 [—O—C_2H_4—C_2**H**$_4$—CH_2—], 1.76 [—O—C_4H_8—**CH**$_2$—], 1.99 [—NH—(O)C—C**H**$_2$—], 2.28 [—O—C_3H_6—**CH**$_2$—CH_2—], 2.94 [PhC**H**$_2$—], 3.56 [—(O)C—O—CH_2—C**H**$_2$—O—], 3.96 [—O—C**H**$_2$—C_4H_8—], 4.11 [—(O)C—O—C**H**$_2$—CH_2—O], 4.45 [—HN—C**H**(CH_2Ph)—], 7.19–7.24 [—**Ph**], 8.24 [—**H**N—CH(CH_2Ph)—]. ^{13}C NMR (DMSO-d_6, ppm, δ): 23.99 [—O—C_2H_4—**C**H_2—C_2H_4—], 24.04 [—O—C_3H_6—**C**H_2—CH_2—], 24.55 [—NH—(O)C—CH_2—**C**H_2—], 27.75 [—O—CH_2—**C**H_2—C_3H_6—], 33.30 [—O—C_4H_8—**C**H_2—], 34.63 [—NH—(O)C—**C**H_2—], 36.67 [Ph**C**H_2—], 53.41 [—HN—**C**H(CH_2Ph)—], 63.46 [—(O)C—O—**C**H_2—CH_2—O—], 63.69 [—(O)C—O—**C**H_2—C_4H_8—], 68.05 [—(O)C—O—CH_2—**C**H_2—O—], 126.42, 128.12, 128.99, 137.13 [—**Ph**], 166.12 [—(O)**C**—O—C_2H_4—O—], 171.65 [—(O)**C**—O—C_5H_{10}—], 172.10 [—**C**(O)—NH—].

SP-PCL530/SP-PCL1250

IR (cm^{-1}), 1736 [—**C(O)**—O—], 1645, 1530 [—**C(O)**—NH—], 1124 (—CH_2—O—CH_2—), 3309 [—C(O)—**NH**—]. ^{1}H NMR (DMSO-d_6, ppm, δ): 1.11 [—NH—(O)C—C_2H_4—C_2**H**$_4$—], 1.37 [—NH—(O)C—CH_2—C**H**$_2$—], 1.48 [—O—CH_2—C_2**H**$_4$—C_2H_4—], 2.01 [—O—C_4H_8—**CH**$_2$—], 2.03 [—NH—(O)C—C**H**$_2$—], 2.27 [—O—C_3H_6—**CH**$_2$—CH_2—], 2.94 [PhC**H**$_2$—], 3.54 [—(O)C—O—CH_2—C**H**$_2$—O—], 3.97 [—O—C**H**$_2$—C_4H_8—], 4.12 [—(O)C—O—C**H**$_2$—CH_2—O], 4.47 [—HN—C**H**(CH_2Ph)—], 7.18–7.24 [—**Ph**], 8.23 [—**H**N—CH(CH_2Ph)—]. ^{13}C NMR (DMSO-d_6, ppm, δ): 23.99 [—O—C_2H_4—**C**H_2—C_2H_4—], 24.03 [—O—C_3H_6—**C**H_2—CH_2—], 25.10 [—NH—(O)C—CH_2—**C**H_2—], 27.75 [—O—CH_2—**C**H_2—C_3H_6—], 28.41 [—NH—(O)C—C_3H_6—**C**H_2—], 28.64 [—NH—(O)C—C_2H_4—**C**H_2—], 33.29 [—O—C_4H_8—**C**H_2—], 34.92 [—NH—(O)C—**C**H_2—], 36.62 [Ph**C**H_2—], 53.35 [—HN—**C**H(CH_2Ph)—], 63.44 [—(O)C—O—**C**H_2—CH_2—O—], 63.69 [—(O)C—O—**C**H_2—], 68.08 [—(O)C—O—CH_2—**C**H_2—O—], 126.38, 128.07, 128.98, 137.19 [—**Ph**], 166.12 [—(O)**C**—O—C_2H_4—O—], 171.67 [—(O)**C**—O—C_5H_{10}—], 172.27 [—**C**(O)—NH—].

FP-PCL530/FP-PCL1250

IR (cm^{-1}), 1730 [—**C(O)**—O—], 1627, 1536 [—**C(O)**—NH—], 1120 (—CH_2—O—CH_2—), 3301 [—C(O)—**NH**—]. ^{1}H NMR (DMSO-d_6, ppm, δ): 1.15 [—O—C_2H_4—C**H**$_2$—C_2H_4—], 1.51 [—O—CH_2—C**H**$_2$—C_3H_6—], 1.99 [—O—C_4H_8—**CH**$_2$—], 2.29 [—O—C_3H_6—**CH**$_2$—CH_2—], 2.99 [PhC**H**$_2$—], 3.55 [—(O)C—O—CH_2—C**H**$_2$—O—], 3.98 [—O—C**H**$_2$—C_4H_8—], 4.14 [—(O)C—O—C**H**$_2$—CH_2—O], 4.56 [—HN—C**H**(CH_2Ph)—], 6.83 [—C(O)—C**H**=], 7.20–7.26 [—**Ph**], 8.88 [—**H**N—CH(CH_2Ph)—]. ^{13}C NMR (DMSO-d_6, ppm, δ): 24.04 [—O—C_2H_4—**C**H_2—C_2H_4—], 24.84 [—O—C_3H_6—**C**H_2—CH_2—], 27.75 [—O—CH_2—**C**H_2—C_3H_6—], 33.30 [—O—C_4H_8—**C**H_2—], 36.57 [Ph**C**H_2—], 53.82 [—HN—**C**H(CH_2Ph)—], 63.44 [—(O)C—O—**C**H_2—CH_2—O—], 63.91 [—(O)C—O—**C**H_2—], 68.06 [—(O)C—O—CH_2—**C**H_2—O—], 126.56, 128.20, 128.99, 136.84 [—**Ph**], 132.51 [—C(O)—**C**H=], 163.51 [—**C**(O)—NH—]. 171.09 [—(O)**C**—O—**C**$_2$ H_4—O—], 172.73 [—(O)**C**—O—C_5H_{10}—].

Materials characterization

For Fourier transform infrared (FTIR) characterization, samples were ground into powder and mixed with KBr at a sample to KBr ratio of 1 : 10 w/w. FTIR spectra were then obtained from a Perkin-Elmer Nicolet Magana 560 (Madison, WI) FTIR spectrometer with Omnic software for data acquisition and analysis.

NMR spectra were recorded by a Varian Unity INOVA-400 400MHz spectrometer (Palo Alto, CA) operating at 400 and 100 MHz for ^{1}H and ^{13}C NMR, respectively. Deuterated dimethyl sulfoxide (DMSO-d_6, Cambridge Isotope laboratories) was used as the solvent.

Thermal property of the synthesized monomers and polymers was characterized by a DSC 2920 (TA Instruments, New Castle, DE), and the scan was carried out from 0 to 300°C at a heating rate of 10°C/min and nitrogen gas flow rate of 25 mL/min. TA Universal Analysis™ software was used for thermal data analysis. The melting point (T_m) was determined at the onset of the melting endotherm. The glass transition value (T_g) was obtained as an average of the onset and end values.

The number and weight averaged molecular weights (M_n and M_w) and (MWD of the PCL-based PEEAs were determined by Model 510 gel permeation chromatography (Waters Associates, Milford) equipped with a high-pressure liquid chromatographic pump, a Waters 486 UV detector and a Waters 2410 different refractive index detector. THF was used as the eluent (1.0 mL/min). The columns were calibrated with polystyrene standards having a narrow MWD.

RESULTS AND DISCUSSION

Synthesis of monomers

Three different types of di-*p*-nitrophenyl esters of dicarboxylic acids, NA, NS, and NF, were used as

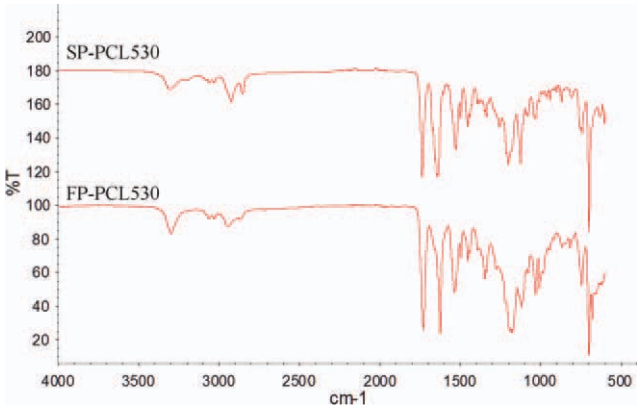


Figure 1 FTIR spectra of two representative PCL-based poly(ether ester amide)s, SP-PCL530, and FP-PCL530. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

monomers **I** in this study to provide the carboxylic ester segment of the PCL-based PEEA. NF has unsaturated double bonds and hence unsaturated, while NA and NS are saturated monomers **I**. All the three monomers were reported in our previous work.[9]

Two PCL-diols of different molecular weights (M_n = 530 Da and 1250 Da) were used in this study to synthesize di-*p*-toluenesulfonic acid salts of *bis*-L-Phe diesters as monomers **II**, and these monomers are synthesized the first time and used as the monomers to provide the amino acid segment of AA-PEEA. Both salts had PCL with ether bonds in the segment.

The chemical structures of the di-*p*-toluenesulfonic acid salts monomers **II**, Phe-PCL530 and Phe-PCL1250, were all confirmed by FTIR and NMR spectra. These two monomers have the similar structure with the only difference in the segment length of PCL (530 Da vs. 1250 Da). Therefore, they have almost the same FTIR and NMR spectra. The FTIR spectra of both Phe-PCL530 and Phe-PCL1250 showed the ester group band around 1737 cm^{-1} and ether group band around 1127 cm^{-1}. Their ^1H and ^{13}C NMR spectra also shared the same characteristic peaks (see the details in Experimental Section). Both monomers were obtained as white powders.

AA-PEEA polymer synthesis

As shown in Scheme 3, six different types of new PCL-based PEEAs were synthesized by the solution polycondensation of different combinations of monomer **I** (**Ia**, **Ib,** or **Ic**) and monomer **II** (**IIa** or **IIb)**. Excess triethylamine was used as the acid receptor for TosOH during the polymerization to regenerate free amino groups in the di-*p*-toluenesulfonic acid salt monomer **II**.[9,16,21] Polymerization took place in a homogeneous phase and the AA-PEEA polymer obtained remained dissolved but became more viscous.

The structures of these AA-PEEAs were all confirmed by both IR and NMR spectra data. Figure 1 shows 2 representative FTIR spectra of the AA-PEEAs (i.e., SP-PCL530 and FP-PCL530). Again, due to the similar structure of Phe-PCL530 and Phe-PCL1250, the polymers also shared the same characteristic IR peaks between AP-PCL530 and AP-PCL1250, SP-PCL530 and SP-PCL1250, or FP-PCL530 and FP-PCL1250. The products had the absorption bands of ester groups ($\sim$ 1740 cm^{-1}), ether groups ($\sim$ 1115 cm^{-1}), and amide groups ($\sim$ 1640 cm^{-1} and $\sim$ 1530 cm^{-1}), while fumaryl-based polymers (FP-PCL530 and FP-PCL1250) also showed unsaturated H—C= bonds ($\sim$ 3030 cm^{-1}).

The NMR spectra (^1H and ^{13}C) of the three AA-PEEAs based on PCL-diol (M_w =530 g/mol) are shown in Figures 2 and 3 (see Experimental Section for detailed spectra peak assignments of all polymers). The spectra data were fully in agreement with the anticipated chemical structure of the PCL-based AA-PEEA polymers shown in Scheme 3. All the polymers showed ^1H peaks of the —NH— bonds of amide (8.88 or 8.24), the ether CH_2—O—CH_2 bonds in the diester unit ($\sim$ 3.55) and —HC= bonds in the amide unit (6.83) for fumaryl based AA-PEEAs. The ^{13}C spectra contained all the peaks for every magnetically different carbon presented in the repeating unit of polymer.

Table II summarizes the fundamental property of the six PCL-based PEEAs synthesized. The PEEAs based on high MW PCL-diol were obtained in much higher yields (83–88%) than those based on low MW PCL-diol (38–51%), which could be due to the more loss of low MW PCL-diol based PEEA in the final purification step.

The M_w of the polymer products varied from 6.9 to 31.0 kg/mol, which are in the similar range of OEG based PEEA reported[11,19] and non-amino acid based PEEA derived from higher molecular weight of PCL.[22] Considering PCL block in each of the polymer repeating unit (530 and 1250 Da), the degree of polymerization could be only about 5 to 20, which suggested the reactivity of these polycondensation reactions are not very high. The molecular weight data of the AP-PCL530 and FP-PCL530 samples, however, were not available because they did not have enough good solubility in THF, the designated eluent for the central GPC facility available to us.

The glass-transition temperatures (T_g) and the melting points (T_m) of the synthesized PCL-based PEEAs were measured by DSC and listed in Table II. Only AP-PCL530 and SP-PCL530 showed a clear glass-transition peak. AP-PCL530 has a higher T_g of 22°C than SP-PCL530's 17°C, which suggested that the more rigid AP-PCL530's molecular backbone

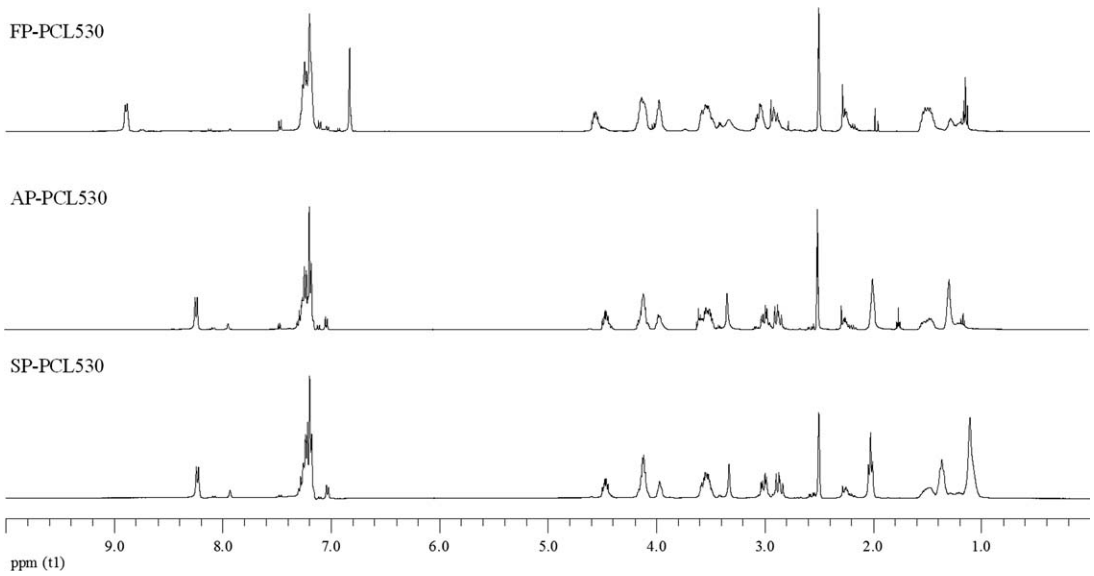


Figure 2 1H NMR spectra of three PCL-based poly(ether ester amide)s in DMSO solvent: AP-PCL530, SP-PCL530, and FP-PCL530.

due to shorter methylene chain length in the diacid segment ($x = 2$). Comparing the results from our previous study of OEG based AA-PEEA,[11] AP-PCL530's T_g is between T_g of AP3EG's (35°C) and AP4EG's (14°C) and SP-PCL530's T_g is between T_g of SP3EG's (23°C) and SP4EG's (12°C). These T_g data indicated the comparable chain flexibility between these two different types of AA-PEEAs, that is, PCL-based AA-PEEA versus OEG based AA-PEEAs. In the Maglio et al. published study,[22,23] however, the non-amino acid-based PEEA synthesized from PCL-OH ($M_n \cong 2$ kDa), polyethylene glycol oligomer (PEG, $M_n = 150$, 300, or 600 Da), trioxy and adipoyl dichloride had T_g as low as from −50 to −58°C due to a more flexible molecular structure with no pendant group. The relatively higher T_g of the PCL-based

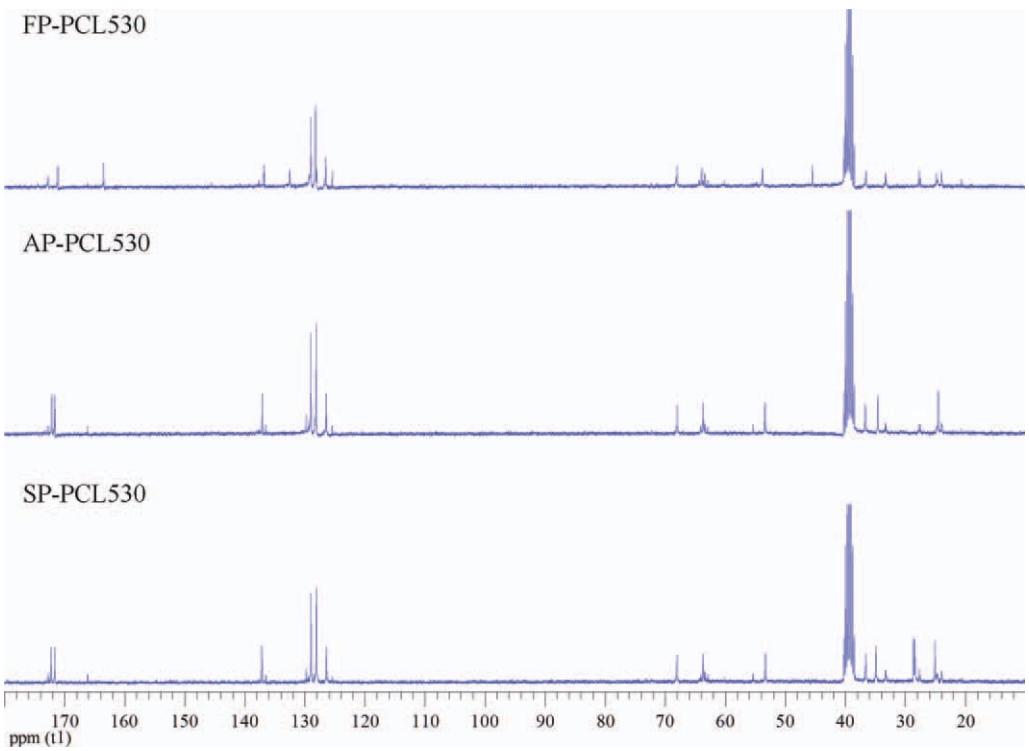


Figure 3 ^{13}C NMR spectra of three PCL-based poly(ether ester amide)s in DMSO solvent: AP-PCL530, SP-PCL530, and FP-PCL530. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II
Fundamental Properties of PCL-Containing AA-PEEAs[a]

	Yield (%)	M_n (kg/mol)	M_w (kg/mol)	M_w/M_n	T_g (°C)	T_m (°C)
AP-PCL530[b]	45	–	–	–	22	75
AP-PCL1250	88	5.6	7.4	1.33	–	56
SP-PCL530	51	4.2	6.9	1.63	17	77
SP-PCL1250	83	8.9	14.1	1.58	–	43
FP-PCL530[b]	38	–	–	–	–	–
FP-PCL1250	85	16.4	31.0	1.89	–	46

[a] Synthesis conditions: $C = 0.90$ mol/L, $T = 70$°C, and DMA as the solvent.
[b] Molecular weight data not available because the polymer cannot dissolved in THF, which is the solvent for the central GPC facility available to us.

AA-PEEAs synthesized in this study was attributed to the presence of pendant aromatic ring structure from the Phe amino acid in each repeating unit of the PCL-based AA-PEEA macromolecules; and it is well-known that a larger pendant ring structure is quite rigid for polymer chain backbone free rotation, that is, decreasing polymer chain flexibility and limiting chain segmental movement, and hence higher T_g.

All the new PCL-based AA-PEEA polymers showed melting peaks, except FP-PCL530. The PCL-based AA-PEEA polymers having a shorter PCL segment (PCL530) showed a higher T_m (75–77°C) than the corresponding ones with a longer PCL segment like PCL1250 (43–56°C), which is expected considering that a longer PCL segment resulted in the more flexible polymer chains. A longer PCL segment in the PCL-based AA-PEEA also reduces the density of amide and ester linkages along the polymer backbone, which, in turn, could reduce the extent of intermolecular hydrogen bond and reflect in a lower T_m. T_m range from the newly developed PCL-based AA-PEEA in this study is much larger than the narrow T_m range from the non-amino acid PCL-based PEEA,[22] which had a T_m range from 49 to 51°C and was lower than T_m of pure PCL (63°C). This difference can be explained by the higher MW of PCL-OH and PEO used in the Maglio et al. study, both of which make the polymers more flexible and easy to melt. When comparing with the OEG based AA-PEEA and their copolymers,[11,19] PCL1250-based PEEA still have a lower T_m, probably due to the high oxygen contents in oligoethylene-based AA-PEEA that the PCL1250 segment does not have, and these oxygen contents could provide intermolecular hydrogen bonds, that is, higher T_m.

As shown in Table III, the solubility of the PCL-based AA-PEEAs (50 mg) in common organic solvents (1.0 mL) at room temperature (25°C) was evaluated. All the PCL-based AA-PEEAs are soluble completely in DMSO, DMF, TFE, THF, and formic acid (except FP2EG), but cannot dissolve in water and ethyl acetate. Except AP-PCL530, the rest can also dissolve in chloroform. The two unsaturated PCL-based AA-PEEAs (FP-PCL530 and FP-PCL1250) share the similar solubility as saturated PCL-based AA-PEEAs in the regular organic solvents tested.

In our previous studies of AA-PEAs derived from aliphatic dialcohols (e.g., SPEA,[16] UPEA,[9] and USPEA[24]) and AA-PEEA derived from OEG,[11,19] the unsaturated polymers usually had poorer solubility than their corresponding saturated ones[9,11] due to the extra conjugation effect between C=C double bonds and carbonyl groups in their structure. For example, FPH, FPB, and FP3EG, which have unsaturated fumaryl group in the polymer-repeating units, cannot dissolve in most common organic solvents, except DMSO and DMF. The incorporation of PCL segment into unsaturated AA-PEEAs, however, improves their solubility in common organic solvents significantly when comparing with prior unsaturated AA-PEAs and AA-PEEAs. This significant improvement in solubility in the PCL-based AA-PEEAs could be attributed to the rather lower degree of polymerization of the PCL-based AA-PEEAs and their relatively high MW of the repeating unit so the polymer properties mainly depended on the PCL blocks. Such an improvement in solubility in common organic solvents would be beneficial for subsequent designing and fabrication of these new polymers for eventual commercial applications.

TABLE III
Solubility of PCL-Containing AA-PEEAs at Room Temperature (25°C)

	H2O	Formic Acid	TFE	DMF	DMSO	THF	MeOH	Ethyl Acetate	$CHCl_3$	Acetone
AP-PCL530	–	+	+	+	+	±	±	–	±	–
AP-PCL1250	–	+	+	+	+	+	±	–	+	+
SP-PCL530	–	+	+	+	+	+	±	–	+	±
SP-PCL1250	–	+	+	+	+	+	±	–	+	+
FP-PCL530	–	+	+	+	+	±	–	–	+	–
FP-PCL1250	–	+	+	+	+	+	±	–	+	+

(+): Soluble; (–): Insoluble; (±): Partially soluble or swell.

CONCLUSIONS

A series of novel biodegradable Phe amino acid-derived unsaturated and saturated AA-PEEAs based on polycaprolactone-diol (PCL-diol) were successfully synthesized by a solution polycondensation. The PCL-containing Phe-PEEA polymers can be obtained with yields ranged from 38 to 88% at 70°C for 48 h in a DMA solvent. The molecular weights (M_n and M_w) measured by GPC could be as high as 31.0 kg/mol and with MWD of 1.89 for FP-PCL1250. The chemical structures of all the six PCL-containing Phe-PEEAs were confirmed by IR and NMR spectra. Two of the saturated PCL-containing Phe-PEEAs showed T_g much higher than that of PCL-based non-amino acid-based PEEAs reported with similar backbone structure. The most important advantage of these new PCL-containing Phe-PEEA polymers is their solubility in common organic solvents, particularly those unsaturated FP-PCL530 and FP-PCL1250, that can dissolve in chloroform, DMA and DMSO, formic acid, and TFE, while unsaturated AA-PEAs based on regular aliphatic diols or OEG based AA-PEEA could not dissolve in any of those common organic solvents. This solubility advantage could facilitate an easier design and fabrication of these new biomaterials for commercial applications.

With the presence of PCL segment in the molecule's backbone, these biodegradable and biocompatible AA-PEEAs may have more promising biomedical applications in tissue engineering, drug/gene delivery, and wound healings as the new family of PCL-containing AA-PEEA integrate the known merits of the FDA-approved PCL biomaterial with the newly developed AA-PEEA. The biodegradability, mechanical properties, and feasibility as a drug/gene carrier for control release are currently still in progress and to be reported later.

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