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ARTICLE

Biodegradable Polyesters Derived from Amino Acids

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ABSTRACT: New optically active polyesters derived from amino acids by replacement of the backbone amino groups for hydroxyl residues are presented. The polyesters described are the following: poly(L)HOAsp-(COOH)−OH, poly(L)HOGlu(COOH)−OH, poly(L)HOSer(OH)−OH, poly(L)HOThr(OH)−OH, poly-(L)HOLys(OH)−OH, and poly(HOAa(X)(OH)-*co*-LA) and some other copolymers of α-hydroxy acids. The polymers were prepared via (a) direct condensation in bulk employing several catalysts as PTSA, boric acid, Mukaiyama's reagent, stannous chloride dihydrate, (b) acyl halide activation, and (c) microwave-assisted polymerization. The obtained polymers reached a molecular weight between 1000 and 4000. The highest molecular weight attained employing polycondensation methods in solution, was either by utilizing polyacid, or metal catalyst (boric acid and stannous chloride respectively). Applying oxalyl chloride for chain extension also showed to be an efficient method. On the other hand, the microwave-assisted polymerization exhibited significant advantages and polymerization could be implemented with lack of solvent (neat). The polymers were characterized by several methods (GPC, CD, DSC, solubility), and tested for their degradability and biocompatibility to cell growth. Most of the polymers displayed a linear correlation between their calculated log *P* values and their experimental contact angles parameters. Transition glass temperatures (T_g) of copolymers with various compositions of LA were correlated to either Gordon Taylor equation or to a three parameters modified Kwei equation. The circular dichroism spectra (CD) of several homo and copolymers were measured. In general, CD curves of the homopolymers of HOSer, HOGlu, HOThr, HOAsp, and HOLys(OH) revealed a significant ester maxima approximately at 205−220 nm while the copolymers of HOSer with HOPhe displayed an additional cotton effect band at 200.6−201.5 nm. This is accounted for polymer rotational isomers and not to a different $\pi\pi^*$ transition at lower wavelength.

Introduction

Biodegradable synthetic polymers propose several advantages over other materials for numerous uses in medical applications. The main advantage reached is the ability to tailor chemical properties as needed for specific uses.[1−7] The introduction of functional groups is an important strategy to shape and modulate properties of materials derived from these highly functionalized polyesters.[8−12]

Derivatives bearing new functional groups along the polymer backbone would be a valuable extension of the present arsenal of biodegradable polymers. In particular, the introduction of hydrophilic functional groups would open a considerable range of potential applications as enhanced hydrophilicity and compatibility with living cells and blood components.

Moreover, it is expected that the degradation time could be framed and that degraded products should be formed through a proper selection of the monomers. Likewise, the functional groups can be further derivatized to yield biodegradable polymeric prodrugs.[13]

Biodegradable polymers can be divided into several categories: (1) natural polymers such as (a) polysaccharides, such as starch, cellulose, chitine, chitosan and alginic acid, and (b) polypeptides of natural origin, such as gelatin; (2) synthetic polymers with *hydrolyzable backbones* such as (a) polyester, polycaprolactone, polyanhydride, poly(amide-enamine), polyacetals, polyketals, polyorthoesters, polycarbonates, polyphosphazenes, and to some extent substituted polyamides and (b) *hydrolyzable pendant groups of* polyvinyl alcohol, polyvinyl acetate, polyacrylate, and polymethacrylate.

Over the past years several functionalized polyesters were described in the literature. These polyesters consist mainly of ε-caprolactone, lactide, or glycolide copolymerized and poly-(hydroxyalkanoates) (PHAs)[14−18] such as polyhydroxy butyrate.

Yet, the selection of nontoxic biodegradable, biocompatible and mechanically strong polymeric materials that can be used in medicine are scant.[19] Poly(lactic acid), poly(glycolic acid), and their combinations have already been used for surgical sutures, scaffolds for tissue engineering and drug delivery systems.[20−22]

Viewing the scope of investigation in the area, reveals that the selection of available chiral hydroxy acids is also limited and most of the work was done either with lactic acid or derivatives of acrylic acid attached to a chiral moiety. Therefore, we have broadened the scope of optically active macromolecules to new poly(α-hydroxy esters) carrying stereogenic centers.

Here in, we present a new series of polymers based on optically active substituted glycolic acid generated through the replacement of the α-amino group of amino acids by a hydroxyl residue. In the present article, our results are focused on hydrophilic polymers originated from serine, threonine, lysine, aspartic acid, and glutamic acid (Figure 1). These α-hydroxy acids were polymerized to form polyesters through backbone and side chain functionality, giving final products of branched polymers, as well as linear ones.

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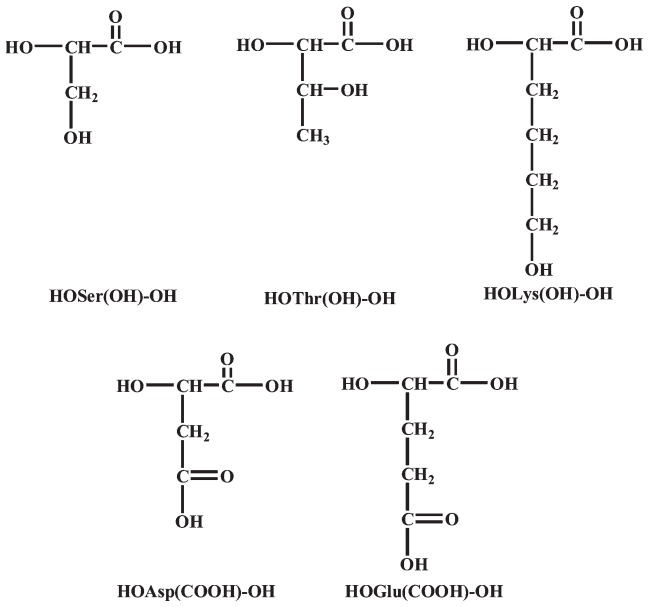


Figure 1. α-Hydroxy acids synthesized by diazotization of natural amino acids.

Polymerization of hydroxy acids can be implemented as is outlined in Figure 2.

According to Figure 2, polymerization can take place via several methods related either to condensation via direct esterification of the α-hydroxy acid or ester or via lactone formation. It should be stressed that most of the work to gain high degree of polymerization was carried out through the formation of 1,4-dioxane-2,5-dione as dilactone (lactide in case of lactic acid),[23−27] or via lactone as β-propiolactone, δ-valerolactone, and ∈-caprolactone[28,29] followed by ring-opening polymerization (ROP). In this regard, a promising method for α-polyester formation takes the advantage of bidentate protected/activated hydroxy acid. The notion is that the α-functionality of the hydroxyl acid and carboxylic group of these compounds heterocyclize in one step by reacting with ketone or aldehyde (step d)[30,31] or with phosgene to form *O*-carboxy anhydride OCA (step e)[32−35] or alternatively with dichlorodimethylsilane to form a cyclic silyl intermediate (step f).[36−38] The later methods are mostly adopted from the peptide synthesis approach and had not yet been fully merged in polymerization processes.

A broad range of organocatalysts (nucleophilic, cationic and bifunctional) and metallic catalysts have been reported for the ROP.[39,40] Nucleophilic catalysts involved: pyridine, dimethylamino pyridine (DMAP), phosphine, carbenes as imidazol-2-ylidenes and imidazolin-2-ylidenes or thiazol-2-ylidenes. Cationic ROP was reported to consist of trifluoromethane sulfonic acid (HOTf) and methyl trifluoromethane sulfonate (MeOTf). Bifunctional organocatalysts seem to be highly efficient catalysts since they can operate in several modes of activation as general acid base catalysis (1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-dimethylamino-cyclohexyl)thiourea) or as combined base-general base catalyst (1,5,7-triazabicyclo(4.4.0)dec-5-ene (TBD)). The commonly used metallic catalysts are tin octanoate ($Sn(Oct)_2$), aluminum alkoxides $Al(OR)_3$, titanium alkoxide ($Ti(OR)_4$), and a wide range of metal cations and rare element derivatives.[40−42]

Direct Condensation. The attainment of polyesters can take place via several reaction routes and catalysts (method a(i−iii,vi)): **(a) Water exclusion** either in the bulk at 150 °C or in solution (Dean−Stark) in the presence of a catalyst selected out of a variety of acid, base, bifunctional and metal catalysts; **(b) Building blocks activation** through the formation of active esters (trans esterification approach), acyl halides (a(v)) and the involvement of coupling reagents (a(iv)). Poly acids such as boric acid and phosphoric acid have some advantage over a monoacid catalyst as PTSA since they can operate as bifunctional catalysts through the formation of cyclic intermediate as is delineated in route a(vii).

In general, direct condensation courses result in low M_w polymers. However, some procedures involving coupling reagents (DCC/ DMAP)[43] or $SnCl_2 \cdot 2H_2O$ as catalysts[44] exhibited relatively high M_w products.

Organic synthesis using microwave heating is a technique that has recently gained broad acceptance in medicinal chemistry laboratories.[45] With microwave heating, certain reactions are complete within seconds or minutes. In the field of synthetic polymer chemistry, microwave energy has been used for the polymerization of vinyl monomers, ring-opening polymerization of caprolactam and caprolactone,[46−48] condensation polymerization of polyesters,[49,50] polyanhydrides,[51] polyamides, and polyimides.[52]

Although microwave-assisted polymerization is gaining growing interest and in some cases became a useful tool in polymerization processes, it is still waiting for further progression and optimization in the sense of irradiation time and power strength, irradiation homogeneity, temperature, pressure, reaction vessel type, stirring, solvent type and solvent free (neat) conditions, and molecular weight controlling parameters. In the light of this perspective, we present here a verity of direct polycondensation experiments shaped through the microwave method.

Experimental Section

Materials. Lactic acid was purchased from J.T. Baker, Deventer, Holland. The amino acids were purchased from Fluka, Buchs, Switzerland and Sigma-Aldrich, Milwaukee, WI (98−99% pure). Sodium nitrite, *p*-toluenesulfonic acid monohydrate, oxalyl chloride, stannous chloride dihydrate, boric acid, pyrophosphoric acid, titanium(IV) isopropoxide, 2-chloro-1-methyl pyridinium iodide, *N*-methyl imidazole, dimethylaminopyridine, dicyclohexylcarbodiimide, 1,5,7-triazabicyclo[4.4.0]dec-5-ene, tributylphosphine, carbonyl diimidazole, disuccinimidyl carbonate, benzaldehyde, and trifluoroacetic anhydride were also purchased from Sigma-Aldrich, Milwaukee, WI (95%−99%). All solvents were analytical-grade from either Biolab, Jerusalem, Israel; Frutarom, Haifa, Israel; or Gadot, Or Akiva, Israel, and were used without further purification.

Techniques. IR (2000 FTIR, PerkinElmer) measurements were performed on tablets of 5% w/w polymer in KBr. The molecular weights of polyesters were estimated on a gel permeation chromatography (GPC) system consisting of a Waters Spectra Series P100 isocratic HPLC pump with an ERMA ERC-7510 refractive index detector and a Rheodyne (Coatati, CA) injection valve with a 20 μL-loop (Waters, MA). The samples were eluted with nitrate buffer 0.05 M through a linear OHPak SB-802.5 HQ column (Shodex) at a flow rate of 1 mL/min. The molecular weights were determined relative to poly (ethylene glycol) standards (Polymer Standards Service-USA, Silver Spring, MD) with a molecular weight range of 100−6000 using a Breeze computer program. ^{1}H NMR spectra (D_2O for the polymers and DMSO-d6 for the hydroxy acids) were obtained on a Varian 300 MHz spectrometer in 5 mm o.d. tubes. Tetramethylsilane served as a reference. Electronspray ionization mass spectrometry was measured on a ThermoQuest Finnigan LCQ-Dou in the positive ion mode. Data was processed using ThermoQuest Finnigan's XcaliburTM biomass calculation and deconvolution software. The optical activity of the monomers and polymers was determined on a PE 343 polarimeter (PerkinElmer). Thermal behavior of the polymers

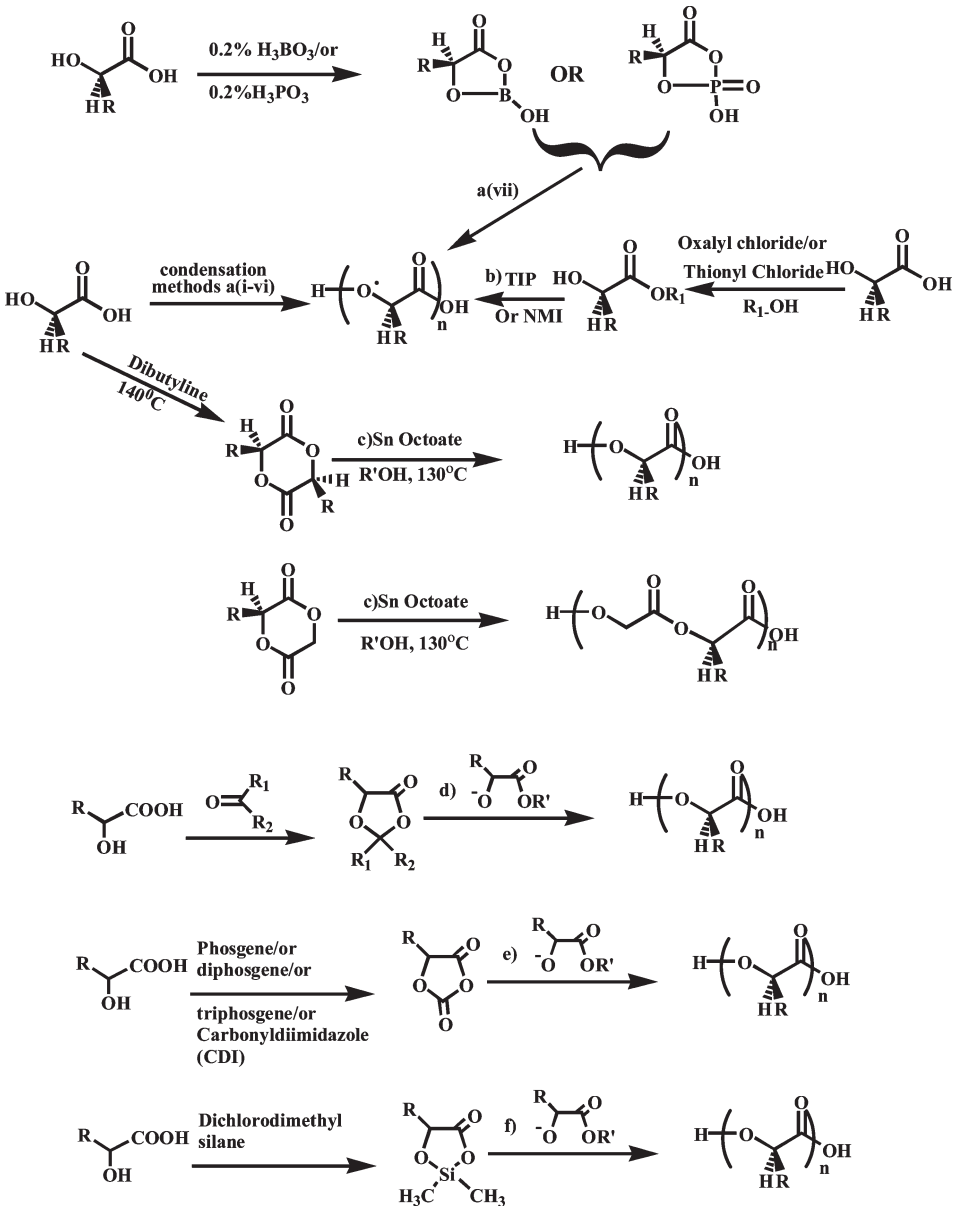
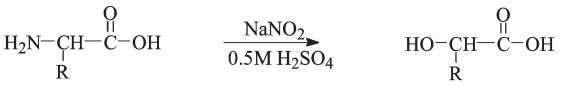


Figure 2. Polymerization methods of polyesters. Condensation conditions: (a) Direct polycondensation. (i) Water exclusion, dry toluene, PTSA, Dean−Stark. (ii) Metal catalyst, $SnCl_2 \cdot 2H_2O$, titanium(IV)(isopropoxide)$_4$ (TIP, also $Ti(OC_4H_9)_4$), or $SiO_2/ZnCl_2$ (80% w/w $ZnCl_2$) as catalysts. (iii) Bifunctional organocatalyst (amidine, guanidine), Triazabicyclodecene (TBD). (iv) Acyl halide formation by thionyl chloride or oxalyl chloride, or triphosgene, in dry toluene, reflux. (v) Coupling reagents as Mukaiyama reagent, DCC/*N*-dimethylamino pyridine (DMAP) or pivaloyl chloride or combination of these couplers with Cs_2CO_3. (vi) Base catalysis: tertiary amines, DMAP, imidazole-2-ylidene, trialkyl phosphine. (vii) Polyacid catalysis: phosphoric acid, boric acid; these methods can be performed also by microwave, slow removal of water (with or without coupling reagents). (b) Alcohol exclusion (trans-esterification) at 180 °C in the presence of traces of TIP as catalyst or *N*-methyl imidazole (NMI). (c) Ring-opening polymerization (ROP): 1,4-dioxane-2,5-dione. (d) 1,3-Dioxalane-4-one. (e) *O*-Carboxyanhydride. (f) 2,2-Dimethyl-1,3,2-dioxasilolan-4-one.

was determined on a Mettler TA 4000-DSC differential scanning calorimeter (Mettler-Toledo, Schwerzzenbach, Switzerland), calibrated with In standard heated at a rate of 10 °C/min under nitrogen atmosphere. Contact angles were measured with a Ramé-Hart model 100 contact angle goniometer on polymer-covered microscope slides. The polymers were dissolved in water or methanol, dropped on the slides, and evaporated. These measurements were repeated three times for each sample, and the average values are reported. The polymers' log *P* values were evaluated by the online ALOGPS 2.1 program as the average values obtained by various methods such as the following: miLogP, ProLogP, ALogP, MlogP, XLogP, etc. Circular dichroism (CD) measurements, CD spectra were recorded using a J-810 spectropolarimeter (Jasco) in acetonitrile using a 1.0-cm quartz cell. Far-UV CD spectra were collected in a spectral range of 190 to 300 nm. Microwave polymerization



R= CH_2COOH, $(CH_2)_2COOH$, CH_2OH, $CH(CH_3)OH$, $(CH_2)_4OH$

Figure 3. α-Hydroxy acids synthesized by diazotization of natural amino acids.

method was done by a Biotage microwave synthesizer (Biotage InitiatorTM) at 120 °C, 0−1 bar, and 200 W for 20 min.

Synthesis of α-Hydroxy Acids by Diazotization of α-Amino Acids. α-Hydroxyl acids were prepared according to the procedure depicted in Figure 3.

A solution of the α-amino acid (10 mmol) in 0.5 M sulfuric acid (40 mL, 20 mmol) was prepared and cooled to 0 °C. Sodium nitrite solution in water ($NaNO_2$, 4.2 g in 15 mL, 60 mmol) was

Table 1. Characterization of the Prepared Polymers According to Method A1

polymer	M_w[a] (Da)	M_n[a] (Da)	M_p[a] (Da)	PDI[b] (M_w/M_n)	optical activity $[\alpha]_D$[c]	solubility (g/L)[e] $CHCl_3/H_2O$	THF/MeOH	ACN
PLA	2800	2600	2400	1.08	−139	250	18	<2%
poly(L)HOAsp	1300	1100	1500	1.18	+2	<2% <2%	<2% <2%	<2%
poly(L)HOAsp−LA (50%)[f]	2000	1900	2100	1.05	−39	>600 <2% >600	<2% <2% >600	<2%
poly(L)HOGlu	1500	1400	1500	1.07	+1	<2% >600	<2% <2%	<2%
poly(L)HOGlu−LA (50%)[d,f]	1200	1100	1300	1.09	−22	<2% >600	<2% >600	<2%
poly(L)HOSer	1100	1000	1000	1.11	1+	<2% >600	<2% <2%	<2%
poly(L)HOSer−LA (50%)[f]	2200	1500	3100	1.47	−22	<2% >600	<2% <2%	<2%
poly(L)HOThr	3300	3200	3600	1.03	−19	<2% >600	<2% <2%	<2%
poly(L)HOThr−LA (50%)[f]	2300	2500	2500	0.92	−25	<2% >600	<2% <2%	<2%
poly(L)HOLys	2200	2200	2300	1.00	+1	<2% >600	<2% >600	<2%
poly(L)HOLys−LA(50%)[d,f]	1900	1800	2000	1.06	−12	<2% >600	<2% >600	<2%

[a]The molecular weights were determined by GPC. [b]Polydispersity index, a measure of the distribution of molecular mass in a given polymer sample. [c]Specific optical rotation ($c = 1-1.2$, in H_2O, at 25 °C), unless mentioned differently. [d]Specific optical rotation ($c = 1-1.2$, in MeOH, at 25 °C). [e]Solubility of the polymers in several solvents. [f]Percentages refer to the last monomer mentioned.

slowly added to the solution.[53−55] Following the addition, the solution was brought to room temperature and stirred overnight. Then, solution was saturated with sodium chloride and extracted with ether. The extracts were dried over Na_2SO_4 and the solvent was evaporated in vacuo, the crude product was dissolved in MeOH (100 mL). The precipitated salts were filtered off and the filtrate was evaporated in vacuo. The diazotization was also carried out using 20% acetic acid as an alternative to 0.5 M sulfuric acid, however the yield in this case was lower. The hydroxyl acids were characterized by ^{1}H NMR (DMSO-d_6), optical activity and mass spectrometry.

(S)-2,3−Dihydroxypropionic Acid [(L)HO−Ser(OH)−OH]. ^{1}H NMR: 3.58 (1H, dd), 3.41 (2H, d). Oily. MS: 151.4 ($+2N_a^+$). [α]($c = 1.28$, MeOH): +1.57. Yield: 60%.

(S)-2,3−Dihydroxybutyric Acid [(L)HO−Thr(OH)−OH]. ^{1}H NMR: 3.63 (1H, dd), 3.45 (1H, d), 0.91 (3H,d). Oily. MS: 165.47 ($+2N_a^+$). [α]($c = 1.05$, MeOH): −4.28. Yield: 60%.

(S)-2-Hydroxysuccinic Acid [(L)HO−Asp(COOH)−OH]. ^{1}H NMR: 3.65 (1H, m), 2.48 (2H, d). Oily. MS: 178.27 ($+2N_a^+$). [α]($c = 1.05$, MeOH): −4.13. Yield: 60%.

(S)-2-Hydroxypentanedioic Acid [(L)HO−Glu(COOH)−OH]. ^{1}H NMR: 3.55 (1H, m), 2.30 (2H, m), 1.87 (2H, t). Oily. MS: 149.45; [α]($c = 1.24$, MeOH): −4.83, Yield: 60%.

(S)-2,6-dihydroxyhexanoic Acid [(L)HO−Lys(OH)−OH]. ^{1}H NMR: 4.09 (1H, t), 2.68 (2H, t), 1.29−1.71 (6H, m). Oily. MS: 148.13. [α]($c = 1.20$,MeOH): +3.76. Yield: 60%.

Polymerization of α-Hydroxy Acids. The hydroxy acids were condensed by direct condensation in bulk, employing diverse methods.

Method A1 (Acid Catalysis). α-Hydroxy acid (1 g, 6.76−9.43 mmol), or a mixture of α-hydroxy acid and lactic acid at 1:1 molar ratio (about 1 g), was suspended in dry toluene (4 mL) under nitrogen atmosphere, and 0.1% w/w of *p*-toluenesulfonic acid (PTSA) was added as a catalyst.[56,57] The solution was refluxed overnight in a Dean−Stark apparatus to remove water. The toluene was then evaporated and the oligomers were heated in bulk at 120 °C for 2 h, following a vacuum of 15 mmHg for 14−20 h.[19,56]

This method was employed for most of the homopolymes and random copolymers (1:1 molar ratio of lactic acid) preparation. The results are summarized in table 1.

Method A2 (Polyacid Catalysis). α-Hydroxy acid (1 g, 6.76−9.43 mmol), or a mixture of α-hydroxy acid and lactic acid at 1:1 molar ratio (about 1 g), was suspended in dry toluene (4 mL) and 0.2% w/w boric acid was added as a catalyst, under nitrogen atmosphere. The solution was then treated as is delineated in method A1.

By this method poly(L)HOAsp was prepared.

Method A3 (Activation via Acyl Halide Formation). This procedure follows the protocol depicted in method A1, however 0.2% w/w oxalyl chloride was used as an acid activator. The reaction was carried out in refluxed toluene (4 mL) in a Dean−Stark apparatus. HCl formed vaporized through the condenser during the reflux and was trapped.

Poly(L)HOSer and poly(L)HOAsp were synthesized according to this method.

Method A4 (Activation by Coupling Reagents). Method A4 was carried out as is outlined in method A1; however Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide (CMPI, 1:1 molar ratio) was introduced as a coupling reagent, instead of PTSA. The product (polyester) was separated from the coupling reagent by chromatography on a silica column (hexane: ethyl acetate 1:1).

The following polymers were synthesized via the A4 approach: poly(L)HOSer, poly(L)HOAsp.

Method A5 (Metal Catalyst). α-Hydroxy acid (1 g) was suspended in m-xylene (2 mL), 0.2% w/w of stannous chloride dihydrate and molecular sieves (3 Å, 5−6 beads). The solution was refluxed overnight with a dean-stark apparatus. After 24 h, the Dean−Stark apparatus was removed and the solution was left under reflux for additional 48 h. The solvent was then evaporated and the resulting polymer, mixed with molecular sieves, was dissolved in chloroform and filtered.[44]

Several other experiments were implemented under similar condition implicating stannous octoate and stannous chloride as metal catalysts in toluene solution.

The following polymers were prepared via this method: poly-(L)HOAsp and poly(L)HOGlu.

Method B (Chain Extension). Poly(α-hydroxy acid) (500 mg) was dissolved in dichloromethane and oxalyl chloride was added (under nitrogen), along with a drop of dimethylforamide. The mixture was stirred for an hour at 40−50 °C. The excess oxalyl chloride was evaporated, along with the solvent.

Then, a second portion of the polymer was added and the polymerization was carried out as is described in method A1.

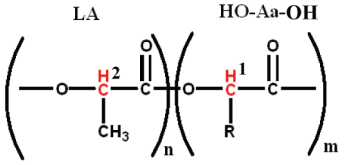
The following polymer was synthesized through method B: poly(L)HOSer.

Method C (Microwave-Assisted Polymerization). All the experiments on the microwave apparatus were implemented either in neat or in DMF solvent. A representative experimental procedure was as follows. A mixture of α-hydroxy acid (300 mg) and one of the selected catalysts were sealed in a 2.0−5.0 mL microwave vial. The reaction was irradiated for 20 min, at 120 °C, at a pressure of 0−1 bar and power of about 200 W.[58] In the case of reaction in solution, the above constituents were dissolved in 0.6 mL DMF prior to irradiation.

The catalysts tested were as follows: PTSA, stannous chloride, boric acid and CMPI, pyrophosphoric acid (0.2% w/w), titanium(IV) isopropoxide (0.2% w/w), *N*-methyl imidazole (1:1 molar), (dimethylamino)pyridine/DCC (1:1 molar), tributylphosphine (1:1 molar), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 0.1% w/w), carbonyl diimidazole (1.5 equiv), disuccinimidyl carbonate (DSC, 1.5 equiv), TFA anhydride (preactivation of the monomer, 1:1).

The following polymers were prepared by microwave assistance: poly(L)HOAsp, poly(L)HOGlu, and poly(L)HOSer.

The polymers were characterized by ^{1}H NMR, IR, GPC, optical activity, and solubility in several solvents. All polymers show a major ester peak of carbonyl stretch (C═O) at 1720−1765 cm^{-1} and a small absorption band around 1640 cm^{-1} due to C═O stretch of −COOH.



^{1}H-NMR (H_2O)

Poly(L)HOAsp(COOH)−OH. ^{1}H NMR: 5.49 (1H, m), 4.52 (1H, m, end OH), 2.92 (2H, m). IR: 1723, 1638 cm^{-1}.

Poly(L)HOAsp(COOH)−OH−LA. ^{1}H NMR: 5.28 (1H, m), 4.66 (1H, m), 2.85 (2H, m), 1.22 (3H, m). IR: 1755, 1641 cm^{-1}.

Poly(L)HOGlu(COOH)−OH. ^{1}H NMR: 4.82 (1H, m), 2.44 (4H, m). IR: 1761, 1645 cm^{-1}.

Poly(L)HOGlu(COOH)−OH−LA. ^{1}H NMR: 5.11 (1H, m), 4.79 (1H, m), 2.42 (4H, m), 1.28 (3H, m). IR: 1760, 1642 cm^{-1}.

Poly(L)HOSer(OH)−OH. ^{1}H NMR: 4.76 (1H, m), 4.01−4.23 (2H, m); IR: 1753, 1638 cm^{-1}.

Poly(L)HOSer(OH)−OH−LA. ^{1}H NMR: 4.68 (1H, m), 4.25 (1H, m), 3.68 (2H, m), 1.39 (3H, m). IR: 1750, 1639 cm^{-1}.

Poly(L)HOThr(OH)−OH. ^{1}H NMR: 5.15 (1H, m), 4.04 (1H, m), 1.25 (3H, m); IR: 1756, 1645 cm^{-1}.

Poly(L)HOThr(OH)−OH−LA. ^{1}H NMR: 5.18 (1H, m), 4.45 (1H, m), 3.58 (1H, m), 1.21−1.41 (6H, m). IR: 1762, 1643 cm^{-1}.

Poly(L)HOLys(OH)−OH. ^{1}H NMR: 4.63 (1H, m), 2.82 (2H, m), 1.34−1.71 (6H, m). IR: 1758, 1644 cm^{-1}.

Poly(L)HOLys(OH)OH−LA. ^{1}H NMR: 4.99 (1H, m), 4.83 (1H, m), 2.76 (2H, m), 1.21−1.74 (9H, m). IR: 1762, 1648 cm^{-1}.

In Vitro Hydrolytic Degradation of the Polymers. The standard analysis of weight loss and the change of molecular weight of five polymers, poly(L)HOSer, poly(L)HOThr, poly(L)HOLys (OH), poly(L)HOAsp, and poly(L)HOGlu, were determined during hydrolysis under physiological conditions. To study the hydrolytic degradation of the polymers, tablets (~200 mg) of the polymers were dropped into 50 mL of phosphate buffer solution pH 7.4 0.1 M at 37 °C, with orbital shaking (100 rpm). Samples were taken from the polymers at each time point, and analyzed by GPC. All experiments were done in duplicate. The degradation of the polymers was followed by GPC for 40 days.

Results and Discussion

Methods of Preparation. The results of method A1, polymerization using PTSA as a catalyst, are summarized in Table 1.

While this method gave low molecular weights, other tried catalysts, such as boric acid (method A2) and stannous chloride (method A5) improved the molecular weights. Furthermore, the copolymerization of the monomers with lactic acid, with the intention of increasing the molecular weights (PLA made using this method has M_w of 3000 Da), showed no improvement in resulting M_w of copolymers.

The hydrophilic side chains of the monomers, hydroxyl and carboxylic acid, provide the prepared polymers a hydrophilic nature, and all of the polymers are indeed soluble in water, but not in hydrophobic solvents. Some of the polymers are soluble in methanol as well. By the presence of solubility, it is demonstrated that the polymers are either branched or linear, but not cross-linked.

Additionally, poly(L)HOAsp and poly(L)HOGlu are firm solid polymers, as opposed to poly(L)HOSer, poly(L)-HOThr and poly(L)HOLys(OH). These solid polymers had melting points in the DSC, in addition to T_g. For poly(L) HOAsp, the Tm is 133.37 °C (ΔH = -420.42 J/g) and for poly(L)-HOGlu the Tm is 81.14 °C (ΔH = -127.20 J/g).

Table 2 shows the results of the microwave-assisted polymerization. The method was used on already tried catalysts and on new catalysts as well. When compared to the lab results of methods A1−A5, higher molecular weights were obtained through the microwave approach. This fact is shown mainly in the polyacid catalysis and the metal catalysis. All new catalysts tried did not show an improvement in weights. Moreover, the lack of solvent does not make a significant change in the results when compared to the experiments done with dimethylformamide.

Figure 4 indicates the comparison between the best polymerization methods tried (in which the results were above 1000 Da), by the molecular weights of the product. All of the results refer to poly(L)HOAsp.

It is shown that the highest molecular weights of polymer were made through acid catalysis and metal catalysis. Furthermore, the molecular weights were improved when using the same catalysts, only by microwave. The microwave approach gives us better results in less time.

Contact Angles. The behavior of interfacial water depends strongly on the properties (curvature roughness, chemistry, and chemical heterogeneity) of the confining surface. For the case of a flat and homogeneous surface, the properties of interfacial water are mainly determined by the confining surface's chemical properties and, in particular, by its hydrophobic/hydrophilic character of the boundary surface. The hydrophobicity of a surface can be enhanced by a chemical modification that lowers the surface energy. This modification leads to an increase in the contact angle of a water drop.

In this context, due to the diversity of α-hydroxy acids and their derived homo and copolymers, prepared in our laboratory we have examined their water contact angle in correlation to their calculated LogP values. The predicted log *P* values presented in Table 3 and Figure 5 are actually the average values obtained by various methods such as miLogP, ProLogP, ALogP, MlogP, XLogP, etc. offered by the online ALOGPS 2.1 program.

Table 2. Molecular Weights of Polymers Made by Microwave[a]

polymer	Solvent	M_w (Da)	M_n (Da)	M_p (Da)
AspOH 300 mg, PTSA[b] 0.1%	neat	1500	1400	1800
AspOH 300 mg, PTSA[b] 0.1%	DMF 0.6 mL	1500	1400	1600
AspOH 300 mg, $SnCl_2$ 0.2%	neat	3500	3700	3900
AspOH 300 mg, $SnCl_2$ 0.2%	DMF 0.6 mL	3500	3500	3500
AspOH 300 mg, boric acid 0.2%	neat	3800	3700	3300
AspOH 300 mg, boric acid 0.2%	DMF 0.6 mL	3300	3700	3900
AspOH 300 mg, pyrophosphoric acid 0.2%	DMF 0.6 mL	1800	1800	1800
AspOH 300 mg, Ti $[OCH(CH_3)_2]_4$ 0.2%	DMF 0.6 mL	1500	1400	1500
AspOH 300 mg, CMPI[c] 1:1 molar	DMF 0.6 mL	700	600	700
AspOH 300 mg, *N*-methyl imidazole 1:1 molar	DMF 0.6 mL	600	500	600
AspOH 300 mg, DMAP[d]/DCC 1:1 molar	DMF 0.6 mL	500	400	600
AspOH 300 mg, Tributyl phosphine 1:1 molar	DMF 0.6 mL	600	400	500
AspOH 300 mg, CDI[e] 1.5 equiv	neat	700	600	600
AspOH 300 mg, DSC[f] 1.5 equiv	neat	600	500	600
AspOH 300 mg, TBD[g] 0.1%	DMF 0.6 mL	900	800	900
AspOH 300 mg, TFA anhydride 1:1 molar	DMF 0.6 mL	700	700	700
GluOH 300 mg, $SnCl_2$ 0.2%	neat	2900	2900	3000
SerOH 300 mg, $SnCl_2$ 0.2%	neat	2700	2700	2700

[a] The vials used: 0.5−2.0 mL Biotage microwave vials. Temperature: 120 °C. Time: 20 min. Pressure: 0−1 bar. Power: up to 200 W (the pressure and power were not set up). [b] PTSA = *p*-toluenesulfonic acid. [c] CMPI = 2-chloro-1-methylpyridinium iodide. [d] DMAP = Dimethylamino pyridine. [e] CDI = Carbonyldiimidazole. [f] DSC = Disuccinimidyl carbonate. [g] TBD = 1,5,7-Triazabicycol[4.4.0]dec-5-ene.

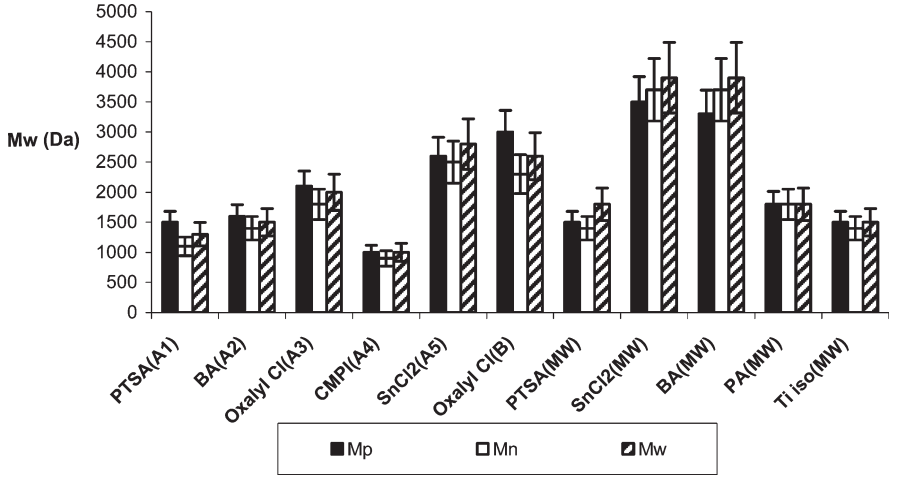


Figure 4. Comparison of molecular weights emerging from the various methods. Each polymer was checked three times, the deviation was ±6−7%.

These log *P* values were evaluated from oligomer units of 10 hydroxyacids $H(OCH(R_1)C(O))_n(OCH(R_2)C(O))_mOH$ where $n+m=10$, composed of polymers composition depicted in Table 3.

The data reveals that the contact angle of all the polyesters derived from amino acids exhibited water contact angles in the range of 10−76 which can be attributed to a mild surface hydrophobicity. Figure 5, indicates a linear correlation between the calculated log *P* and the water contact angle value θ of the homo and copolymers tested (slope = 0.2433, SD = 1.676, $N = 21$, $R = 0.957$).

Glass Transition Temperature (T_g). The T_g data reported in the literature do not permit formulation of precise structure property relationships. Similar polymer systems can show significant variation since the observed T_g depends on many factors such as: their molecular weights, degree of crystallinity, polymer architecture: "random" copolymers, block copolymers, stars, combs, etc., tacticity (isotactic and syndiotactic), stereoregularity, cross-linking, and substituents (steric size).

High T_g materials generally have rigid backbones and are usually synthesized by including rigid elements in the backbone, such as para-substituted aromatic rings, or by restricting bond rotation along the polymer backbone. Chain-chain interactions as dipole−dipole interactions caused by polar moieties in the polymer structure also enhance T_g value of polymers.

On the other hand, low T_g polymers employing opposite features which make polymer backbones more flexible, and decline chain−chain interactions.

In the case of copolymerization and ignoring the effects of stereochemistry and crystallization, copolymerization usually provides polymers with T_g values that smoothly vary with composition between the T_gs of the two homopolymers.

Our data does not consist with this view and the transition glass temperatures of the determined copolymers strongly deviate from being positioned between the two T_g values of the pure components.

Actually, the data reveal some relationship patterns between the T_g values and the composition of the copolymer. In the case of poly(L)HOSer-*random*-LA, poly(L)HOThr-*random*-LA, and poly(L)HOAsp-*random*-LA (category A) the T_g tends to ascend moderately with the increase of the weigh fraction of LA up to a composition of 80% LA (ΔT_gs are 6.2, 14.7, and 29.2 °C respectively). Beyond this value, in the range of 80−100% LA there is a sharp increase in the T_g from −52, −73, and −35 °C in the case of HOSer, HOThr and HOAsp to 49 °C of 100% LA .The respective ΔTg are 101, 122, and 84 °C. On the other hand in polymers with extended side chains as poly(L)HOGlu-*random*-LA and poly-(L)HOLys(OH)-*random*-LA (category B), the behavior of the T_g as a function of the polymer composition is in an opposite direction. In the range of 0−80% LA the T_g values

Table 3. Contact Angles θ and Calculated LogP Values of Various Polyesters

hydroxy acids homo and copolymers	contact angle θ^a	average log P (calcd)^b
PLA	37.10	−0.49
poly(L)HOVal[c,e]	73.70	7.12
poly(L)HOIle[c,e]	74.71	10.48
poly(L)HOLeu[c,e]	76.17	10.12
poly(L)HOAsp	17.22	−5.38
poly(L)HOAsp−LA(80%)[d]	25.61	−0.55
poly(L)HOGlu	26.40	−3.61
poly(L)HOGlu−LA(80%)[d]	36.02	0.13
poly(L)HOSer	11.40	−7.15
poly(L)HOSer−LA(70%)[d]	37.91	−1.62
poly(L)HOThr	14.72	−4.17
poly(L)HOThr−LA(90%)[d]	28.41	0.57
poly(L)HOLys	19.90	−0.82
poly(L)HOLys−LA(70%)[d]	25.6	0.21
poly(L)HOSer−HOVal (80%)[d,f]	58.5	5.15
poly(L)HOSer−HOIle (80%)[d,f]	61.9	8.22
poly(L)HOSer−HOAsn (80%)[d,f]	9.63	−9.13
poly(L)HOSer−HOGln (80%)[d,f]	10.04	−6.22
poly(L)HOSer−HOMet (80%)[d,f]	47.22	3.59
poly(L)HOSer−HOArg (80%)[d,f]	15.81	−4.98
poly(L)HOSer−HOHis (80%)[d,f]	18.20	−3.73

[a] Water contact angles were determined on a contact angle goniometer. [b] LogP was calculated for oligomers of 10 hydroxyacid according to stated compositions. [c] Hydrophobic polymers. [d] Percentages refer to the last monomer mentioned. [e] Published elsewhere.[59] [f] Unpublished results.

of the copolymers tend to descend to-58 °C ($\Delta T_g = -47.3$ °C) and −70 °C ($\Delta T_g = -23.8$ °C) for poly(L)HOGlu and poly (L)HOLys(OH) respectively and then sharply to increase to 49 °C ($\Delta T_g = 107$ and 119 °C, respectively).

These results clearly indicate the complexity in evaluating T_g values of copolymers bearing functional side chains.

Several equations are currently applied to correlate between the glass transition temperature and the copolymer composition. The first is the Fox equation which assigns a symmetric contribution by the copolymer constituents to the T_g value. Fox equation delineate a linear correlation between the reciprocal value of T_g and the weight fraction of the copolymer components (eq 1)[60]

$$\frac{1}{T_g} = \frac{X_1}{T_{g1}} + \frac{(1-X_1)}{T_{g2}} \quad (1)$$

where T_g referred to the copolymer, T_{g_1} and T_{g_2} to the pure components, and X_1 to the weight fraction of component 1. The equation is valid when $T_{g_2} > T_{g_1}$.

Another equation is related to the Gordon−Taylor correlation (eq 2).[61]

$$T_g = \frac{T_{g1}X_1 + K_1 T_{g2}(1-X_1)}{X_1 + K_1(1-X_1)} \quad (2)$$

This is a nonsymmetrical equation where K_1 represents an unequal contribution of T_{g2} to T_g value of the copolymer. An additional equation, referred to as the Kwei equation, consists of two parameters to be fit: K_1 and K_2.[62]

$$T_g = \frac{T_{g1}X_1 + K_1 T_{g2}(1-X_1)}{X_1 + K_1(1-X_1)} + K_2 X_1(1-X_1) \quad (3)$$

It is apparent that the T_gs of polymers of category A are in accordance with the Gordon−Taylor equation (Figure 6).

In contrast to these three polymers, the T_g values as a function of composition of the copolymers derived from HOGlu with LA and HOLys(OH) with LA (category B) could not be fitted to any of eqs 1, 2, or 3 (see Figure 7). However, it was established that the T_g data of these polymers fit a modified Kwei equation where the parameter K_2 is replaced by a quadratic polynomial (eq 4). The equation derived is of three parameters K_0, K_1 and K_2.

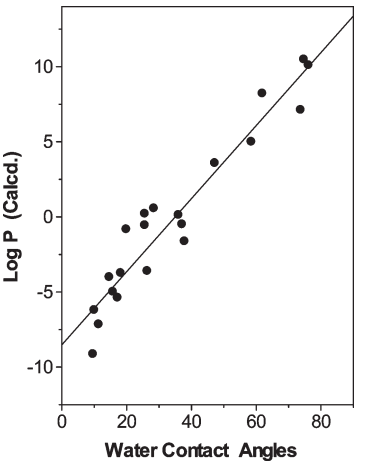


Figure 5. Linear correlation between log P (calcd) and water contact angle θ.

$$T_g = T_{g1}X_1 + K_1 T_{g2}(1-X_1) + X_1(1-X_1)[K_0 + K_1(2X-1) + K_2(2X-1)^2] \quad (4)$$

Several parameters were ascribed in the literature to high T_g materials. Between them are rigidity of the backbone (chain stiffness) due to high rotational barriers along the polymer backbone. This can be reached by introducing rigid elements or bulk side chains along the polymer strand. Another important parameter is the dipole−dipole interaction between the polymer chains. In the case of alkyl side chains, it has been demonstrated that steric effect of substituents might screen the ester group of the polymer and thus lead to a decrease in dipole−dipole interaction between chains and consequently to a decrease of polymers T_gs. As above-mentioned, the T_g behavior of the present data fall into two categories A and B. The distinction between them is not due to differences in their phase state since both involve solids as polyHOAsp and polyHOGlu and oils as polyHOSer, polyHOThr, and polyHOLys(OH). The variation is also not due to differences in functional groups of the side chain since both consist of carboxy and hydroxy side chain. The only apparent difference is referred to the length of the side chains, where in category B they are extended at least by one methylene group. This might point toward the deliberation that category B is less ordered. In our view, the functional group plays an important role in molding the transition glass temperature. In both categories, they may form either inter or intrahydrogen bonds, which consequently disrupt the dipole−dipole interaction between the polymer chains. In category B, replacement of HOLys(OH) or HOGlu by LA along the composition range of 0−80% does not yet brings the polymer chains to closed interaction proximity due to the side chain arms that keep them apart. However, substitution of the native side chain for methyl group alleviate the rotational barriers along the polymer backbone. Thus, the polymer backbone becomes more flexible and reflects a declination of T_g.

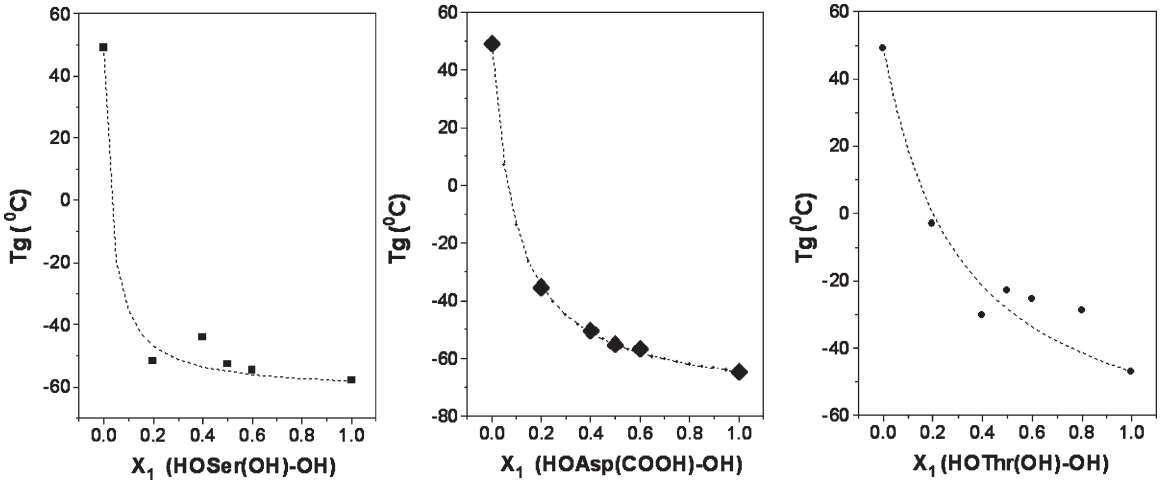


Figure 6. Dependence of T_g: on HOSer composition (■) in polyHOSer−LA (left); on HOAsp composition (♦) in polyHOAsp−LA (middle); on HOThr composition (●) in polyHOThr−LA (right). The theoretical curves were derived from the Gordon−Taylor equation. The respective K_1 values for polyHOSer−LA, polyHOAsp−LA, and polyHOThr−LA are 0.0293, 0.0897, and 0.2390.

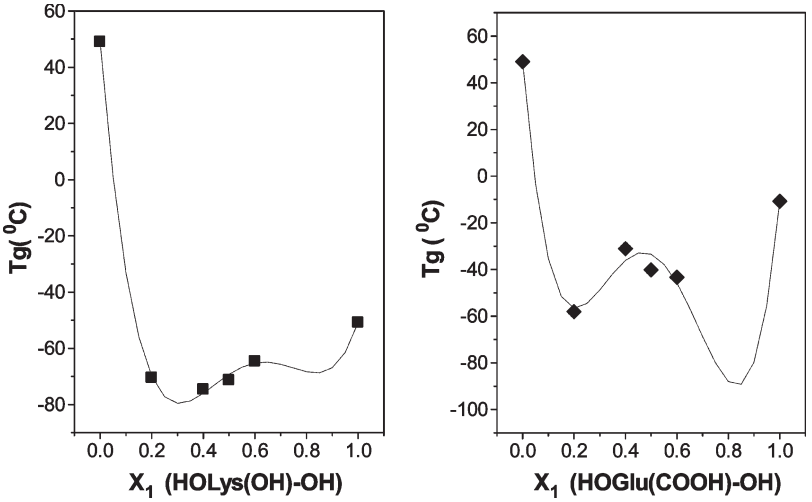


Figure 7. Dependence of T_g on HOLys composition (■) in polyHOLys−LA (left) and on HOGlu composition (♦) in polyHOGlu−LA (right). The theoretical curves derived from eq 4. The respective K_0, K_1, and K_2 values for polyHOLys−LA are as follows: −273, 320.3, −425 and for polyHOGlu−LA are −210, 235, and 1003.

In the case of category A, the arms that separate between the polymer chains are shorter. Hence, in the copolymer structure, local dipole−dipole interactions between chains may contravene the counter forces that repel the chains to form rigid islands of chain interactions. This of course will raise the T_g value of the polymer.

Circular Dichroism. The CD data were fit to one or two terms of eq 5 by a nonlinear regression method.

$$A_\lambda = A_{01}\mathrm{Exp}-\left(\frac{\lambda_1-\lambda_{1\max}}{\Delta_1}\right)^2 + A_{02}\mathrm{Exp}-\left(\frac{\lambda_2-\lambda_{2\max}}{\Delta_2}\right)^2 \quad (5)$$

$A\lambda$ is the CD amplitude at the wavelength λ, A_{01} and A_{02} are the maximum amplitudes at $\lambda_{\max 1}$ and $\lambda_{\max 2}$ respectively, Δ_1 and Δ_2 are the widths of the curves at A_0/e. The CD spectra of poly(L)HOSer-*co*-(L)HOPhe (20%, 50%, and 80%) display overlapping bands with two maxima at 218−219 and 201 nm (Table 5 and Figure 8A, red line), which are probably attributed to nπ* transition of the ester bond. It is apparent that the two maxima (A_{01} and A_{02}) of the copolymers increase with the increase of HOPhe percentage in the polymer, whereas the first CD absorbance associated with A_{01} disappears in the pure poly(L)HOPhe (Figure 8B). It should be also noted that the pure poly(L)HOSer (Figure 8C) disclose a CD-absorbance maxima at 209 nm and not at 201 nm and that the pure poly(L)HOPhe presents a high A_{02} value of 115 mdeg compared to 6−18 mdeg displayed in the copolymers (Figure 8A). This suggests that the introduction of the HOSer component to the polymer sequence induced some conformational changes reflected by the magnitude of the amplitude (A_{02}) and the appearance CD band at 201 nm.

It is thus proposed that the existence of rotational isomers account for the presence of two overlapping cotton effects in the nπ* absorption region of the optically active copolymer, and not to two different transitions of the ester group, nπ* transition at higher wavelength and a $\pi\pi$* band at lower wavelength.

The increase in rotational strength of the poly(L)HOPhe can be due to the structural alignment of the attached phenyl groups which is interrupted in the case of the copolymer.

In analogy to poly(L)HOSer, poly(L)HOAsp displayed a positive CD maximum at 211 nm while the polymer composed of the D configuration demonstrated as expected a

negative cotton effect (Table 5 and Figure 9). The shift in λ_{max} from 222 nm for poly(L)HOPhe to 209−211 nm for poly(L)HOSer and poly(L)HOAsp can be assigned to the electron withdrawal property of the side chain substituents.

Table 4. T_g Values of Polyesters at Various Compositions with Lactic Acid (LA)

polyesters composition[a]	T_g (°C)[b]	ΔH (J/g)[b]	M_w (Da)[c]
PLA	49.00		3000
poly(L)HOAsp	−64.66	−12.86	1300
poly(L)HOAsp−LA (40%)	−56.86	−8.54	1000
poly(L)HOAsp−LA (50%)	−55.21	−10.03	1300
poly(L)HOAsp−LA (60%)	−50.44	−6.86	1000
poly(L)HOAsp−LA (80%)	−35.45	−10.27	2000
poly(L)HOGlu	−10.78	−6.22	1500
poly(L)HOGlu−LA (40%)	−43.32	−5.77	1000
poly(L)HOGlu−LA (50%)	−40.12	−6.53	1000
poly(L)HOGlu−LA (60%)	−31.09	−11.44	1000
poly(L)HOGlu−LA (80%)	−58.07	−14.61	1000
poly(L)HOLys	−50.80	−7.05	2200
poly(L)HOLys−LA(40%)	−64.58	−11.88	1000
poly(L)HOLys−LA(50%)	−71.33	−10.21	1000
poly(L)HOLys−LA(60%)	−74.62	−19.41	1900
poly(L)HOLys−LA(80%)	−70.43	−15.98	1000
poly(L)HOSer	−58.00	−12.37	1500
poly(L)HOSer−LA (40%)	−54.61	−10.01	1000
poly(L)HOSer−LA (50%)	−52.66	−8.65	1400
poly(L)HOSer−LA (60%)	−43.92	−7.22	1300
poly(L)HOSer−LA (80%)	−51.81	−11.53	1500
poly(L)HOThr	−46.92	−14.26	1642
poly(L)HOThr−LA (20%)	−28.88	−18.79	1841
poly(L)HOThr−LA (40%)	−25.55	−7.36	1192
poly(L)HOThr−LA (50%)	−22.94	−6.07	1915
poly(L)HOThr−LA (60%)	−30.19	−11.27	1293
poly(L)HOThr−LA (80%)	−30.19	−11.27	1293

[a] Percentages refer to the last monomer mentioned. [b] T_g and ΔH were determined by DSC at 10 °C/min. [c] The molecular weights were determined by GPC.

In the case of poly([*R*]-(−)-3-hydroxybutyrate) (PHB) the CD curve centered also at 210 nm, however the amplitude (A_0) and the curve width (Δ) were shown to be much larger (155 mdeg and 54 nm respectively).[63]

In Vitro Hydrolytic Degradation of the Polymers. The standard analysis of weight loss and the change of molecular weight of five polymers, poly(L)HOSer, poly(L)HOThr, poly(L)HOLys(OH), poly(L)HOAsp, and poly(L)HOGlu, were determined during hydrolysis under physiological conditions. The results are summarized in Figure 10.

The molecular weight decrease of the polymers was faster in the first days of the degradation. In the following weeks of the degradation the molecular weight decrease was very slow.

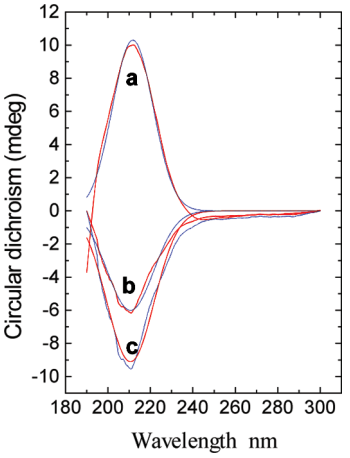


Figure 9. CD curves: (a) poly(L)HOAsp, 0.5 mmol/mL; (b) poly(D)-HOAsp, 0.3 mmol/mL; (c) poly(D)HOAsp, 0.5 mmol/mL. Red lines and blue dots refer to the experimental and predicted curves, respectively.

Table 5. Calculated Parameters (A_0, λ_{max}, and Δ) Emerged from CD Absorbance Curve Fitting Using Eq 5

polyesters	A_{01} (mdeg)	λ_{1max} (nm)	Δ_1 (nm)	A_{02} (mdeg)	λ_{2max} (nm)	Δ_2 (nm)
copoly(L)HOSer-(L)HOPhe (20%)[a]	2.7	201.0	3.9	6.3	218.9	11.2
copoly(L)HOSer-(L)HOPhe (50%)[a]	4.3	200.6	3.8	13.1	218.9	11.3
copoly(L)HOSer-(L)HOPhe (80%)[a]	9.1	201.5	4.9	18.0	218.4	10.8
poly(L)HOPhe				115.1	220.1	9.5
poly(L)HOSer				5.8	209.1	13.3
poly(L)HOAsp				10.3	211.7	13.6
poly(D)HOAsp				−9.1	210.6	15.7
poly(L)HOGlu				12.8	206.1	12.6
poly(L)HOThr				8.64	209.6	14.2
poly(L)HOLys				6.14	205.5	14.3

[a] Percentages refer to the last monomer mentioned.

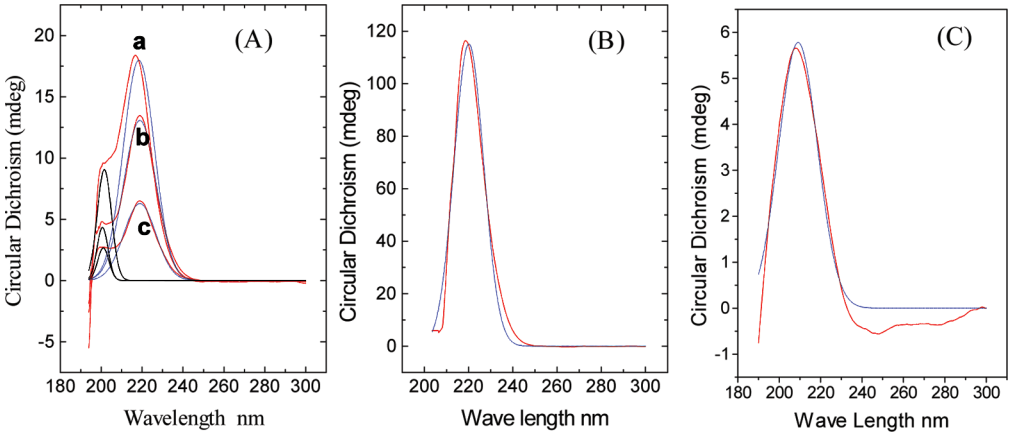


Figure 8. CD curves of various polyesters at 0.5 mmol/mL. (A) (a) poly(L)HOSer-*co*-(L)HOPhe 80%, (b) 50%, and (c) 20%, where percentages refer to the last monomer mentioned. Red lines refer to the experimental curves. Blue dots and black lines of the second and first bands respectively are the predicted curves. (B and C) observed (red) and predicted (blue dots) CD spectra of the homopolymers poly(L)HOPhe and poly(L)HOSer, respectively.

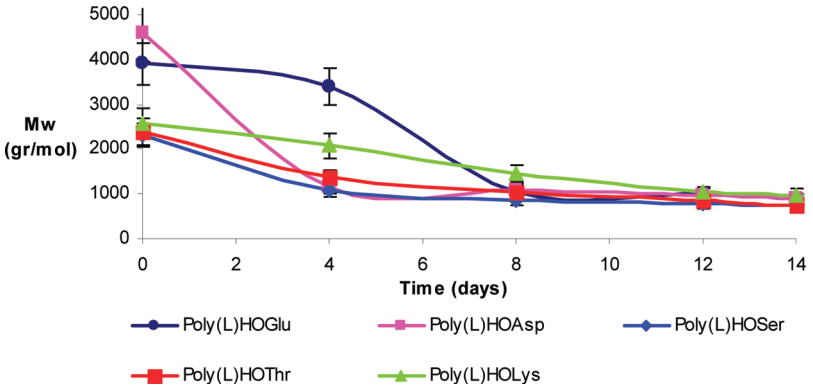


Figure 10. Molecular weight change during hydrolysis of the polymers. Hydrolysis was conducted in 0.1 M phosphate buffer (pH 7.4) at 37 °C.

Generally, the polymers with a smaller side chain, containing less methylene groups are less stable than the polymers with a longer side chain, toward the hydrolysis. PolyHOAsp, for instance, loses most of its weight during the first 5 days of degradation, whereas the high weight loss of polyHOGlu takes four more days.

Conclusions

Five trifunctional hydroxy acids derived from amino acids were prepared by a straightforward, reliable and inexpensive chemical method of diazotization. The hydroxy acids were obtained in relatively good yields from common amino acids and served as building blocks for polyester synthesis, displaying hydrophilic properties and preserved chirality. The polymers were prepared via direct condensation in bulk, acyl halide activation and microwave-assisted polymerization applying a variety of catalysts. In the case of polycondensation in solution molecular weights in the range of 2000−3000 were attained in the presence of the catalyst $SnCl_2$ and via acyl halide formation mediated by oxalyl chloride. In the case of the microwave method higher molecular weights of 2700−3500 were reached in neat and solution, with the same catalyst ($SnCl_2$). However, the polyacidic catalyst H_3BO_3 revealed also an efficient catalytic property yielding M_w of 3300−3800. These new biodegradable polymers can be used for biomedical applications which require hydrophilic properties.

In addition: (1) the polyesters displayed enhanced CD rotational strength as compared to their building blocks (data not shown); (2) the contact angles of a series of poly-HOAa and their copolymers prepared in our laboratory indicated a mild surface hydrophobicity and a linear correlation with their calculated log *P* values; (3) the transition glass temperatures (T_g) of poly(HOAa-(X)(OH)-*co*-LA) were in accord with Gordon−Taylor equation or with modified Kwei equation; (4) the degradation rate of the homopolymers is fast during the first week and slow afterward.

Note Added after ASAP Publication. This article was published ASAP on June 9, 2009. A small text change has been made in the Abstract. The correct version was published on June 17, 2009.

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