

Synthesis of biodegradable chiral poly(ester-imide)s derived from valine-, leucine- and tyrosine-containing monomers

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Received: 14 August 2010 / Accepted: 26 October 2010 / Published online: 11 November 2010
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Abstract The present demand for a drastic reduction in environmental pollution is extended to qualitative change in the approach to development of biodegradable polymers. The aim of this article is to focus on the synthesis of biodegradable optically active poly(ester-imide)s (PEI)s, which compose of different amino acids in the main chain as well as in the side chain. These polymers were synthesized by polycondensation of diacid monomers such as 5-(2-phthalimidyl-3-methyl butanoylamino) isophthalic acid (1), 5-(4-methyl-2-phthalimidyl pentanoylamino)isophthalic acid (2) with *N,N'*-(pyromellitoyl)-bis-*L*-tyrosine dimethyl ester (3) as a phenolic diol. The direct polycondensation reaction was carried out in a system of tosyl chloride, pyridine and *N,N*-dimethylformamide as a condensing agent under conventional heating conditions. The optically active PEIs were obtained in good yield and moderate inherent viscosity. The synthesized polymers were characterized by means of FT-IR, ¹H-NMR, elemental and thermo gravimetric analysis techniques. In addition, in vitro toxicity and soil burial test were employed for assessing the

sensitivity of these compounds to microbial degradation. To this purpose, biodegradability behavior of the monomers and polymers were investigated in culture media and soil condition. The results of this study revealed that synthesized monomers and their derived polymers are biologically active and probably microbiologically biodegradable.

Keywords Biodegradable polymers · Polymers containing amino acid · Optically active material · Poly(ester-imide)

Introduction

Today the urgency of reducing environmental pollution with non-biodegradable plastics is a good reason for the intensive efforts to develop new biodegradable polymers. It is now widely accepted that the significance of polymers in our life is unquestioned but the use of long-lasting polymers for short-lived applications is not sustainable. Therefore, biodegradable polymers are finding their way into a variety of applications in material science. Biodegradation is defined as an event in which enzymatic and/or chemical decomposition takes place in associated with living organisms (bacteria, fungi, etc.) or their secreted products (Amass et al. 1998). Naturally occurring biopolymers formed in nature during the growth cycles of all organisms such as polysaccharides, polypeptides and bacterial polyesters are first class of biodegradable polymers. Polymer with hydrolysable backbones such as polyesters, polycaprolactone, polyamides, polyurethanes and polyureas or polymer with carbon backbones such as poly(vinyl alcohol) and polyacrylates are biodegradable synthesized polymers (Chandra and Rustgi 1998). Poly (α -amino acid)s (PAA)s as a new biomaterials have received much attention

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because of incorporating α -amino acids in these compounds. They have generated significant properties which make them structurally tissue-compatible, easily metabolized by living organisms and with nontoxic degradation products (Pitarresi et al. 2008). However, due to their unfavorable mechanical and thermal properties, all of PAAs could not be considered as potential biomaterials (Yu et al. 1999; Huang 2005). To improve the poor physical-mechanical properties of most PAAs, amino acids have been used to design monomers with a different structure from conventional backbone found in peptides containing amino acid. These materials are referred to as 'non-peptide amino-acid-based polymers' or as 'amino-acid-derived polymers' with modified backbones. These have previously been classified into four major groups by Kenmitzer and Kohn (1997). It is worth pointing out that the most important and diffusible biological polymers are optically active. The presence of amino acid in the polymer chains as a chiral group competent induces optical activity into macromolecules (Mallakpour and Kolehdozan 2008; Mallakpour and Mirkarimi 2010; Mallakpour 2010). Amino acids as constitutional components of proteins with a high degree of functionality and chirality play crucial role in the synthesis of biocompatible and biodegradable polymers (Metselaar et al. 2007; Wezenberg et al. 2006). As an example, poly(ester-amide)s containing amino acids, such as phenylalanine, leucine, and alanine, have been synthesized and they have been degraded by enzymes (Fan et al. 2001; Suarez et al. 1998; Tsitlanadzei et al. 2004). Of these, macromolecules that contain amino acid units are potentially useful in many different medical applications such as bio-erodible sutures, tissue engineering scaffolds and drug delivery matrices (Wathier et al. 2006; Gigante et al. 2003; Guo et al. 2007; Yu et al. 2007; Tosi et al. 2007; Brown et al. 2003). Valine is an amino acid obtained by hydrolysis of proteins. It is a branched-chain amino acid (BCAA) that works with the other two BCAAs, isoleucine and leucine, to promote normal growth, repair tissues, regulate blood sugar, and provide the body with energy. The importance of leucine as the primary amino acid responsible for protein synthesis has been confirmed in many studies. This amino acid has the capability to be consumed to exert regulatory influences on carbohydrate and protein metabolism, providing gluconeogenic precursors via the formation of alanine in muscle, regulating glucose homeostasis and decreasing protein breakdown. L-Tyrosine is the only major natural nutrient amino acid containing an aromatic hydroxyl group. This kind of the amino acid has the ability to be used to improve memory and mental alertness, to act as an appetite suppressant, to control depression and anxiety and to enhance physical performance (Garlick 2005; Layman and Baum 2004; Eversloh et al. 2007).

Polyimides have attained a unique position in material systems that can compete with other structural materials, mechanical fasteners, higher voltage connectors and chemically resistant parts because of their excellent thermal, mechanical and physical properties (Wang and Chen 2010). However, some drawbacks remain to be addressed, particularly in the perspective of their difficulties in melting processing. One way to decrease the melting point is by adding of a flexible linking group in the main chain (Wang and Leub 2000). Another approach involves the synthesis of copolyimides such as poly(ester-imide)s (PEI)s (Hasegawa et al. 2010; Shabbir et al. 2010) and poly(amide-imide)s by incorporating amide or ester functionality at regular intervals in the polyimide chain (Chern et al. 1998; Behniafar et al. 2009).

The direct step-growth polymerization reaction involves the use of free carboxylic acid and diols under mild conditions using activating reagents. Several condensing agents suitable for the direct polycondensation reaction such as diphenyl chlorophosphate and arylsulfonyl chlorides have been developed in the past decades (Higashi et al. 2001; Higashi and Mashimo. 1986). It was found that Vilsmeier adduct derived from arylsulfonyl chlorides and *N,N*-dimethylformamide (DMF) in pyridine (Py) was successfully used as a suitable condensing agent for the synthesis of aromatic polyesters by direct polycondensation of aromatic dicarboxylic acids and bisphenols (Higashi et al. 1999).

Follow by our past success in generating optically active polymers based on amino acids; we were encouraged to consider the approach mentioned above to predict experiment in order to address the question that can this method succeed in yielding biodegradable polymers if we use two biodegradable monomers. Our main interest in synthesizing biodegradable polymers relies on the fact that both monomers have α -amino acids which can act as a biodegradable segment in the polymer chain. In this study the amino acids are functionalized to produce diacid and diol monomers. The structure of the resulting polymers was investigated by FT-IR, $^1\text{H-NMR}$, elemental analysis techniques and subsequently, their biodegradation and thermal properties was evaluated.

Experimental

Materials

The amino acids of synthetic grade were used as purchased from Merck Chemical without further purification. *N,N*-Dimethylacetamide (DMAc), DMF, Py, *N*-methyl-2-pyrrolidone (NMP) and triethylamine (TEA) were procured from Fluka (dried over barium oxide (BaO) and then

distilled under reduced pressure). Pyromellitic dianhydride (benzene-1,2,4,5-tetracarboxylic dianhydride) and phthalic anhydride were the product of Merck Chemicals and purified by recrystallization from a mixture of acetic anhydride and acetic acid (1:4). 5-Aminoisophthalic acid was obtained from Aldrich and recrystallized from H₂O/DMF (4/1) mixture.

Instrument and measurement

The structure of PEIs was characterized by proton nuclear magnetic resonance (¹H-NMR, 500 MHz) and spectra were recorded in dimethyl sulfoxide (DMSO)-*d*₆ solution using a Bruker Avance 500 instrument (Bruker, Germany) and FT-IR spectra were also recorded on spectrophotometer (Jasco-680, Japan). The spectra of solids were obtained using KBr pellets. The vibrational transition frequencies are reported in wavenumbers (cm⁻¹). Band intensities were assigned as weak (w), medium (m), strong (s) and broad (br). Inherent viscosities were measured by using a Cannon–Fenske Routine Viscometer (Germany) at concentration of 0.5 g dl⁻¹ at 25°C. Specific rotations were measured by a Jasco Polarimeter (Japan). Quantitative solubility was determined using 0.05 g of the polymer in 1 ml of solvent. Thermal gravimetric analysis (TGA) data for polymers were taken on Perkin Elmer at a heating rate of 10°C min⁻¹ under argon (Ar) atmosphere. Elemental analyses were performed by Leco, CHNS-932. Images from cultured samples in Petri plate were captured using a binocular equipped with a digital canon (DS126181, Japan) camera.

Monomer synthesis

Optically active diacid monomers such as: 5-(2-phthalimidyl-3-methyl butanoylamino)isophthalic acid (**5a**), 5-(4-methyl-2-phthalimidylpentanoylamino)-isophthalic acid (**5b**) and also *N,N'*-(pyromellitoyl)-bis-L-tyrosine dimethyl ester (10) as a phenolic diol were prepared according to our previous works (Mallakpour and Kolahdoozan 2007; Mallakpour and Dinari 2008; Mallakpour et al. 2010a, b).

Polymer synthesis

The PEIs were prepared by the following procedure: a Py (0.20 ml) solution of tosyl chloride (TsCl) (0.37 g; 1.94 × 10⁻³ mol), after 30 min stirring at room temperature was treated with DMF (0.14 ml; 1.94 × 10⁻³ mol) for 30 min and the resulting solution was added drop wise to a solution of diacid (**5a**) (0.10 g; 2.44 × 10⁻⁴ mol) in Py (0.20 ml). The mixture was maintained at room temperature for 30 min, after that diol 10 (0.14 g; 2.44 × 10⁻⁴ mol) was added to this mixture. Later on the whole

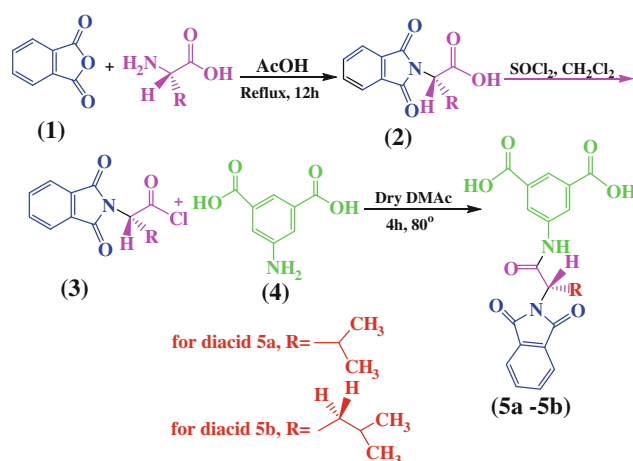
solution was stirred at room temperature for 30 min and then it was stirred at 120°C for 4 h. As the reaction was proceeded, the solution became viscous and then at this point the viscous liquid was precipitated in 20 ml of methanol to give 0.20 g of PEI1 (86% yield). PEI2 was prepared by a similar procedure (Mallakpour and Asadi 2010).

Soil biodegradability test

To study of soil biodegradation, 30 mg of each compound including 5-aminoisophthalic acid, diacid **5a** and bisphenol A (as reference) were separately mixed with 1.5 g clay-loam soil. The mixture was transferred into 2-ml plastic vials in three replications. Samples of soil without any added compounds were also tested in these experiments as negative controls. Vials were incubated at temperature of 23–25°C, with a saturated humidity and at dark condition for 3 months. In this part of study days to 50% disappearance of materials was recorded. Then water extracts of soil samples were inoculated by streak culture on Potato Dextrose Agar (PDA) as culture media. The number of bacterial and fungal colonies formed on the media was counted and noted as colony forming units (CFUs) per 100 µl of water extract.

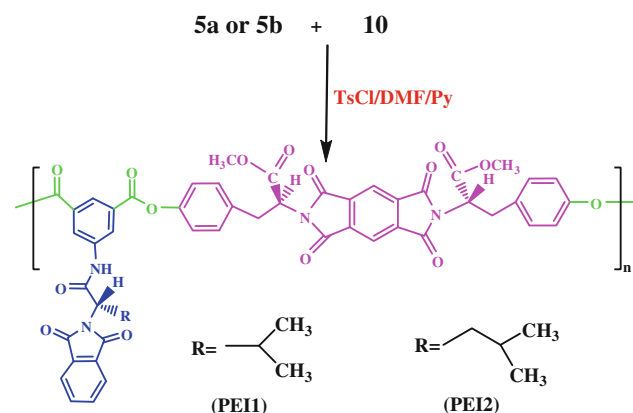
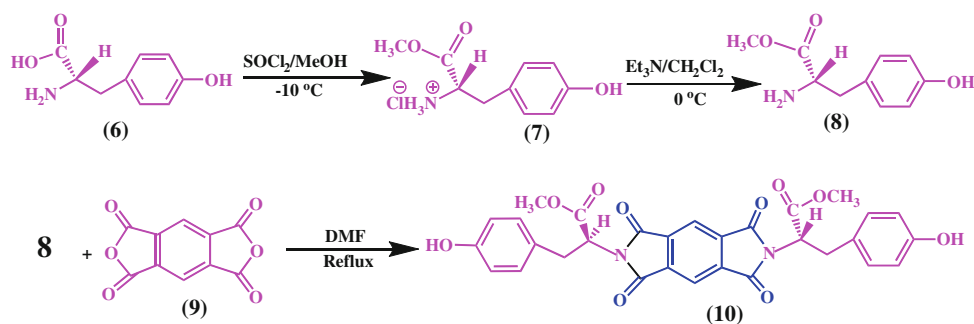
Investigation of in vitro toxicity

In vitro assessment of polymeric compounds has been used as a rapid, cost effective and reliable test for their toxicity studies (Mallakpour et al. 2010a, b). In vitro toxicity of 5-aminoisophthalic acid, diacid (**5a**), PE1 and PE2 to airborne fungal saprophytes was evaluated on PDA as culture media in three replications for 3 weeks. For this purpose, 20 to 50 mg of 5-aminoisophthalic, diacid **5a** and obtained polymers were put on PDA. Media were inoculated with



Scheme 1 Preparation of amino acid containing diacid monomers

Scheme 2 Preparation of *N,N'*-(pyromellitoyl)-bis-(*L*-tyrosine dimethyl ester) (10) as an optically active phenolic diol



Scheme 3 Polycondensation reactions of diol (10) with diacids **5a** and **5b**

spores of *Penicillium* spp. and *Aspergillus* spp. saprophytic fungi maintained at $28 \pm 1^\circ\text{C}$ and material invasion by fungi were noted and photographed using a binocular equipped with a digital canon camera.

Result and discussion

Monomer synthesis

Diacid monomers were synthesized by the condensation reaction of an equimolar amount of phthalic anhydride (1) and different amino acids (*S*-valine and *L*-leucine) in reflux acetic acid solution to obtain imide acid (2) which was reacted with thionyl chloride in dichloromethane to get related diacid chloride (3). At the final step, 3 was converted to diacid compounds (**5a** and **5b**) thorough reaction with 5-amino isophthalic acid (4) in dry DMAc in the presence of TEA. (Mallakpour and Kolahdoozan 2007; Mallakpour and Dinari 2008) (Scheme 1).

N,N'-(Pyromelliticdiimido)-bis-*L*-tyrosine dimethyl ester (10) was synthesized as described below (Scheme 2). *L*-Tyrosine was added to a methanol solution containing thionyl chloride and stirred at room temperature to obtain white, powdery, *L*-tyrosine methyl ester hydrochloride which was de-protected with TEA to obtain *L*-tyrosine

Table 1 Optimum conditions for preparation of PEIs

Optimum conditions	
TsCl/diacid (mmol/mmol)	8
Aging time (min)	30
Reaction time (h)	4
Temperature	120
DMF/diacid (mmol/mmol)	8

Table 2 Reaction conditions for the polymerization of diacid monomers with diol (10) and some physical properties of PEIs^a

Polymer	Diacid	Yield (%)	η_{inh} (dL/g) ^b	$[\alpha]_D^{25}$ (b)	Color ^c
PEI1	5a	86	0.33	-19.2	PB
PEI2	5b	90	0.35	-17.7	PY

^a TsCl/DMF/Py was used as a condensing agent

^b Measured at a concentration of 0.5 g/dl in DMF at 25°C

^c PB Pale-brown, PY Pale-yellow

methyl ester. This compound was reacted with pyromellitic dianhydride in DMF under refluxing conditions to obtain diol monomer 10.

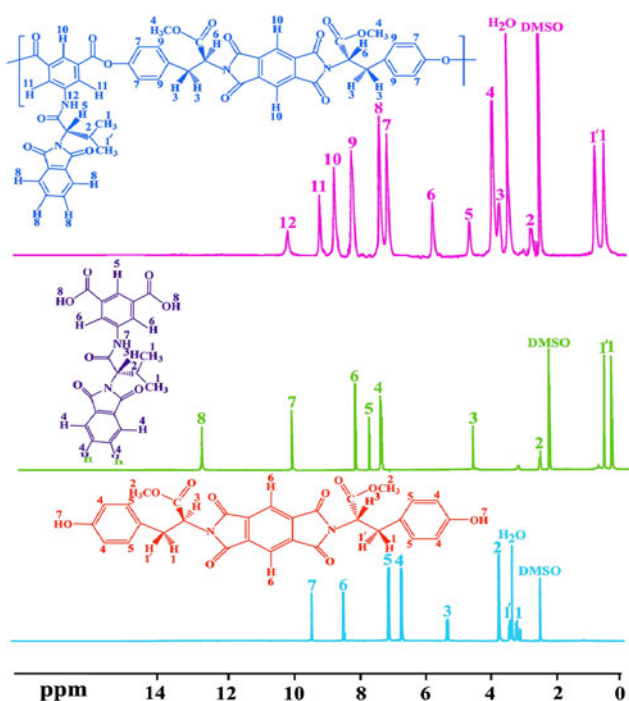
Polymer synthesis

Vilsmeier adduct was used for the polycondensation of aromatic diacids (**5a** and **5b**) with diol (10) in the following way: (Scheme 3) TsCl was dissolved in Py to yield sulfonium salt and after a certain period of time (aging time) the solution was treated with DMF to form Vilsmeier adduct. The reaction mixture was added to a solution of diacid in Py to form activated acid. Then powder of diol was added and after a period of time passed PEIs were produced. All the reaction parameters such as aging times, reaction time, temperature and molar ratio of chemical additives to diacid had significant effect on the reaction progress. The optimum conditions for the preparation of PEIs are shown in Table 1.

The synthesis and some physical properties of these novel optically active PEIs are listed in Table 2. The inherent viscosities of PE1 and PEI2 under optimized

Table 3 $^1\text{H-NMR}$, FT-IR and elemental analysis of PEIs

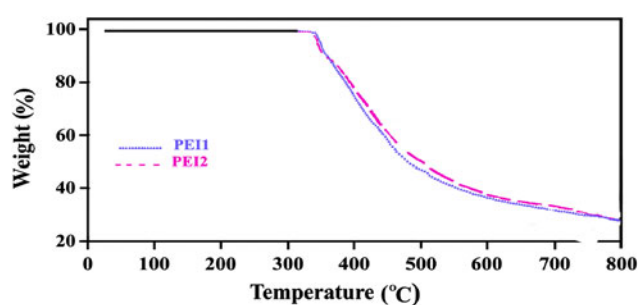
Polymer	Spectra data
PEI1	FT-IR Peaks (KBr): 3419 (m, br), 2954 (m), 1778 (m), 1724 (s), 1678 (m), 1548 (w), 1505 (m), 1452 (m), 1382 (m), 1364 (s), 1215 (m), 1184 (w), 1167 (m), 1112 (m), 1018 (m), 917 (w, br), 887 (w), 833 (w), 712 (w), 633 (w), (cm^{-1}). ($\text{C}_{51}\text{H}_{38}\text{N}_4\text{O}_{15}$): calcd. C 64.69, H 4.02, N 5.91; Found: C 63.64, H 4.34, N 6.15.
PEI2	FT-IR Peaks (KBr): 3383 (m, br), 3074 (m), 2965 (m), 2930 (m), 1777 (m), 1723 (s), 1605 (m), 1548 (w), 1507 (m), 1453 (m), 1382 (m), 1365 (s), 1214 (m), 1193 (w), 1167 (m), 1112 (m), 1070 (m), 1017 (m), 953 (w, br), 836 (w), 721 (w), 631 (w), (cm^{-1}). ($\text{C}_{52}\text{H}_{40}\text{N}_4\text{O}_{15}$): calcd. C 65.00, H 4.20, N 5.83; Found: C 65.69, H 4.48, N 6.57.

**Fig. 1** $^1\text{H-NMR}$ (500 MHz) spectra of diol (10), diacid (5a) and PEI1 in $\text{DMSO-}d_6$ at R.T

conditions were 0.33 and 0.35 dl/g, respectively, and both of polymerization reaction had a good yield. The incorporation of amino acids as a chiral unit into the polymer backbone was confirmed by measuring the specific rotations of the obtained polymers. As shown in Table 2, the polymers demonstrate a relatively high optical rotation and are therefore optically active.

Polymer characterization

The structures of synthesized polymers were confirmed by means of FT-IR spectroscopy. The FT-IR spectra of

**Fig. 2** TGA thermograms of PEI1 and PEI2 under Ar atmosphere and a heating rate of $10^\circ\text{C}/\text{min}$

polymers showed absorptions of amide N–H bonds appeared around $3363\text{--}3419\text{ cm}^{-1}$ (hydrogen bond) and the peaks at 1778 cm^{-1} (C = O imide group), 1721 cm^{-1} (C = O ester group) and 1605 cm^{-1} (C = O, amide group) confirming the presence of different carbonyl groups in the polymers structure. Also these PEIs exhibited absorptions at 1382 and $712\text{--}721\text{ cm}^{-1}$ which indicate the presence of the imide heterocycle in the polymers structures (Table 3).

The $^1\text{H-NMR}$ (500 MHz) spectra of PEI1 is shown in Fig. 1. The appearance of the N–H proton of amide groups around 10.30 ppm indicates the amide group in the polymer's chain. The proton of the chiral centers for *S*-valine and *L*-tyrosine appeared at 4.54 and 5.32 ppm , respectively. Furthermore, the other peaks in the spectrum confirmed and prove the structure of PEI1 (Table 3).

The elemental analyses results for PEIs are also in agreement with calculated values of carbon, hydrogen and nitrogen in the polymers (Table 3).

Solubility of PEIs

The solubility properties of PEIs were studied quantitatively in various solvents. The results revealed that these polymers are soluble in organic polar solvents such as

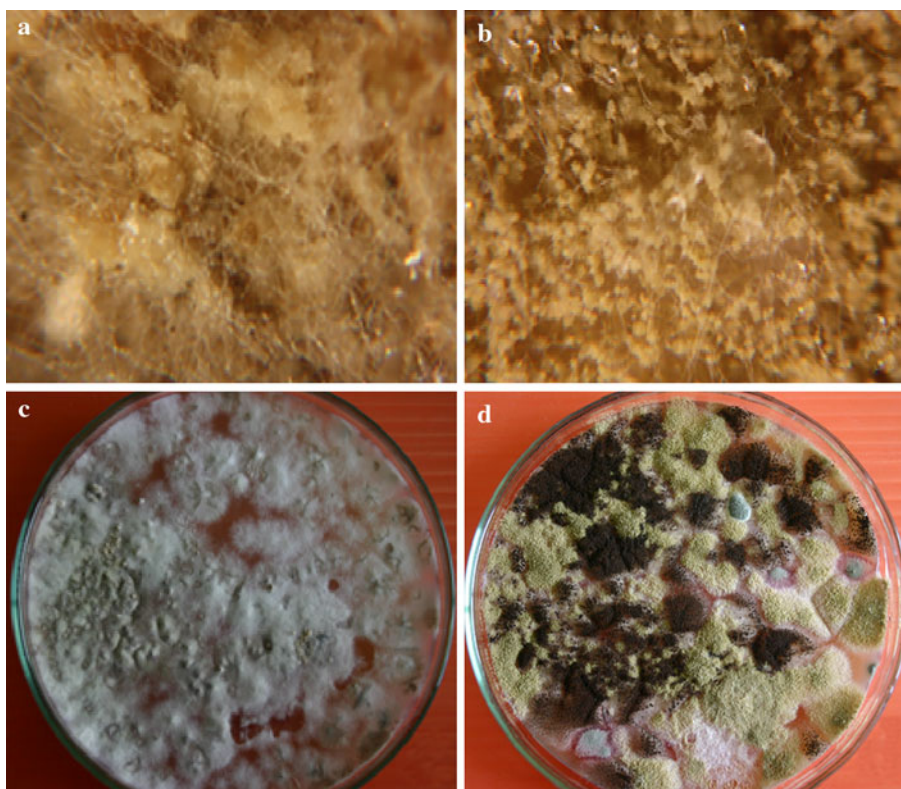
Fig. 3 Fungal colonies grown from soil water extract, 6 days after inoculation on PDA Petri plates. **a** lack of fungal growth from extract of soil containing bisphenol A as a reference, **(b)** 5-aminoisophthalic acid and **(c)** diacid (**5a**)



Table 4 The number of bacterial and fungal colony forming units (CFUs) in water extract of soil containing bisphenol A, diacid (**5a**), and 5-aminoisophthalic acid

Compound	Bacterial CFUs ($n/100 \mu\text{l}$)	Fungal CFUs ($n/100 \mu\text{l}$)
BPA (positive control)	0 ± 0	0 ± 0
Diacid (5a)	8 ± 14	80 ± 12
5-Amino isophthalic	36 ± 18	98 ± 16
Soil (negative control)	32 ± 10	74 ± 8

Fig. 4 Invasion and growth of saprophytic fungi 3 weeks after inoculation on **(a)** 5-aminoisophthalic acid, **(b)** diacid (**5a**), **(c)** PEI1 and **(d)** PEI2 in culture media co-cultivated with *Aspergillus* spp. and *Penicillium* spp. fungal spores



DMAc, DMF, NMP, and in sulfuric acid at room temperature. These polymers are insoluble in solvents such as chloroform, methylene chloride, acetone, cyclohexane, tetrahydrofuran and water. The good solubility of these PEIs is due to the presence of bulky group in side chain which prevents the packing of the macromolecules and facilitates the diffusion of solvent molecules among the polymer chains.

Thermal properties

The thermal properties of the PEIs were evaluated by TGA techniques at a heating rate of $10^\circ\text{C}/\text{min}$ under Ar atmosphere (Fig. 2). Thermal stability of the polymer was investigated based on 5% and 10% weight loss (T_5 , T_{10}) of the polymers and residue at 800°C (char yield). T_{10} of PEIs was 367 and 356 for PEI1 and PEI2, respectively.

The amount of residue (char yield) in an Ar atmosphere was around 27 at 800°C. TGA thermograms of above polymers mention that they are thermally stable and this is in agreement with wholly aromatic polymers backbone which increases the stability of the polymers toward heating. Although the existence of pendant group may cause the loss of thermal stability, but introducing of heat resistant phthalimide groups as well as the presence of imide and amide groups can counterbalance it.

Soil biodegradability test

5-Aminoisophthalic acid and diacid (**5a**) were disappeared to 50% after 1 month and they were often almost disappeared under experimental condition after 2 months. This observation shows that both 5-aminoisophthalic acid and diacid (**5a**) are biologically active and biodegradable under soil burial. PDA Petri plates containing fungal colonies grown from different soil water extract are shown in Fig. 3. Results of counting fungal and bacterial colonies showed that the highest number of colonies was counted from water extracts of soil containing 5-aminoisophthalic acid. Based on this result, it could be concluded that this compound is more biologically active than diacid (**5a**). This can be related to simpler and smaller structure of this compound which makes nitrogen more available for microorganism growth. Interestingly, there was no colonial growth of fungal and bacterial saprophytes from water extracts of BPA containing soil as a reference due to probable toxic properties of this compound for soil microorganisms (Table 4).

In vitro toxicity test

Fungal growth on 5-aminoisophthalic acid, diacid (**5a**), PEI1 and PEI2 co-cultivated with *Aspergillus* and *Penicillium* spores on PDA culture media is shown in Fig 4. Since they were completely invaded and colonized by fungal mycelium, it seems that these compounds didn't have any toxicity for saprophytic activity of fungi.

It is worth mentioning that, to prepare biodegradable polymers, we used the diol 10 which its biodegradability has been previously testified and reported by our research group (Mallakpour et al. 2010a, b). Regarding to biodegradability of diacid, we also expected synthesized polymers to be biodegradable. This is in agreement with the structure of synthesized polymers, because these types of polymers contain nitrogen which is needed for the growth of microorganisms. They also contain naturally occurring amino acids which make them structurally close to natural polypeptide and possess potentially degradable linkages suitable as biomaterials.

Conclusions

In this study we investigated different polymer structures that can be used to develop biodegradable polymers in order to reduce environmental pollution and help mankind to achieve sustainable developments. Thus, by applying amino acids, two biodegradable optically active PEIs using TsCl/DMF/Py as a condensing agent were synthesized and characterized by different techniques. Due to the presence of amino acids as biological chiral resources in these polymers structures, we expected these polymers to be biodegradable. To ensure real biodegradability and safe incorporation of these materials in the geochemical life cycle, soil biodegradability and in vitro toxicity test was performed. The results illustrated that synthesized polymers could be probably decomposed by soil microorganisms and therefore they are biodegradable. The TGA measurements demonstrated that the obtained polymers were stable up to 350°C under Ar atmosphere. The introduction of the bulky pendant groups into the PEIs backbone gave them remarkable solubility in common organic solvents.

Acknowledgments We wish to express our gratitude to the Research Affairs Division Isfahan University of Technology (IUT), Isfahan, for partial financial support. Further financial support from Center of Excellency in Sensors and Green Research (IUT) is gratefully acknowledged. Special thanks to Mr. Iman E Mallakpour (University of Arizona, USA) for his valuable time for excellent proofreading of this manuscript.

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