

Polyurethanes Made from Bile Acids^{*}

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Abstract New polyurethanes based on bile acids were synthesized from alcohol derivatives of cholic and lithocholic acids and hexamethylene diisocyanate, in an effort to improve the biocompatibility and biodegradability of polyurethanes through the use of natural compounds. The hydrogen bonding in the polymers is confirmed by IR spectral analysis. The glass transition temperatures of the polymers are in the range of 82–138 °C and degradation temperatures in the range of 267–298 °C as studied by thermal analyses. Thermogravimetric studies indicate that the comonomers are of equimolar amounts in the polyurethanes derived from both bile acids.

Keywords: Polyurethanes; Bile acids; Hydrogen bonding; Glass transition temperature.

INTRODUCTION

Polyurethanes (PUs) are an important family of polymers that find applications as fibers, paint, dye, leather as well as in medical devices^[1–3]. They contain a carbamate-linked segment of polyol (soft segment) and an amide-linked segment (hard segment)^[4]. The formation of the different segments is due to the intermolecular hydrogen bonding between the amine or alcohol groups and the carbonyl groups. The extensively hydrogen-bonded structure yields stronger and tougher materials, making them particularly useful as fibers or leather^[1, 2]. Less hydrogen bonding leads to softer materials, also useful in medical devices^[3]. Their biomedical applications make use of their interesting properties such as adhesion, elasticity, flexibility and biodegradability^[5–7]. Researchers focused recently on the use of renewable sources of monomers in the preparation of PUs, mostly using vegetable oil as starting materials or as additives^[8–10]. For example, castor oil may be included in the structure of polyurethane to enhance its cytocompatibility or antibacterial effects^[11, 12].

In response to the need of bio-based polymers, we have used bile acids, a family of biological compounds abundant in all animals with a digestive tract, in the preparation of polyesters^[13], polyamides^[14], block copolymers^[15], and oligomers^[16]. We report here the first synthesis of PUs based on cholic (PUCA) and lithocholic acids (PULCA) (Fig. 1), two representatives of bile acids.

EXPERIMENTAL

Hexamethylene di-isocyanate (HDI) was distilled under reduced pressure. The catalyst di-*n*-butyltin dilaurate (Fluka) was used as received without purification. Solvents such as dimethyl acetamide (DMA, from Merck), dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) were dried with MgSO₄ for two days. Cholic acid methyl ester^[17, 18], the alcohol derivatives of cholic^[17, 18] and lithocholic^[19, 20] acids CA and LCA were synthesized according to literature. The conditions used for the synthesis of polyurethane samples are summarized in Table 1.

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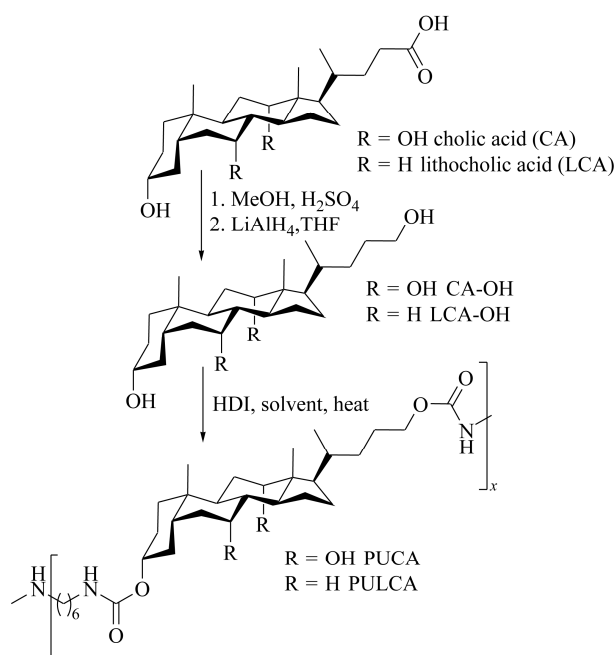


Fig. 1 Synthesis of polyurethanes from hexamethylene diisocyanate (HDI) and cholic acid (CA) and lithocholic acid (LCA)

Table 1. Synthetic conditions and physical properties for the polyurethanes made from bile acid derivatives

Polymer	Solvent used	T_{rxn} (°C)	T_g (°C)	TGA weight loss				Weight ratio	Physical appearance
				T_d (°C)	%	T_d (°C)	%		
PULCA1	DMF	110	123	273	40	405	60	1.5	White paste
PULCA2	DMSO	70	104	267	38	425	52	1.4	Transparent gum paste
PULCA3	DMSO	110	103	275	35	415	58	1.6	Transparent gum paste
PULCA4	DMA	110	85	284	37	413	51	1.4	Soft gum
PUCA6	DMF	70	121	276	36	391	54	1.5	White gum
PUCA7	DMSO	70	117	272	33	411	57	1.7	
PUCA8	DMSO*	110	128	298	27	405	43	1.6	
PUCA9	DMA	70	125	278	32	396	46	1.4	
PUCA10	DMA*	110	138	277	37	396	55	1.5	

Note: T_{rxn} : reaction temperature, T_g : glass transition temperature, determined by DSC, T_d : decomposition temperature for the 2nd or 3rd weight loss and the percentage of the weight loss and the ratio of the last 2 stages of weight loss, determined by TGA (HDI/BA weight ratio is about 1.6 for PULCA and 1.7 for PUCA. *2 eq. of HDI used. The rest all used equimolar amounts of HDI and CA-OH or LCA-OH.)

Polyurethanes Based on Bile Acid Derivatives

To make the PU based on cholic acid (PUCA), a solution of alcohol derivatives of cholic acid CA-OH (500 mg, 1.26 mmol) was dissolved in 3 mL of solvent (DMA, DMF or DMSO), followed by the addition of 2 drops of di-*n*-butyltin dilaurate and hexamethylene di-isocyanate (205 μ L, 1 eq.). The reaction mixture was stirred at high temperatures (70 or 110 °C) for 10 h. The product was then washed with ethyl acetate (EtOAc) and dichloromethane (DCM), and dried in a vacuum oven for 10 h at room temperature. A white solid was obtained. The reaction was repeated by using 2 eq. of HDI (410 μ L). For the synthesis of the PU based on lithocholic acid (PULCA), the same procedure was used with the exception of the quantities of LCA-OH (500 mg, 1.38 mmol) and HDI (220 μ L, 1 eq.).

Dissolution Study

Various solvents were tested to dissolve the new PUs, including DCM, chloroform, methanol, ethanol, EtOAc, THF, acetone, DMF, DMA, *N*-methylpyrrolidine, pyridine, DMSO, water, acetic acid, hydrochloric acid, sulfuric acid, xylene, toluene, *m*-cresol, polyethyleneglycol, castor oil and glycerol (1 mg/mL) without success, even with the help of ultrasounds, heat, additives such as urea and solvent mixtures. Only aniline dissolved the PUs.

Analyses

Thermal degradation was analyzed on a Hi-Res TGA 2950 thermogravimetric analyzer (TGA from TA Instruments). The method employed for all samples uses a ramp at 10 K/min up to 600 °C. Before DSC analysis, all samples underwent a preparative TGA in order to remove all traces of solvents. In the TGA experiments the samples were heated at 10 K/min from room temperature to 160 °C and left isothermal for 120 min. The glass transition temperatures (T_g) of the polymers were analyzed by differential scanning calorimetry (DSC) on a Q2000 DSC instrument (TA Instruments). Three DSC thermograms were recorded for each sample starting with cooling to -70 °C with a 10 K/min ramp, an isotherm for 5 min, a heating ramp at 10 K/min until 200 °C, followed by an isotherm for 5 min. The T_g 's shown are the averages of the last two unchanged cycles. The attenuated total reflectance (ATR) infrared (IR) spectra were taken with 32 scans on a Nicolet FTIR 6700 spectrometer (Thermo Scientific). Dynamic mechanical analysis (DMA) measurements were conducted on a DMA 2980 dynamic mechanical analyzer from TA Instruments. For the experiment, a preload force of 0.005 N, an amplitude of 10 μ m, a heating rate of 1 K/min, and force track of 125% were used. The T_g determined by DMA was defined as the inflection point in the change of storage modulus.

RESULTS AND DISCUSSION

Various polyurethanes were synthesized from the alcohol derivatives of bile acids CA-OH and LCA-OH under different reaction conditions by changing the temperature, time, and solvent of the reaction (Table 1). LCA-OH yielded a gum paste in 10 h (transparent or white). PULCA2 was made at 70 °C in DMSO. Higher reaction temperature was required for the other samples in DMF and DMSO. In the reactions with CA-OH only one equivalent of HDI was used to avoid cross-linking (PUCA 6, 7 and 9), and then two equivalents were also tested for the reaction (PUCA 8 and 10). All polymers were obtained as gummy solid. PUCA7 needed only 30 min.

With the exception of aniline, the PU samples were found to be insoluble in common organic solvents. Additives such as urea^[21, 22] did not help with the dissolution. Degradation occurred when pure sulfuric acid was used. Due to their poor solubility, GPC analysis could not be performed to determine their molar masses. The products were thus characterized by ¹³C and ¹⁵N solid state NMR, IR spectroscopy and thermal analyses (TGA and DSC). Copolymerization was also attempted with CA-OH, PEG 400 and HDI (1/1/2). The polyurethane obtained was soluble in DMSO and NMP, but the molar mass determined by GPC was low (around 8000 Da).

Figure 2 shows solid state ¹³C- and ¹⁵N-NMR spectra of PUCA7 and PULCA2. These polymers are representative of the PU sample derived from cholic and lithocholic acids, and the difference between them is small^[23]. Solid state ¹³C-NMR spectrum where the carboxylic acid CO peak at δ = 170 shifts to 150 for the amide or carbamate CO peak of the bile acid derivative which is the case in both polymers (Fig. 2 spectra a and spectra b)^[24, 25]. PUCA7 shows also a peak at δ = 170. Solid state ¹⁵N-NMR spectra show a unique peak around δ = 100^[26], corresponding to samples of amorphous polyurethane.

Preparative TGA was done for the samples before the DSC experiments, to remove the residual amounts of solvents. Some of the solids obtained were difficult to break and pulverize, causing some solvent to be trapped inside the polymer. Figure 3(a) shows that all the thermograms displayed a transition between 82 °C and 120 °C and between 115 and 140 °C for the PUs based on CA-OH and LCA-OH, respectively. No weight loss was detected on TGA at these temperatures (Fig. 3b). For PULCA, the reproducibility of the reaction was tested (Table 1, PULCA4), and the thermal properties obtained were identical, suggesting that the synthesis is reproducible. The reaction temperature (Table 1, PULCA 2 and 3) had no effect on the results, as the same T_g was obtained (104 and 103 °C, respectively).

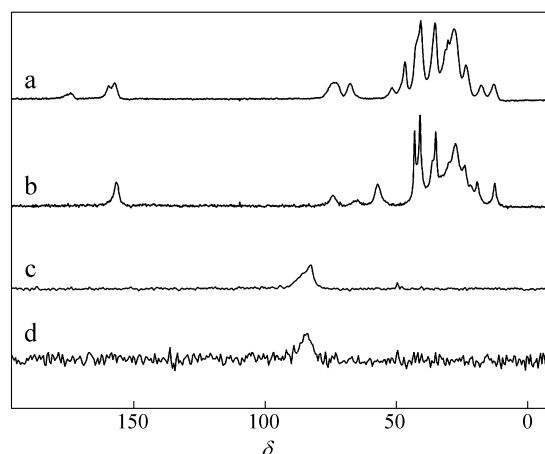


Fig. 2 Solid state ^{13}C -NMR spectra of PUCA 7 (a) and PULCA 2 (b) and solid state ^{15}N -NMR spectra of PUCA 7 (c) and PULCA 2 (d)

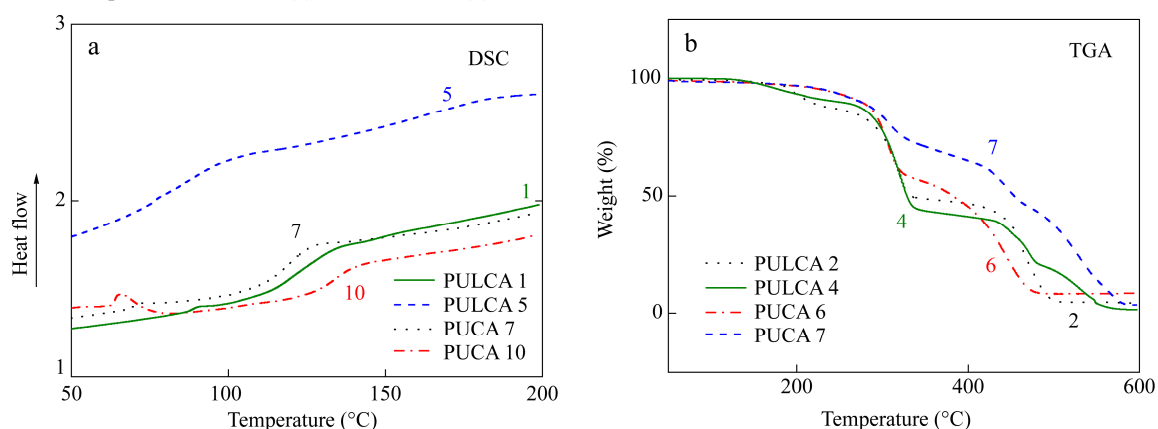


Fig. 3 (a) DSC and (b) TGA traces of selected polyurethane samples made of cholic acid (PUCA) and lithocholic acid (PULCA)

The weakest bond in the PU samples is the ester bond, which should be easier to break. The step-wise weight loss for the PUs is expected to correspond to the linear bis-amine followed by the bile acid core. The polymers synthesized with equimolar amounts of HDI and the bile acid derivatives should therefore exhibit HDI/BA weight ratios of about 1.7 and 1.6 for PUCA and PULCA, respectively. Figure 3(b) shows four representative thermograms of the PUs, each exhibits two or three weight loss steps. The first weight loss step, between 160 and 200 °C, corresponds to the loss of residual solvent (around 5%–10%). These solvents have relatively high boiling points: DMA, DMSO and NMP are at 165, 189 and 202 °C, respectively. The second step, around 280 °C, corresponds to a weight loss of 27%–40%, and the third step, around 400 °C, shows a weight loss of 43%–60%. The bond energy of the O–C=O bond of the carbamate group is about 300 kJ/mol in comparison to that of the N–C=O bond (600 kJ/mol)^[27], it would be the first component to degrade, leading to a bis-amide (estimated molar mass 171). Therefore, we can estimate the weight ratio between these two components from the weight loss, which yields around 1.5 for PULCA and 1.6 for PUCA, as shown in Table 1. We may expect some experimental error in the weight loss measured, but the numbers obtained fall within the expected range. Further, the weight loss ratios of the two steps follow closely the weight ratio of the two comonomers. The weight loss ratio of the PULCA samples tends to be systematically less than that of the PUCA samples. Dynamic mechanical analysis was conducted on the PULCA 2. T_g of 98 °C was obtained (Fig. 4), which is consistent with the results observed in DSC measurements.

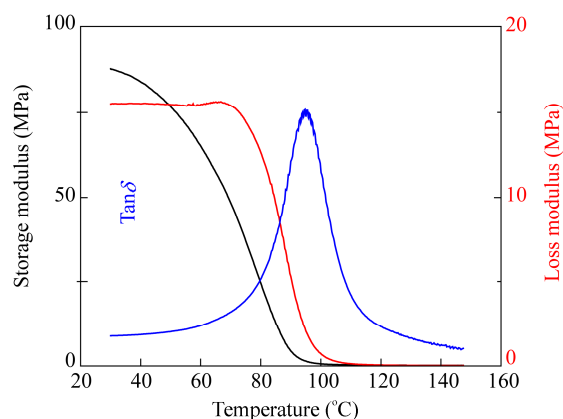


Fig. 4 Dynamic mechanical analysis on PULCA 2

Figure 5 shows the IR spectra of selected PUs. Two kinds of hydrogen bonds can be observed in the hard-hard and hard-soft sections of PUs^[28–31]. Usually, the IR spectra of PUs present two distinct areas of interest: the first corresponding to the N–H stretching vibration (3300 cm^{-1}), and the second to the C=O bonds (1700 cm^{-1}). There are 3 kinds of C=O stretching vibration bands as shown in the enlarged insets of Fig. 5. those without hydrogen bonding (I, $1720\text{--}1740\text{ cm}^{-1}$), those with hydrogen bonding in the soft segments (II, $1700\text{--}1720\text{ cm}^{-1}$) and in the hard segments (III, $1680\text{--}1700\text{ cm}^{-1}$). The starting material, HDI, cannot be seen in the spectra ($2100\text{--}2200\text{ cm}^{-1}$). For PULCA (Fig. 5 inset), three peaks in the region of carbonyl bond stretching vibration can be seen: the first around 1715 cm^{-1} ; the second around $1690\text{--}1700\text{ cm}^{-1}$; and the third around 1670 cm^{-1} . This last peak can be clearly seen in the case of PULCA1, less so in PULCA2, but is absent in PULCA4. In the PUCA samples (Fig. 5 inset), 3 peaks can also be observed at 1740 , 1705 (PUCA7) and 1720 cm^{-1} for the second and 1695 cm^{-1} for the third. This last one corresponds to the CO bond stretching vibration with hydrogen bonding in the hard segments, but is present only for PUCA6 and PUCA9.

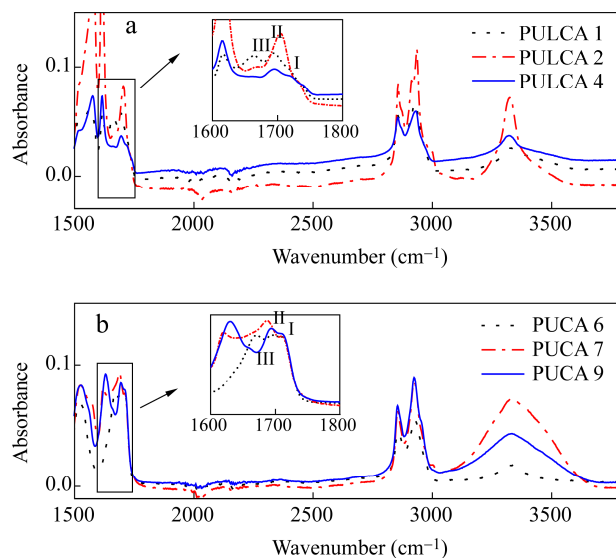


Fig. 5 FTIR spectra of polyurethanes based on (a) lithocholic acid (PULCA) and (b) cholic acid (PUCA)

The C=O stretching vibration bands are shown in the insets: I ($1720\text{--}1740\text{ cm}^{-1}$), without hydrogen bonding, II ($1700\text{--}1720\text{ cm}^{-1}$), with hydrogen bonding in the soft segments, and III ($1680\text{--}1700\text{ cm}^{-1}$), with hydrogen bonding in the hard segments.

The IR spectra of PULCA1 show more hydrogen bonding in the hard segments and a higher T_g was also obtained for this series (123 °C). The PUCA samples with the highest intensity in the IR spectra (PUCA 5 and 9) showed the highest T_g (121–125 °C). When more HDI was added to reach 2 equivalents, an increase in T_g (PUCA 8–10) was also observed (to 128–138 °C). The samples made in the other solvents had a lower T_g . The PUCA samples generally had a narrow glass transition temperature in the range of 117–125 °C.

CONCLUSIONS

Polyurethanes were made from derivatives of cholic and lithocholic acids and HDI, and they were hard to dissolve in common solvents. TGA analyses showed that the two comonomers were of equimolar amounts, and extensive hydrogen bonding was evidenced by IR studies. Their T_g ranged from 80 °C to 140 °C depending on the reaction conditions as evidenced by DSC experiments. The solid state NMR spectroscopy confirms the structure of the polyurethanes. More soluble PU samples based on bile acids are being prepared by incorporating more flexible moieties in the polymer chains.

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