The Configuration Statistics of Random Poly(lactic acid) Chains. I. Experimental Results[1]

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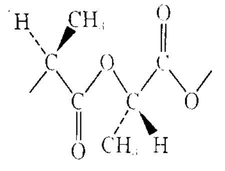
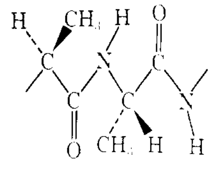
Received January 31, 1969

ABSTRACT: The characteristic ratio $C_\infty = \lim_{x\to\infty}(\langle r^2\rangle_0/xl_u^2)$ of poly(L-lactic acid) (where $\langle r^2\rangle_0$ is the mean-square end-to-end length of the chain comprising x units of structural length l_u = 3.70 Å), is *ca.* 2.0 according to light scattering and intrinsic viscosity $[\eta]$ measurements at 85° on C_6H_5Br solutions of two polymers of molecular weights 4.9 and 0.80 × 10^5. This result is less than one-fourth the value of C_∞ for analogous polypeptides. Temperature coefficients d ln$[\eta]$/dT of −5 and -7×10^{-3} deg^{-1} in C_6H_5Br and in $CHCl_3$, respectively, are indicative of an unusually large decrease in $\langle r^2\rangle_0$ with temperature. Smaller negative temperature coefficients are observed for stereoirregular poly(DL-lactic acids).

The configurational statistics of the poly(L-lactic acid) (P-L-LA) chain are of special interest because of the structural similarity of this molecule to poly-L-alanine (P-L-Ala). Like the amide group, the ester linkage is planar and *trans*,[2-4] owing to the partial double-bond character of the C—O skeletal bond. The polyester chain may therefore be treated as a succession of virtual bonds[4,5] of fixed length connecting successive α-carbon atoms. These virtual bonds are 3.70 Å in length,[4] compared with 3.80 Å for the corresponding virtual bonds in the polypeptide chain.[5] The geometrical description of the two chains is thus closely similar.


P-L-LA


P-L-Ala

There are important differences as well. The absence in P-L-LA of a hydrogen corresponding to the amide hydrogen in P-L-Ala is at once apparent. The residues in the former chain are thus deprived of the capability of forming hydrogen bonds with other residues. In the form of the random coil here considered, such hydrogen bonds do not play a significant role even for P-L-Ala. Hence, the absence of a pendant hydrogen at the position of the skeletal oxygen atom in P-L-LA is not a fact of major importance for our purposes. It does, however, eliminate certain steric interactions affecting rotations about the C^α—CO bond.[6,7] More important is the valence angle at the skeletal oxygen atom, which is 10° smaller than the corresponding angle at NH in the polypeptide chain. This difference enhances steric interactions hindering rotation about the O—C^α bond.[6,7] Finally, the dipole moment of the ester group is barely half of that of the amide. The dipolar interactions between neighboring residues, which play such an important role in polypeptides,[5] are thus diminished in the analogous polyester chain;[4,6] their effect on the conformation is nevertheless significant according to the analysis presented in the following paper.[7]

In the present paper we report the results of experiments on the characteristic ratio $\langle r^2\rangle_0/xl_u^2$ for P-L-LA, $\langle r^2\rangle_0$ being the mean-square end-to-end distance for the unperturbed chain comprising x units (virtual bonds) of length l_u = 3.70 Å. Also included are measurements yielding the temperature coefficients of intrinsic viscosities of P-L-LA, and also of the predominantly racemic (*i.e.*, atactic) polymer, which afford indications of the temperature coefficient of $\langle r^2\rangle_0$ and its dependence on stereoregularity. The full interpretation of these results, in light of conformational energy calculations, is withheld for the paper which follows.[7]

Experimental Section

Polymers. Polymer A was made available through the courtesy of C. H. Boehringer u. Sohn, Ingelheim am Rhein, West Germany. Its high melting point, 185–190°, and optical rotation, $[\alpha]_D$ −151°, confirmed its stereoregularity.

Polymer B was prepared from the cyclic dimer, L(+)-lactide, according to the method of Kleine and Kleine.[8] Lactide was prepared from L(+)-lactic acid (grade L-1, the Sigma Chemical Co.). The acid was heated at 120–140° under nitrogen at reduced pressure, *ca.* 15 mm, for 10 hr. A trace of zinc dust was added to the clear, viscous mass, and the cyclic dimer, L(+)-lactide, was gradually removed by sublimination with further heating at 200° at a pressure of 5 mm. Several recrystallizations of the sublimate from ethyl acetate yielded the pure product melting at 98°, $[\alpha]_D$ −270° in $CHCl_3$ at 25°.

The lactide was placed in dry toluene in the ratio of 1 g of the cyclic diester to 3 cc of dry toluene, and a trace of PbO was added. Care was exercised to avoid contamination by moisture. The solution was refluxed under dry

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[1] From the thesis submitted by A. E. Tonelli in fulfillment of the requirements for the degree of Doctor of Philosophy, Stanford University, 1968.

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[3] R. F. Curl, *J. Chem. Phys.*, **30**, 1529 (1959); J. M. Riveros and E. B. Wilson, Jr., *ibid.*, **46**, 4605 (1967).

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[6] P. J. Flory, "Statistical Mechanics of Chain Molecules," Interscience Publishers, New York, N. Y., 1969, Chapter VII.

[7] D. A. Brant, A. E. Tonelli, and P. J. Flory, *Macromolecules*, **2**, 228 (1969).

[8] J. Kleine and H. H. Kleine, *Makromol. Chem.*, **30**, 23 (1959).

Table I

Characteristics of Lactic Acid Polymers in Dilute Solutions

Polymer	$[\alpha]_D$ in $CHCl_3$ at 25°, deg	$[\eta]$, dl g^{-1} In $CHCl_3$ at 30°	$[\eta]$, dl g^{-1} In C_6H_5Br at 85°	$M_w \times 10^{-3}$	$A_2 \times 10^4$, cc mol g^{-2}
A	−151	2.63	1.38	490 ± 50	3.2 ± 0.3
B	−150		0.295	80 ± 10	3.5 ± 0.3
C	−90	0.473	0.277	(65)[a]	
D	−3	0.249	0.135	(25)[a]	

[a] Estimated from the intrinsic viscosity by extrapolation from the data for polymers A and B.

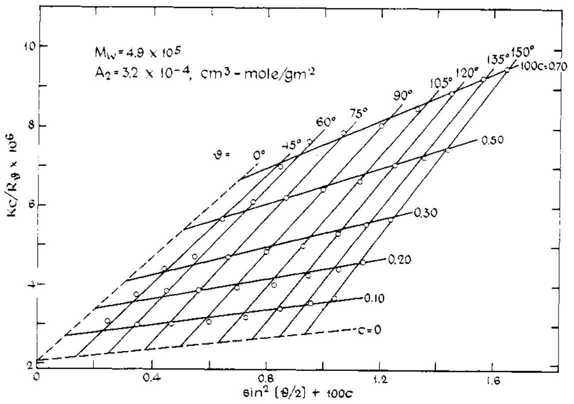

Figure 1. Light-scattering results for polymer A in C_6H_5Br at 85°. The concentration c is in grams per milliliter, R_ϑ is the reduced scattering intensity at angle ϑ, and $K = 2\pi^2(n\,dn/dc)^2/N_A\lambda^4$.

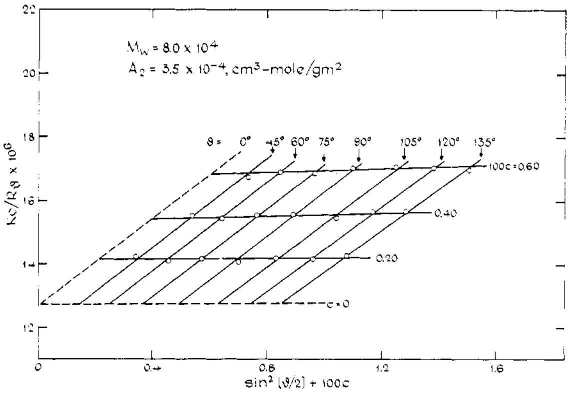

Figure 2. Light-scattering results for polymer B in C_6H_5Br at 85°.

nitrogen for 48 hr. Poly(L-lactic acid) crystallized from the solution upon cooling. It was removed by filtration, then dried at 80° under vacuum: mp 165–170°; $[\alpha]_D$ −150° in $CHCl_3$ at 25°. Kleine and Kleine[8] report the same rotation, −150°, for a polymer in which 98.5% of the units were L(+), from which we conclude that polymers A and B are stereoregular in like degree.

Samples C and D were prepared similarly, but without stringent exclusion of moisture. They were clear, viscous liquids. Their low softening points indicated racemization, which is confirmed by their smaller optical rotations; see Table I.

Solvents. Spectroquality chloroform and superior quality bromobenzene and *m*-cresol (Matheson Coleman and Bell) were used without further purification. They were filtered to remove suspended matter which would have interfered with the light scattering and viscosity measurements.

Intrinsic Viscosities. Viscosities of dilute polymer solutions were determined with Cannon–Ubbelohde viscometers, the temperature being controlled to ±0.01°. Flow times exceeded 200 sec. They were measured in triplicate. Results at several concentrations, determined in each instance from the weight of the sample and the density of the solvent at the temperature of the measurement, were extrapolated in the usual manner to obtain $[\eta] = \lim_{c \to 0}(\eta_{sp}/c)$.

Light Scattering. A SOFICA instrument, operated with unpolarized light of wavelength 5461 Å from a mercury vapor lamp, was used. Optical alignment was confirmed by observing the scattering envelope for pure benzene at 26°, and by carrying out measurements on a well-characterized sample of polystyrene dissolved in benzene.

P-L-LA is soluble at room temperature in only a few solvents such as $CHCl_3$, *m*-cresol, and dichloroacetic acid. None was found for which the refractive increment was sufficient for accurate determination of molecular weight and second virial coefficient. Bromobenzene, in which the polymer exhibits limited solubility above 50°, was eventually chosen as the solvent and light-scattering measurements were carried out at 85°. The hot solutions were filtered into the light scattering cells under dry nitrogen. Temperatures were maintained by circulating ethylene glycol from an external thermostat through the jacket surrounding the cell.

The refractive increment for P-L-LA in bromobenzene at 85° was determined with a Brice–Phoenix differential refractometer adapted for operation at controlled, elevated temperatures. The accuracy of the result, $dn/dc = -6.0\ (\pm 0.2) \times 10^{-2}$ cm³ g^{-1}, was limited by the low solubility of the polymer which precluded measurements above a concentration of about 0.8 g/100 cm³.

Optical Rotations. Molar optical rotations $[\alpha]_D$ were determined at 25° using a Zeiss polarimeter equipped with a monochromatic sodium D line source.

Results

Zimm plots of the light-scattering measurements on solutions of polymers A and B in bromobenzene at 85° are shown in Figures 1 and 2, respectively. Weight average molecular weights M_w and second virial coefficients A_2 deduced from the intercepts and slopes of the lines for scattering angle $\theta = 0$ are recorded in Table I, together with results of other measurements on these polymers. The slope of the line for $c = 0$ for polymer A in Figure 1 gives $\langle s^2 \rangle_z = 7.6\ (\pm 1.5) \times 10^4$ Å² for the z average of the squared radius of gyration. The dissymetry for polymer B (Figure 2) was too small for reliable determination of $\langle s^2 \rangle_z$.

The perturbation α of the mean dimensions of the chain may be estimated from the relation[9]

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(9) T. A. Orofino and P. J. Flory, *J. Chem. Phys.*, **26**, 1067 (1957).

$$A_2M/[\eta] = (2^{5/2}\pi N_A/3^3\Phi)\ln[1 + (\pi^{1/2}/2)(\alpha^2 - 1)] \quad (1)$$

where N_A is Avogadro's number and Φ is a constant approximately equal to[10] 2.6×10^{21} with $[\eta]$ expressed in deciliters per gram, and

$$\alpha^2 = \langle s^2\rangle/\langle s^2\rangle_0 \cong \langle r^2\rangle/\langle r^2\rangle_0 \quad (2)$$

$\langle s^2\rangle_0$ and $\langle r^2\rangle_0$ being the values for the unperturbed chain. Introducing A_2, M_w, and $[\eta]$ for polymer A in bromobenzene at 85° into eq 1, we obtain $\alpha^2 = 2.25$, or $\alpha = 1.5$. Thus $\langle s^2\rangle_0 = 7.6 \times 10^4/2.25 = 3.4 \times 10^4$ Å^2, and $\langle r^2\rangle_0 = 6\langle s^2\rangle_0 = 20 \times 10^4$ Å^2. The value of the characteristic ratio $C_x = (\langle r^2\rangle_0/xl_u^2)$ obtained in this manner for polymer A is 2.2 ± 0.4. In view of the degree of polymerization of the chain, this result may be identified with the limiting value C_∞ for $x \longrightarrow \infty$. It is to be noted that this approximate result is subject to vitiation by the molecular heterodispersity of the polymer. Inasmuch as the weight average $\langle s^2\rangle_w$, which should be used in conjunction with M_w, is smaller than $\langle s^2\rangle_z$ by an amount dependent upon the unknown degree of heterodispersity of the polymer, the foregoing result is to be regarded as an upper limit.

The characteristic ratio may be deduced from the intrinsic viscosity by resort to the relation

$$C_x = ([\eta]/\Phi M)^{2/3}/\alpha^2 x l_u^2 \quad (3)$$

where ϕ and l_u are assigned their respective values, 2.6×10^{21} and 3.70×10^{-8} cm, introduced above. The values of α for polymers A and B in bromobenzene at 85° are 1.5 and 1.35, respectively, according to eq 1. From eq 3 we obtain $C_x = 2.0 \pm 0.2$ and 1.8 ± 0.2 for polymers A and B, respectively. Agreement with the result obtained directly from $\langle s^2\rangle_z$ for polymer A is satisfactory; the difference is in the direction expected from failure to correct $\langle s^2\rangle_z$ for molecular heterodispersity. The values deduced from eq 3 are more reliable. Accordingly, we conclude that $C_\infty = 2.0 \pm 0.2$, this value being accepted as the limiting result for $x = \infty$, subject of course to the indicated experimental uncertainty. The characteristic ratio of P-L-LA is much lower than the value, *ca.* 9.0, found for analogous polypeptides.[11] We reserve the interpretation of this result, and the contrast it presents in comparison to structurally similar polypeptides, for the following paper.[7]

Intrinsic viscosities were determined at several temperatures for each of the polymers in bromobenzene and for three of them in chloroform. Measurements in the former solvent were carried out at 65, 75, and 85°; in the latter solvent, in which the polymer remains soluble at ordinary temperatures, the viscosities were determined over the range 25–50° in 5° intervals. Temperature coefficients obtained from slopes of the straight lines drawn through the experimental points are given in Table II. They are subject to errors of about 10%. Included in the second column are the fractions f_L of L(+)-lactic acid units in the polymer, as estimated from the optical rotations (see Table I) interpreted according to the results of Kleine and Kleine[8] cited above.

TABLE II
TEMPERATURE COEFFICIENTS OF INTRINSIC VISCOSITIES AND OF CHAIN DIMENSIONS

Polymer	f_L	$(\mathrm{d}\ln[\eta]/\mathrm{d}T) \times 10^3$		$(\mathrm{d}\ln\langle r^2\rangle_0/\mathrm{d}T) \times 10^3$ from results in C_6H_5Br
		In C_6H_5Br at *ca.* 75°	In $CHCl_3$ at *ca.* 35°	
A	0.99	−4.8	−7.1	−6
B	0.98	−5.6		−6
C	0.79	−3.6	−4.0	−4
D	0.51	−1.8	−2.8	−2

It will be observed that the temperature coefficients of $[\eta]$ are negative in all cases and large in magnitude. In chloroform, an exceptionally good solvent, they are even larger than in bromobenzene. The magnitudes of the temperature coefficients diminish with decrease in stereoregularity, but remain negative.

Equation 3 in conjunction with the well-known relationship

$$\alpha^5 - \alpha^3 = 3^3(2\pi)^{-3/2}(\bar{v}/N_AV_1)(\langle r^2\rangle_0/M)^{-3/2}M^{1/2}\psi_1 \times (1 - \Theta/T) \quad (4)$$

affords a basis for evaluating $\mathrm{d}\ln\langle r^2\rangle_0/\mathrm{d}T$ from $\mathrm{d}\ln[\eta]/\mathrm{d}T$ and the estimated values of α. (In eq 4, $\bar{v}$ is the partial specific volume of the polymer, V_1 is the molar volume of the solvent, ψ_1 is the entropy of dilution parameter, and Θ is the ideal temperature at which $A_2 = 0$ and $\alpha = 1$.) Equation 4 serves to relate α^2 to temperature, as is required if eq 3 is to be used to relate $\mathrm{d}\ln C_x/\mathrm{d}T = \mathrm{d}\ln\langle r^2\rangle_0/\mathrm{d}T$ to $\mathrm{d}\ln[\eta]/\mathrm{d}T$. The result obtained[12] is

$$\mathrm{d}\ln\langle r^2\rangle_0/\mathrm{d}T = \left(\frac{5}{3} - \frac{1}{\alpha^2}\right)\frac{\mathrm{d}\ln[\eta]}{\mathrm{d}T} - \left(1 - \frac{1}{\alpha^2}\right)\left[\frac{\mathrm{d}\ln(v^2/V_1)}{\mathrm{d}T} + \frac{\Theta}{T(T - \Theta)}\right] \quad (5)$$

The quantities in brackets in the second term of eq 5 may be neglected in comparison with the large values of $-\mathrm{d}\ln[\eta]/\mathrm{d}T$. Accordingly, we take

$$\mathrm{d}\ln\langle r^2\rangle_0/\mathrm{d}T \approx [(5/3) - (1/\alpha^2)]\,\mathrm{d}\ln[\eta]/\mathrm{d}T \quad (6)$$

Values of the temperature coefficient of $\langle r^2\rangle_0$ calculated according to this relation are listed in the last column of Table II. In partial confirmation of the results thus obtained, the same value is found for the two stereoregular polymers A and B ($f_L \approx 1$), a sixfold difference in chain lengths notwithstanding. Smaller values are obtained for stereoirregular polymers C and D. The unexpectedly large temperature coefficients found for P-L-LA in halogenated solvents is discussed in the following paper.[7]

Acknowledgment. This work was supported by the Air Force Office of Scientific Research, Contract No. AF 49(638)-1341.

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(11) D. A. Brant and P. J. Flory, *J. Amer. Chem. Soc.*, **87**, 2788, 2791 (1965); see also ref 6.

(12) P. J. Flory, A. Ciferri, and R. Chiang, *J. Amer. Chem. Soc.*, **83**, 1023 (1961).