Polylactides in Channels

Alan E. Tonelli

Fiber and Polymer Science Program, College of Textiles, North Carolina State University, Raleigh, North Carolina 27695-8301

Received November 19, 1991

ABSTRACT: The conformations of stereoregular poly(L-lactide) (PLLA, optically active) and regularly alternating poly(L,D-lactide) (PLDLA, optically inactive) confined to occupy cylinders of varying radii were determined in an effort to learn if either polylactide could be incorporated in the narrow channels of its inclusion compound (IC) with urea. Only PLLA chains in the extended, nearly planar zigzag, all-trans conformation fit in cylinders whose diameters D correspond closely to those observed in polymer–urea–IC's, namely, $D \sim 5.5$ Å. PLDLA chains were not able to fit in cylinders with $D < 7.5$ Å. Thus, we might anticipate making PLLA–urea–IC but not PLDLA–urea–IC. Because in its IC with urea the PLLA chains are nearly all-trans, while in bulk crystalline PLLA and in the 1:1 crystalline complex formed between PLLA and PDLA the chains adopt 10_3 and 3_1 helical conformations, respectively, we would expect significant differences between their high-resolution, solid-state CPMAS/DD ^{13}C NMR spectra.

Introduction

Polylactides are biodegradable polymers that have utility as prosthetic devices and sutures,[1] as matrix material in bioresorbable composites[2] and for controlled release of drugs and agrochemicals,[3] and as nontoxic, environmentally safe, degradable plastics. Stereoregular poly(L- and poly(D-lactides) (PLLA and PDLA) are crystalline, high-melting (180 °C) polyesters,[4–7] while the stereoregular, regularly alternating poly(L,D-lactide) (PLDLA) and the stereoirregular polylactides (random sequence of D and L lactide units) are completely amorphous[7–9] (see Figure 1 for the chemical structure of polylactides). Recently[10–13] crystalline stereocomplexes of PLLA and PDLA (PLLA*PDLA) have been formed from their equimolar mixtures in solution and were observed to melt at 230 °C, some 60 °C above the crystals of pure PLLA and PDLA.

X-ray diffraction studies of PLLA[6] and the 1:1 PLLA*PDLA complex[10,12] crystalline fibers have revealed that the polylactide chains in both crystalline environments adopt approximate $g^+t[(\phi,\psi) = 120°, 0°]$ conformations, which result in 10_3 and 3_1 helices, respectively, with crystalline fiber repeats of 27.8 and 8.7 Å. Brant, Tonelli, and Flory (BTF)[14] have calculated the conformational energy of a L-lactyl residue in PLLA, and their results are redisplayed in Figure 2 as a (ϕ,ψ) energy contour map, so often utilized in polypeptide and protein studies.[15–22] Note that in the L-lactyl residue (ϕ,ψ) energy map four low-energy regions, or domains (III′, I′, III, and I), appear and correspond approximately to the tt, tg^+, g^+t, and g^+g^+ conformations, respectively. The conformations of PLLA chains in their pure crystals (10_3 helix)[6] and in the crystalline complex with PDLA (3_1 helix)[10,12] correspond to the lowest energy region/conformation (III/g^+t) of the (ϕ,ψ) energy map. Apparently differences in the energies of packing the polylactide chains in both crystals lead to their distinct helical conformations.

Preliminary to an attempt at making the crystalline inclusion compound (IC) between guest PLLA or PDLA chains and the host clathrate urea, we have modeled the conformational behavior of polylactide chains in the narrow channels characteristic of polymer–urea–IC's. This was achieved through simulation of the channels in the urea matrix[23] as narrow cylinders with a diameter $D \sim 5.5$ Å. Six-residue fragments of PLLA and PLDLA were permitted to adopt conformations consistent with the (ϕ,ψ) energy map of BTF.[14] Only the stereoregular, optically active PLLA and PDLA chains were found able to fit in cylinders with a diameter approximating the one observed[23] in polymer–urea–IC's, while the regularly alternating PLDLA could not be placed in cylinders whose diameters were smaller than 7.5 Å. Unlike the bulk crystalline phases of PLLA, PDLA, and PLLA*PDLA, the stereoregular polylactides were restricted to the nearly planar, zigzag, tt conformation of the (ϕ,ψ) energy map, i.e., region III′ (see Figure 2), when constrained to occupy cylinders with 5.2 Å $< D <$ 7.0 Å, which encompass the narrow channels in polymer–urea–IC's.

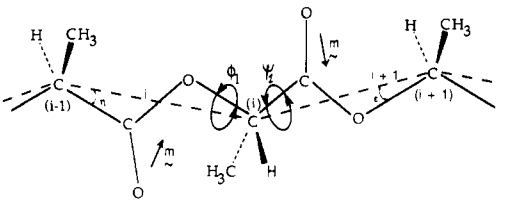

Figure 1. Diagram showing L-lactyl residue i, portions of residues $i-1$ and $i+1$, and virtual bonds (dashed) i and $i+1$ of a PLLA chain. The ester group dipole moments are indicated by arrows m.

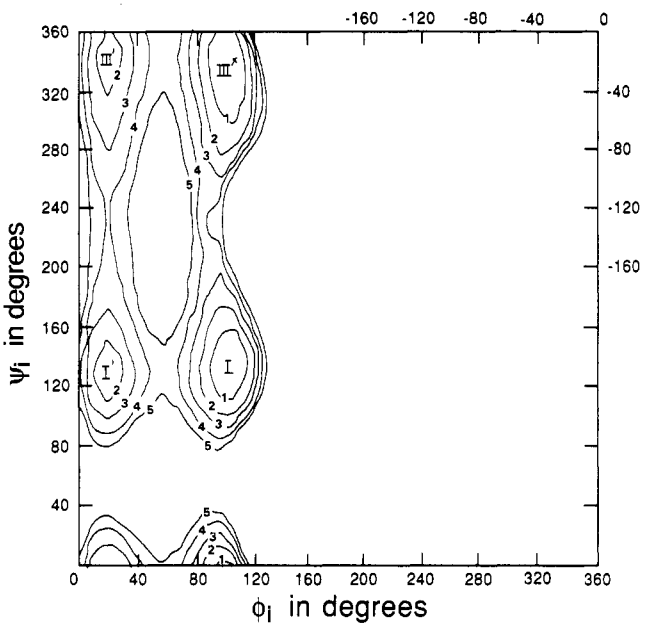

Figure 2. Conformational energy map for the L-lactyl residue as calculated by BTF.[14] Contours are drawn at intervals of 1.0 kcal/mol relative to the lowest energy minimum at X in domain III.

0024-9297/92/2225-3581$03.00/0

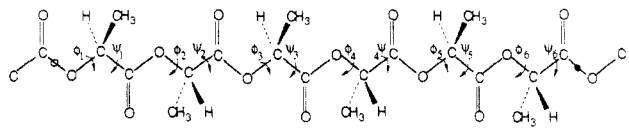

Figure 3. Six-residue fragment of polylactide used to derive its channel-bound conformers. Though only the fragment for stereoregular PLLA is drawn, the regularly alternating PLDLA was also considered, where the hydrogen atom and methyl group on every other asymmetric carbon are interchanged.

Table I
Structural Parameters[a]

bond length, Å	bond angle, deg
O–C$^{\alpha}$, 1.44	O–C$^{\alpha}$–C, 110
C$^{\alpha}$–C, 1.52	C$^{\alpha}$–C–O, 114
C–O, 1.34	C–O–C$^{\alpha}$, 113
C=O, 1.22	C$^{\alpha}$–C=O, 121
C$^{\alpha}$–C$^{\beta}$, 1.54	O–C$^{\alpha}$–C$^{\beta}$, 110
C$^{\alpha}$–H$^{\alpha}$, 1.07	O–C$^{\alpha}$–H$^{\alpha}$, 110

[a] $\eta = 18.9°$; $\xi = 19.9°$.

Table II
Statistical Weights for Various Minima

minimum, M	z_M/z	statistical wt, w_M
I	0.362	0.368
III	0.540	0.550
I′	0.039	0.040
III′	0.041	0.042
total	0.982	1.000

Modeling Polylactide Chains in Cylinders

Figure 3 presents the six-residue fragment of polylactide employed in the modeling of PLLA and PLDLA chains confined to cylinders. Though only the stereoregular all poly(L-lactide) fragment is drawn, we did consider the L,D,-L,D,L,D-six-residue fragment as well. The molecular geometry appropriate to poly(lactic acid) and presented by BTF[14] was adopted here and is given in Table I. In addition, the description of the conformational characteristics of a lactyl residue as embodied in the (ϕ,ψ) conformational energy map (see Figure 2) calculated by BTF was employed in the search for channel-bound conformers of the polylactide fragments (see Figure 3). As noted by BTF,[14] the occurrence of four discrete energy minima (I, I′, III, and III′) in the (ϕ,ψ) energy map of the L-lactyl residue suggests treatment of the polylactide chain conformational characteristics in the rotational isomeric state (RIS) approximation.[14,22] Each L-lactyl residue may be considered to be confined to occupy the four RIS states tt (III′), tg$^+$ (I′), g$^+$t (III), and g$^+$g$^+$ (I) independent of the conformations adopted by neighboring L-lactyl residues. The neighbor independence of lactyl residue conformations stems from their separation by trans, planar ester bonds.[13,21]

In Table II statistical weights, w_m, calculated for each of the four energy minima of the L-lactyl residue are presented. These statistical weights were obtained by evaluation of the residue partition functions, $z_m = \Sigma_{\phi\psi} \exp(-E(\phi,\psi)/RT)$, using 10° increments of $\Delta\phi$ and $\Delta\psi$ within the 3 kcal/mol energy contours about each of the minima, and $w_m = z_m/\Sigma_m z_m$. Note that the total residue partition function z evaluated over the complete range of (ϕ,ψ) values, once again using 10° increments, is only slightly larger than $\Sigma_m z_m$ (1.0 vs 0.982, see Table II). On the basis of this analysis, we treat each L-lactyl residue as able to independently adopt the tt, tg$^+$, g$^+$t, and g$^+$g$^+$ conformations with probabilities 0.042, 0.040, 0.550, and 0.368, respectively.

From BTF's analysis, we assign to the tt, tg$^+$, g$^+$t, g$^+$g$^+$ rotational states the angles (ϕ,ψ) = 20°, 340°; 20°, 132°; 107°, 340°; and 107°, 132° for the L-lactyl residue, where all rotations are right-handed and begin from $\phi = \psi = 0°$ in the trans (t) conformation. By symmetry, a D-lactyl residue energy map also displays four energy minima located at $(\phi,\psi)_D = (-\phi,-\psi)_L$.

A Cartesian coordinate system was affixed to the middle of the first ester bond (see Figure 3) and was used as a reference frame for expressing the x, y, and z coordinates of each atom in the polylactide fragment. These atomic coordinates depend upon the conformations, (ϕ,ψ)'s, of the six constituent lactyl residues, each of which is constrained to adopt one of the four conformations defined by the conformational energy map shown in Figure 2 with probabilities given in Table II. Consequently, $(4)^6 = 4096$ conformations in all are permitted for the six-residue polylactide fragment. For each of these conformers the x, y, and z coordinates of all fragment atoms were calculated and transformed to the Cartesian coordinate system x', y', and z' whose z' axis connects the midpoints (○,●) of the terminal ester bonds. The radius, r, of the corresponding cylindrical coordinate system with coincident z' axis is $r = (x'^2 + y'^2)^{1/2}$.

When selecting channel conformers, we simply determined if $r = (x'^2 + y'^2)^{1/2} < r_c$, where r_c is the radius of the cylindrical channel. If each atom in the six-residue polylactide fragment passed this test, then the conformation was considered a channel conformer.

If we define the statistical weight matrices $\mathbf{U}_e$, $\mathbf{U}_{ph}$, and $\mathbf{U}_{ps}$, corresponding to the conformations adopted by the ester, O–C, and C–C backbone bonds, respectively, as

$$\mathbf{U}_e = \begin{array}{c} \psi\backslash e \\ t \\ g^+ \end{array} \begin{array}{c} \begin{array}{cc} t & x \end{array} \\ \begin{bmatrix} 1 & 0 \\ 1 & 0 \end{bmatrix} \end{array} \qquad \mathbf{U}_{ph} = \begin{array}{c} e\backslash\phi \\ t \\ x \end{array} \begin{array}{c} \begin{array}{cc} t & g^+ \end{array} \\ \begin{bmatrix} 1 & 1 \\ 0 & 0 \end{bmatrix} \end{array}$$

$$\mathbf{U}_{ps} = \begin{array}{c} \phi\backslash\psi \\ t \\ g^+ \end{array} \begin{array}{c} \begin{array}{cc} t & g^+ \end{array} \\ \begin{bmatrix} 0.042 & 0.040 \\ 0.550 & 0.368 \end{bmatrix} \end{array}$$

then the partition function of the six-residue polylactice fragment is simply $z_6 = (\mathbf{U}_e\,\mathbf{U}_{ph}\,\mathbf{U}_{ps})^6$. Notice the ester bond is fixed in the trans conformation, and the elements of $\mathbf{U}_{ps}$ (ϕ,ψ rotations) are obtained from the statistical weights in Table II. Let us suppose that the polylactide fragment adopts the III′, I, III, III′, I′, I or tt, g$^+$g$^+$, g$^+$t, tt, tg$^+$, g$^+$g$^+$ conformation. Its probability of occurrence is given by $\{[U_e(1,1)U_{ph}(1,1)U_{ps}(1,1)]*[U_e(1,1)U_{ph}(1,2)U_{ps}(2,2)]*[U_e(2,1)U_{ph}(1,2)U_{ps}(2,1)]*[U_e(1,1)U_{ph}(1,1)U_{ps}(1,1)]*[U_e(1,1)U_{ph}(1,1)U_{ps}(1,2)]*[U_e(2,1)U_{ph}(1,2)U_{ps}(2,2)]\}/z_6$.

Results and Discussion

The channel conformers found for the six-residue fragments of PLLA and PLDLA are partially characterized in Tables III and IV, where their numbers, probabilities, and average central residue conformations $[(\phi,\psi)_3;(\phi,\psi)_4]$ are compared for various assumed constraining cylinder diameters, D. Because in the search for channel conformers each atom was considered a volumless point, a channel conformer found to fit in a cylinder of diameter $D' = 2r_c$ would actually fill a cylinder with a diameter $D = D' + 1$ Å, if van der Waals spheres of radius 0.5 Å are assigned to each hydrogen bond. Consequently, the results presented in Tables III and IV reflect the 0.5-Å radius

Table III
PLLA Channel Conformers

D, Å	no. of channel conformers	probability of channel conformers	population of central residue conformations in channel conformers			
			tt (III′)	tg^+ (I′)	g^+t (III)	g^+g^+ (I)
4.0	0	0				
4.5	0	0				
5.0	0	0				
5.2	2	7.7×10^{-8}	1.0	0.0	0.0	0.0
5.5	2	7.7×10^{-8}	1.0	0.0	0.0	0.0
6.0	4	1.3×10^{-7}	1.0	0.0	0.0	0.0
7.0	8	1.8×10^{-6}	1.0	0.0	0.0	0.0
8.0	38	0.0546	0.0	0.002	0.998	0.0
9.0	118	0.0653	0.002	0.005	0.993	0.0
10.0	278	0.120	0.021	0.008	0.903	0.068
12.0	1106	0.311	0.060	0.044	0.776	0.120
16.0	3220	0.849	0.045	0.037	0.603	0.315
20	4090	0.99992	0.042	0.040	0.550	0.368
free chain	4096	1.0	0.042	0.040	0.550	0.368

Table IV
PLDLA Channel Conformers

D, Å	no. of channel conformers	probability of channel conformers	population of central residue conformations in channel conformers			
			tt (III′)	tg^+ (I′)	$g^{\pm}t$ (III)	$g^{\pm}g^{\pm}$ (I)
4.0	0	0				
4.5	0	0				
5.0	0	0				
5.5	0	0				
6.0	0	0				
7.0	0	0				
7.5	12	0.00149	0.002	0.500	0.260	0.240
8.0	50	0.00495	0.009	0.335	0.340	0.316
9.0	238	0.0393	0.011	0.075	0.298	0.616
10.0	576	0.100	0.019	0.069	0.210	0.702
12.0	1410	0.253	0.029	0.060	0.333	0.578
16.0	3182	0.725	0.044	0.050	0.487	0.419
20.0	4092	0.99998	0.042	0.040	0.550	0.368
free chain	4096	1.0	0.042	0.040	0.550	0.368

assigned to hydrogen atoms, and, for example, in the search for $D = 5.5$ Å channel conformers the x', y', and z' atomic coordinates were tested against $r_c = 2.25$ Å.

A comparison of the channel conformations generated for the six-residue fragments of PLLA and PLDLA appearing in Tables III and IV indicates clearly that only PLLA chains in the nearly planar zigzag, all-trans conformation [III′, $(\phi,\psi) = 20°, 340°$] are able to fit in narrow channels with $5.2 \text{ Å} < D < 7.0$ Å, while $D > 7.5$ Å channels are required for accommodation of the regularly alternating PLDLA chains. It would appear that neither regularly alternating nor stereochemically random polylactides would be able to form crystalline IC's with urea, whose channels[23] are cylindrical with $D \sim 5.5$ Å. At the same time, stereoregular PLLA and PDLA in the extended (III) conformation could be accommodated in the channels provided by the host clathrate urea. Thus, complexation with urea might be a potential means for fractionating polylactide samples on the basis of their stereochemical purity.

In Figure 4 Newman projections along the ester oxygen to asymmetric carbon bond are presented, illustrating the ϕ-rotation angle adopted by PLLA (a) when crystallized in bulk, as in pure PLLA or in the 1:1 stereocomplex with PDLA, and (b) in cylinders commensurate with the narrow channels found[23] in polymer–urea–IC's. Note that when $\phi = g^+$ the carbonyl carbons are in a gauche arrangement, while for $\phi = t$ the methyl carbon and its γ-carbonyl carbon are gauche to each other. On the basis of our experience with the conformationally-sensitive γ-gauche effects[24-27] on ^{13}C chemical shifts, we would expect the methyl carbons in the bulk crystals of PLLA and PLLA*PDLA to resonate

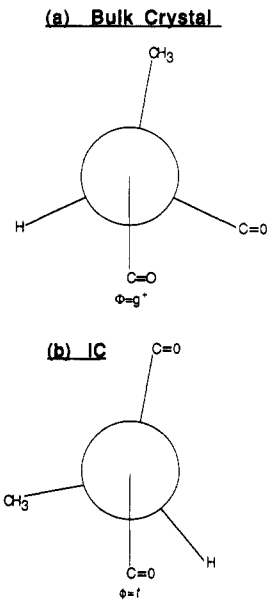

Figure 4. Newman projections along the ester oxygen to asymmetric carbon bond in PLLA illustrating the ϕ-rotation angle adopted (a) in the bulk crystals of PLLA, PDLA, and PLLA*PDLA and (b) in the channels of the potential PLLA–urea–IC.

several ppm upfield from the methyl carbons of PLLA in its crystalline IC with urea. We hope to test this suggestion by forming the crystalline IC of PLLA with urea and observing its CPMAS/DD ^{13}C NMR spectrum.

On the basis of our previous study[28] of the channel conformers of the corresponding aliphatic polyester and

polyamide, poly(ϵ-caprolactone) (E-6) and nylon-6 (N-6), we may by analogy extend the results found here for the polylactides to the simplest polypeptides. Both E-6 and N-6 were found to fit in cylindrical channels with $D \geq 4.5$ Å, suggesting the possibility that both polymers could form IC's with urea. Subsequently,[29] the E-6–urea–IC was formed and studied by a variety of means including X-ray diffraction, DSC, and FTIR and CPMAS/DD ^{13}C NMR spectroscopies. E-6 and N-6 were found to adopt very similar numbers and types of channel-bound conformers, with the all-trans, planar zigzag conformer accounting for at least 40% of the probabilities of all channel-bound conformers when both polymers were confined to narrow channels with $D \leq 5.5$ Å. The remarkable similarity between the channel-bound conformers of E-6 and N-6 suggests that we might extend our findings on the polylactides, as reported here, to analogous polypeptides like the polyalanines and polyglycine.

We would expect stereoregular poly(L- and poly(D-alanine) and polyglycine to fit in channels with $D = 5.5$ Å, thereby permitting the formation of IC's with the host clathrate urea. On the basis[20,22] of the significantly increased number of low-energy conformations accessible to the glycine residue, relative to the lactyl residue, and the absence of a protruding methyl side group, we might expect polyglycine conformations, in addition to the all-trans conformer, to fit and populate the channels of its IC with urea. Polyalanine, whose residue conformational energy map[20,22] and side group are similar and identical, respectively, to those of polylactide, would be expected to be limited to the all-trans conformation in its urea–IC.

References and Notes

(1) Kulkarni, R. K.; Moore, E. G.; Hegyeli, A. F.; Leonard, F. J. *Biomed. Mater. Res.* **1971**, *5*, 169.
(2) St. John, K. R. *Biocompatible Polymers, Metals, and Composites*; Szycher, M., Ed.; Technomic Publishing Co.: Lancaster, PA, 1983; p 861.
(3) Wood, D. A. *Int. J. Pharm.* **1980**, *7*, 1.
(4) Kleine, J.; Kleine, H. H. *Makromol. Chem.* **1959**, *30*, 23.
(5) Schulz, V. C.; Schwaab, J. *Makromol. Chem.* **1965**, *87*, 90.
(6) Desantis, P.; Kovacs, A. J. *Biopolymers* **1968**, *6*, 299.
(7) Tonelli, A. E.; Flory, P. J. *Macromolecules* **1969**, *2*, 225.
(8) Schindler, A.; Harper, D. *J. Polym. Sci., Polym. Lett. Ed.* **1976**, *14*, 729.
(9) Chabot, F.; Vert, M.; Chapelle, S.; Granger, P. *Polymer* **1983**, *24*, 53.
(10) Ikada, Y.; Jamshidi, K.; Tsuji, H.; Hyon, S.-H. *Macromolecules* **1987**, *20*, 904.
(11) Loomis, G. L.; Murdoch, J. R.; Gardner, K. H. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1990**, *31* (2), 55.
(12) Okihara, T.; Tsuji, M.; Kawaguchi, A.; Katayama, K.-I. *J. Macromol. Sci., Phys.* **1991**, *B30* (1, 2), 119.
(13) Tsuji, H.; Hyon, S.-H.; Ikada, Y. *Macromolecules* **1991**, *24*, 5651, 5657.
(14) Brant, D. A.; Tonelli, A. E.; Flory, P. J. *Macromolecules* **1969**, *2*, 228.
(15) Sasisekharan, V. *Collagen*; Ramanathan, N., Ed.; Interscience: New York, 1962.
(16) Ramachandran, G. N.; Ramakrishnan, C.; Sasisekharan, V. *J. Mol. Biol.* **1963**, *7*, 95.
(17) Ramakrishnan, C.; Ramachandran, G. N. *Biophys. J.* **1965**, *5*, 909.
(18) Ramachandran, G. N.; Venkatachalam, C. M.; Krimm, S. *Biophys. J.* **1966**, *6*, 849.
(19) Venkatachalam, C. M.; Ramachandran, G. N. *Conformation of Biopolymers*; Ramachandran, G. N., Ed.; Academic Press: New York, 1967; Vol. 1, p 83.
(20) Brant, D. A.; Flory, P. J. *J. Am. Chem. Soc.* **1965**, *87*, 663, 2791.
(21) Brant, D. A.; Miller, W. G.; Flory, P. J. *J. Mol. biol.* **1967**, *23*, 47.
(22) Flory, P. J. *Statistical Mechanics of Chain Molecules*; Interscience: New York, 1969; Chapters I, IV, and VII.
(23) Fetterly, L. C. *Non-Stoichiometric Compounds*; Mandelcorn, L., Ed.; Academic Press: New York, 1964; Chapter 8.
(24) Tonelli, A. E. *J. Am. Chem. Soc.* **1980**, *102*, 7635.
(25) Tonelli, A. E.; Schilling, F. C. *Acc. Chem. Res.* **1981**, *14*, 233.
(26) Tonelli, A. E. *Biopolymers* **1984**, *23*, 819.
(27) Tonelli, A. E. *NMR Spectroscopy and Polymer Microstructure: The Conformational Connection*; VCH: New York, 1989.
(28) Tonelli, A. E. *Macromolecules* **1991**, *24*, 1275.
(29) Choi, C.; Schilling, F. C.; Davis, D. D.; Song, K.; Tonelli, A. E., in preparation.