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Communications to the Editor

Preparation of New α-Hydroxy Acids Derived from Amino Acids and Their Corresponding Polyesters

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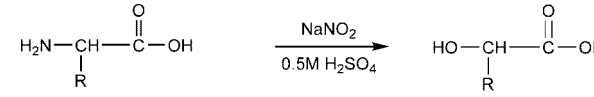
Background. Degradable polymers have been used for fixation of fractures, bone replacement, cartilage repair, menisci repair, fixation of ligaments,[1] drug delivery carriers,[2] and scaffolds for tissue engineering.[3] Absorbable materials have been used in the form of screws, pins, plugs, and plates for orthopedic, oral, and craniofacial surgery. Required features designated to biodegradable polymers are (1) the polymer should degrade in water into small water-soluble, nontoxic molecules, (2) rate of hydrolysis should be adjustable within a wide range by simple manipulation of polymer structure, (3) erosion rate of the polymer should follow the rate of the entrapped active agent, and (4) mechanical properties should be adjustable by simple changes in polymer.[4] Since nontoxicity is an inherent prerequisite for biodegradable polymers that are designed for medical applications, the starting materials, the final product, and the optional breakdown products of such biodegradable polymers should be nontoxic and benign.[5]

When used in medical applications, the biodegradable polymer of choice for the intended use is selected according to its properties. Thus, for example, semicrystalline polymers (e.g., poly(L-lactic acid)) are typically used in medical devices that require good mechanical properties such as sutures, devices for orthopedic and cardiovascular surgery, and stents. Amorphous polymers, on the other hand (e.g., poly(DL-lactic-*co*-glycolic acid)), are attractive in drug delivery applications, where it is important to have homogeneous dispersion of the active species within the polymeric matrix.[6]

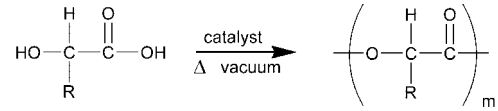
In general, synthetic polymers may offer greater advantages than natural materials in that they can be tailored to provide a wide range of properties and more predictable lot-to-lot uniformity than can materials from natural sources.

Scheme 1. Synthesis of the α-Hydroxy Acids



R= CH_2CONH_2, CH_2COOH, CH_2SH, $CH_2CH(CH_3)_2$, $(CH_2)_4OH$, $CH_2C_6H_5$, CH_2OH...

Scheme 2. Direct Condensation of the α-Hydroxy Acids



R= CH_2CONH_2, CH_2COOH, CH_2SH, $CH_2CH(CH_3)_2$, $(CH_2)_4OH$, $CH_2C_6H_5$, CH_2OH...

Methods of preparing polymeric materials are well-known.[7] However, synthetic methods that successfully lead to the preparation of polymeric materials that exhibit adequate biodegradability, biocompatibility, mechanical strength, and minimal toxicity for medical use are scarce. The restricted number and variety of biopolymers currently available attest to this.[8] The biodegradable polymers that have been most intensively investigated are aliphatic polyesters made from the following hydroxy acids: lactic acid, glycolic acid, butyric acid, and caprolactone. Their polyesters and copolyesters represent the main group of interest due to their long history of safety. Interestingly, little was reported on other hydroxy acid-based polyesters, probably due to the limited availability of other hydroxy acids from natural sources or complication in their synthesis.

Biodegradable polymers that have one or more stereogenic center(s) in the repeat unit (namely, optically active polymers) offer advantageous features when used as carriers for drug delivery.[9] In light of the above it is our intention to expand the scope of biodegradable polymers to new poly(hydroxy acids) carrying various stereogenic centers. Viewing the scope of this work in the area reveals that the selection of available chiral hydroxy acids is limited, and most of the work been done with either lactic acid or derivatives of acrylic acid attached to chiral moiety.

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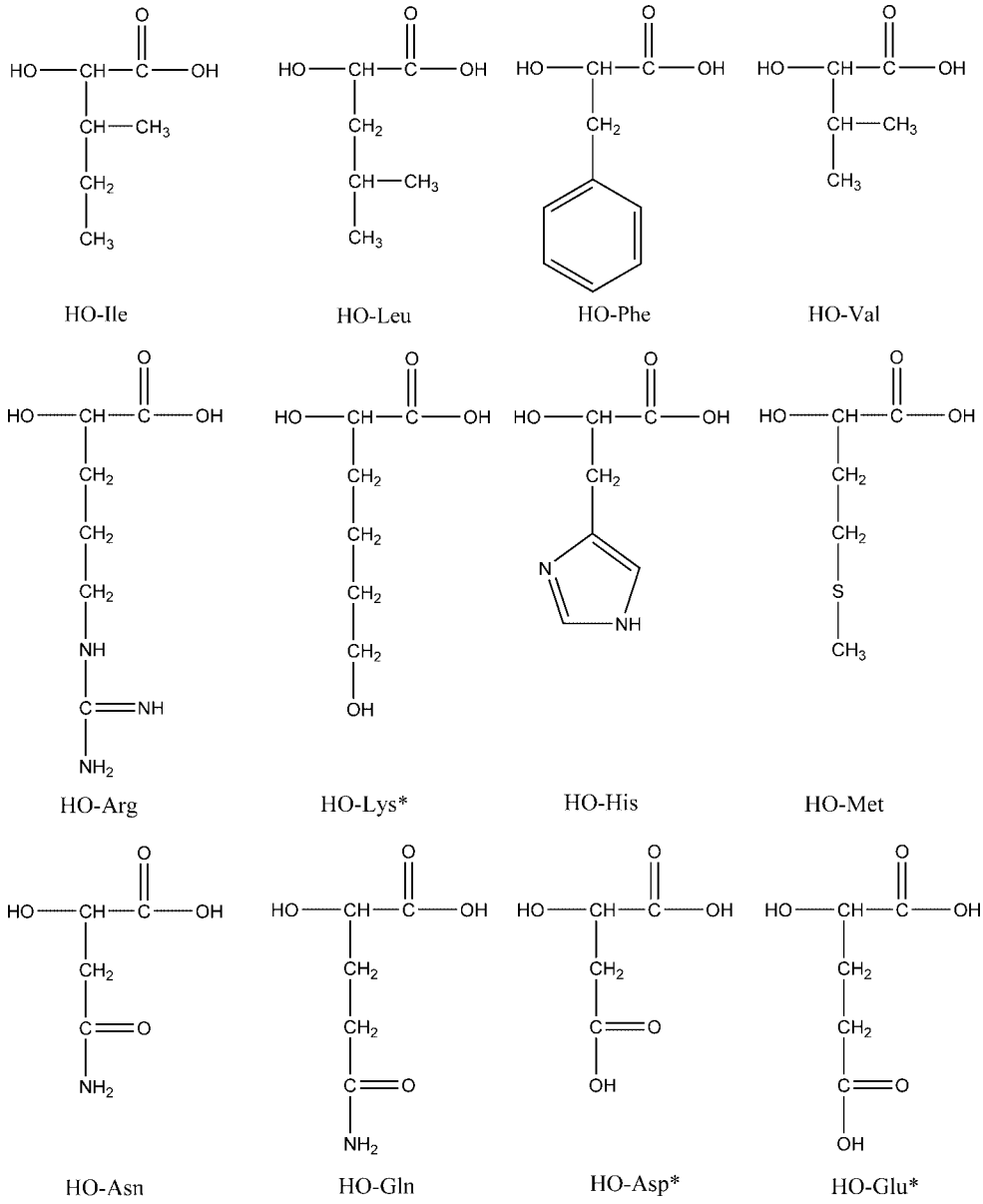

Figure 1. α-Hydroxy acids synthesized by diazotization of natural amino acids (a separate article will be published on these five hydroxy acids which are trifunctionnal monomers).

Therefore, we present here a new approach based on optically active substituted glycolic acid derived from amino acids. α-Hydroxy acids have been synthesized from natural α-amino acids using a straightforward, reliable, and inexpensive method of diazotization of α-amino acids.[10] Biopolymers based on positively charged, negatively charged, hydrophobic, and hydrophilic chiral building blocks or any designed combination of these constituents are proposed.

The α-hydroxy acids prepared from the amino acids are listed in Figure 1.

Linear homopolyesters and copolymers with lactic acid (1:1) were prepared from the hydroxy acids of the following amino acids: isoleucine, L- and D-leucine, L- and D-phenylalanine, L- and D-valine, arginine, histidine, methionine, asparagine, and glutamine.

The polymers were prepared by direct condensation in bulk.

Results and Discussion. *Hydroxy Acids Synthesis.* Hydroxy acids of the amino acids isoleucine, leucine, phenylalanine, valine, methionine, arginine, lysine, histidine, methionine, asparagine, glutamine, glutamic acid, aspartic acid, serine, and threonine were prepared from the reaction of the amino acid with sodium nitrite in an acidic aqueous medium.[11,12] They were obtained in good yields (60−70%). Attempts were made to prepare hydroxy acids from cysteine, tryptophan, and tyrosine. Cysteine gave a very hydrophilic product that is hard to extract and not clean according to ^{1}H NMR analysis. Tryptophan and tyrosine are hardly oxidized by the reaction, and protecting groups do not help. Trp(For) (formyl-protected tryptophan) is hardly oxidized, and Tyr(Bzl) (benzyl-protected tyrosine) yielded multiple products.

Polymer Synthesis. Polyesters were synthesized from the hydroxy acids and from the hydroxy acids with lactic acid, with a molar ratio of 1:1. The polyesters were prepared by direct condensation in bulk with *p*-toluenesulfonic acid as catalyst.[13,14] The hydrophobic polymers have a molecular weight around 2000 whereas the hydrophilic ones give low molecular weight oligomers. The synthesized hydrophobic polymers are viscous-yellow to off-white ointment like at room temperature. A separate work is conducted on polymers derived from the

Table 1. Characterization of the Prepared Polymers

	polymer	M_w[a] (Da)	M_n[a] (Da)	Mp[a]	optical activity $[\alpha]_D$ [b](lit. value)	solubility (g/L)[c] $CHCl_3$	THF	ACN	T_g (°C)[e](lit. value)	ΔH (J/g)[e]	water contact angle (θ)[g]
1	PLA	2800	2600	2400	−139 (−141)[15]	250	18	<2%	49.0 (49−60)[15]	−6.3	37.1
2	Poly(L)HOIle	1000	800	800	−10	>600	150	60	−10.7	−4.1	53.0
3	Poly(L)HOIle-LA (50%)	1800	1600	1500	−53	>600	32	75	5.4	−3.0	67.4
4	Poly(L)HOLeu	2300	1900	2800	−43	>600	80	120	−8.8	−3.7	76.2
5	Poly(L)HOLeu-LA (50%)	2300	1900	2500	−60	>600	147	59	11.2	−5.3	78.4
6	Poly(L)HOPhe	2500	2200	2600	−37	>600	37	47	32.0[h] (38−50)[16]	−5.9	85.8
7	Poly(D)HOPhe	2200	2300	2400	+32	>600	37	47	31.9	−6.0	85.8
8	Poly(L)HOPhe-LA (50%)	2500	2300	2700	−55[i] (−66)[16]	>600	410	41	25.9[i] (38−50)[16]	−11.8	99.1
9	Poly(L)HOVal	1000	700	700	−32	>600	122	65	16.8	−4.3	73.7
10	Poly(D)HOVal	1100	800	700	+10	>600	330	65	16.6	−4.4	73.7
11	Poly(L)HOVal-LA	1700	1400	1500	−70	>600	78	33	29.2	−6.8	87.7

[a] The molecular weight were determined by GPC. [b] Specific optical rotation (c = 1−1.2, in $CHCl_3$, at 25 °C). [c] Solubility of the polymers in several organic solvents. [e] T_g and ΔH were determined by DSC at 10 °C/min. [g] Water contact angle was determined using a contact angle goniometer. [h] The molecular weight of the PolyHOPhe corresponding to the literature value is higher than 3000 Da. [i] The polymer corresponding to the literature value contains 70% HOPhe monomer.

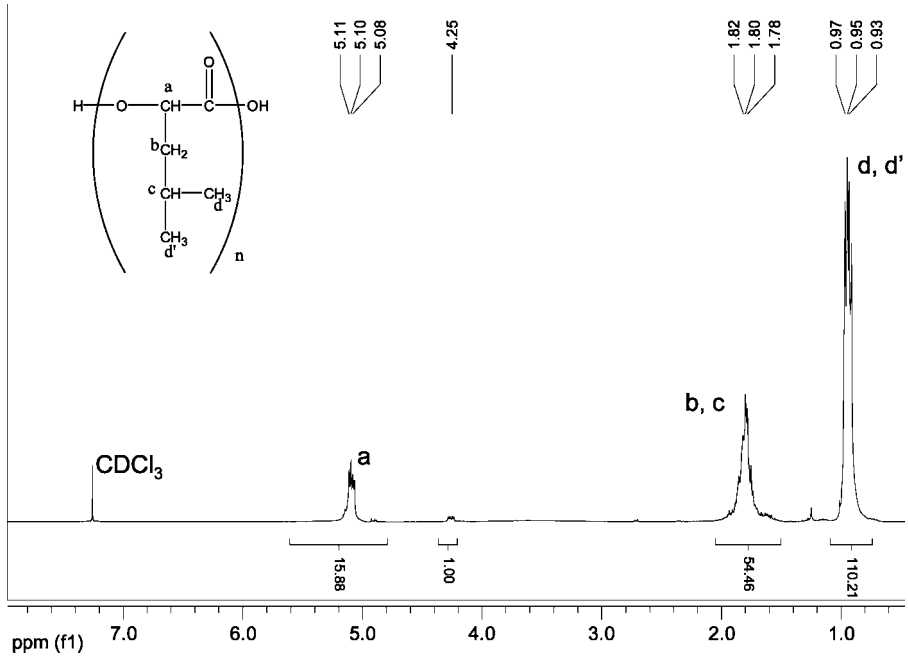

Figure 2. ^{1}H NMR spectrum of PolyHOLeu. Obtained in 5 mm diameter tubes. $CDCl_3$ containing tetramethylsilane served as solvent and shift reference.

trifunctional monomers as HOSer, HOThr, HOAsp, HOGlu, and HOLys. The characterization of the polymers obtained is summarized in Table 1. The introduction of lactic acid in the hydrophobic polymers increases the molecular weight of the polymer. In general, the polymerization potential of hydrophobic α-hydroxy acids is a little lower than the one of lactic acid, whereas most of the hydrophilic hydroxy acids are quite hard to polymerize by this condensation method. As known, it is often difficult to prepare high molecular weight polyesters using the polycondensation method. Oligomeric products with a molecular weight in the range of a few thousands can be obtained.[8]

The polymers are soluble in chloroform, even more than PLA itself. They are also soluble in THF and ACN. The polymers are not soluble in water.

^{1}H NMR Spectra of the Polyesters. ^{1}H NMR spectroscopy confirm the polymerization of the monomers by the appearance of a C*H* peak between 5.1 and 5.3 ppm, corresponding to the ester group CH−COO−C*H*, and the significant disappearance of the C*H*OH peak of the hydroxy acid at 4−4.3 ppm. From ^{1}H NMR data M_n of the polymer can also be calculated. The ratio between the integration of the two CH signals (of the main chain groups at 5.10 ppm, and of the end group at 4.25 ppm) gives the degree of polymerization, 15.88. Since the molecular weight of the monomeric unit is 114.14, M_n of the analyzed polymer is found to be 1830 (including the H and OH end groups). This calculated data is close to the M_n determined by GPC (1900).

IR Spectroscopy. All polymers show major ester peak between 1750 and 1765 cm^{-1} and a small acid peak around 1640 cm^{-1}.

In Vitro Hydrolytic Degradation of the Polymers. The standard analysis of weight loss and the change of molecular weight of two polymers, PolyHOLeu and PolyHOleu-LA, were determined during hydrolysis under physiological conditions (phosphate buffer, pH 7.4, 37 °C, 100 rpm). The weight loss analysis is summarized in Figure 4. In the first days the weight loss rate of the polymers was quite high, whereas during the following weeks the degradation rate of the polymers was slow. Generally, PolyHOLeu is less stable than PolyHOLeu-LA toward hydrolysis, although HOLeu is a more hydrophobic monomer than lactic acid. The difference in the stability of the polymers can be attributed to their tacticity. It could be that

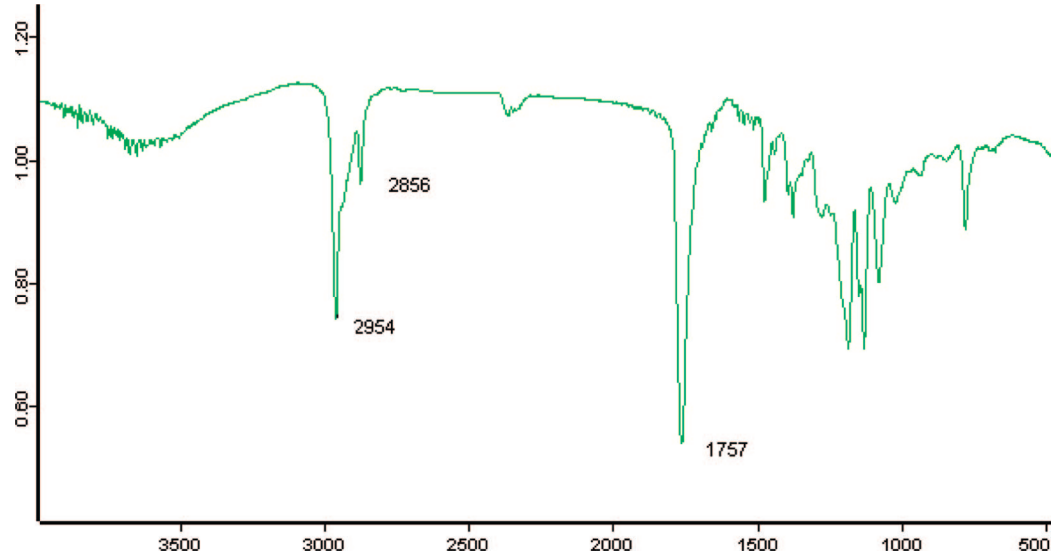

Figure 3. IR spectrum of PolyHOLeu. The typical ester peak is 1757 cm^{-1}. IR spectroscopy was performed on polymer sample cast on NaCl plate from a chloroform solution.

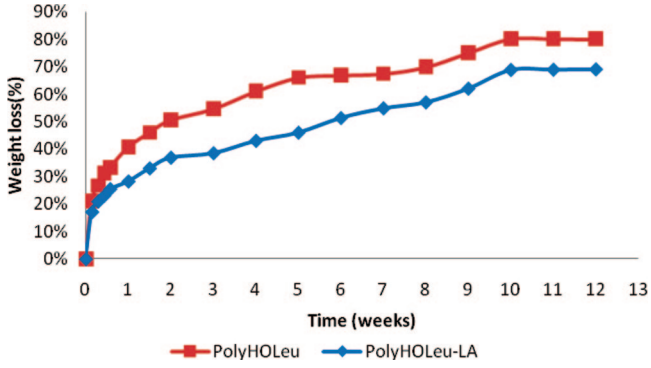

Figure 4. Hydrolysis of PolyHOLeu and PolyHOLeu-LA monitored by weight loss of the degraded polymers. Hydrolysis was conducted in 0.1 M phosphate buffer (pH 7.4) at 37 °C. At each time point, the remaining polymer was dried and weighted.

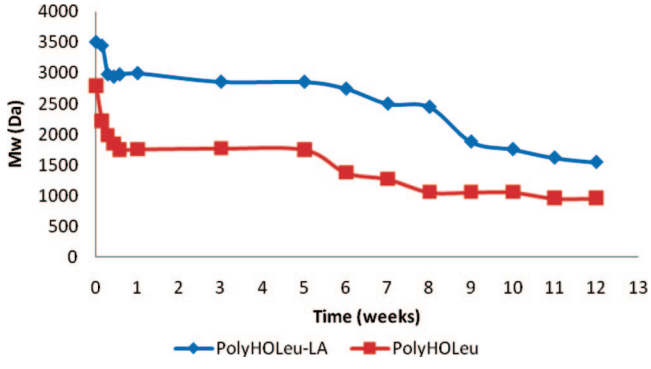

Figure 5. Molecular weight change during hydrolysis of the polymers. The hydrolysis conditions are described in Figure 1.

there are hydrophobic interactions between the alkyl side chains of PolyHOLeu which lead the substituents to be located on the same side of the macromolecular backbone. If so, the other side of the backbone may be exposed to degradation by water molecules. In PolyHOLeu-LA the alkyl chains of HOLeu are separated by the methyl groups of LA, and likely the side-chain substituents are distributed all around the backbone, so that the polymer is more stable to degradation.

Molecular weight decrease of the polyHOLeu and PolyHOLeu-LA was monitored by GPC and is summarized in Figure 5.

As it was seen in the weight loss analysis, the molecular weight decrease of the polymers was faster in the first days of the degradation. In the following weeks the molecular weight decrease was very slow. The molecular weight decrease of PolyHOLeu was faster than the one of PolyHOLeu-LA.

Conclusion. It was demonstrated that 14 hydroxy acids derived from amino acids can be prepared by a straightforward, reliable, and inexpensive chemical method of diazotization. The hydroxy acids are obtained in relatively good yields from common amino acids and can serve as building blocks for polyester synthesis, displaying positively charged, negatively charged, hydrophobic, and/or hydrophilic properties and chirality.

It was demonstrated that homopolyesters can be prepared from the hydroxy acids and copolymers with lactic acid by direct condensation in bulk. The obtained polymers have a molecular weight between 1000 and 3000. There is a need to improve the polymerization procedure in order to get higher molecular weight polyesters.

These new biodegradable polymers can be used for medical needs like stands, drug delivery carriers, and scaffolds for tissue engineering.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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