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Polyurethanes Derived from Carbohydrates and Cystine-Based Monomers

Belén Begines, Francisca Zamora, M. Violante de Paz, Khalid Hakkou, Juan A. Galbis
Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, 41012 Sevilla, Spain
Correspondence to: J. A. Galbis (E-mail: jgalbis@us.es)

ABSTRACT: Linear [*m,n*]-type polyurethanes (PUs) fully based on renewable materials are synthesized by interfacial polycondensation reaction of diamines derived from the amino-acid cystine with (bis)chloroformates derived from alditols having L-*arabino* or *xylo* configuration. The degradability of the new PUs has been enhanced by the introduction of disulfide linkages into the polymer backbone leading to a new group of stimulus-responsive sugar-based polyurethanes able to be degraded by glutathione under physiological conditions. All these polyurethanes are stable up to around 245°C, decomposing at higher temperatures through a one-stage mechanism. The new materials display high chemical homogeneity and degradability in both hydrolytic and reductive environments, with reductions of above 90% in M_w. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 41304.

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INTRODUCTION

Significant progress has been made in the development of biodegradable polymeric materials for biomedical applications such as temporary prostheses, scaffolds for tissue engineering, and vehicles for controlled/sustained drug release.[1] Nevertheless, due to the complexity and variety of applications of polymeric biomaterials used at present, there is not a single polymeric system available that could be considered an ideal biomaterial. Thus, efforts in biodegradable polymer synthesis have been focused on developing novel tailor-made synthetic polymers to broaden the variety of polymer structures available with adapted properties for specific applications, circumventing many of the disadvantages of natural polymers.[1,2]

Polyurethanes (PUs) are moldable, strong, hydrolytically degradable polymers that possess labile carbamate functional groups in their structure.[3] They present degradation rates similar to polyesters and polycarbonates.[4,5] Extensive research into their use as long-term medical devices such as tracheal tubes, vascular grafts, and cardiac pacemakers has been made,[6–9] due to the excellent biocompatibility and mechanical properties of these polymers. However, they are resistant to degradation under most conditions, and hence, poor candidates for drug delivery and some tissue engineering applications. Therefore, owing on their good biological performance and chemical versatility, new methods have been developed to increase their biological degradability,[10–12] in order to make them applicable in the preparation of nonpermanent medical devices.

Although hydrolytic degradation of PUs has been extensively reported, a faster degradation method under milder degradation conditions has been described by our research group.[13] This method is based on glutathione-mediated lysis under physiological conditions of disulfide bonds incorporated into the polymer skeleton. The general validity of this strategy has been supported by previously published works related with various HMDI- and MDI-PUs.[13,14]

Linear PUs are generally prepared by the polymerization reaction of diisocyanates with diols.[15] However, due to the use of toxic stannous catalysts and the toxicity of common aromatic diisocyanates such as 4,4'-methylenediphenyl diisocyanate (MDI) and toluene diisocyanate (TDI), some synthetic changes are needed when developing biodegradable polyurethanes for application as biomaterials, such as, for example, the use of biocompatible aliphatic diisocyanates. In this way, efforts are being carried out to develop biocompatible PUs based on renewable and biocompatible building blocks.[16–21]

Another alternative is presented here, in which the use of diisocyanates and metal catalysts is avoided. In this case, the reactive (bis)chloroformates were formed from sugar-based diols, and polymerized with selected diamines. In contrast with the diisocyanate method, a wide range of PUs can be freshly

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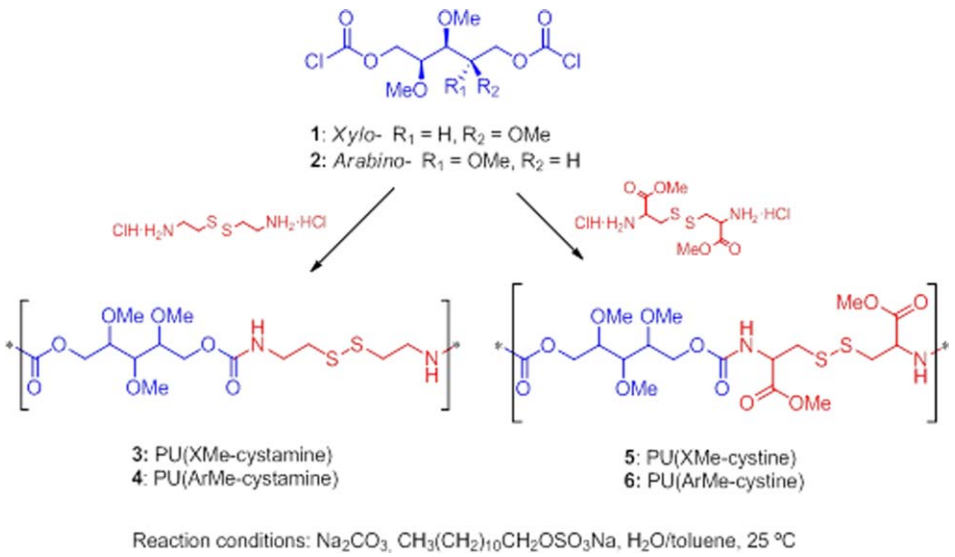

Scheme 1. Synthesis of polyurethanes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

prepared from a large set of commercial diamines, and hence the chemical versatility of the new materials may be highly improved. In the present work, all the monomers are nature-based materials. The diamines used are derivatives of the natural amino acid L-cysteine, and were chosen as bearing the labile disulfide bond in their structure. This may confer enhanced degradability on the novel polymers. The preparation of bis(chloroformate)s monomers by means of phosgene is safe—despite the toxicity exhibited by this reactant—since its excess can be completely removed prior the polymerization process.

EXPERIMENTAL

Materials and Methods

Commercial reagents and solvents were purchased from Aldrich Chemical Co. and used as received. The bis(chloroformate) monomers 2,3,4-tri-O-methylxylitol bis(chloroformate) (**1**) and 2,3,4-tri-O-methyl-L-arabinitol bis(chloroformate) (**2**) (Scheme 1) were synthesized from the freshly prepared 2,3,4-tri-O-methyl-xylitol and 2,3,4-tri-O-methyl-L-arabinitol, respectively. These diols were obtained following the synthetic method previously described by our group.[22] Both bis(chloroformate)s were handled under inert atmosphere. Optical rotations were measured at (20 ± 5)°C on a Perkin-Elmer 341 polarimeter. Elemental analyses were determined in the Microanalysis Laboratories of the IIQ Service, cicCartuja, Seville. IR spectra were recorded on a JASCO FT/IR-4200 spectrometer equipped with ATR. NMR spectra were recorded at 300 K on either a Bruker Advance AV-500 or a Bruker AMX-500 in the Centro de Investigación Tecnología e Innovación de la Universidad de Sevilla (CITIUS, Seville). Chemical shifts (δ) are reported as parts per million downfield from Me_4Si. Gel permeation chromatography (GPC) analyses were performed using a Waters apparatus equipped with a Waters 2414 refractive-index detector and two Styragel® HR columns (7.8 × 300 mm) linked in series, thermostatted at 60°C, using N-methyl-2-pyrrolidone (NMP) as the mobile phase, at a flow rate of 0.5 mL min^{-1}. Molecular weights were estimated against polystyrene standards. Intrinsic viscosity was determined in dichloroacetic acid (DCA) with an AMVn Automated Microviscosimeter of Anton Paar. The thermal behavior of the polyurethanes was examined by differential scanning calorimetry (DSC), using a TA DSC Q-200 Instrument calibrated with indium. DSC data were obtained from samples of 4–6 mg at heating/cooling rates of 10°C min^{-1} under a nitrogen flow. The glass transition temperatures (T_g) were determined at a heating rate of 20°C min^{-1} from rapidly melt-quenched polymer samples. Thermogravimetric analyses (TGAs) were performed under nitrogen atmosphere (flow rate 100 mL min^{-1}) with a Universal V4.3A TA Instrument at a heating rate of 10°C min^{-1}.

Synthesis of Bis(chloroformate) Monomers

2,3,4-Tri-O-Methylxylitol Bis(chloroformate) (1). A solution of phosgene in toluene (10 mL, 20% w/v, 20 mmol) was charged in a round-bottom flask, saturated with argon, and cooled to −10°C; 2,3,4-tri-*O*-methylxylitol[22] (1.94 g, 10 mmol) in THF (4 mL) was added under stirring, as well as an excess of phosgene (20 mL, 20% w/v in toluene, 40 mmol). When the temperature rose to 0°C, the reaction mixture was allowed to warm up to room temperature and stirred for 4 hr. The excess of phosgene was removed by passing an argon stream through the reaction solution for 12 hr, and the solution was concentrated to give the title bis(chloroformate) (**1**) as a pure colorless oil (2.74 g, 84%). IR: ν (cm^{-1}) 1770 (C=O); ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.47 (t, 1 H, H-3, $J_{2,3} = J_{3,4} = 4.4$ Hz), 3.51 (s, 6 H, 2 OCH_3), 3.54 (s, 3 H, OCH_3), 3.74–3.77 (m, 2 H, H-2, H-4), 4.46 (dd, 2 H, H-1a, H-5a, $J_{1a,1b} = J_{5a,5b} = 11.5$ Hz, $J_{1a,2} = J_{4,5a} = 6.4$ Hz), 4.59 (dd, 2 H, H-1b, H-5b, $J_{1b,2} = J_{4,5b} = 4.0$ Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ (ppm) 59.0, 60.0 (3 OCH_3), 70.9 (C-1, C-5), 77.3 (C-2, C-4), 79.2 (C-3), 150.6 (C=O); Anal. Calcd. for $C_{10}H_{16}Cl_2O_2$: C, 37.63; H, 5.05. Found: C, 37.97; H, 4.69.

2,3,4-Tri-O-Methyl-L-Arabinitol Bis(chloroformate) (2). The reaction of 2,3,4-tri-*O*-methyl-L-arabinitol[22] (0.77 g, 4 mmol) with phosgene (12 mL, 20% w/v in toluene, 24 mmol) was carried out as described above for compound **1** to give the title compound as a white solid after recrystallization from ethanol (1.16 g, 91%). $[\alpha]_D$ −9° (*c* 1.0, chloroform); IR: *v* (cm^{-1}) 1775 (C=O); ^{1}H-NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 3.33 (dd, 1 H, H-3, $J_{2,3}$ = 7.9 Hz, $J_{3,4}$ = 2.7 Hz), 3.45 (s, 3 H, OCH_3), 3.47 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 3.56–3.60 (m, 1 H, H-4), 3.73–3.75 (m, 1 H, H-2), 4.34 (dd, 1 H, H-5a, $J_{5a,5b}$ = 11.8 Hz, $J_{4,5a}$ = 4.1 Hz), 4.46 (dd, 1 H, H-1a, $J_{1a,1b}$ = 11.1 Hz, $J_{1a,2}$=5.4 Hz), 4.55 (dd, 1 H, H-1b, $J_{1b,2}$ = 6.6 Hz), 4.79 (dd, 1 H, H-5b, $J_{4,5b}$ = 2.5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz): *δ* (ppm) 58.2, 59.6, 60.9 (3 OCH_3), 69.1, 70.4 (C-1, C-5), 77.7, 77.8 (C-2, C-4), 79.2 (C-3), 150.8 (C=O); Anal. Calcd. for $C_{10}H_{16}Cl_2O_2$: C, 37.63; H, 5.05. Found: C, 37.60; H, 5.14.

Synthesis of Polymers

PU(XMe-cystamine) (3). A mixture of cystamine dihydrochloride (0.25 g, 1.13 mmol), sodium carbonate (0.29 g, 2.26 mmol), and sodium lauryl sulfate (0.034 g) was placed in a round-bottom flask and dissolved in distilled water (7 mL). Next, a solution of 2,3,4-tri-*O*-methylxylitol bis(chloroformate) (**1**, 0.36 g, 1.13 mmol) in toluene (5 mL) was added dropwise to the aqueous solution under vigorous stirring (1000 rpm). The reaction was allowed to proceed for 30 min and the polyurethane was filtered off, washed several times with distilled water to remove the salts and the emulsifier, and dried under vacuum. The polymer was further purified by dissolving it in the minimum amount of CH_2Cl_2, and the solution was added dropwise into cold *tert*-butyl methyl ether (150 mL), where the polymer PU(XMe-cystamine) precipitated as a white solid (0.18 g, 40%). IR: *v* (cm^{-1}) 3329 (NH), 1696 (C=O, urethane), 1524 (NH, *δ*); ^{1}H-NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 2.86 (t, 4 H, CH_2-S, *J* = 6.5 Hz), 3.48 (s, 6 H, 2 OCH_3), 3.55 (s, 3 H, OCH_3), 3.40–3.61 (m, 7 H, H-2, H-3, H-4, CH_2NH), 4.06–4.50 (m, 4 H, H-1a, H-1b, H-5a, H-5b), 5.56 (bs, 2 H, NH); ^{13}C-NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 38.1 (CH_2S), 39.9 (CH_2NH), 58.7, 60.6 (3 OCH_3), 63.8 (C-1, C-5), 79.1 (C-2, C-4), 80.6(C-3), 156.4 (C=O); Anal. Calcd. for $C_{14}H_{26}N_2O_7S_2$: C, 42.20; H, 6.58; N, 7.03; S, 16.09. Found: C, 42.28; H, 6.70; N, 7.38; S, 16.59.

PU(ArMe-cystamine) (4). This polymer was prepared from a mixture of cystamine dihydrochloride (0.34 g, 1.5 mmol), sodium carbonate (0.32 g, 3 mmol), sodium lauryl sulfate (0.045 g), and 2,3,4-tri-*O*-methyl-L-arabinitol bis(chloroformate) (**2**, 0.48 g, 1.5 mmol), at 25°C, to give the title compound as a white solid (0.27 g, 45%). $[\alpha]_D$ +9° (*c* 1.0, chloroform); IR: *v* (cm^{-1}) 3328 (NH), 1697 (C=O, urethane), 1524 (NH, *δ*); ^{1}H-NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 2.86 (bs, 4 H, CH_2-S), 3.44 (s, 3 H, OCH_3), 3.48 (s, 3 H, OCH_3), 3.50 (s, 3 H, OCH_3), 3.36–3.64 (m, 7 H, H-2, H-3, H-4, CH_2NH), 4.07–4.63 (m, 4 H, H-1a, H-1b, H-5a, H-5b), 5.58 (bs, 2 H, NH); ^{13}C-NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 38.2 (CH_2S), 39.9 (CH_2NH), 57.7, 59.1, 60.1 (3 OCH_3), 62.2, 63.1 (C-1, C-5), 77.2, 78.1 (C-2, C-4), 79.5 (C-3), 156.3, 156.4 (C=O); Anal. Calcd. for $C_{14}H_{26}N_2O_7S_2$: C, 42.20; H, 6.58; N, 7.03; S, 16.09. Found: C, 42.18; H, 6.73; N, 7.00; S, 15.97.

PU(XMe-cystine) (5). This polymer was prepared from a mixture of L-cystine dimethyl ester dihydrochloride (0.34 g, 1 mmol), sodium carbonate (0.21 g, 2 mmol), sodium lauryl sulfate (0.03 g), and 2,3,4-tri-*O*-methylxylitol bis(chloroformate) (**1**, 0.32 g, 1 mmol),) at 25°C, to give the title compound as a white solid (0.18 g, 40%). IR: *v* (cm^{-1}) 3315 (NH), 1716 (C=O, ester and urethane), 1521 (NH, *δ*); ^{1}H-NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 3.14–3.19 (m, 4 H, CH_2-S), 3.35–3.84 (m, 3 H, H-2, H-3, H-4), 3.44 (s, 6 H, 2 OCH_3), 3.50 (s, 3 H, OCH_3), 3.75 (s, 6 H, $COOCH_3$), 4.12–4.40 (m, 4 H, H-1a, H-1b, H-5a, H-5b), 4.63 (bs, 2 H, CHCOOCH_3), 6.12 (bs, 2 H, NH); ^{13}C-NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 40.7 (CH_2S), 52.8 (COOCH_3), 53.2 (CHCOOCH_3), 58.7, 60.6 (3 OCH_3), 64.1 (C-1, C-5), 78.7, 80.0 (C-2, C-3, C-4), 155.7 (NHCOO), 171.0 (C$OOCH_3$); Anal. Calcd. for $C_{18}H_{30}N_2O_{11}S_2$: C, 42.01; H, 5.88; N, 5.44; S, 12.46. Found: C, 42.13; H, 5.91; N, 5.47; S, 12.70.

PU(ArMe-cystine) (6). This polymer was prepared from a mixture of L-cystine dimethyl ester dihydrochloride (0.35 g, 1.03 mmol), sodium carbonate (0.22 g, 2.06 mmol), sodium lauryl sulfate (0.03 g), and 2,3,4-tri-*O*-methyl-L-arabinitol bis(chloroformate) (**2**, 0.33 g, 1.03 mmol), at 25°C, to give the title compound as a white solid (0.23 g, 50%). $[\alpha]_D$ +28° (*c* 1, chloroform); IR: *v* (cm^{-1}) 3317 (NH), 1715 (C=O, ester and urethane), 1521 (NH, *δ*); ^{1}H-NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 3.21 (bs, 4 H, CH_2-S), 3.36–3.66 (m, 3 H, H-2, H-3, H-4), 3.42 (s, 3 H, OCH_3), 3.47 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 3.78 (s, 6 H, $COOCH_3$), 4.10–4.58 (m, 4 H, H-1a, H-1b, H-5a, H-5b), 4.62 (bs, 2 H, CHCOOCH_3), 5.97 (bs, 2 H, NH); ^{13}C-NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 40.7 (CH_2S), 52.8 (COOCH_3), 53.4 (CHCOOCH_3), 57.7, 59.1, 60.9 (3 OCH_3), 62.7, 63.5 (C-1, C-5), 78.0, 78.1 (C-2, C-4), 79.3 (C-3), 155.6, 155.8 (NHCOO), 171.0 (C$OOCH_3$); Anal. Calcd. for $C_{18}H_{30}N_2O_{11}S_2$: C, 42.01; H, 5.88; N, 5.44; S, 12.46. Found: C, 42, 15; H, 6.03; N, 5.41; S, 12.36.

Degradation Assays

For degradation studies, the polymer disks (160 ±10 *μ*m of thickness) were prepared by the application of 10 ton cm^{-2} pressure on powdered polymer (20 ± 5 mg) for 5 min, at 25°C.

Hydrolytic Degradation Assays. In the hydrolytic degradation studies, each polymer disk was submerged in separate sealed vials containing 5 mL of an aqueous buffer solution (at pH 7.02 or pH 8.02) and heated at 37°C for an exact period of time. The samples were then rinsed thoroughly with double-distilled water and then, the aqueous solutions were dried under vacuum. Gel permeation chromatography (GPC) were used to study the molecular weights (M_n and M_w) and polydispersity indices (M_w/M_n) of the degraded polymers. The weight loss of the polymer disks was also monitored, as well as the molecular weights of the aqueous soluble residues, by gravimetric and GPC measurements, respectively.

Reductive Degradation Assays with Glutathione. In the reduction degradation assays, each polymer disk was submerged in a reduced glutathione solution (10 mL, 0.1 *M*, 1 mmol), at pH 7.02. An argon flow was passed through the solution for 5 min to avoid the presence of oxygen in the media and the vial was sealed and heated at 37°C, for an exact period of time. The

Table I. Viscosity and Molecular Weights of Polyurethanes

PU	η^a (dL g^{-1})	$M_w{}^b$	$M_n{}^b$	$M_w/M_n{}^b$
PU(XMe-cystamine) (**3**)	0.16	10,900	6,500	1.7
PU(ArMe-cystamine) (**4**)	0.30	51,100	21,900	2.4
PU(XMe-cystine) (**5**)	0.20	6,700	5,200	1.3
PU(ArMe-cystine) (**6**)	0.38	22,500	10,400	2.2

[a] Intrinsic viscosity, in dL/g, determined in dichloroacetic acid at 25°C.
[b] Determined by GPC analysis against polystyrene standards using NMP as mobile phase.

degradation experiments were quenched to stabilize the degraded polymer fragments.[13] The evolution of the process was followed as described for the hydrolytic degradation assays.

RESULTS AND DISCUSSION

Synthesis and Characterization of Monomers and Polymers

In the present paper, we describe the preparation of new biodegradable polyurethanes from renewable resources such as carbohydrates and amino acids and their derivatives. The synthesis of the new PUs was carried out by interfacial polycondensation of freshly prepared pentitol-based (bis)chloroformates with cystine-based diamines. The structures proposed for the monomers and polyurethanes were validated by FTIR and NMR spectroscopies; these data are fully detailed in the experimental section. Both ^{1}H-NMR and ^{13}C-NMR spectra were elucidated with the aid of other NMR experiments, such as COSY, DEPT, and heteronuclear correlation.

The starting diol compounds 2,3,4-tri-*O*-methylxylitol and 2,3,4-tri-*O*-methyl-L-arabinitol used for the synthesis of the bis(chloroformate)s 2,3,4-tri-*O*-methylxylitol bis(chloroformate) (**1**) and 2,3,4-tri-*O*-methyl-L-arabinitol bis(chloroformate) (**2**), respectively, were prepared as previously described from the commercially available pentitols xylitol and L-arabinitol.[22] For the preparation of the bis(chloroformate)s **1** and **2**, an excess of phosgene at low temperature was required, and the reactions proceeded efficiently with high yields in both cases. The new compounds exhibit the carbonyl stretching band at about 1,770 cm^{-1} and the signals corresponding to the carbonyl groups at about 151 ppm in their IR and ^{13}C-NMR spectra, respectively.

Reduction-sensitive polyurethanes were prepared straightforwardly[23] by polycondensation reaction of the commercial diamine dihydrochlorides cystamine dihydrochloride and L-cystine dimethyl ester dihydrochloride with the analytically pure freshly prepared bis(chloroformate)s (**1**) and (**2**) (**Scheme 1**). The new materials are homopolymers with a disulfide linkage in the skeleton that could potentially be reduced by the natural tripeptide reduced glutathione (GSH) under physiological conditions. This method imparts greater uniformity to the sample than the methods described to date, in which the introduction of the sensitive disulfide linkage into the polymer is carried out by the incorporation of a second monomer to the polymerization media. Moreover, with the method attempted here, the use of a metal-based catalyst is avoided, in contrast to the more common synthetic procedure of linear PUs, in which the polymerization takes place between a reactive diisocyanate and a diol in the presence of a tin-based catalyst such as dibutyltin dilaurate.

The polymerizations were carried out by interfacial polycondensation[24] in a mixture of toluene/water using sodium carbonate as a base and sodium lauryl sulfate as an emulsifier. The reaction mixtures were vigorously stirred (1,000 rpm), and foaming emulsions were formed. The new materials precipitated from the media within 30 min. The polymers were then isolated and purified. Moderate yields (40–50%) were attained, and weight-average molecular weights (M_w) were in the range of 6,700–51,100 Da. Both viscosity and molecular-weight data for the set of synthesized polyurethanes are recorded in Table I.

Characteristic IR absorption bands of urethane groups were observed at the expected ranges of wavenumber and intensity. Thus, the NH stretching bands appeared at about 3,320 cm^{-1} in every polyurethane, and the C=O stretching bands between 1,696 and 1,715 cm^{-1} (Figure 1). Likewise, ^{1}H- and ^{13}C-NMR spectra were in full agreement with the proposed chemical structures. ^{1}H-NMR spectra of novel polyurethanes show two or three singlet signals between 3.42 and 3.50 ppm for the methoxy groups of the polymers with *xylo* or *L-arabino* configurations, respectively [Figure 2 exhibits the ^{1}H NMR spectrum of PU(XMe-cystamine) (**3**)]. The polymers with cystine units display the signal corresponding to the protons CH_2S at lower field (~3.2 ppm) than those corresponding to the cystamine segments (~2.86 ppm, polymers **3** and **4**), because of the presence of the neighboring methyl carboxylate groups. ^{1}H-NMR spectra of polymers **5** and **6** also presented two peaks at 4.62 and 3.75 ppm, corresponding to the methyne protons ($\underline{CH}COOCH_3$) and the methyl ester group, respectively. ^{13}C-NMR spectra exhibited a characteristic peak at around 156 ppm, corresponding to the carbon of the urethane moiety. Furthermore, polymers **5** and **6** presented an extra peak at 171 ppm, due to the carbonyl ester group.

Thermal Properties

The thermal behavior of polyurethanes has been studied by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Detailed data for each compound are given in Table II. For comparative purposes, the calorimetric data for the new homopolymers are given together with the values obtained for HMDI-based xylitol and L-arabinitol PUs.[25] The presence of disulfide linkages involves a decrease in the thermal stability under nitrogen atmosphere—the decomposition onset temperature with an associated 10% weight loss (T_d 10%) ranged from

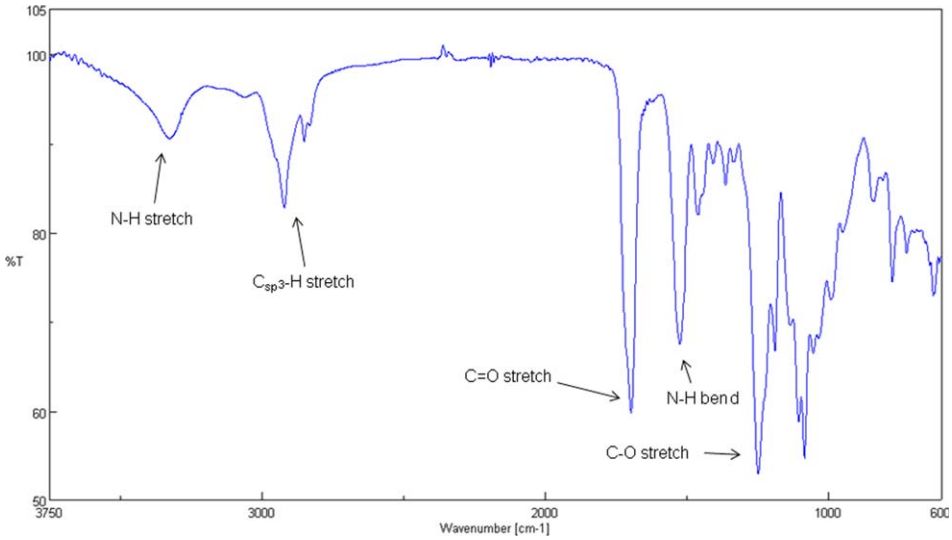

Figure 1. FTIR spectrum of PU(ArMe-cystamine) (**4**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

244°C to 261°C, whereas the HMDI-based polymers underwent the same 10% weight loss at temperatures above 280°C. The degradation under nitrogen atmosphere proceeded in one stage, with a maximum associated weight loss at temperatures ranging from 282°C to 300°C, and an observed weight loss of above 89%. These values follow a general trend observed in other synthetic polyurethanes[13,14,25] and the weight loss could reach 100 wt % when an oxidative atmosphere is used.

DSC studies showed that all new materials are semicrystalline. In contrast, hexamethylene chain incorporated in the model polymers **7** and **8** make these materials essentially amorphous. Also, cystine-based PUs displayed lower melting entalphy values than their cystamine counterparts, probably due to the presence of the side methoxycarbonyl groups which may influence the packing of the polymer chains. However, the low values of the measured melting enthalpies indicated a reduced presence of well-packed crystalline segments in all the polymers. This is in accordance with the good degradability of the materials studied. Moreover, L-arabinitol-based polymers **4** and **6** exhibit higher T_g values than their xylitol-based analogs **3** and **5**; this trend was already reported by us in a previous work[25] and can also be observed in polymers **7** and **8**. Furthermore, the incorporation of a pendant methoxycarbonyl group into the diamine unit (polymers **5** and **6**) results in a more rigid material (higher T_gs).

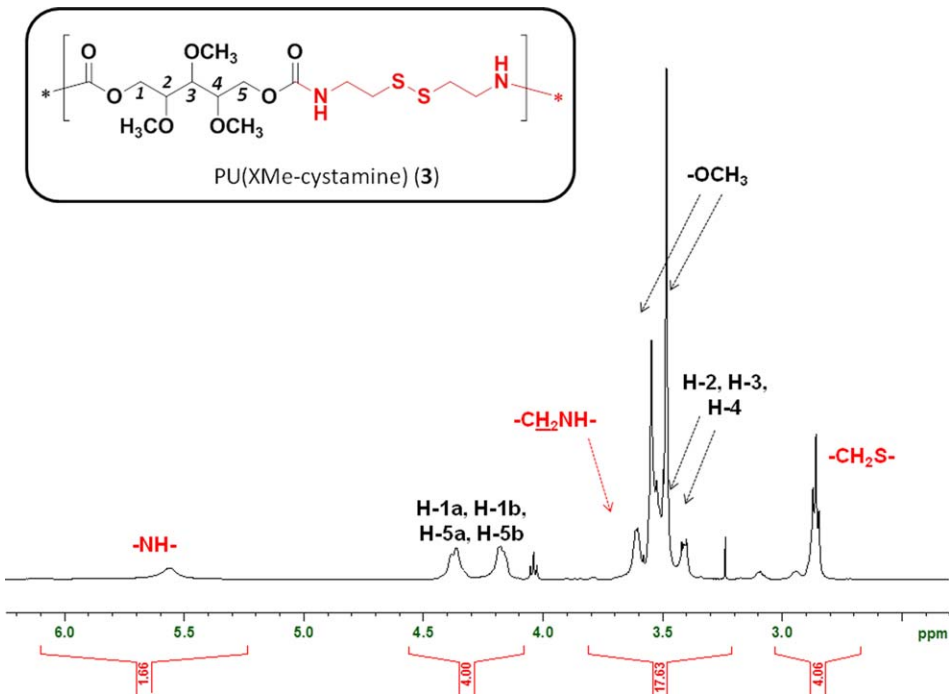

Figure 2. ^{1}H NMR spectrum of PU(XMe-cystamine) (**3**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table II. Thermal Properties of Polyurethanes

PU	DSC[a] T_g (°C)	T_m (°C)	ΔH_m (J g^{-1})	TGA[b] $^{\circ}T_d$ (°C)	$^{max}T_d$ (°C)	−ΔW (%)
PU(XMe-cystamine) (3)	35	78	11	244	299	89
PU(ArMe-cystamine) (4)	43	83	16	259	300	91
PU(XMe-cystine) (5)	57	76	1	261	282	91
PU(ArMe-cystine) (6)	63	80	9	256	290	96
PU(XMe-HMDI)[c] (7)	22	–	–	283	301/366/468	56/20/13
PU(ArMe-HMDI)[c] (8)	35	–	–	282	304/370/468	53/23/12

[a] Glass transition temperature (T_g), melting temperature (T_m), and enthalpy measured by DSC.
[b] Onset decomposition temperature corresponding to 10% of weight loss ($^{\circ}T_d$), maximum rate decomposition temperatures ($^{max}T_d$), and weight loss at the respective decomposition step [-ΔW (%)] determined by TGA.
[c] Data recorded in Ref. 25.

Degradation Studies

Degradation studies were carried out for polymers **4** and **6** (L-*arabino* configuration), since previous works of our group showed dependence between degradability and the configuration of the sugar units: the homo- and co-polymers having *xylo* configuration appeared to be more degradable than their L-*arabino* counterpart.[25–27]

Hydrolytic Degradation of New Polyurethanes. The hydrolytic degradation of PUs **4** and **6** was evaluated at 37°C and pH 7.0 and 8.0 following the method previously used by us.[10–12] The evolution of the process was followed by measuring changes in the mass of the polymer disks and in the average molecular weights of the residual polymers. Results from this study are displayed in Figure 3.

The novel homopolymers contain a high proportion of polar groups, imparting greater hydrophilicity to the new PUs synthesized as compared with HMDI-based PUs. Moreover, L-arabinitol-based PUs proved to be degradable under physiological conditions; the degradation curves show two well-defined regions in which the greatest reduction in molecular weight was observed within the first 10 days of incubation. From the 11th day to the 40th day, the slope of the curve diminished significantly. The hydrolytic cleavage of the polymers studied was enhanced at pH 8.0. Significant reductions were observed in the mass of the cystine-based polymer disks (**6**, between 40% and 50% in 40 days); however, no significant losses in mass occurred in the polymer disks derived from cystamine (polymer **4**), which can be explained by the nonsolubility of the degradation products in the incubation media. The concentrated aqueous solutions were examined by GPC; the retention times for those fractions were very high, indicating that only small moieties, such as water-soluble molecules, were part of it. It is well documented that the urethane groups are hydrolytically cleaved by the O–CO bond leading to a carbamic acid and an alcohol. The carbamic acids are not stable and decompose giving CO_2 and the corresponding amines. The residues are, therefore, aliphatic amines related to L-cysteine and sugar-based diols.[28]

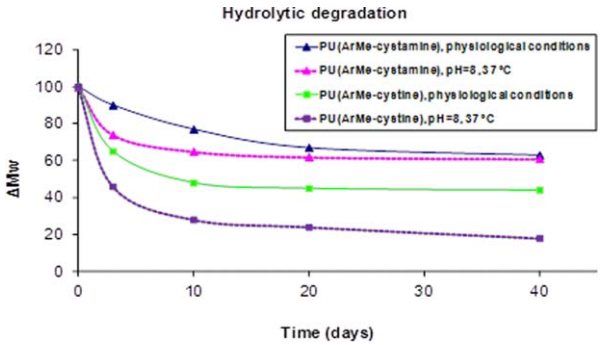

Figure 3. Hydrolytic degradation of polyurethanes. Reductions in weight average molecular weights (%) are plotted against time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

With regard to the molecular-weight loss, the greatest reductions were observed for PU(ArMe-cystine) **6** (ΔM_w of 82% and 56% at pH 8.0, 37°C and pH 7.0, 37°C, respectively), leading to oligomers of low molecular weight at pH 8.0. The profiles of the average molecular-weight data of PU(ArMe-cystamine) **4** during the degradation studies were very similar in both reaction conditions explored (ΔM_w of 39% and 37%, at pH 8.0, 37°C and physiological conditions, respectively).

Glutathione-Mediated Degradation of New Polyurethanes. In the present study, the incorporation of disulfide linkage into the polymer bond makes the new PUs exceptionally biodegradable under physiological conditions in the presence of the natural tripeptide glutathione (the most abundant low-molecular-weight biological thiol). Disulfide bonds are prone to rapid cleavage under a reductive environment through the fast and readily reversible thiol-disulfide exchange reactions.[29,30] In some previous works, we investigated the glutathione-mediated degradation pathway of 2,2'-dithiodiethanol-based copolyurethanes, where the second diol monomers used were 2,3,4-tri-*O*-benzyl-L-arabinitol or 2,3,4-tri-*O*-methyl-L-arabinitol[13] and the degradation was under reductive conditions of multiallyl- and multiamine-based copolyurethanes, useful as carriers of anionic drugs (at physiological pH) or gene materials.[14] After a fixed incubation period, the degraded polymeric fragments were stabilized by entrapping the newly generated free thiol groups as methyl thioether by treatment of the degraded disk with MeI in aqueous-THF media.

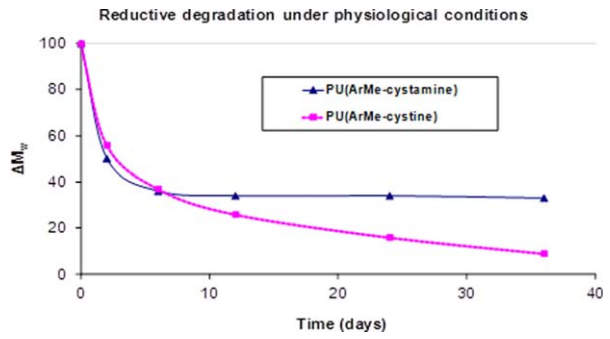

Figure 4. Reductive degradation of polyurethanes. Reductions in weight average molecular weights (%) are plotted against time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

For PUs **4** and **6**, a significant reduction in M_w of some 66% was observed for the cystamine-based homopolymer **4** and 74% for the cystine-based one (polymer **6**) in 12 days (Figure 4). We can assume that the small size of the tripeptide glutathione facilitates its dispersion into the polymer disk throughout the trials, with degradation effects not only over the surface of the polymer disks but also inside them. In all cases, the degradation in the presence of glutathione was more pronounced than the hydrolytic degradation.

CONCLUSIONS

The preparation of two sugar-based (bis)chloroformate monomers—having L-*arabino* and *xylo* configuration—with the secondary hydroxyl groups protected as methyl ether was successfully achieved. Their use in the synthesis of new linear sugar-based polyurethanes was accomplished by interfacial polycondensation using cystine-based diamines as comonomers. In these systems, the activation of the polymerization process by a metal catalyst is avoided. The presence of disulfide linkages in the polymer structures led to a reduction in their thermal stability under nitrogen atmosphere, with an associated 10% weight loss (T_d 10%) at around 245°C, in contrast with the analogous HMDI-based polymers, with T_d 10% above 280°C. They also confer greater stiffness on the new materials compared with HMDI-based polymers, as well as significant degradability under reductive conditions. The presence of methoxycarbonyl side groups in L-cystine dimethyl ester-based homopolymer **6** makes it more degradable not only in the hydrolytic trials but also in the degradation under reductive environments, probably due to its lower crystallinity and a better water/glutathione penetration in its structure. In all cases, the degradation in presence of glutathione was more pronounced than the hydrolytic degradation (for polymer **6**, the reductions in M_w under hydrolytic (pH 8.0) and reductive conditions were 82% and 91%, respectively, within 40 days).

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