Biomacromolecules **2007,** *8,* 905−911

Synthesis of Highly Elastic Biodegradable Poly(urethane urea)

J. O. Basse Asplund,[†] Tim Bowden,[†] Torbjörn Mathisen,[‡] and Jöns Hilborn*[,†]

Department of Materials Chemistry, Uppsala University, Lägerhyddsvägen 1, 751 21 Uppsala, Sweden,
and Radi Medical Systems AB, Palmbladsgatan 10, 754 50 Uppsala, Sweden

Received November 7, 2006; Revised Manuscript Received December 8, 2006

Linear poly(urethane urea) containing a biodegradable soft segment and a hard segment built solely from methyl-2,6-diisocyanatehexanoate (LDI) is presented, using a procedure where no chain extender is required. By having LDI in excess, together with a soft segment, and adding water in the vapor phase continuously creates amines in situ resulting in hard segments containing multiple LDI units linked via urea linkages. As soft segments, polymers of trimethylene carbonate (TMC) and copolymers of TMC, ϵ-caprolactone, and D,L-lactic acid (DLLA) were used. High inherent viscosity, 0.95−1.65 dL/g, was afforded even when DLLA-containing soft segments were used, which usually undergo aminolysis. With a hard segment content between 12% and 18%, all of the materials showed very high elongation at breakage, ranging from 1600% to 4700%, and an elastic modulus from 2.1 to 140 MPa. This one-pot synthesis is simple and has now been shown to be applicable to a large number of systems.

Introduction

A new strategy for synthesizing segmented poly(urethane urea) (PUU) where the hard segment (HS) is formed during the addition of water in the vapor phase resulting in non-cross-linked biodegradable PUU was earlier reported.[1] The method is based on the use of excess diisocyanate that is partially hydrolyzed, creating an amine in situ, allowing subsequent reaction with remaining isocyanate units to form urea bonds. Hence, the isocyanate is partially used as a protecting group for the amine. By varying the ratio between diisocyanate and poly(caprolactone), used as the soft segment (SS), the HS length and therefore the mechanical properties of the polymer can be altered. It was also demonstrated that the strategy works with different diisocyanates and that the HS length could easily be varied.[1] No chain extender is needed, and the linear HS is derived solely from the diisocyanate.

Segmented polyurethanes (PUs) and PUUs, in general, are a commercially important group of polymers since they can have rubberlike behavior and can be easily processed. They contain a SS with a T_g below working temperature and a HS with a T_g/T_m above working temperature. These segments are able to phase-separate into domains where the soft domains give the material its elastic properties while the hard domains provide physical integrity. Materials with a low HS content can exhibit a morphology where the hard segments are dispersed in the SS matrix, while a high HS content can result in an interconnected and continuous morphology.[2] Lately, Yilgör et al. and Wilkes et al. have shown however that even PU/PUU with HS content as low as 8% can result in highly phase-separated systems with good mechanical properties.[3,4] Hence, the mechanical properties are highly dependent on the HS/SS ratio and the phase separation.[5−7]

When applying stress to a PU or PUU polymer the soft segments are initially deformed elastically, and when fully extended significant loads are transferred to the hard segments. These then start to rotate to align with the strain direction, and upon continued elongation plastic deformation of the hard domains occurs. If the stress is removed, then the soft segments recoil while the hard segments retain their new positions. This causes the material to obtain a lower modulus by the phenomenon described as strain-softening.[5−7]

PU and PUU have been shown to be hemocompatible, and successful transfers to diverse vascular applications have been made.[8,10,11] Biodegradable PUs and PUUs have, however, been questioned due to the risk of harmful diamine-containing degradation products.[12] Therefore, research focus has shifted toward diisocyanates that hold a latent diamine functionality, such as methyl-2,6-diisocyantohexanoate (LDI) and 1,4-butane diisocyanate, that degrade to the amino acid lysine[13] and the naturally occurring putrescine, respectively.[14] This opened a new door in biodegradable polymer research, with linear and cross-linked structures from these diisocyanates being developed that have shown very promising results in vitro and in vivo.[13−15]

Through changes in the composition of the SS, the mechanical as well as biodegradable properties can be altered. Poly(caprolactone) (PCL), which is a semicrystalline rigid polymer that degrades through hydrolysis and intracellular mechanisms,[16,17] was previously used.[1] By using semicrystalline SS, the PUU will be rigid with a high elastic modulus. Also, when stretching the material the soft segments will align and crystallize by strain crystallization. This leads to a higher degree of plastic deformation either due to irreversible deformation of the hard segments[6,7] or due to sustained crystal structure.

In this study, four different polymers were used as soft segments, poly(trimethylene carbonate) (PTMC), poly(TMC-*co*-TMC), poly(TMC-*co*-DLLA), and poly(CL-*co*-DLLA). PTMC is an amorphous polymer that degrades in vivo through surface erosion[18] and has a lower elastic modulus compared to that of poly(caprolactone),[19] which gives the PUU more rubberlike properties. To tune both the stress−strain and biodegradable properties a copolymer of trimethylene carbonate/ϵ-caprolactone (50/50) was used. To facilitate an increased rate of degradation, compared to the relatively slow degrading PCL and PTMC, and to study the effect on strain crystallinity for PTMC, copolymers of PCL and PTMC with DLLA were prepared. Earlier studies

---

* Author to whom correspondence should be addressed. Phone: +46 18 4713 839. Fax: +46 18 4713 477. E-mail: jons.hilborn@polymer.uu.se.

[†] Uppsala University.

[‡] Radi Medical Systems AB.

10.1021/bm061058u CCC: $37.00

have shown that PUU with DLLA was not possible to synthesize due to the competing side reaction of aminolysis when adding a diamine as a chain extender.[20] However, through the use of a copolymer with a low content of DLLA together with PCL and PTMC, respectively, the aminolysis during synthesis could be kept to a minimum, allowing the formation of high molecular weight polymers.

It is generally accepted that one of the driving forces for phase separation is strong hydrogen bonding between urethane and urea groups.[21,22] With this new way of synthesizing PUU, a large fraction of urea groups will be found in the HS. Previous quantum mechanical calculations have shown that the urea−urea hydrogen bonding is stronger, 58.5 kJ mol^{-1}, than the corresponding urethane−urethane hydrogen bonding, 46.5 kJ mol^{-1}.[23] Hence, we presumed that as a result of the higher bond strength and a higher driving force for phase separation shorter hard blocks and lower HS content would result in improved elasticity of the resulting polymers. In this article, we take advantage of that when applying the new strategy of synthesizing PUU using other biodegradable soft segments and study the impact that they have on the mechanical properties. The aim of this work was to demonstrate the possibilities of this new synthetic approach by preparing highly elastic biodegradable materials using the inherent strong hydrogen bonding of urea groups.

Experimental Section

Materials. LDI (Kyowa Hakko Europe GmbH) was distilled at 100 °C and 0.1 Torr. Trimethylene carbonate (TMC) (Böhringer) was used as received and kept in a glovebox. ϵ-Caprolactone (CL) (Sigma Aldrich), butanol (Sigma-Aldrich), and 1,4-butanediol (Merck) were distilled at reduced pressure from CaH_2 and stored in a glovebox. Butanol (Sigma-Aldrich) was distilled from $MgSO_4$ (Merck). Stannous 2-ethylhexanoate (Sn(Oct)$_2$) (Sigma Aldrich) and D,L-lactic acid (DLLA) (Böhringer) were used as received but opened inside a glovebox. 1,4-Diazabicyclo[2.2.2]octane (DABCO) (Merck) was sublimated at reduced pressure. *N,N*-Dimethylformamide (DMF) (HPLC, Sigma Aldrich), DMF-d_7 (Sigma-Aldrich), and chloroform-*d* ($CDCl_3$) (Chemtronica) were kept over molecular sieves (4 Å). Chloroform (HPLC, Sigma Aldrich), 1,1,1−3,3,3-hexafluoro-2-propanol (HFIP) (Acros), methanol (Sigma Aldrich), ethanol (99.5%, Solveco), D_2O (Chemtronica), 1,1,1−3,3,3-hexafluoro-2-propanol-d_2 (HFIP-d_2) (Acros), and phosphorus pentoxide (P_2O_5) (Fluka) were used as received.

Soft Segment Synthesis. The soft segments were synthesized using 1,4-butanediol as the initiator. All chemicals were added inside a glovebox, and the reactions were conducted at 110 °C. HS content was calculated based on the average number of LDI units obtained from NMR measurements as described below. The final proportions, presented below, of the monomers in the copolymers are derived from $\overline{\mathrm{DP}}_{\mathrm{SS}}$ ratios obtained from NMR.

Poly(trimethylene carbonate), PTMC (1). To a washed and dried 250 mL round-bottom flask were added TMC (72.55 g, 711 mmol), the initiator butanediol (1.62 g, 18 mmol), and Sn(Oct)$_2$ (0.20 g). After the mixture was stirred for 30 h chloroform was added to dissolve the polymer before precipitation with 500 mL of methanol. The filtered product was dried in vacuum at 100 °C over P_2O_5. Yield 88%, $\bar{M}_w$ (GPC) of 8000 g/mol, $\bar{M}_n$ (NMR) of 4200 g/mol, and PDI of 1.53. ^{1}H NMR ($CDCl_3$): δ 4.05 (t, 4H, CH_2O), 3.73 (t, 2H, *CH*$_2$OH end group), 2.02 (m, 2H, CH), 1.90 (m, 2H, *CH*$_2$CH$_2$OH), and 1.76 (m, 4H, CH_2, initiator).

Poly(trimethylene carbonate-*co*-caprolactone), P(TMC-CL) (2). When copolymerizing trimethylene carbonate and ϵ-caprolactone, CL (26.32 g, 230.6 mmol), TMC (23.59 g, 231.3 mmol), and 1,4-butanediol (1.04 g, 11.5 mmol) were added to a round-bottom flask inside a glovebox; Sn(Oct)$_2$ (0.1 g) was added as a catalyst. The reaction was stirred at 110 °C for 40 h; before precipitation with methanol the resulting polymer was dissolved in 100 mL of chloroform. The isolated product was dried in vacuum at 100 °C over P_2O_5. Yield 89%, $\bar{M}_w$ (GPC) of 10,000 g/mol, $\bar{M}_n$ (GPC) of 6,500 g/mol and PDI 1.59, TMC:CL (NMR) 1:1. ^{1}H NMR ($CDCl_3$): δ 4.30−4.00 (m, 6H, CH_2O), 2.28 (m, 2H, CH), 2.02 (m, 2H, CH), 1.64 (m, 4H, CH_2), and 1.37 (m, 2H, CH_2).

Poly(trimethylene carbonate-*co*-D,L-lactic acid), P(TMC-DLLA) (3). For copolymerization of TMC with DLLA, TMC (20.44 g, 200 mmol) and DLLA (0.69 g, 4.80 mmol) were added to a dry round-bottom flask together with 1,4-butanediol (0.48 g, 5.29 mmol) and Sn(Oct)$_2$ (0.18 g) as a catalyst. The polymerization was performed at 110 °C for 24 h, and 40 mL of chloroform was added before precipitation with ethanol. To remove ethanol residues, a 10 wt % polymer solution in chloroform was made followed by solvent removal by rotary evaporation. The product was dried in vacuum at 100 °C over P_2O_5. Yield 84%, $\bar{M}_w$ (GPC) of 4900 g/mol, $\bar{M}_n$ (NMR) of 4400 g/mol, PDI of 1.35, and TMC/DLLA (NMR) of 40:1. ^{1}H NMR ($CDCl_3$): δ 4.99 (m, 1H, O*CH*(CH$_3$)CO), 4.22 (m, 2H, CH_2O), 3.73 (t, 2H, *CH*$_2$OH end group), 2.04 (m, 2H, CH), 1.91 (m, 2H, *CH*$_2$CH$_2$OH), 1.76 (m, 4H, CH_2, initiator), and 1.53 (d, 3H, *CH*$_3$CH).

Poly(caprolactone-*co*-D,L-lactic acid), P(CL-DLLA) (4). The synthesis of P(CL-DLLA) was performed as described above, for **3**, by adding CL (20.34 g, 178 mmol) and DLLA (0.54 g, 3.76 mmol) to a washed and dried round-bottom flask. 1,4-Butanediol (0.49 g, 5.49 mmol) and Sn(Oct)$_2$ (0.16 g) were added as the initiator and catalyst, respectively. All chemicals were added inside a glovebox. Yield 85%, $\bar{M}_w$ (GPC) of 8300 g/mol, $\bar{M}_n$ (NMR) of 7600 g/mol, PDI of 1.31, and CL/DLLA (NMR) 32:1. ^{1}H NMR ($CDCl_3$): δ 5.05 (m, 1H, O*CH*(CH$_3$)-CO), 5.05 (m, 1H, O*CH*(CH$_3$)CO), 4.04 (m, 2H, CH_2O), 3.63 (t, 2H, *CH*$_2$OH end group), 2.29 (m, 2H, CH), 1.63 (m, 4H, CH), 1.47 (d, 3H, *CH*$_3$CH), and 1.36 (m, 2H, CH).

Synthesis of Poly(urethane urea). The formation of poly(urethane urea) is a one-pot synthesis where no intermediate isolation steps are required. Each synthesis is described separately below, but the synthesis of PUU with PTMC is described in more detail to show the general principle. All reactions were performed at room temperature (20 °C).

Poly(2,6-diisocyantohexanoate-*block*-poly(trimethylene carbonate)), PUU−PTMC (5). *Prepolymer Synthesis.* LDI (3.112 g, 14.67 mmol) was added to a washed and oven-dried three-necked round-bottom flask. PTMC **(1)** (11.92 g, 116.9 mmol) dissolved in DMF (41 mL) was added dropwise during 7 h, and the reaction was left with stirring overnight.

Poly(urethane urea) Synthesis. To the prepolymer was added DABCO (0.90 g, 8.0 mmol), dissolved in DMF (10 mL). Water vapor was subsequently added to the reaction by letting nitrogen pass through water that was heated at 45 °C; inside the reaction flask the vapor held room temperature. As the synthesis continued the viscosity increased, and more DMF was added to facilitate formation of a high molecular weight product. The polymerization was judged complete when the viscosity began to increase drastically, usually at ∼10% solid composition. The product was isolated through precipitation in methanol and filtered. To remove residual DMF, the isolated product was stirred with methanol at 50 °C overnight. The isolated product was dried in vacuum over P_2O_5. Yield 82%. ^{1}H NMR (HFIP-d_2): δ 4.70 (t, 4H, CH_2O), 4.22 (s, 3H, CH_3O), 3.57 (m, 2H, *CH*$_2$NH), 2.51 (m, 2H, CH), and 2.30−1.84 (m, 6H, CH_2).

Poly(2,6-diisocyantohexanoate-*block*-poly(trimethylene carbonate-*co*-caprolactone)), PUU−P(TMC-CL) (6). *Prepolymer Synthesis.* To a three-necked round-bottom flask containing LDI (2.428 g, 11.44 mmol) was added P(TMC-CL) **(2)** (12.21 g,1.88mmol) in DMF (42 mL) over 6 h.

Poly(urethane urea) Synthesis. Before connection of the water vapor, DABCO (0.5 g) dissolved in 14 mL of DMF was added, with the oil bath held at a temperature of 45 °C. The polymer was precipitated in methanol and washed with methanol overnight during stirring and heating. Isolated product was dried in vacuum over P_2O_5. Yield 84%.

^{1}H NMR (HFIP-d_2): δ 4.71−4.54 (m, 6H, CH_2O), 4.22 (s, 3H, CH_3O), 3.57 (m, 2H, CH_2NH), 2.83 (m, 2H, CH_2CO), 2.51 (m, 2H, CH), and 2.29−1.85 (m, 12H, CH_2).

Poly(2,6-diisocyantohexanoate-*block*-poly(trimethylene carbonate-*co*-D,L-lactic acid)), PUU−P(TMC-DLLA) (7). *Prepolymer Synthesis.* P(TMC-DLLA) **(3)** (5.17 g, 1.08 mmol) dissolved in 16 mL of DMF was added to an excess of LDI (1.478 g, 6.96 mmol) over 6 h.

Poly(urethane urea) Synthesis. DABCO (0.39 g) was dissolved in 3 mL of DMF and added to the prepolymer. The vapor was connected, and the oil bath temperature was set to 45 °C. The product was isolated by precipitation in ethanol; the filtered product was washed with ethanol during stirring before drying in vacuum. Yield 85%. ^{1}H NMR (HFIP-d_2): δ 5.52 (m, 1H, $OCH(CH_3)CO$), 4.71 (t, 4H, CH_2O), 4.22 (s, 3H, CH_3O), 3.59 (m, 2H, CH_2NH), 2.52 (m, 2H, CH_2CO), and 2.30−1.85 (m, 13H, CH_2 and $CH(CH_3)CO$).

Poly(2,6-diisocyantohexanoate-*block*-poly(caprolactone-*co*-D,L-lactic acid)), PUU−P(CL-DLLA) (8). *Prepolymer Synthesis.* To a washed and oven-dried three-necked round-bottom flask was added LDI (1.033 g, 4.87 mmol) followed by the addition of P(CL-DLLA) **(4)** (3.664 g, 0.76 mmol) in DMF (12 mL) over 8 h.

Poly(urethane urea) Synthesis. DABCO (0.26 g) in DMF (4 mL) was added to the prepolymer, and then the water vapor was connected. The product was precipitated and washed, with stirring, in ethanol for a couple of hours. The isolated product was dried in vacuum over P_2O_5. Yield 85%. ^{1}H NMR (HFIP-d_2): δ 5.55 (m, 1H, $OCH(CH_3)CO$), 4.55 (m, 2H, CH_2O), 4.22 (s, 3H, CH_3O), 3.58 (m, 2H, CH_2NH), 2.80 (m, 2H, CH_2CO), 2.23−1.74 (m, 12H, CH), and 1.66 (d, 3H, CH_3CH).

Model Reaction of Prepolymer Synthesis. To identify when to connect the vapor apparatus to the reaction flask it is necessary to know that all or most of the soft segments have been end-capped with isocyanates and the prepolymers have been formed. To study the conversion with ^{1}H NMR, model reactions using butanol and LDI were performed. The reactions were conducted in bulk, DMF-d_7, and in $CDCl_3$. The solid solution concentration (for DMF-d_7 and $CDCl_3$) and the isocyanate/hydroxyl ratio were the same as those in the PUU synthesis, ∼25% and 6:1. Consumption of the hydroxyl groups and the shifts of the α-methyl group were monitored after 4, 8, 12, and 24 h. For the bulk synthesis $CDCl_3$ was added just before the measurement.

Characterization by NMR. The SS and HS compositions of the PUUs were determined by ^{1}H NMR at 400 MHz (JEOL ECP-400). The reason for determining $\overline{\mathrm{DP}}_{\mathrm{SS}}$ and M_n (NMR) for the SS from NMR is that it is used to calculate $\overline{\mathrm{DP}}_{\mathrm{HS}}$. The soft segments were dissolved in $CDCl_3$, while for the PUUs HFIP-d_2 was used. To lock the NMR signal, when using HFIP-d_2, a capillary with D_2O was inserted into the NMR tube. The average degree of polymerization ($\overline{\mathrm{DP}}_{\mathrm{SS}}$) for the SS was determined through the ratio between a selected integral from the main chain (I_{polymer}) and the integral from the methylene end group ($I(\delta$ 3.63−3.73$)$) according to eq 1

$$\overline{\mathrm{DP}}_{\mathrm{SS}} = 2\,\frac{I_{\mathrm{polymer}}}{I(\delta\ 3.63 - 3.73)} \qquad (1)$$

For the copolymers the $\overline{\mathrm{DP}}_{\mathrm{SS}}$ was calculated as the sum of the two monomer units $\overline{\mathrm{DP}}_{\mathrm{SS}}$. For P(TMC-DLLA) **(3)** and P(CL-DLLA) **(4)** the α methylene resonance at δ 2.04 (t, 2H, CH_2CO) and δ 2.29 (t, 2H, CH_2CO) were used for the PTMC and PCL parts, respectively. The resonance at δ 5.05−4.99 (m, 1H, $OCH(CH_3)CO$) was used for the PDLLA fraction. For the homopolymer PTMC **(1)**, I_{polymer} was the α methylene resonance at δ 2.02 (t, 2H, CH_2CO). The end group resonance, $I(\delta$ 3.72−3.63$)$, for P(TMC-CL) **(2)**, could not be detected due to the relatively high molecular weight, and $\overline{\mathrm{DP}}_{\mathrm{SS}}$ was therefore determined by GPC.

The length of the HS was calculated from eq 2

$$\overline{\mathrm{DP}}_{\mathrm{HS}} = \overline{\mathrm{DP}}_{\mathrm{SS}}\,\frac{I(\delta\ 3.58)}{I_{\mathrm{polymer}}} \qquad (2)$$

where $I(\delta_{\mathrm{DI}}$ 3.58$)$ is from LDI (t, 2H, CH_2NH). I_{polymer} is the methyl resonance at δ 2.51 (m, 2H, CH), δ 2.28 (m, 2H, CH) for PUU−PTMC **(5)** and PUU−P(TMC-DLLA) **(7),** and δ 2.80 (m, 2H, CH_2CO) for PUU−P(TMC-CL) **(6)** and PUU−P(CL-DLLA) **(8)**, respectively.

HS content was obtained using eq 3

$$\mathrm{HS}(\%) = \frac{\bar{M}_{\mathrm{nHS}}}{(\bar{M}_{\mathrm{nHS}} + \bar{M}_{\mathrm{nSS}})} \qquad (3)$$

The proportions of monomers for the copolymers were calculated from the ratio for the two individual $\overline{\mathrm{DP}}_{\mathrm{SS}}$ values. Molecular weights (M_n) for the hard and soft segments are based on $\overline{\mathrm{DP}}_{\mathrm{HS}}$ and $\overline{\mathrm{DP}}_{\mathrm{SS}}$, respectively, and the monomer ratio.

Molecular Weight and Inherent Viscosity. Soft segments were characterized using a Waters Alliance GPCV 2000 with refractive index and viscometer detectors. The system is equipped with three Styragel columns (HR5E, HR4, and HR1), and calculations were based on polystyrene standards. Each SS was dissolved in chloroform to a concentration of 1−2 mg/mL. The measurements were performed at 40 °C and at a flow rate of 1 mL/min.

Inherent viscosity (IV) was used for the PUUs since they were difficult to dissolve in solvents other than HFIP and tend to stick to GPC columns due to the strong hydrogen bonding. Samples for IV measurements were taken from compression-molded samples prior to the stress−strain measurements. Each sample was dissolved in 10 mL of HFIP to give a concentration of 0.1 dL/100 mL and filtered using a 0.45 μm polytetrafluoroethylene filter. The measurements were conducted at 25 °C using an Ubbelohde capillary 0_c. Each sample was measured four times, and the IV was calculated using eq 4

$$\mathrm{IV} = \frac{\ln\left(\dfrac{t_p}{t_s}\right)}{c_p} \qquad (4)$$

where t_p is the time, in seconds, for the polymer solution, t_s is the time for the pure solvent, and c_p is the polymer concentration in g/dL.

Thermal Analysis. A Perkin-Elmer Q1000 differential scanning calorimeter was used to study the glass transition (T_g) and melting (T_m) temperatures for the PUUs. Samples of 4−6 mg were cycled between 180 and −80 °C at a heating rate of 10 °C/min. All calculations are based on the second heating.

Tensile Properties. Stress−strain measurements were conducted on 300−500-μm-thick samples using an Instron 5544 equipped with Merlin software. Dog-bone-shaped samples (5 mm in width, 10 mm in length) were punched from films and compression-molded at 170 °C for 20 s. Three to seven samples were measured at a deformation rate of 100 mm/min. For PUU−PTMC **(1)**, only two of the samples broke; the others slipped out from the grips. The presented results for elongation at breakage and tensile stress at maximum, for these samples, are therefore the values where the samples slipped out.

Permanent set, i.e., the degree of plastic deformation after the stress has been removed, was determined after the stress−strain measurement by measuring the lengths of the pieces.

Hydrogen-Bonding Characterization by Fourir Transform Infrared Spectroscopy. Hydrogen bonding was studied using a Fourier transform infrared spectrometer from Perkin-Elmer (Spectrum One) equipped with a ZnSe crystal. The measurements were done on the compression-molded samples and scanned 64 times at a resolution of 2 cm^{-1}. The degree of hydrogen bonding was calculated from the peak height ratio of hydrogen-bonded to non-hydrogen-bonded carbonyl/carbonate groups. The peak height was calculated from the peak baseline.

Results and Discussion

A new group of potentially biodegradable PUUs was synthesized. Biodegradable polyesters and carbonates were used

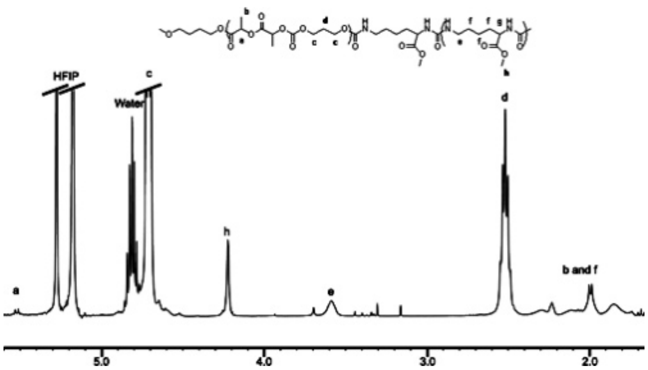
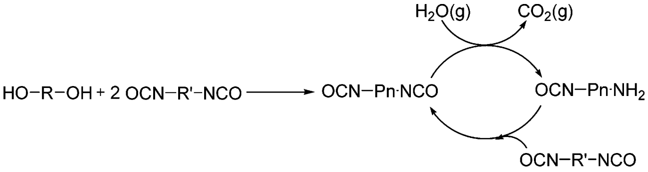


Figure 1. ^1H NMR spectrum for PUU−P(TMC-DLLA) **(7)**.

Scheme 1. General Reaction Scheme of PUU Synthesis through Vapor Addition of Water[a]



[a] Water could also first react with free diisocyanate and then with the growing chain.

as soft segments while the HS was built up solely by LDI through a simple one-pot synthesis.

SS synthesis was performed through ring-opening polymerization initiated from 1,4-butanediol. The average degree of polymerization ($\overline{DP}_{SS}$) for the different soft segments was determined using GPC and NMR and was between 40% and 66%, which was an acceptable dispersity. The molar compositions of the copolymers were as follows: TMC/CL, 1:1; TMC/DLLA, 40:1; and CL/DLLA 32:1.

The synthesis strategy is to first create a diisocyanate end-capped prepolymer by letting a diol react with an excess of diisocyanate and then chain-extend it by adding water in the vapor phase. The corresponding amine is formed in situ upon reaction with water. The amine then reacts with an isocyanate, thus resulting in a urea linkage (Scheme 1). Thereby, a HS will be formed that will contain only urea-linked LDI units (Figure 1). Any remaining isocyanate is consumed during precipitation in water or ethanol.

A model reaction was studied to determine the conversion of hydroxyl groups to urethane in the prepolymer synthesis. Butanol acted as the SS and was added to a 6:1 excess of LDI. The reaction was performed in bulk and in solution (DMF-d_7 and $CDCl_3$). In Figure 2 the proton NMR for bulk and DMF-d_7 are shown, and as can be seen the bulk reaction is much faster than the reaction performed in solution. However, after 24 h, which is the prepolymer reaction time, 90% of the hydroxyl groups (e) are consumed in DMF-d_7. In chloroform only 60% have reacted after 24 h. Interestingly, the secondary isocyanate is much more reactive than the primary isocyanate, which can be determined by comparing the shifts of the α (c to c′) and ε (b to b′) methylene groups in LDI. Earlier studies on asymmetric 2,4-toluene diisocyanate have shown that the isocyanate in position 2 adjacent to the alkyl constituent experiences approximately 12% of the reactivity of the isocyanate in position 4. The reason for this is steric hindrance.[24] Here, LDI shows a higher reactivity for the isocyanate closest to the methyl ester substituent despite the expected steric hindrance. This could be explained by the fact that the ester group is an electron-withdrawing group, which would lead to an increase in the nucleophilicity of the isocyanate.

Table 1. Results from PUU Synthesis

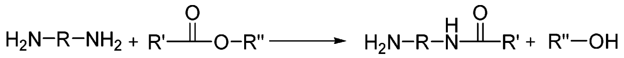
poly(urethane urea)	HS content (%)	HS length (NMR)	inherent viscosity (dL/g)	isolated yield (%)
PUU−PTMC	18	4.4	1.65	89
PUU−P(TMC-CL)	13	4.8	1.63	84
PUU−P(TMC-DLLA)	18	4.6	0.95	85
PUU−P(CL-DLLA)	12	4.8	1.22	87

Table 2. Glass Transition and Melting Temperature[a]

poly(urethane urea)	glass transition (°C)	melting temperature (°C)
PUU−PTMC	−12	
PUU−P(TMC-CL)	−43	
PUU−P(TMC-DLLA)	−12	
PUU−P(CL-DLLA)	−55	43

[a] Calculations were based on the second heating.

Scheme 2. Mechanism of Aminolysis, a Competitive Reaction to Urethane and Urea Formation



$$H_2N{-}R{-}NH_2 + R'{-}\overset{\overset{O}{\|}}{}{-}O{-}R'' \longrightarrow H_2N{-}R{-}\overset{H}{N}{-}\overset{\overset{O}{\|}}{}{-}R' + R''{-}OH$$

With the reactions performed at the same concentrations and the same hydroxyl to isocyanate ratios as in the PUU synthesis, the conclusion is that after 24 h, when the water apparatus is connected, 90% of the potential prepolymers are formed. It should also be noted that even during the addition of water the prepolymer synthesis continues for the remaining 10%.

The syntheses of PUUs were successful and were confirmed with NMR and IV measurements showing HS lengths of just under five LDI units and viscosities between 1.22 and 1.62 dL/g (Table 1). The NMR spectrum in Figure 1 shows the methylene protons (denoted B and F) from LDI and DLLA as a group of peaks around 2 ppm. The resonance from the α methylene protons, D, in the SS were used together with the resonance from the ε-methylene protons, E, in the hard segment to obtain the HS length. The singlet at δ 4.22 ppm is from the methylene ester protons. Residual DMF is visible as a trace signal just above 3 ppm, water gives a peak at δ 4.8, and HFIP (*CH*OH) appears as a doublet at δ 5.2 ppm. As shown later, this PUU was able to be compression-molded and showed excellent mechanical properties; therefore cross-linking could be excluded.

Noticeably, this strategy was also applicable to DLLA-containing PUU. However, the DLLA content was very low, 3%, and the contribution it has to the aminolysis could be argued; nonetheless PUU with high IV and good mechanical properties could be synthesized. And, which is shown below, there is a difference in tensile strength between PUU−PTMC and PUU−P(TMC-DLLA). Generally, due to aminolysis (Scheme 2), PUU with DLLA in the SS is problematic to synthesize.[20] Any residual amine will be short-lived due to an excess of isocyanate. In fact, the nucleophilic amine may react with either an ester or a more reactive isocyanate group, but since in this strategy the amine will be in deficit compared with isocyanate the risk of aminolysis is minimized. In addition, any alcohol created as a result of aminolysis can react with excess isocyanate, meaning the system is somewhat self-repairing.

Glass Transition and Melting Temperatures. As expected, the only PUU that showed a melting peak was PUU−P(CL-DLLA) **(8)** due to the crystallinity of PCL. For PUU−PTMC **(5)** and PUU−P(TMC-DLLA) **(7)** a sharp glass transition was seen at −12 °C. Pure PTMC usually exhibits a slightly lower T_g while the transition for the copolymer corresponds well with

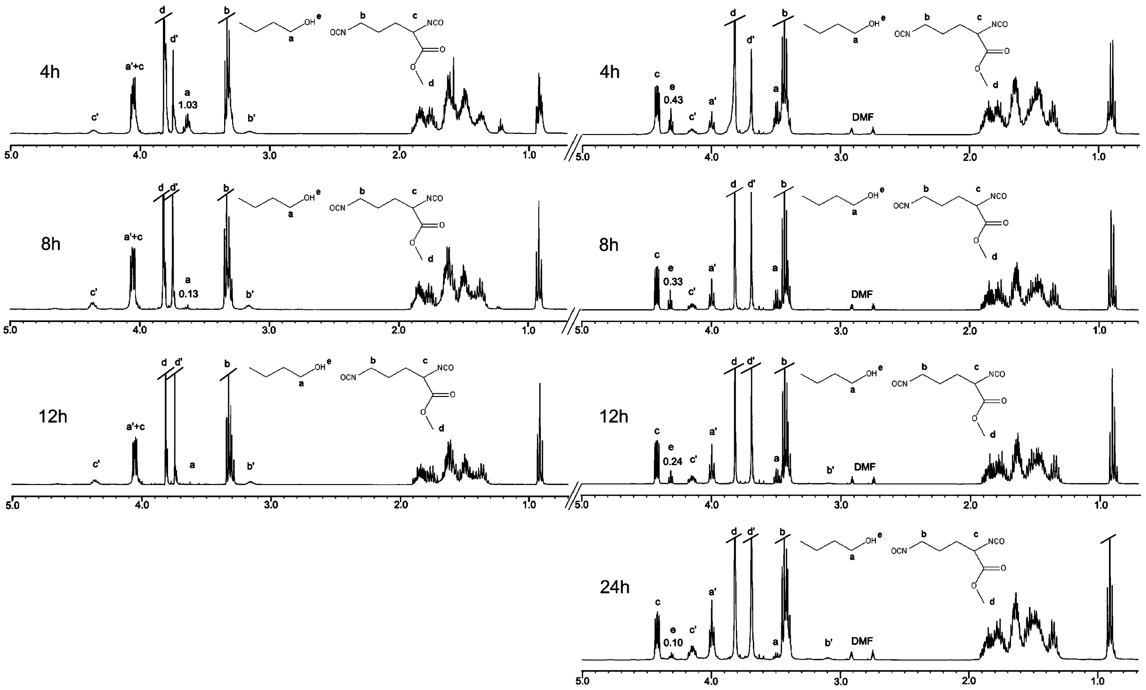


Figure 2. ^{1}H NMR spectra from the reaction between butanol and LDI in bulk (left) and DMF-d_7 (right).

Table 3. Stress−Strain Properties and Permanent Set for PUU[a]

poly(urethane urea)	HS content (%)	elongation at breakage (%)	elastic modulus (MPa)	tensile strength (MPa)	permanent set (%)
PUU−PTMC	18	1900 (240)[b]	4.5 (0.6)	14 (1.5)[b]	16 (13)
PUU−P(TMC-CL)	13	4700 (540)	2.1 (0.3)	5.4 (0.60)	47 (13)
PUU−P(TMC-DLLA)	18	1900 (280)	6.1 (0.9)	6.8 (0.75)	13 (7)
PUU−P(CL-DLLA)	12	1600 (560)	140 (16)	18 (2.2)	400 (31)

[a] Three to seven samples of each composition were tested. Standard deviations are given within parentheses. [b] The sample did not break. Elongation at breakage is from when the sample slipped out from the grip.

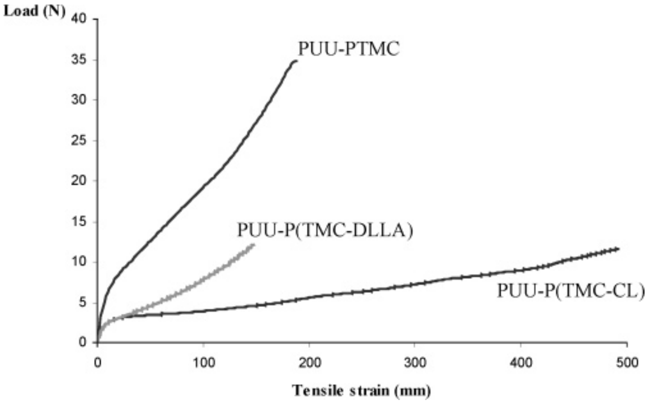


Figure 3. Stress−strain curves for PUU−PTMC, PUU−P(TMC-DLLA), and PUU−P(TMC-CL). A decrease in strain crystallinity is seen when PTMC is copolymerized.

Table 4. IR Spectroscopy Data[a]

poly(urethane urea)	N−H (cm^{-1})	amide I (cm^{-1})	amide II (cm^{-1})	hydrogen bonding (%)
PUU−PTMC	3341	1633	1563	6.3
PUU−P(TMC-CL)	3356	1640	1563	5.3
PUU−P(TMC-DLLA)	3356	1634	1562	6.9
PUU−P(CL-DLLA)	3361	1638	1563	3.5

[a]Amide II is a combination of N−H bending and C−N stretching.

that in the literature.[25] The T_g for the PUU−P(TMC-CL) **(6)** was found at −43 °C, which was expected for a SS with 1:1 TMC/CL.[22] No transitions for the HS could be detected.

Stress−Strain Properties. The measurements were conducted on dog-bone-shaped samples with a thickness range of 300−500 μm. All materials showed very high elongation at breakage; PUU−P(TMC-CL) **(6)** could be extended by almost 5000% (Table 3 and Figure 3). In comparison with other studies, these materials showed higher elongation at breakage, regardless of the HS content.[16,26−28] Skarja et al., who used poly(ϵ-caprolactone) as the SS, reported an elongation at breakage of just below 700%, also similar to what Guan et al. reported.[16,28] Storey et al. studied PU networks with poly(caprolactone), poly(caprolactone-*co*-trimethylene carbonate), and poly(D,L-lactic acid-*co*-trimethylene carbonate); these materials showed an elongation at breakage ranging from 213% to 861%.[27]

TMC-containing PUU (PUU−PTMC) **(5)** showed a much lower elastic modulus compared to the caprolactone-containing PUU shown in a previous study,[1] which is in accordance with the literature.[16] As a result of that the melting temperature of the semicrystalline SS of PUU−P(CL-DLLA) is above room temperature, 43 °C, and the crystalline segments hinder phase separation the material becomes stiffer, with a much higher elastic modulus as a result, Table 3. In a completely phase-separated system the elastic modulus is dependent on the discrete SS, so a higher extent of phase mixing will lead to more hydrogen bonding between HS and SS. The higher frequency of the N−H stretching and the lower hydrogen-bonding degree seen for PUU−P(CL-DLLA) could be a result of phase mixing (Table 4). PUU−P(CL-DLLA) also exhibited necking upon

Figure 4. Photos showing the elongation and permanent set of PUU−PTMC: (a) dog-bone-shaped sample before measurement, (b) the sample elongated 2500%, and (c) permanent set of the sample.

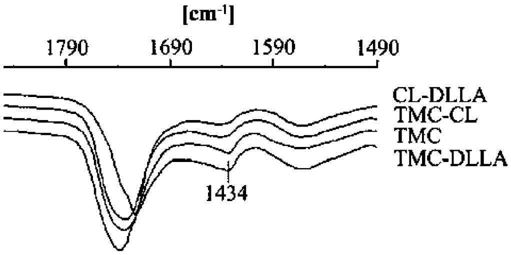


Figure 5. FTIR spectra over the carbonyl vibration region. the expected peak around 1690 cm^{-1} originating from the non-hydrogen-bonded-ureas could not be determined.

deformation that is due to the alignment of the polymeric chains. This was not seen for the amorphous PUU.

The higher elongation at breakage for PUU−P(TMC-CL) **(6)** compared with that for PUU−PTMC **(5)** can be partially explained by the higher molecular weight of the SS. The relatively high tensile strength for PUU−PTMC **(5)** is attributed to strain crystallization of the SS (Figure 3). This ability to crystallize upon strain for PTMC is most likely affected by the copolymerization with ϵ-caprolactone and D,L-lactic acid, and therefore they show a lower tensile strength. PUU−P(CL-DLLA) shows as expected a higher tensile strength than the other PUU, which is a result of the crystalline domains, but it is lower than expected[1] and could be explained by a decrease in strain crystallinity ability due to the DLLA part but also due to a lower degree of hydrogen bonding (Table 4).

The samples with amorphous SS returned almost to their original length after the stress was removed (Figure 4 and Table 3). The low permanent set of PUU−PTMC **(5)** could be explained by the fact that only two of the samples broke and therefore little or no plastic deformation of the hard domains had occurred. For PUU−P(CL-DLLA) **(8)** the permanent set was higher due to the melting temperature of the SS crystal structure, partly derived from strain crystallization, and remains after stress removal, thus hindering the recovery.

At the moment we are not able to clearly explain the extremely high elongation and excellent recovery in these copolymers.

Hydrogen-Bonding Study with IR Spectroscopy. Hydrogen bonding and the extent of the same are important to PU and PUU. The physical cross-links that the HS creates are derived from hydrogen bonding. When studying these secondary bondings with IR spectroscopy there are two major regions of interest, namely, the carbonyl region (amide I) located between ∼1620 and 1760 cm^{-1} and the N−H region found between 3100 and 3500 cm^{-1}. The amide II region, ∼1560 cm^{-1}, can also be of interest. Peak shape also reveals the strength of the hydrogen bonding; the sharper the peak, the more pronounced it is. Coleman and Painter have shown that higher bond strength will lead to a decrease in frequency for the carbonyl and the N−H peak while the amide II peak should increase in frequency.[29] Here, PUU−PTMC **(5)** had an N−H peak at 3341 cm^{-1} and a carbonyl peak at 1633 cm^{-1}, with sharp peaks indicating pronounced hydrogen bonding. PUU−P(TMC-CL) **(6)**, PUU−P(TMC-DLLA) **(7)**, and PUU−P(CL-DLLA) **(8)** showed similar IR spectra with an N−H peak around 3360 cm^{-1} and a carbonyl peak between 1634 and 1640 cm^{-1} (Table 4). The amide II peak was found at 1563 cm^{-1} for all of the PUUs. This could be another explanation for the much higher tensile stress at maximum for PUU−PTMC **(5)** in comparison to the other TMC-containing PUUs (Figure 5). The hydrogen-bonding degree is fairly similar except for that of crystalline PUU−P(CL-DLLA), which indicates a less phase-separated system.

Conclusions

Here we have presented a one-pot synthesis for poly(urethane urea) using biodegradable soft segments and a hard segment derived solely from a lysine-derived diisocyanate. The HS has a high density of hydrogen-bonding urea groups, giving the material unprecedented stress−strain properties. The tensile strength for PUU−PTMC was clearly affected when PTMC was copolymerized, even at very low degree. Interesting is that the synthesis strategy, where urea linkages are built up from the amine produced in situ through vapor phase addition of water, is also applicable to DLLA-containing soft segments. This way of synthesizing PUU has earlier been shown to be applicable to both aliphatic and aromatic diisocyanates. It has now been demonstrated to be generally applicable for a number of various polyesters and polycarbonates. It is a very simple one-pot synthesis that requires no isolations steps and no chain extender.

Acknowledgment. We thank Radi Medical Systems AB for their support and interest in our research. We also thank VINNOVA, Sweden (Project No 20436-1), and EU-project 013602 3G-SCAFF for financing our research.

Supporting Information Available. ^{1}H NMR spectra from the model study of butanol and LDI. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Asplund, B.; Bowden, T.; Mathisen, T.; Hilborn, J. *Macromolecules* **2006**, *39*, 4380−4385.
(2) Martin, D. J.; Meijs, G. F.; Gunatillake, P. A.; Yozghatlian, S. P.; Renwick, G. M. *J. Appl. Polym. Sci* **1999**, *71*, 937−952.
(3) Sheth, J. P.; Klinedinst, D. B.; Wilkes, G. L.; Yilgör, I.; Yilgör, E. *Polymer* **2005**, *46*, 7317−7322.
(4) Klinedinst, D. B.; Yilgör, E.; Yilgör, I.; Beyer, F. L.; Wilkes, G. L. *Polymer* **2005**, *46*, 10191−10201.
(5) Seymour, R. W.; Estes, G. M.; Cooper, S. L. *Macromolecules* **1970**, *3*, 579−583.
(6) Estes, G. M.; Seymour, R. W.; Cooper, S. L. *Macromolecules* **1971**, *4*, 452−457.
(7) Christenson, E. M.; Anderson, J. M.; Hiltner, A.; Baer, E. *Polymer* **2005**, *46*, 11744−11754.
(8) Boretos, J. W.; Pierce, W. S. *Science* **1967**, *158*, 1481−1493.
(9) Lyman. D.; Knutson. K.; McNeil. B.; Shibatani, T. *Trans. Am. Soc. Artif. Intern. Organs* **1975**, *21*, 49−54.
(10) Khorasani, M. T.; Shorgashti, S. *J. Biomed. Mater. Res., Part A* **2006**, *77*, 235−260.
(11) Zhang, Z.; Wang, Z.; Liu, S.; Kodama, M. *Biomaterials* **2004**, *25*, 177−187.
(12) Tang, Y. W.; Labow, R. S.; Santerre, J. P. *Biomaterials* **2003**, *24*, 2805−2819.
(13) Zhang, J. Y.; Beckman, E. J.; Piesco, N. P.; Agarwal, S. *Biomaterials* **2000**, *21*, 1247−1258.
(14) Guan, J.; Sacks, M. S.; Beckman, E. J.; Wagner, W. R. *J. Biomed. Mater. Res.* **2001**, *61*, 493−503.
(15) Saad, B.; Hirt, T. D.; Welti, M.; Uhlschmidt, G. K.; Neuenschwander, P.; Suter, U. W. *J. Biomed. Mater. Res.* **1997**, *36*, 65−74.
(16) Woodward, S. C.; Brewer, P. S.; Moatmed, F.; Schindler, A.; Pitt, C. G. *J Biomed. Mater. Res.* **1985**, *19*, 437−444.
(17) Pitt, C. G.; Gratzl, M. M.; Kimmel, G. L.; Surles, J.; Schindler, A. *Biomaterials* **1981**, *2*, 215−220.
(18) Pêgo, A. P.; van Luyn, M. J. A., Brouwer, L. A., van Wachem, P. B., Poot, A. A., Grijpma, D. W.; Feijen, J. *J. Biomed. Mater. Res., Part A* **2003**, *67*, 1044.
(19) Pêgo, A. P.; Poot, A. A.; Grijpma, D. W.; Feijen, J. *J. Biomater. Sci., Polym. Ed.* **2001**, *12*, 35−53.
(20) de Groot, J. H.; Spaans, C. J., Dekens, F. G., Pennings. A. J. *Polym. Bull.* **1998**, *41*, 299−306.
(21) Lee, H. S.; Wang, Y. K.; Hsu, S. L. *Macromolecules* **1987**, *20*, 2089−2095.
(22) Ning, L. N.; De-Ning, W.; Sheng-Kang, Y. *Macromolecules* **1997**, *30*, 4405−4409.
(23) Yilgör, E.; Yilgör, I.; Yurtsever, E. *Polymer* **2002**, *43*, 6551−6559.
(24) Tremblay, P.; Lesage, J.; Ostiguy, C.; Tra, H. V. *Analyst* **2003**, *128*, 142−149.
(25) Pêgo, A. P.; Poot, A. A.; Grijpma, D. W.; Feijen, J. *Macromol. Biosci.* **2002**, *2*, 411−419.
(26) Yang, J. H.; Chun, B. C.; Chung, Y.-C.; Cho, J. H. *Polymer* **2003**, *44*, 3251−3258.
(27) Storey, R. F.; Hickey, T. P. *Polymer* **1994**, *35*, 830−838.
(28) Skarja, G. A.; Woodhouse, K. A. *J. Appl. Polym. Sci* **2000**, *75*, 1522−1534.
(29) Coleman, M. M.; Sobkowiak, M.; Pehlert, G. J.; Painter, P. C.; Iqbal, T. *Macromol. Chem. Phys.* **1997**, *198*, 117−136.

BM061058U