

Rapid synthesis of new block copolyurethanes derived from L-leucine cyclodipeptide in reusable molten ammonium salts: novel and efficient green media for the synthesis of new hydrolysable and biodegradable copolyurethanes

Fatemeh Rafiemanzelat · Elahe Abdollahi

Received: 25 May 2011 / Accepted: 7 June 2011 / Published online: 25 June 2011
© Springer-Verlag 2011

Abstract This study concerns the synthesis of novel multi block polyurethane (PU) copolymers containing cyclodipeptide, taking the advantage of ionic liquids (ILs) under microwave irradiation. For this, L-leucine anhydride cyclodipeptide (LACP) was prepared and then a new class of poly(ether-urethane-urea)s (PEUUs) was synthesized in molten ammonium type ILs. ILs were used as reaction media and PUs were prepared via two-step polymerization method. In the first step, 4,4'-methylene-bis-(4-phenylisocyanate) (MDI) was reacted with LACP to produce isocyanate-terminated oligo(imide-urea) as hard segment (NCO-OIU). Chain extension of the aforementioned prepolymer with polyethyleneglycol (PEG) of molecular weights of 1000 (PEG-1000) was the second step to furnish a series of new PEUUs. These multiblock copolymers are thermally stable, soluble in amide-type solvents, hydrolysable and biodegradable. PEUUs prepared in ILs under microwave irradiation showed more phase separation and crystallinity than PEUUs prepared under conventional method. The protocol presented here has the merits of environmentally benign, simple operation, convenient work-up, short reaction time and good yields without using volatile organic solvents, and catalysts. Ammonium type reaction media were air and water stable, and relatively cheap, which makes them suitable for application. The results demonstrate that they can be easily separated into water and reused without losing activity. Reusability of tetrabutylammonium bromide as reaction media makes the method a cost effective and environmentally benign

method under microwave irradiation. Thus, we could prepare environmentally friendly polymers via environmentally benign method.

Keywords Amino acid cyclodipeptide · Ionic liquids · Thermally stable polymers · Poly(ether-urethane-urea)s · Microwave assisted copolymerization · Green chemistry

Introduction

Amino acid anhydride cyclopeptides are the smallest cyclic peptides known, which are commonly biosynthesized from amino acids by different organisms, and are considered as side products of terminal peptide cleavage (Delaforge et al. 2001). They attracted attention due to their biological properties such as alteration of cardiovascular and blood-clotting functions (Long et al. 2001; Einholm et al. 2003). They also have activities as anti-tumor, antiviral, anti-fungal, and antibacterial (Nicholson et al. 2006; Houston et al. 2004; Sugie et al. 2001; Kozlovsky et al. 2003; Song et al. 2003; Imamura and Prasad 2003). Some of their chemical properties are very interesting for medicinal chemistry, such as resistance to proteolysis, mimicking of peptidic pharmacophoric groups, conformational rigidity and their donor–acceptor properties for hydrogen bonding with biological targets (Wang et al. 2002; Martins and Carvalho 2007).

Degradable polymers have been used in biomedical applications, or as environmental friendly polymers. In addition in response to public concern about the effects of plastics in the environment and damaging effects of plastic wastes, it has become a widely accepted opinion that degradable polymers have a well-grounded job in solving waste problem (Rutkowska et al. 2002; Okada 2002).

F. Rafiemanzelat (✉) · E. Abdollahi
Organic Polymer Chemistry Research Laboratory,
Department of Chemistry, University of Isfahan,
81746-73441 Isfahan, I.R. Iran
e-mail: Frafiemanzelat@chem.ui.ac.ir

Degradable polymers are generally achieved by incorporating labile moieties susceptible to degradation into the polymer chain. Some important classes of degradable polymers are poly(α -hydroxy acid)s, poly(α -amino acid)s, and their different copolymers (Okada 2002). Amino acid anhydride cyclopeptides derived from amino acids may be good candidates for preparation of degradable polymers (Nakano et al. 1997). In addition, copolymers of PEG and peptide sequences were also designed in which PEG is highly water-soluble, non-immunogenic, degradable and relatively non-toxic (Matthews et al. 2000).

Segmented polyurethanes (SPU)s consist of hard and soft segments that their variable structure and properties make them suitable for many kinds of applications. Various chemical and/or physical factors may modify their properties such as hydrolysis, biodegradability, thermal properties, thermo oxidation, and, etc. (Sharma et al. 2005; Martin et al. 1996).

Ionic liquids (ILs) are molten salts that have attracted much attention in recent years, because they have good solubility for a wide range of organic, inorganic and organometallic materials. ILs benefit from properties such as high thermal stability, almost zero vapor pressure, non-flammability, high ionic conductivity and sometimes reusability. Compared with common organic solvents that have an unfavorable impact on environment, ILs can be considered some times as environmentally friendly green solvents (Xing et al. 2007). In recent years, ILs have been used in polymer science, mainly as polymerization media in several types of polymerization processes (Mallakpour and Rafiee 2008). In some cases, the use of IL in place of conventional organic solvent was lead to enhancement in reaction rate, higher molecular mass or useful separation of polymer from catalyst residues (Mori et al. 2007; Harrisson et al. 2003). However, the high cost of most conventional room temperature ILs and concern about their toxicity have led researchers to investigate the use of more benign and cheaper salts in the molten state as practical alternatives. Recently, molten ammonium type ILs were used as a low toxic and cost-effective ILs in a number of useful synthetic transformations (Mallakpour and Dinari 2007; Mallakpour and Rafiee 2007).

The application of microwave heating in synthetic chemistry using a commercial domestic oven is a fast-growing area of research. Since the first report of microwave-assisted synthesis in 1986, the technique has been accepted as a method for reducing reaction times and for increasing yields of products compared to conventional heating methods (Gedye et al. 1986). Microwave, supplies a clean and inexpensive alternative to conventional oil baths (Bogdal and Gorczyk 2004; Melo-Junior et al. 2009; Wiesbroc et al. 2005). Microwave irradiation, in polymer chemistry, is used for developing different types of polymerizations including addition polymerization, condensation

polymerization, and so on (Hoogenboom and Schubert 2007; Mallakpour and Zadehnazari 2010).

In connection with our interest in preparation and studying degradable polymers, this study concerns the synthesis of novel multi block PU copolymers containing ecofriendly, degradable segments via a green method. Here, we study the reliability of using microwave irradiation in the presence of ammonium salts as reaction media for the preparation of these kinds of polymers containing cyclopeptide moiety.

Experimental

Materials and methods

All chemicals were purchased from Fluka, Aldrich (Ald), Riedel-deHaen AG and Merck. 4,4'-methylene-bis-(4-phenylisocyanate) (MDI) (Ald) was used without further purification. 1,4-butanediol and PEG were dried under vacuum at 80°C for 6 h. Ethylene glycol (EG) and *N*-methyl pyrrolidone (NMP) were distilled under reduced pressure over CaO. ILs including tetrabutylammonium bromide (TBAB) (Merck), tetrapropylammonium bromide (TPAB) (Merck), benzyl tributyl ammonium chloride (BztBAC) (Merck), hexadecyltrimethylammonium bromide (HexDectMAB) (Merck), *n*-dodecylpyridinium chloride (DodecPyCl) (Merck), were dried between 80 and 100°C under reduced pressure for 3 h.

Proton nuclear magnetic resonance $^1\text{H-NMR}$ (400 MHz) spectra were recorded on a Bruker, Avance 400 instrument in dimethyl sulfoxide (DMSO-*d*₆) at room temperature (RT). Multiplicities of proton resonance were designated as singlet (s), doublet (d), doublet of doublet (dd), multiplet (m), and broad (br). FT-IR spectra were recorded on a Jasco FT-IR spectrophotometer. IR spectra of solids were carried out using KBr pellets. Vibrational transition frequencies are reported in wave number (cm^{-1}). Band intensities and designations are assigned as weak (w), medium (m), shoulder (sh), strong (s) broad (br), stretching (st.) and bending (bend). Inherent viscosities were measured by a standard procedure using a Cannon-Fensk Routine Viscometer. Thermal gravimetric analysis (TGA) data for polymers were taken on a Mettler-Toledo TG-50 Thermal Analyzer under N_2 atmosphere at heating rate of $20^\circ\text{C min}^{-1}$. Differential Scanning Calorimetry (DSC) data for polymers were recorded on a DSC-30/S instrument under N_2 atmosphere. Glass transition temperatures (T_g) were read at the middle of the transition in the heat capacity taken from heating DSC traces. A sample was first scanned from room temperature to 140°C and maintained for 1 min followed by quenching to -80°C at a cooling rate of $10^\circ\text{C min}^{-1}$, and then a second heating scan was

used to measure sample's Tg of soft (T_{gs}) or hard segment (T_{gh}) at a heating rate of 10°C min⁻¹. Wide angle X-ray diffraction measurements (WAXS) were carried out with a Bruker, D8ADVANCE XRD Diffractometer using a graphite monochromatized Cu K α radiation (40 kV; 40 mA). Microwave experiments were carried out at atmospheric pressure using a focused microwave reactor (CEM DiscoverTM). The target temperature (110°C) was reached with a ramp of 2 min and the microwave power and irradiation intervals set so that to hold the mixture at this temperature. Polycondensation reaction was also conducted using a domestic microwave oven with operator selectable power output from 0 to 850 W and operator selectable time in porcelain dishes. The results were to some extent the same after adjusting optimized irradiation power and time.

Monomer synthesis

LACP was prepared and characterized according to a previous procedure (Rafiemanzelat and Abdollahi 2010). Into a dried 25 mL round bottom flask occupied with a reflux condenser, drying tube and N₂ balloon, L-leucine (**1a**) (1 g, 7.62 × 10⁻³ mol) was heated in dried ethylene glycol (EG) (10 mL) at 180°C for 10 h then cooled ethanol was added at RT. Precipitate was filtered and recrystallized from hot ethanol–water (5/1) and dried under vacuum at 80°C for 6 h to give LACP in 54% yield. m.p. >280°C (dec.) determined by DSC. α_D^{25} : -0.34 [0.02 g in 5 mL of DMF at RT]. ¹H-NMR Peaks for LACP, DMSO-*d*₆ at RT, δ ppm: 8.01 (br, 2H, NH), 4.53 (m, 2H, CH ring), 1.81 (m, 2H, CH side chain), 1.77 (m, 4H, CH₂ side chain), 1.03 (m, 12H, CH₃ side chain). FT-IR Peaks (cm⁻¹) (KBr pellet) for LACP: 3,317 (m) NH st., 3,199 (s, br) NH st., 3,091 (s) NH st., 3,056 (s) NH st., 2,956 (s) CH st., 2,923 (s) CH st., 2,871 (s) CH st., 1,681 (m) C=O (amide I) (non-H-bonded) st., 1,630 (s) C=O (amide I) (H bonded) st., 1,530 (m) C–N st + NH bend (amide II), 1,512 (w) C–N st. + NH bend (amide II), 1,455 (s) C–N st., 1,407 (m), 1,386 (m), 1,368 (m), 1,347 (m), 1,324 (s), 1,261 (w) C–N st. + NH bend, 1,234 (w), 1,172 (w), 1,142 (m), 1,122 (m), 1,093 (m), 899 (m), 822 (m, br), 805 (m, br) NH bend., 766 (m), 487 (m). CHN analysis for LACP: calculated: C% = 63.7, N% = 12.4, H% = 9.7. Found: C% = 63.61, N% = 11.74, H% = 9.53.

Polymer synthesis in molten ammonium salts under microwave irradiation (method I)

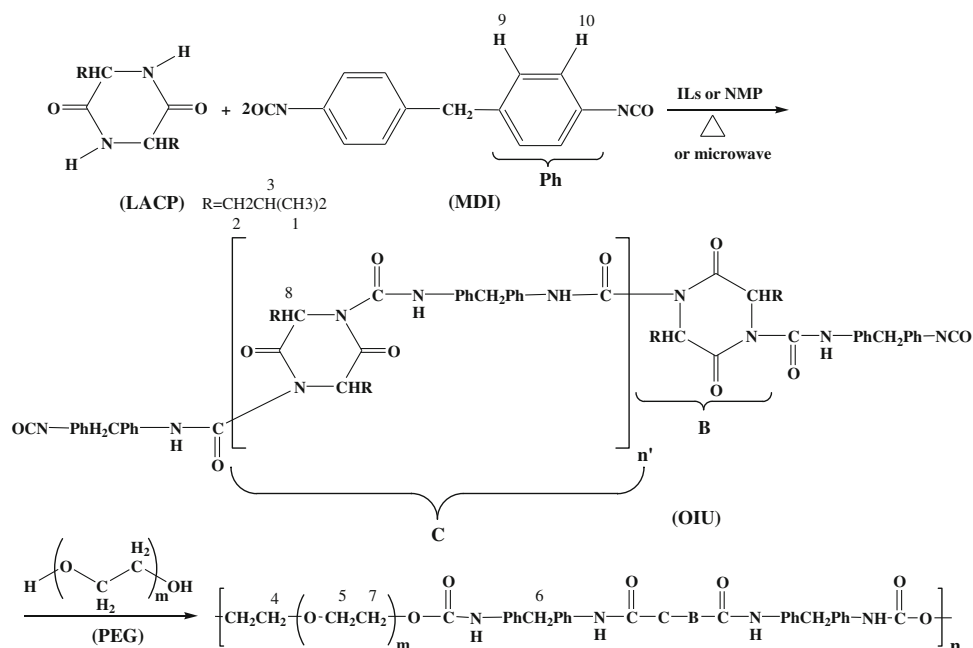
Polymerization reaction was performed in the presence of different molten ammonium salts. A typical preparation of PEUUs by two-step polymerization method in TBAB is as

follow: mixture of LACP 0.023 g (9.99 × 10⁻⁵ mol), MDI 0.05 g (1.99 × 10⁻⁴ mol) and TBAB 0.56 g (1.736 × 10⁻³ mol) were placed in a porcelain dish and the mixture was ground completely. The reaction mixture was irradiated in a microwave oven for a period of 8.5 min (**t_m** + **t₁**), including every 2 min interval of irradiation at 850 W of power level until a viscose solution was obtained. Then, PEG 0.099 g (9.99 × 10⁻⁵ mol) was added to the above mixture. Reaction mixture was pulverized completely and was irradiated in a microwave oven for a period of 2.5 min (**t₂**) at 850 W of power level. The resulting polymer was isolated by addition of 5 mL of distilled water. The white-cream solid was filtered off, dried under vacuum at 50°C to give 0.094 g (83%) of **P5**, whose inherent viscosity was 0.66 (dL g⁻¹). The FT-IR spectra were consistent with the assigned structure. FT-IR Peaks (cm⁻¹) (KBr pellet) for **P5**: 3,316 (s, N–H), 2,871 (m, C–H, CH₂), 1,707 (s, C=O), 1,644 (s, C=O), 1,600 (s, C=C), 1,540 [s, C–N, + N–H (bending)], 1,500 (s, C=C), 1,413 (m), 1,232 (s, C–O), 1,107 (s, C–O), 950 (w, C=C, opp), 816 (w, C=C, opp). ¹H-NMR spectrum of **P5**, DMSO-*d*₆ at RT, δ ppm: 0.90–0.95 [distorted d, *J* = 17 Hz, 6 H, CH₃ (1, 1')], 1.4–1 [m, 2 H, diastereotopic hydrogens of CH₂ (2, 2')], 1.8–1.9 (m, 1 H, CH (3)), 3.2–3.4 (br t, CH₂S (4) of PEG), 3.6–3.8 (br t, CH₂S (5) of PEG), 3.8–4.2 (m, 2 + 2 H, CH₂ (6) of MDI moiety and CH₂ (7) of urethane linkages), 4.4–4.6 (m, CH (8)), 7.1–7.4 (d, aromatic protons), 8.1–8.6 (br, NH of urea and urethane groups) (see Scheme 1 for each assigned hydrogen).

Polymer synthesis in molten ammonium salts under conventional heating, in an oil bath (method II)

Polymerization reaction was performed in the presence of different molten ammonium salts. A typical preparation of PEUUs by two-step polymerization method in TBAB is as follow: mixture of LACP 0.023 g (9.99 × 10⁻⁵ mol), MDI 0.05 g (1.99 × 10⁻⁴ mol) and TBAB 0.56 g (1.736 × 10⁻³ mol) were placed in a 25 mL round bottom flask and the mixture was ground completely for 2 min. The reaction mixture was heated in an oil bath gradually from RT up to 110°C, above melting temperature of molten salt, for a period of 8 h. Then, PEG 0.099 g (9.99 × 10⁻⁵ mol) was added to the above viscose mixture and was heated for a period of 6 h at 110°C. The resulting product was isolated by addition of 10 mL of distilled water. The white-cream solid was filtered off, dried under vacuum at 50°C to give 0.068 g (40%) of **P18**, whose inherent viscosity was 0.43 (dL g⁻¹). The FT-IR spectra were consistent with the assigned structure. FT-IR peaks (cm⁻¹) (KBr pellet) for **P-18**: 3,317 (s, N–H), 2,874 (m, C–H, CH₂), 1,707 (s, C=O), 1,646 (s, C=O), 1,602 (s, C=C), 1,541 (s, C–N, + N–H

Scheme 1 Synthesis of PEUUs by two step polymerization method



(bending)), 1,502 (s, C=C), 1,414 (m), 1,230 (s, C–O), 1,107 (s, C–O), 950 (w, C=C, opp), 817 (w, C=C, opp).

Polymer synthesis in conventional organic solvent under conventional heating, in an oil bath (method III)

A typical preparation of PEUUs is as follow: into a dried 25 mL round bottom flask with an addition inlet, occupied with drying tube and N_2 balloon, LACP (0.055 g, 2.43×10^{-4} mol) was dissolved in 0.15 mL of NMP 1% (NMP containing 1% w/w LiCl as solubility assistant) at 110°C , after decreasing temperature a solution of MDI (0.122 g, 4.87×10^{-4} mol) in 0.15 mL of NMP 1% was added at 80°C . The solution was heated between 80 and 90°C for 4 h, for 2 h at 100°C and finally for 1 h at 120°C . During this period appropriate amounts of NMP 1% were added upon viscosity build-up of the reaction mixture. Then, it was cooled to 50°C , and a solution of PEG (0.243 g, 2.43×10^{-4} mol) in 0.2 mL of NMP 1% was added. The reaction mixture was stirred between 50 and 70°C for 1 h then it was heated up to 80 – 110°C over a period of 6 h and NMP 1% was also added. The total solid content of reaction mixture was kept at about 50% w/v. Then, the viscous solution of reaction mixture was poured into 5 mL of methanol–water. After vigorous grinding and stirring for 0.5 h, precipitated polymer was isolated. For additional purification, fractional precipitation method was applied by re-dissolving and re-precipitation of polymer in DMF and methanol–water, respectively. The precipitated polymer was collected by filtration, dried at 80°C for 6 h under vacuum to give 0.192 g (70%) of polymer **Pcon**. α_D^{25} : +0.4 [0.05 g in 10 mL of DMF at RT]. The FT-IR and $^1\text{H-NMR}$

spectra were consistent with the assigned structure. **FT-IR Peaks (cm^{-1}) (KBr pellet) for Pcon:** 3,350 (m, br) NH st., 3,200 (m, br) NH st., 3,100 (m) NH st., 3,060 (m) CH aromatic st., 2,960 (m) CH st., 2,926 (m) CH st., 2,872 (m) CH st., 1,772 (w, sh) C=O urethane st., 1,705 (m, sh) C=O urethane-amide st., 1,672 (s) C=O urea st., 1,599 (m) C=C st., 1,540 (m) C–N st. + NH bend, 1,510 (s) C=C st., 1,460 (m) C=C st., 1,412 (m) C–N st., 1,400 (m) CH bend, 1,385 (m), 1,370 (w), 1,347 (w), 1,313 (m), 1,236 (m) C–N st. + NH bend, 1,203 (m), 1,201 (w), 1,180 (w), 1,144 (w), 1,117 (m) C–O–C ether st, 1,042 (m) O = C–O–C st., 1,018 (w), 917 (w), 850 (w), 808 (w) NH bend, 764 (w) O=C–O, 663 (w), 509 (w), 482 (w). **$^1\text{H-NMR}$ spectrum of Pcon**, DMSO- d_6 at RT, δ ppm: 0.90–0.95 (distorted d, $J = 17$ Hz, 6 H, CH_3 (1, 1')), 1.4–1 (m, 2 H, diastereotopic hydrogens of CH_2 (2, 2')), 1.8–1.9 (m, 1 H, CH (3)), 3.2–3.4 (br t, CH_2s (4) of PEG), 3.6–3.8 (br t, CH_2s (5) of PEG), 3.8–4.2 (m, 2 + 2 H, CH_2 (6) of MDI moiety and CH_2 (7) of urethane linkages), 4.4–4.6 (m, CH (8)), 7.1–7.4 (d, aromatic protons), 8.1–8.6 (br, NH of urea and urethane groups).

Results and discussion

Amino acid anhydride containing amide moiety, LACP, was synthesized via cyclization reaction of L-leucine (LL) in refluxing EG. Chemical structure and purity of LACP was confirmed by melting point measurement, CHNS analysis, thin layer chromatography (TLC), FTIR and H-NMR spectroscopy. Then, LACP was reacted with MDI diisocyanate to establish NCO terminated hard segment containing urea linkages.

Table 1 Preparation of PEUU in TBAB under optimized irradiation power level of 100% and IL/(MDI + LACP) = 5/1 w/w (method I); optimization of **t1** and **t2**

Polymer ^a	Solvent for viscosity	η_{inh} (dL g ⁻¹) ^b	Yield%	t2 min	t1 min ^d
P1	DMF 1% ^c	0.78	57	4	3
P2	DMF 1%	0.67	65	4.5	4
P3	DMF	0.55	48	4.5	5
P4	DMF 2%	1.27	49	4.5	6
P5	DMF	0.66	83	2	4.5
P6	DMF	0.27	82	3	4.5
P7	DMF	0.67	54	5	4.5
P8	DMF	0.67	65	4 min and 20 s	4
P9	DMF	0.315	98	2.5	3
P10	DMF	0.39	74	2	3.5
P11	DMF 1%	0.66	66	2.5	5
P12	DMF	0.1	87	2.5	6
P13	DMF	0.225	90	3	3

Step 1: preparation of NCO-terminated oligo-imide-urea pre-polymer. **t1**, reaction time for step 1. Step 2: copolyurethane formation by reaction of PEG with NCO-terminated oligo-imide-urea pre-polymer. **t2**, reaction time for step 2

^a PX polymer sample code, X = polymer number

^b Inherent viscosity (dL g⁻¹), measured at a concentration of 0.5 g dL⁻¹ in solvent mentioned in column 2 at RT

^c Numbers represent percentage (w/w) of LiCl dissolved in solvent to increase its polarity and solubility

^d Calculated after the time taken for melting IL

PEUU multiblock copolymers were synthesized according to Scheme 1 via two-step method. In the two-step procedure, a NCO-terminated oligo(imide-urea) OIU was prepared by the reaction of two mole excess of MDI with LACP in molten ammonium salts. Then, PEG-diol as soft segment was added and reaction was continued, affording PEG based PEUU multiblock copolymers whose OIU blocks connected with urethane linkages (Table 1). Polymerization reactions were performed via different methods. In this study, we used molten ammonium salts as reaction media under conventional as well as microwave heating and study reliability of these methods and compare them with polymerization reaction in conventional organic solvent under conventional heating method.

Optimizing reaction condition

Polymerization reactions were performed under different reaction conditions including different molten ammonium salts as reaction media, different ratio (w/w) of each salt to (LACP + MDI), different irradiation power and irradiation time during step 1 and step 2. **t1** was considered as irradiation time during step 1, and **t2** was considered as

irradiation time during step 2, after addition of PEG. **t1** was calculated after melting of related salt (**tm**). Optimized reaction conditions for each salt considering resulting yields, viscosities and product appearance via one variable at the time were obtained and some resulting data are summarized in Tables 1 and 2. It was shown that in the case of ammonium salts with melting points ranging 100–270°C optimum power level of 100% (850 W) can be used for step 1 and 2 of polymerization reaction. Using TBAB (m.p. = 100–103°C), at **t1** = 4 min and **t2** = 4 min under 100% of irradiation power, the optimized IL/(MDI + LACP) = 5/1 (w/w) was obtained. It is worthy to mention that it took 3.5 min (**tm**) to melt TBAB under obtained reaction condition. Thus **t1**, the reaction time for step 1, was calculated after melting TBAB. Then, the effect of various **t1** at **t2** = 4 min under the same reaction conditions on viscosities and yields of resulting polymers was studied. It was shown that **t1** = 4 min resulted in the highest yields and **t1** = 6 min resulted in the highest viscosities. Then, the effect of various **t2** at **t1** = 4.5 min under the same reaction conditions on viscosities and yields of resulting polymers was studied. It was shown that **t2** = 2–3 min resulted in higher yields and **t2** = 2, 4 or 5 min resulted in higher viscosities at **t1** = 4.5 min. It was also shown that at any above mentioned **t2** irradiation time, increasing **t1** from 4 up to 6 min or decreasing it from 4 to 3 min resulted in a drastic drop off in viscosities and yields of resulting polymers. Therefore, **t1** = 4.5 min and **t2** = 3 min were selected as favorite reaction time for other studies under the obtained optimized reaction conditions including 100% of irradiation power, and IL/(MDI + LACP) = 5/1 (w/w). It was shown that the above mentioned reaction conditions was in accordance with reaction temperature of about 110–120°C.

Under the aforementioned reaction conditions polymers were formed only in the presence of TBAB (m.p. = 100–103°C), BztBACl (m.p. = 152–159°C) and TBAI (m.p. = 143–146°C). Reactions in the presence of other ammonium salts with higher m.p. because of higher **tm**, lead to decomposition of reaction mixture under irradiation.

TBAB (m.p. = 100–103°C), BztBACl (m.p. = 152–159°C) and TBAI (m.p. = 143–146°C) were used for polymerization reaction via method II. Reaction temperature was set above melting point of each ammonium salt. It was shown that under conventional heating method, PEUU with reasonable viscosity and yield was formed only in TBAB (**P18**). However, its resulting yield and viscosity was lower than that of method I (**P18**, Table 2).

Furthermore, our study showed that TBAB can be easily recovered and reused for at least four cycles without losing its activity. The product of the reaction resulted in a one phase system after reaction. Water–Ethanol (50/50) was added into this system once the reaction was completed.

Table 2 Preparation of PEUUs in different ammonium molten salt ILs, under optimized irradiation power level of 100% and IL/(MDI + LACP) = 5/1 w/w ratio (method I); at **t1** = 4.5 min (calculated after the time taken for tm) and **t2** = 2 min

Polymer ^a	IL	Yield %	η_{inh} (dL g ⁻¹) ^b	tm (min) ^c	IL's m.p. (°C)
P14	Benzyl tributylammonium chloride	87	0.12	4.5	152–159
P15	Tetra-butylammonium iodide	73	0.1	4	143–146
P16	Tetrapropylammonium bromide	–	– ^c	15	265–274
P17	Hexadecyletrimethyl ammonium bromide	–	–	13	237–243
P18	Tetra-butylammonium bromide	40	0.43	3.5	100–103 ^d

Step 1: preparation of NCO-terminated oligo-amide-urea pre-polymer. t1, reaction time for step 1, step 2: copolyurethane formation by the reaction of PEG with oligo-amide-urea pre-polymer

^a PX polymer sample code x = polymer number

^b Inherent viscosity (dL g⁻¹), measured at a concentration of 0.5 g dL⁻¹ in DMF at RT

^c Decomposition of the reaction mixture

^d Prepared under conventional heating method in an oil bath at 110°C for 14 h

^e The time taken for melting IL

Table 3 Effect of reused TBAB on the preparation of PEUU

Entry	Recycling	Yield (%) ^a	Viscosity (dL g ⁻¹) ^b	Recovered TBAB%
1	0	83	0.66	–
2	1	80	0.63	90
3	2	79	0.57	85
4	3	76	0.54	80

Reactions were performed under optimized irradiation power, irradiation time and TBAB to MDI + LACP (w/w)

^a Yield was calculated after filtration and drying of reaction product

^b Inherent viscosity (dL g⁻¹), measured at a concentration of 0.5 g dL⁻¹ in DMF at RT

Filtration was sufficient to remove products from the reaction mixture because TBAB could dissolve in water–ethanol while reaction product could not. TBAB could be recycled after separating away most of the water–ethanol under vacuum at 80°C for 24 h. The polymerization reaction was repeated seven times. The yields were calculated

after filtration and drying of reaction product. It can be seen (Table 3) that the yield was not reduced too much after being reused four times and TBAB could have the potential to be used more than four times. The same studies were conducted for other molten ammonium salts, e.g. BztBACl (m.p. = 152–159°C) and TBAI (m.p. = 143–146°C). The results reveal that they can be easily reused without losing their activity too much.

Thermal properties

Thermal properties of PEUUs were evaluated with TGA and DSC techniques (Table 4).

TGA curves show smooth stepwise manner which their slopes are relatively similar (Fig. 1). If stability parameters of PEUUs are taken as the temperature at which 5 and 10% weight loss were occurred, it can be concluded that PEUU prepared in TBAB under microwave irradiation show higher thermal stability than that prepared under conventional heating method (method II). **P5** shows to some

Table 4 Thermal properties data of PEUUs prepared via different methods

Polymer	Reaction media	T5% (°C) ^a	T10% (°C) ^b	Char yield % ^c	Tgs (°C) ^d	Tgh (°C) ^e	$\Delta Tg = Tgh - Tgs$ (°C)
P5	TBAB	215	260	20	20	210	180
Pcon^f	NMP1% ^g	212	275	23	60	175	95
P18^h	TBAB	208	240	18	36	190	154

^a Temperature at which 5% weight loss was occurred by TGA in N₂ atmosphere

^b Temperature at which 10% weight loss was occurred by TGA in N₂ atmosphere

^c The percentage of weight residue of polymer sample at 600°C in N₂ atmosphere by TGA

^d Glass transition temperature of soft segment recorded by DSC in N₂ atmosphere

^e Glass transition temperature of hard segment recorded by DSC in N₂ atmosphere

^f Polymer prepared in conventional organic solvent in an oil bath

^g N-methyl pyrrolidone containing 1% w/w LiCl as solubility assistant

^h Polymer prepared in TBAB in an oil bath

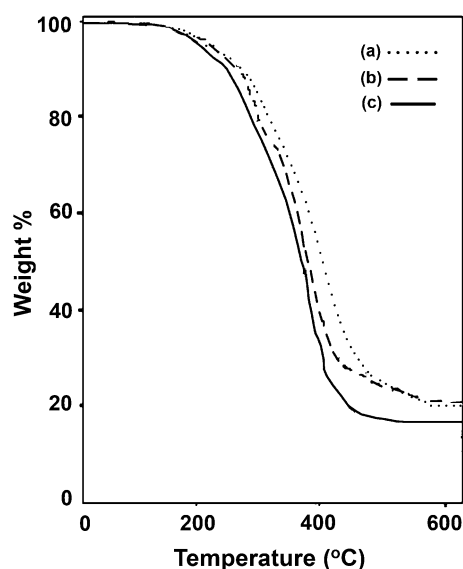


Fig. 1 TGA thermograms of **a P5**, **b Pcon**, and **c P18** under N_2 atmosphere at heating rate of $20^\circ C \text{ min}^{-1}$

extent thermal stability similar to polymer prepared in NMP under conventional heating (**Pcon**). Table 4 also shows thermal properties of PEUUs prepared in TBAB via methods I and II as well as PEUU prepared in NMP. **P5** shows higher char yield% and higher Tgh (glass transition temperature of hard segment) comparing with **P18**. Thermal stability of **P5** and **Pcon** are relatively similar, however, **P5** shows more phase separation than both **P18** and **Pcon** (ΔT_g , Table 4). It can be said that the final weight residue and Tgh are more related to hard segment residue, hard segment incorporation and hard segment cohesiveness in polymer chain, respectively. Thus, it can be implied that polymer prepared in TBAB under microwave irradiation has higher final thermal stability and hard segment cohesiveness and more micro-phases separation than other polymers prepared under conventional methods.

DSC curves for PEUUs are shown in Fig. 2. Peak temperatures for Tgs and Tgh of each sample are presented in Table 4. DSC curve of **Pcon** shows broad transitions associated with Tgs and Tgh between $27\text{--}97^\circ C$ and $137\text{--}210^\circ C$, respectively. DSC curve of **P5** showed broad-deep transitions associated with Tgs and Tgh at about 20 and $210^\circ C$, respectively. By comparing $\Delta T_g = T_{gh} - T_{gs}$ better information about interaction between soft and hard segments could be indicated. Comparing polymers prepared in TBAB, it can be seen that ΔT_g of **P5** are greater than ΔT_g of **P18**. Comparing polymers prepared under conventional heating method, it can be seen that ΔT_g of **P18** are greater than ΔT_g of **Pcon**. These results indicate that there is more interaction between hard segments of polymers prepared in molten ammonium salts than that of polymer prepared in conventional solvent, NMP. This may

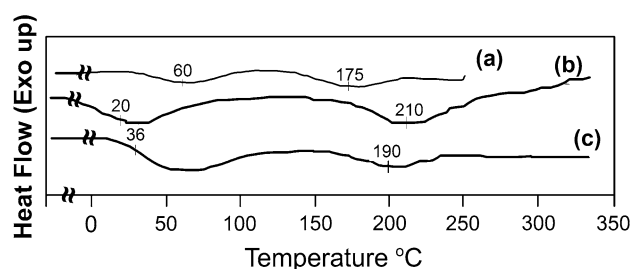


Fig. 2 DSC trace of PEUUs **a Pcon**, **b P5**, **c P18** at heating rate of $10^\circ C \text{ min}^{-1}$ under N_2 atmosphere

be due to relatively better hard segments chain growth and better phase separation in the former polymers. In additions it can be said that hard segment interaction and phase separation in polymer prepared under microwave (**P5**) is higher than those of polymers prepared under conventional heating method (**P18**, **Pcon**). Comparing these transitions data (Table 4), with Tgs of pure PEGs (ranging from -60 to $-53^\circ C$) great shifts of Tgs to higher temperatures can be observed. Such results indicate that the presence of LACP in PU backbone resulted in more interaction and compatibility between hard and soft segments.

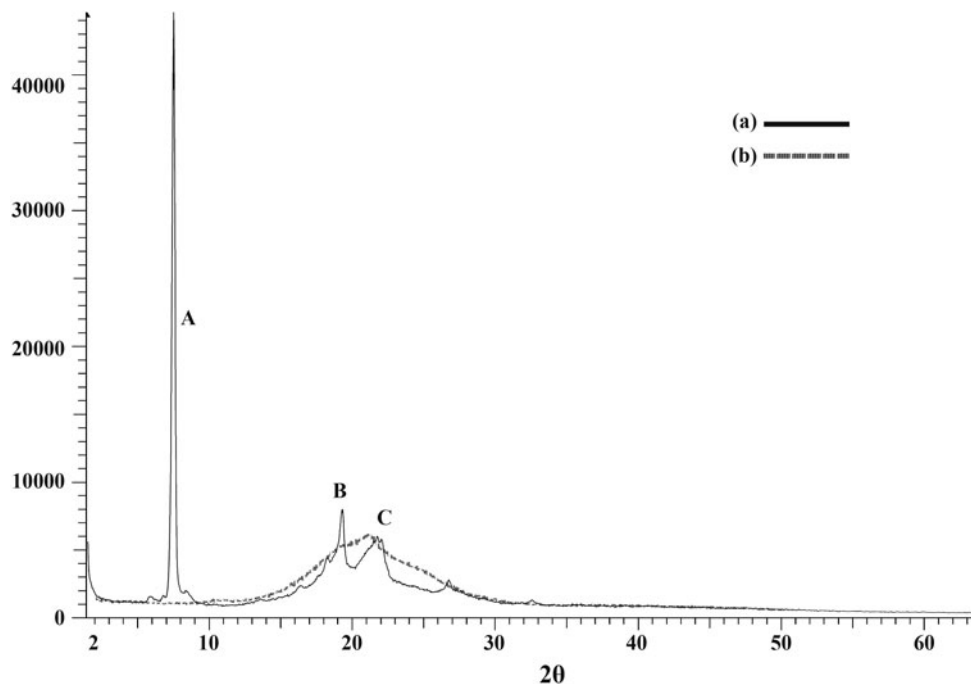
WAXS studies

WAXS measurements were carried out for PEUUs prepared via different methods. The percentage of crystallinity was calculated through graphical integration of the diffracted intensity data in the 2θ range $10\text{--}60^\circ$ and subtraction of the amorphous scattering band intensity.

Diffraction patterns for PEUUs show two main crystalline regions A, B. Figure 3 presents WAXS diffractograms of **P5** and **Pref** (the reference sample was prepared under the same reaction condition by the reaction of MDI, BD, and PEG). WAXS diffractogram of **P5** shows two crystal reflection patterns at A, B and C regions with maximum at about $2\theta = 7, 19$ and 22° , respectively. However, WAXS diffractogram of **Pref** shows a broad diffusion scattering pattern (amorphous halo) at about $2\theta = 19\text{--}22^\circ$ at B–C region. **Pref** can be considered as an amorphous polymer. These results suggest that the crystalline phase which develops at A region in PEUUs containing LACP is associated with crystallization of MDI-LACP hard segment. WAXS diffractograms of **Pcon** and **P18** show reflection patterns the same as **P5**. The percentage of crystallinity obtained for **Pcon** at A, and B–C regions are 17 and 30%, respectively, for **P5** at A and B–C regions are 22 and 40%, respectively, for **P18** at A, and B–C regions are 20 and 35%, respectively.

These data show that crystalline phases which developed in A regions of PEUUs associated with crystallization of their hard segments show the following order: **P5** > **P18** \geq **Pcon**. The observed crystallization trend is similar to

Fig. 3 WAXS spectra of **a** P5 and **b** Pref



their total crystallinity order and the observed T_g order. Crystalline phases which developed in B–C regions of PEUUs can be associated with crystallization of their soft segments and MDI-PEG. It shows the following order: **P5** > **P18** > **Pcon**. On account of total crystallinity of PEUUs, it can be said that polymer prepared in TBAB under microwave shows more crystallinity than polymers prepared in TBAB and NMP under conventional heating method.

Degradation study

The biodegradation studies of above PEUUs were carried out by using soil burial test and immersion test method under simulated controlled laboratory conditions. Biodegradation was monitored by FTIR, DSC, TGA, SEM, GPC analysis and weight loss measurements. Our studies confirm hydrolyze-ability and biodegradability of these polymers. Resulting data show that degradability of PEUUs can be controlled by the length and/or type of soft segments, composition and morphology of PEUUs and their method of preparation. Detailed results of our studies will be published in our impending papers.

As an example weight loss measurements data are presented in Fig. 4. Weight loss is one of the main parameters which determine the degradation of the polymer. The percentage weight loss data of the polymers in different environments after 150 days are shown in Fig. 4. Our studied showed that PEUUs based on MDI, LACP and PEG-1000 biodegraded at a rate of 10% per week in activated sludge, 10% per week in land field soil, 10.2% per week in Zayand-e-Rood river water and 1% per week in

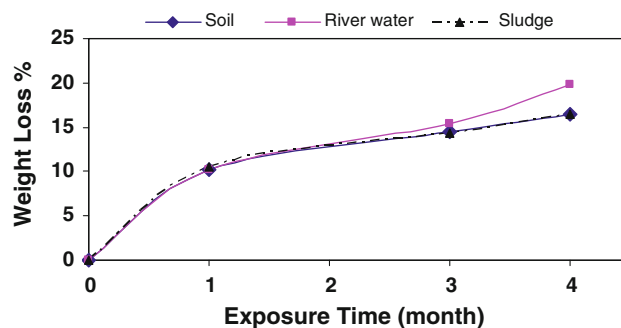


Fig. 4 The percentage weight loss of PEUUs versus exposure time in different environment during 150 days. Weight loss% = $(W_{t1} - W_{t2}) / W_{t1} \times 100$, in which W_{t2} and W_{t1} are weights of polymer sample measured after and before exposure to different environment for every 5 days intervals of weight measurements

water during the first 30 days of exposure. The polymer films immersed in activated sludge showed 11 and 18% weight loss in 30 and 150 days, respectively. Soil buried samples showed 10 and 18% weight loss in 30 and 150 days, respectively. River water deployed films showed 11 and 22% weight loss in 30 and 150 days, respectively.

Conclusions

New segmented PEUUs based on cyclopeptide were successfully synthesized by the reaction of NCO terminated OIU consisting of MDI-LACP with PEG as soft segment. OIU was prepared from the reaction of an amino acid based monomer having a preformed amide ring with MDI. Polymerization reactions were performed under microwave

irradiation in molten ammonium salts. Some experimental results were compared with polymerization reactions in NMP as a conventional organic solvent. Polymerization reactions in ILs under conventional heating method and microwave irradiation were compared as well. Polymers prepared via different methods showed different thermal resistance as well as different inter-chain interaction, phase miscibility, crystallinity and degradability. Thermal properties studies indicate that all of these PEUUs are thermally stable. They show higher T₅, T₁₀ and char residue due to the presence of imide, urea and aromatic groups in the polymer chains in comparison with typical PUs. The resulting PEUUs have cyclopeptide moiety in polymer chain and they are soluble in amide type solvents. Thus, they could be considered as new processable high-performance, thermally stable and ecofriendly polymers. PEUUs prepared under microwave irradiations in TBAB are more crystalline than PEUUs prepared under conventional method in conventional organic solvent. In addition, it was found that the synthesis of PEUUs in ILs via microwave-assisted method provided a very rapid means of synthesizing a peptide based hydrolysable copolyurethane. This method has been shown a reduced reaction time, and at the same time shows comparable yields and viscosities of the desired products of conventional methods. It also shows the advantages of using ILs as solvents in green chemistry processes. This study shows ability of microwave irradiation and ILs as reaction media as fast and green method for efficient co-polyurethanes preparations. Molten TBAB as a low toxic and cost-effective IL combined with microwave-assisted method shows a promising synthetic transformation for PU preparation. The procedure presented here has the worth of environmentally benign, simple operation, convenient work-up, short reaction time and good yields without using volatile organic solvents, and catalysts. Ammonium type reaction media were air and water stable, and relatively cheap, which makes them suitable for application. The results demonstrate that they can be easily separated by water and reused without losing activity. Reusability of TBAB as reaction media makes the method a cost effective and environmentally benign method under microwave irradiation. Thus, we could prepare environmentally friendly polymers via environmentally benign method.

Acknowledgments Financial support of this work by the Research Affairs Division of University of Isfahan (UI), is gratefully acknowledged.

References

- Bogdal D, Gorczyk J (2004) Synthesis and characterization of epoxy resins prepared under microwave irradiation. *J Appl Polym Sci* 94:1969–1975
- Delaforge M, Bouill'e G, Jaouen M, Jankowski CK, Lamouroux C, Bensoussan C (2001) Recognition and oxidative metabolism of cyclodipeptides by hepatic cytochrome P450. *Peptides* 22:557–565
- Einholm AP, Pedersen KE, Wind T, Kulig P, Overgaard MT, Jensen JK, Bodker JS, Christensen A (2003) Biochemical mechanism of action of a diketopiperazine in-activator of plasminogen activator inhibitor-1. *Biochem J* 373:723
- Gedye R, Smith F, Westaway K, Humera A, Baldsera L, Laberge L, Rousel L (1986) The use of microwave ovens for rapid organic synthesis. *Tetrahedron Lett* 27:279–282
- Harrisson S, Mackenzie SR, Haddleton DM (2003) Pulsed laser polymerization in an ionic liquid: strong solvent effects on propagation and termination of methyl methacrylate. *Macromolecules* 36:5072–5075
- Hoogenboom R, Schubert US (2007) Microwave-assisted polymer synthesis: recent developments in a rapidly expanding field of research. *Macromol Rapid Commun* 28:368–386
- Houston DR, Synstad B, Eijsink VGH, Stark MJR, Eggleston IM, Van Aalten DMF (2004) Structure-based exploration of cyclic dipeptide chitinase inhibitors. *J Med Chem* 47:5713–5720
- Imamura M, Prasad C (2003) Cyclo (His-Pro) potentiates GABA/ethanol-mediated chloride uptake by neurosynaptosomes. *Peptides* 24:445–448
- Kozlovsky AG, Zhelifonova VP, Adanin VM, Antipova TV, Ozerskaya SM, Ivanushkina NE, Grafe U (2003) Penicillium aurantio-griseum dierckx 1901: producer of diketopiperazine alkaloids (roquefortine and 3, 12-dihydroroquefortine), isolated from permafrost. *Appl Biochem Microbiol* 39:393–397
- Long DD, Tennant-Eyles RJ, Estevez JC, Wormald MR, Dwek RA, Smith MD, Fleet GWJ (2001) Carbopeptoids: peptides and diketopiperazines incorporating the anomeric centre of mannopyranose. *J Chem Soc Perkin Trans* 1:807–813
- Mallakpour S, Dinari M (2007) Molten salt as a green reaction medium: synthesis of polyureas containing 4-phenylurazole moiety in the main chain in the presence of tetrabutylammonium bromide as an ionic liquid. *e-Polymer* 035
- Mallakpour S, Meratian S (2009) Preparation and characterization of thermostable chiral extended polyamides bearing N-phthaloyl-L-leucine pendent architectures in green media. *J Appl Polym Sci* 111:1209–1215
- Mallakpour S, Rafiee Z (2007) Tetrabutylammonium bromide: an efficient, green and novel media for polycondensation of 4-(4-dimethylaminophenyl)-1, 2, 4-triazolidine-3, 5-dione with diisocyanates. *Eur Polym J* 43:1510–1515
- Mallakpour S, Rafiee Z (2008) Use of ionic liquid and microwave irradiation as a convenient, rapid and eco-friendly method for synthesis of novel optically active and thermally stable aromatic polyamides containing N-phthaloyl-L-alanine pendent group. *Polym Degrad Stab* 93:753–759
- Mallakpour S, Zadehnazari A (2010) Microwave irradiation as a versatile tool for increasing reaction rates and yields in synthesis of optically active polyamides containing flexible L-leucine amino acid. *Amino Acids* 38:1369–1376
- Martin DJ, Meijs GF, Renwick GM, McCarthy SJ, Gunatillake PA (1996) The effect of average soft segment length on morphology and properties of a series of polyurethane elastomers.1. Characterization of the series. *J Appl Polym Sci* 62:1377–1386
- Martins MB, Carvalho I (2007) Diketopiperazines: biological activity and synthesis. *Tetrahedron* 63:9923–9932
- Matthews SE, Pouton CW, Threadgill MD (2000) A biodegradable multiblock co-polymer derived from an alpha, omega-bis(methylamino)peptide and an alpha, omega-bis(oxiranylmethyl)poly(ethylene glycol). *J Control Release* 67:129–139
- Melo-Junior C, Albuquerque C, Fortuny M, Dariva C, Egues S, Santos AF, Ramos A (2009) Use of microwave irradiation in the

- noncatalytic esterification of C18 fatty acids. *Energy Fuel* 23:580–585
- Mori H, Iwata M, Ito S, Endo T (2007) Ring-opening polymerization of gamma-benzyl-L-glutamate-*N*-carboxyanhydride in ionic liquids. *Polymer* 48:5867–5877
- Nakano K, Sumitomo Y, Kondo K (1997) Tautomerism polymerization: new degradable polyethers and polythioethers from nucleic acid base derivatives. *Macromolecules* 30:852–856
- Nicholson B, Lloyd GK, Miller BR, Palladino MA, Kiso Y, Hayashi Y, Neuteboom STC (2006) NPI-2358 is a tubulin-depolymerizing agent: in vitro evidence for activity as a tumor vascular-disrupting agent. *Anti Cancer Drugs* 17:25–31
- Okada M (2002) Chemical syntheses of biodegradable polymers. *Prog Polym Sci* 27:87–133
- Rafiemanzelat F, Abdollahi E (2010) Synthesis and characterization of hydrolysable poly(ether-urethane-urea)s derived from L-leucine anhydride cyclopeptide; a green synthetic method for monomer. *Polym Degrad Stab* 95(6):901–911
- Rutkowska M, Krasowska K, Heimowska A, Steinka I, Janik H (2002) Degradation of polyurethanes in sea water. *Polym Degrad Stab* 76(2):233–239
- Sharma B, Ubaghs L, Keul H, Hocker H, Loontjens T, van Benthem R (2005) Synthesis and characterization of alternating poly(amide urethane)s from epsilon-caprolactone diamines and diphenyl carbonate. *Polymer* 46:1775–1783
- Song MK, Hwang IK, Rosenthal MJ, Harris DM, Yamaguchi DT, Go Yip I, LW V (2003) Anti-hyperglycemic activity of zinc plus cyclo (his-pro) in genetically diabetic Goto-Kakizaki and aged rats. *Exp Biol Med* 228:1338–1345
- Sugie Y, Hirai H, Inagaki T, Ishiguro M, Kim YJ, Kojima Y, Sakakibara T, Sakemi S, Sugiura A, Suzuki Y, Brennan L, Duignan J, Huang LH, Sutcliffe J, Kojima N (2001) A new antibiotic CJ-17,665 from *Aspergillus ochraceus*. *J Antibiot* 54:911–916
- Wang DX, Liang MT, Tian GJ, Lin H, Liu HQ (2002) A facile pathway to synthesize diketopiperazine derivatives. *Tetrahedron Lett* 43:865–867
- Wiesbroc F, Hoogenboom R, Leenen MAM, Meier MAR, Schubert US (2005) Investigation of the living cationic ring-opening polymerization of 2-methyl-, 2-ethyl-, 2-nonyl-, and 2-phenyl-2-oxazoline in a single-mode microwave reactor. *Macromolecules* 38:5025–5034
- Xing GW, Li FY, Ming C, Ran LN (2007) Peptide bond formation catalyzed by alpha-chymotrypsin in ionic liquids. *Tetrahedron Lett* 48:4271–4274