The Configurational Statistics of Random Poly(lactic acid) Chains. II. Theory

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ABSTRACT: The conformational energy of the L-lactyl residue of poly(L-lactic acid), P-L-LA, is calculated as a function of rotation angles φ and ψ about the O—C$^\alpha$ and C$^\alpha$—C bonds, respectively, the ester bond being planar *trans*. Methods of calculation correspond to those applied previously to various polypeptides. Despite the close structural similarity of P-L-LA to poly-L-alanine, differences in the conformational energy result from the difference of $-10°$ between the COC$^\alpha$ angle compared with the CNC$^\alpha$ angle of the latter chain. Dipolar interactions, though much smaller than in the polypeptides, are significantly important. The conformational energy contour map over φ and ψ is dominated by four well-defined minima. The two of lowest energy, situated approximately at the g^+t and g^+g^+ conformations, suffice for interpretation of the configurational characteristics of the chain. The calculated characteristic ratio agrees very well with that observed. The temperature coefficient d ln $\langle r^2\rangle_0/dT$ is predicted to be negative, but much smaller in magnitude than experiments indicate.

Structural similarities between poly(L-lactic acid) and poly-L-alanine have been cited in the preceding paper.[1] Methods applied previously[2,3] to the successful interpretation of the configurational characteristics of polypeptides may readily be adapted therefore to the poly(lactic acid) chain. Conformational rigidity of the amide linkage ensures rotational independence of neighboring amino acid residues in polypeptides, and this circumstance reduces the statistical mechanical problem to one of deducing partition functions for individual residues.[2-4] These functions were evaluated[2,3] from approximate conformational energy calculations which take into account the rotational interdependence about bonds within a given residue. Conformational energy functions originally established[2,3] to account for the unperturbed coil dimensions of a series of four peptide homopolymers were applied subsequently, without readjustment of parameters, to the calculation of the configurational properties of other peptide homopolymers,[5] copolymers,[6,7] and oligopeptides.[8] Modified to account for the possibility of intramolecular hydrogen bonding, the same functions have been used to calculate the properties of polypeptide helices.[9]

With modifications described below to render the previous treatment appropriate for the lactyl residue, the methods used to establish the connection between polypeptide backbone structure and chain configuration are employed here to treat poly(L-lactic acid) and poly(DL-lactic acid).

Theoretical Treatment

Structural Parameters. Microwave spectroscopic analysis of methyl formate[10] and electron diffraction studies of methyl formate and methyl acetate[11] provide the most complete structural data for the ester group. Corroboration of these results is found in other work.[12,13] A fully extended segment of the poly(L-lactic acid) chain with all ester groups *trans* is shown in Figure 1. Rigid planarity of the ester group C$^\alpha$COOC$^\alpha$ in its *trans* configuration is assumed; virtual exclusion of the *cis* configuration for the ester bond is indicated by the infrared spectral data[14] and the structural analyses previously cited.[10-12] Bond lengths and angles have been assigned by considering values determined in structural analyses of esters[10,11] and the accepted standard values of these parameters in organic molecules.[15] These quantities are given in Table I.

All bond angles and bond lengths given in Table I are taken to be constant for the calculations presented here. Thus configurations of the chain are defined completely in terms of the torsional angles φ_i, ψ_i associated with each lactyl residue. Torsional rotations are measured from the *trans* conformation depicted for each bond in Figure 1; torsional angles are

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(1) A. E. Tonelli and P. J. Flory, *Macromolecules*, **2**, 225 (1969).

(2) D. A. Brant and P. J. Flory, *J. Amer. Chem. Soc.*, **87**, 2791 (1965).

(3) D. A. Brant, W. G. Miller, and P. J. Flory, *J. Mol. Biol.*, **23**, 47 (1967).

(4) P. J. Flory, "Statistical Mechanics of Chain Molecules," Interscience Publishers, New York, N. Y., 1969, Chapter VII.

(5) P. R. Schimmel and P. J. Flory, *Proc. Nat. Acad. Sci., U.S.*, **58**, 52 (1967).

(6) W. G. Miller, D. A. Brant, and P. J. Flory, *J. Mol. Biol.*, **23**, 67 (1967).

(7) P. R. Schimmel and P. J. Flory, *ibid.*, **34**, 105 (1968).

(8) P. J. Flory and P. R. Schimmel, *J. Amer. Chem. Soc.*, **89**, 6807 (1967).

(9) D. A. Brant, *Macromolecules*, **1**, 291 (1968).

(10) R. F. Curl, Jr., *J. Chem. Phys.*, **30**, 1529 (1959).

(11) J. M. O'Gorman, W. Shand, Jr., and V. Schomaker, *J. Amer. Chem. Soc.*, **72**, 4222 (1950).

(12) J. M. Riveros and E. B. Wilson, Jr., *J. Chem. Phys.*, **46**, 4605 (1967).

(13) T. Ukaji, *Bull. Chem. Soc. Jap.*, **32**, 1266, 1270, 1275 (1959)

(14) T. Miyazawa, *ibid.*, **34**, 691 (1961).

(15) H. J. M. Bowen and L. E. Sutton, Ed., "Tables of Interatomic Distances and Configuration in Molecules and Ions," The Chemical Society, London, 1958; Supplement, 1965.

TABLE I

STRUCTURAL PARAMETERS[a]

Bond length, Å	Bond angle, deg
O—C^α, 1.44	O—C^α—C, 110
C^α—C, 1.52	C^α—C—O, 114
C—O, 1.34	C—O—C^α, 113
C═O, 1.22	C^α—C═O, 121
C^α—C^β, 1.54	O—C^α—C^β, 110
C^α—H^α, 1.07	O—C^α—H^α, 110

[a] $\eta = 18.9°$; $\xi = 19.9°$.

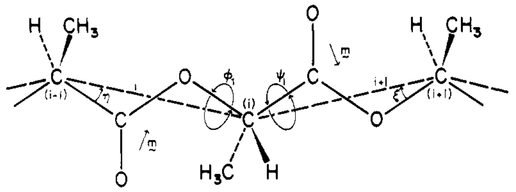

Figure 1. Diagram showing L-lactyl residue *i*, portions of residues *i* − 1 and *i* + 1, and virtual bonds (dashed) *i* and *i* + 1 of a P-L-LA chain. The dipole moments are indicated by arrows **m**.

taken to be positive for right-handed rotations. Neglect of bond stretching and bond angle bending is justified for random chains because the almost equal probability for occurrence of positive and negative distortions from the equilibrium values nullifies their importance.[4]

Curl's microwave structural analysis[10] of methyl formate locates the molecular dipole moment approximately on the line joining the carbonyl and ester oxygens and directed so as to make an angle of 39° with the carbonyl bond. The magnitude is 1.77 D, a value confirmed by results for other esters.[16] On the other hand, vector addition of conventional bond dipole moments[17] for each of the bonds C═O, C—O, O—C^α yields a resultant virtually parallel with the C═O bond. If, however, we attribute a moment of 2.05 D to the C═O bond (compared to the conventional value 2.3 D) and the usual value 0.75 D to the O—C^α bond while assuming that any inherent moment for the intervening C—O bond is effectively accounted for by the foregoing representation of the polarization of C═O and O—C^α, the resultant group moment makes an angle of 21° with C═O and has the observed magnitude 1.77 D. This moment, represented in the point monopole approximation[3] by four partial charges assigned to the participating atoms (see Table II), is employed to represent the poly(L-lactic acid) backbone polarity in the calculations which follow. It is represented by the vector **m** in Figure 1, where it has been located at the approximate center of charge for the four partially charged atoms. Adopting coordinate basis systems described previously in the treatment of polypeptide chains,[2] the coordinates of the center of charge are found to be 0.126, 0.545, 0.0 in the reference frame associated with the skeletal C—O bond, in which the group dipole moment vector has components 1.47, −0.99, 0.0.

TABLE II

ATOMIC AND GROUP PARAMETERS

Atom/group	r_j^0, Å	α_j, Å^3	N_j	δ_j, electronic charges
H^α	1.20	0.42	0.9	0.0
C	1.70	1.23	5	0.350
C^α	1.70	0.93	5	0.109
O (ester)	1.50	0.70	7	−0.109
O (carbonyl)	1.50	0.84	7	−0.350
CH_3	1.80–2.00	1.77	7	0.0

Conformational Potential Functions. Conformational energies have been evaluated using the function[3]

$$V(\varphi, \psi) = V_\varphi(\varphi) + V_\psi(\psi) + \sum_{jk}[V_{r,jk}(\varphi, \psi) + V_{l,jk}(\varphi, \psi) + V_{c,jk}(\varphi, \psi)] \quad (1)$$

Terms $V_\varphi(\varphi)$ and $V_\psi(\psi)$ account for the potential barriers to torsion about bonds O—C^α and C^α—C, respectively, which arise from electronic features of the chemical bonding and are assumed independent of van der Waals or coulombic interaction of nonbonded substituents on these atoms.[2,18] Contributions to the energy from interactions of nonbonded atoms or groups j and k comprise the remaining terms: $V_{r,jk}$ is the van der Waals repulsion; $V_{l,jk}$ is the van der Waals (London) attraction; $V_{c,jk}$ is the coulombic interaction of partially charged atoms. The summation in eq 1 is carried over all atoms the mutual separation of which is governed only by φ_i and/or ψ_i; rotational interdependence of φ_i and ψ_i is thereby acknowledged.

Inherent torsional barriers for both of the bonds O—C^α and C^α—C probably are threefold, with the conformation shown in Figure 1 corresponding to one of the minima for each bond. Other minima occur at φ_i, ψ_i = 120°, 240°. Barrier heights V_φ^0 and V_ψ^0 are anticipated to be near 1 kcal mol^{-1}. Evidence for these conclusions in the case of the C^α—C bond has already been presented,[2] and we take $V_\psi(\psi) = (V_\psi^0/2)(1 - \cos 3\psi)$. Torsional potentials found experimentally for bonds of the type O—C^α in methyl formate[10] and ethyl formate[12] confirm the occurrence of a minimum at $\varphi = 0$. Hence, we let $V_\varphi(\varphi) = (V_\varphi^0/2)(1 - \cos 3\varphi)$. In the formate esters the observed barrier heights for O—C^α rotations are 1.1–1.2 kcal mol^{-1}. Curl[10] argues, however, that this value in methyl formate may reflect a significant contribution from van der Waals interaction of the carbonyl oxygen with the methyl hydrogens.

The energy of interaction between dipole moments of ester groups which are nearest neighbors is evaluated in the point monopole approximation[3] using the terms $V_{c,jk} = 332\delta_j\delta_k/\epsilon r_{jk}$. Partial charges δ_j consistent with bond dipoles and bond lengths quoted above are given in Table II. Here r_{jk} is the internuclear distance for atoms j and k, ϵ is the local dielectric constant, and the numerical factor produces energies in kilocalories per mole for distances expressed in ångström units and

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(16) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Co., San Francisco, Calif., 1963.

(17) C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, pp 244–245.

(18) R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, **42**, 2209 (1965).

partial charges in fractions of an electronic charge. Internuclear distances are readily evaluated functions of the angles φ_i, ψ_i by methods previously described.[2] From experience with conformational energy calculations for polypeptides, we anticipate that a value of ϵ close to the high-frequency value for solid esters or polyesters will be appropriate, *i.e.*, 2.5–4.0. A similar choice of ϵ for the polypeptides has invariably produced the best agreement between theory and experiment.[2,9,19] The electric field intensity is greatest in the region between the two interacting dipoles, and a value of ϵ reflecting appreciable contributions from bulk solvent would be expected to be incorrect on this basis alone.

The parameters c_{jk} of the London terms $V_{l,jk} = -c_{jk}/r_{jk}^6$ are evaluated in the usual manner from atomic polarizabilities α_j and the effective numbers of valence electrons N_j using the Slater–Kirkwood equation.[20] With polarizabilities expressed in Å^3 and London parameters c_{jk} in kcal Å^6 mol^{-1}, this equation is

$$c_{jk} = \frac{360\alpha_j\alpha_k}{\left(\dfrac{\alpha_j}{N_j}\right)^{1/2} + \left(\dfrac{\alpha_k}{N_k}\right)^{1/2}} \tag{2}$$

The polarizabilities listed in Table II are chosen in accordance with assignments suggested by Ketelaar[21] with due recognition of enhanced polarizability arising from the carbonyl double bond. A double bond adds about 0.58 Å^3 to the molecular polarizability.[21] Values given by Ketelaar for hydroxyl, ether, and carbonyl oxygens suggest that 0.22 Å^3 of this double bond contribution may be taken to reside on the oxygen of the carbonyl group. Of the remaining 0.36 Å^3, an additional 0.30 Å^3 is apportioned to the carbonyl carbon relative to aliphatic carbon, and 0.06 Å^3 is assigned to the ester oxygen relative to aliphatic (ether) oxygen in recognition of the partial double bond character of the ester linkage.[10] Values for the effective numbers of valence electrons, given also in Table II, are chosen following Pitzer[20] as described previously.[2]

A firm theoretical basis upon which to choose the form of the van der Waals repulsion term is lacking, and existing experimental evidence does not yield a clear choice in this regard. The form $V_{r,jk} = a_{jk}/r_{jk}^{12}$ is selected here in consonance with frequent practice; comparison of this potential with the alternative Buckingham form $V_{r,jk} = a_{jk}\exp(-b_{jk}r_{jk})$ is offered elsewhere.[3] The scale factors a_{jk} are always evaluated by requiring the complete potential function, or more commonly some component thereof, to conform to experimentally determined criteria. In favorable cases, *e.g.*, the alkenes, alkanes, and cycloalkanes, for which extensive and accurate experimental conformational energies and geometries are known, the requirement may be imposed that the complete potential function reproduce these experimental quantities.[22–24]

For most systems, including the poly(lactic acid) chain and low molecular weight ester analogs, experimental data of this sort are scarce or lacking altogether. The difficulties consequently confronting evaluation of the a_{jk} are compounded by the occurrence in the present molecules of longer range dipolar interactions. The usual procedure in such cases has been to force the nonbonded interaction terms (*i.e.*, van der Waals and dipolar terms) to display a minimum at the normal equilibrium contact distances for atoms j and k in molecular crystals. To achieve this end it is not sufficient, as is sometimes supposed, merely to minimize the individual atom pair potentials at the sum of their respective crystallographic van der Waals radii, owing to the existence of interactions, principally attractive, of other nearby atoms attached in covalent connection.[3,23,25] These additional interactions will inevitably produce minima in the total potential function for interaction of two groups of connected atoms at distances less than the combined van der Waals radii of abutting atom pairs, if the nonbonded potential functions for individual atom pairs have been so minimized. It has been shown[3] by considering electrically neutral groups of partially charged atoms that the role of neighboring atoms can be taken reasonably into account if the parameters a_{jk} are fixed by requiring the van der Waals functions $V_{jk} = V_{r,jk} + V_{l,jk}$ for each atom pair to be minimized at a distance 0.20 Å greater than the combined van der Waals radii of atoms j and k. This procedure is adopted here to establish the parameters a_{jk}.

Values of the van der Waals radii[26] for the atoms of the lactyl residue are tabulated in Table II. The rotation angle about the C$^\alpha$—C$^\beta$ bond is not subject to systematic variation in the present calculations; hence, the β-methyl group is taken as spherical, and its van der Waals radius is treated as a variable parameter. The range of $r_{CH_3}{}^0$ quoted in Table II is generally below that accepted for methyl and methylene, 2.00 Å, in recognition of the minimization of steric overlaps involving methyl hydrogens which can be achieved by adjustment of the angle of rotation about the C$^\alpha$—C$^\beta$ bond.

Configurational Statistics. Structural features assigned above render the distance between adjacent α carbons constant. In analogy with the polypeptides the chain may consequently be treated as a sequence of independent virtual bonds of length 3.70 Å, and these are shown as dashed lines in Figure 1. Angles η and ξ describing the mutual orientation of virtual and chemical bonds are defined in Figure 1, and the respective values are given in Table I. For homopolymeric species comprising x virtual bonds of length l_u the characteristic ratio $C_x = \langle r^2\rangle_0/xl_u{}^2$ of the mean square unperturbed end-to-end distance $\langle r^2\rangle_0$ is given by[2,6]

$$C_x = \left\{(\mathbf{E} + \langle\hat{\mathbf{T}}_i\rangle)(\mathbf{E} - \langle\hat{\mathbf{T}}_i\rangle)^{-1} - (2/x)(\langle\hat{\mathbf{T}}_i\rangle - \langle\hat{\mathbf{T}}_i\rangle^{x+1})(\mathbf{E} - \langle\hat{\mathbf{T}}_i\rangle)^{-2}\right\}_{11} \tag{3}$$

where $\mathbf{E}$ is the identity matrix of order 3 and $\langle\hat{\mathbf{T}}_i\rangle$ is the averaged matrix $\mathbf{T}_i(\varphi_i, \psi_i, \theta, \xi, \eta)$ which relates coordinate bases affixed to adjacent virtual bonds;

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(19) T. Ooi, R. A. Scott, G. Vanderkooi, and H. A. Scheraga, *J. Chem. Phys.*, **46**, 4410 (1967).

(20) K. S. Pitzer in "Advances in Chemical Physics," I. Prigogine, Ed., Vol. II, Interscience Publishers, New York, N. Y., 1959, p 59.

(21) J. Ketelaar, "Chemical Constitution," Elsevier Publishing Co., New York, N. Y., 1958, p 91.

(22) A. Abe, R. L. Jernigan, and P. J. Flory, *J. Amer. Chem. Soc.*, **88**, 631 (1966).

(23) J. B. Hendrickson, *ibid.*, **89**, 7036 (1967).

(24) J. E. Mark, submitted for publication.

(25) N. L. Allinger, M. A. Miller, F. A. VanCatledge, and J. A. Hirsch, *J. Amer. Chem. Soc.*, **89**, 4345 (1967).

(26) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).

the subscript on the brackets designates the required matrix element. Owing to rotational independence of neighboring residues,[2,3] it suffices to obtain the statistical mechanical average over the conformation space of residue i given by[7,8]

$$\langle \hat{\mathbf{T}}_i \rangle = \frac{\int_0^{2\pi}\int_0^{2\pi} \hat{\mathbf{T}}_i(\varphi_i, \psi_i, \theta, \xi, \eta) \exp[-V(\varphi_i, \psi_i)/RT]\, d\varphi_i d\psi_i}{\int_0^{2\pi}\int_0^{2\pi} \exp[-V(\varphi_i, \psi_i)/RT]\, d\varphi_i d\psi_i} \tag{4}$$

The stipulated integrations are invariably approximated by summation over an appropriate set of discrete conformations.[2,5,8]

Chain dimensions of random, Markoffian, and ordered copolymers of stereoisomeric lactic acids are subject also to calculation by methods established to treat peptide copolymers.[6] In particular, for random copolymers of L- and D-lactic acid occurring in proportions f_L and $f_D = 1 - f_L$, respectively, C_x is calculated using eq 3 with $\langle \hat{\mathbf{T}}_i \rangle$ replaced by $\langle \hat{\mathbf{T}} \rangle$ where

$$\langle \hat{\mathbf{T}} \rangle = f_L \langle \hat{\mathbf{T}}_L \rangle + f_D \langle \hat{\mathbf{T}}_D \rangle \tag{5}$$

The matrix $\langle \hat{\mathbf{T}}_D \rangle$ is obtained immediately from $\langle \hat{\mathbf{T}}_L \rangle$, specified in eq 4, by changing the signs of elements 13, 23, 31, and 32 of the latter matrix.[6]

The unperturbed mean square dipole moment of the P-L-LA chain may be calculated from eq 4, 6, and 7.[4,8]

$$\langle \mu^2 \rangle_0 = [2\ 0\ 0\ 0\ 0] \prod_{i=1}^{x} \mathcal{G}_i \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} \tag{6}$$

$$\mathcal{G}_i = \begin{bmatrix} 1 & \mathbf{m}^{\mathrm{T}}\langle \hat{\mathbf{T}} \rangle & m^2/2 \\ \mathbf{0} & \langle \hat{\mathbf{T}} \rangle & \mathbf{m} \\ 0 & \mathbf{0} & 1 \end{bmatrix}_i \tag{7}$$

The index $i = 1, 2, \cdots x$ is understood to apply to **m**, m, and $\hat{\mathbf{T}}$ which appear in the 5 × 5 matrix $\mathcal{G}_i$. Null matrices **0** are of orders required to conform. Limits on i differ from those of Flory and Schimmel[8] because the P-L-LA chain is not zwitterionic, and only the ester group dipoles **m** are taken into account. Representation of **m** in the coordinate system of a virtual bond is assumed in the formulations of eq 6 and 7. In this reference frame the components of **m** become 1.07, −1.41, 0.

Results and Discussion

Calculations of Unperturbed Dimensions. Calculations of the unperturbed dimensions of P-L-LA were carried out using eq 1, 3, and 4 and parameters given in Tables I and II. Interaction energies for all atom pairs whose mutual separation is governed only by φ_i and/or ψ_i were included in the sum in eq 1. The parameters $r_{\mathrm{CH_3}}{}^0$, ϵ, $V_\varphi{}^0$, and $V_\psi{}^0$ were varied throughout reasonable ranges to assess the sensitivity of the calculated dimensions to uncertainties in the values finally chosen. The averaged transformation matrix $\langle \hat{\mathbf{T}}_L \rangle$ was calculated by replacing the integrations in eq 4 by summation over 144 terms evaluated at intervals of 30° in φ_i and ψ_i.[2] An asymptotic theoretical value $C_\infty = 2.13$, in good agreement with the experimental result 2.0 ± 0.2,[1] is obtained for the following "final" values of the variable parameters: $r_{\mathrm{CH_3}}{}^0 = 1.90$ Å, $\epsilon = 3.0$, $V_\varphi{}^0 = V_\psi{}^0 = 1.0$ kcal mol^{-1}. Parameters of the final van der Waals potential functions are summarized in Table III.

TABLE III
FINAL VAN DER WAALS POTENTIAL FUNCTIONS

$$V_{jk} = a_{jk}/r_{jk}{}^{12} - c_{jk}/r_{jk}{}^6$$

j	k	$a_{jk} \times 10^{-5}$, kcal Å^{12} mol^{-1}	c_{jk}, kcal Å^6 mol^{-1}
H$^\alpha$	H$^\alpha$	0.717	46.4
H$^\alpha$	C	7.01	158
H$^\alpha$	C$^\alpha$	5.59	126
H$^\alpha$	O (ester)	3.15	106
H$^\alpha$	O (carbonyl)	3.66	123
H$^\alpha$	CH$_3$	14.6	226
C	C	59.9	550
C	C$^\alpha$	48.3	444
C	O (ester)	29.5	382
C	O (carbonyl)	34.1	442
C	CH$_3$	118	787
C$^\alpha$	C$^\alpha$	39.3	361
C$^\alpha$	O (ester)	24.3	314
C$^\alpha$	O (carbonyl)	28.0	362
C$^\alpha$	CH$_3$	95.7	636
O (ester)	O (ester)	15.0	279
O (ester)	O (carbonyl)	17.2	320
O (ester)	CH$_3$	59.4	546
O (carbonyl)	O (carbonyl)	19.7	367
O (carbonyl)	CH$_3$	68.8	632
CH$_3$	CH$_3$	230	1125

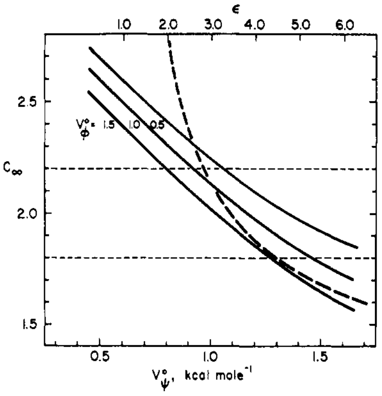

Figure 2. The characteristic ratio C_∞ calculated for P-L-LA as a function of $V_\psi{}^0$ (solid curves) for the three values of $V_\varphi{}^0$ indicated (in kilocalories per mole), with the $\epsilon = 3.0$ and $r_{\mathrm{CH_3}}{}^0 = 1.90$ Å in each case. The dashed curve shows C_∞ as a function of the effective dielectric constant ϵ (upper scale) with $V_\varphi{}^0 = V_\psi{}^0 = 1$ kcal mol^{-1} and $r_{\mathrm{CH_3}}{}^0 = 1.90$ Å. Horizontal dashed lines indicate limits of the experimental range for C_∞ according to results of the preceding paper.[1]

Whereas the calculated dimensions of P-L-Ala depend rather strongly on the choice of $r_{\mathrm{CH_3}}{}^0$, this is not found for the present polymer. The calculated value of C_∞ varies in the range 2.13–2.16 as $r_{\mathrm{CH_3}}{}^0$ varies from 1.80 to 2.00 Å, with other variable parameters fixed as above. The sensitivity of the calculated value of C_∞ to ϵ with other variable parameters assigned their final values is shown by the dashed line in Figure 2.

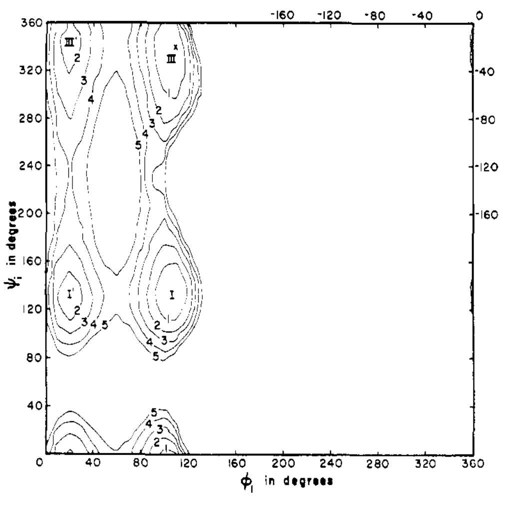

Figure 3. The conformational energy map for the L-lactyl residue calculated as described in the text. Contours are drawn at intervals of 1.0 kcal mol^{-1} relative to the lowest minimum at × in domain III. Dipolar interactions are included.

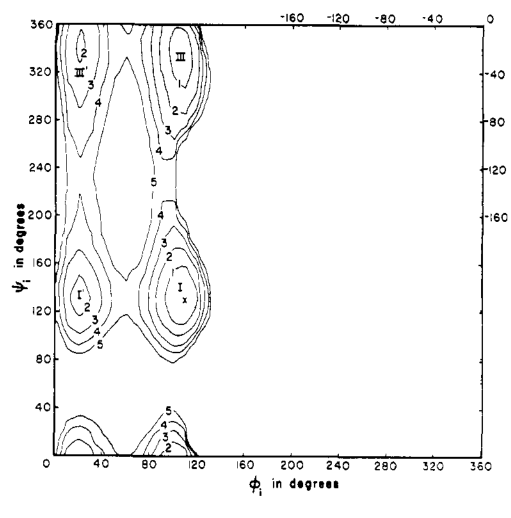

Figure 4. The conformational energy contour map for the L-lactyl residue calculated with omission of dipolar interactions. The lowest minimum occurs at × in domain I.

The asymptotic value for $\epsilon = \infty$, *i.e.*, for no dipolar interactions, is 1.24, which is less than the result, 1.92, for free rotation about the O—C$^\alpha$ and C$^\alpha$—C bonds. The influence of dipolar interactions on the configuration of P-L-LA is thus qualitatively similar to their effect in the case of the polypeptide chain. The influence of dipolar interactions will be interpreted in the discussion to follow. Figure 2 shows also a family of curves giving C_∞ as calculated with $r_{\mathrm{CH_3}}{}^0 = 1.90$ Å and $\epsilon = 3.0$ for several choices of the parameters $V_\varphi{}^0$ and $V_\psi{}^0$. It is evident that increasing either $V_\varphi{}^0$ or $V_\psi{}^0$ leads to a reduction in C_∞ with the more pronounced effect being observed for changes in $V_\psi{}^0$, the intrinsic barrier to rotation about the bond C$^\alpha$—C. This effect is subject to interpretation in terms of the conformational energy maps presented below.

Conformational Energy Contour Diagrams. The total conformational energy was recalculated according to eq 1 at intervals of 10° in φ_i and ψ_i using the parameters given in Tables I and II in conjunction with the "final" values of the variable parameters, $r_{\mathrm{CH_3}}{}^0$, ϵ, $V_\varphi{}^0$, and $V_\psi{}^0$. A contour diagram of the energy thus determined is plotted against φ_i and ψ_i in Figure 3. Contours are drawn at intervals of 1 kcal mol^{-1} relative to the lowest minimum marked ×; contours above 5 kcal mol^{-1} are not shown. Four distinct energy minima appear, and these are designated I, I', III, and III' in extension of the scheme used previously[3] for enumeration of the minima in the corresponding diagram for the L-alanyl residue. The calculated energies at these minima are 0.08, 1.40, 0, and 1.52 kcal mol^{-1}, respectively. Energetically acceptable conformations do not exist for which $130° < \varphi_i < 360°$. The region centered at $\varphi_i = 180°$ is excluded by conflict of adjacent carbonyl groups, and around $\varphi_i = 300°$ intolerable steric interference of (CO)$_{i-1}$ with (CH$_3$)$_i$ arises (see Figure 1). Allowed conformers do occur for the L-Ala residue in the upper right-hand quadrant of the corresponding diagram[3] near the line $\varphi_i = 240°$, because the angle C—N—C$^\alpha$ exceeds by 10° the C—O—C$^\alpha$ angle in the lactyl residue, and repulsions which exclude this region to polymers of the latter residue are reduced substantially in the former. Moderate steric conflict of (CO)$_{i-1}$ with H_i, in conjunction with a maximum in $V_\varphi(\varphi)$, produces a ridge at $\varphi_i = 60°$ which divides the allowed regions into the subsidiary minima at I, I' and III, III'. A similar ridge in the L-Ala map[3] is much less pronounced because of the larger bond angle at the nitrogen atom.

Throughout the accessible range of φ_i, the energy is comparatively insensitive to ψ_i. Only near $\psi_i = 60°$ does the energy become excessive owing to repulsion of (CH$_3$)$_i$ and O$_{i+1}$, and this region of high energy is narrower than its counterpart on the L-Ala map[3] because of the absence of an amide hydrogen atom. A second consequence of this structural difference is the absence of a high-energy swath near $\psi_i = 180°$ which occurs in polypeptides owing to interaction of neighboring amide groups.

That the coulombic energy effects little discrimination within the sterically allowed conformation space is apparent from comparison of Figure 3 with the contour diagram in Figure 4, which was calculated with neglect of dipolar interactions. Minima I' and III' in Figure 4 retain the relationships respective to I and III evident in Figure 3. In Figure 4, however, the marginal stability of III relative to I, seen in Figure 3, is reversed, and this preference for the more compact conformations in minimum I in the absence of dipolar interactions accounts for the previously cited dependence of C_∞ upon the value of the dielectric constant used in the calculations. Relocation of the absolute minimum from III to I with suppression of coulombic terms parallels the results obtained for the polypeptides.[3] The larger dipole moment, 3.7 D, and its somewhat different orientation in the latter polymer produce a greater difference between the coulombic energies at minima I and III. Consequently, the calculated unperturbed dimensions of polypeptides are affected to a greater degree by inclusion of the coulombic interaction. Nevertheless, even the marginal energy differences between minima I and III for P-L-LA in Figures 3 and

4 obviously have an important effect upon the calculated value of C_∞, and they will be shown below to affect also the temperature coefficient of C_∞.

It is evident from comparison of Figures 3 and 4 that the principal features of these diagrams arise from van der Waals interactions of constituents of the P-L-LA chain. Thus, the +20° displacement of minima I′ and III′ from the standard *trans* (*t*) position for O—C$^\alpha$ rotation at $\varphi_i = 0$ is attributable to steric interaction of $(CO)_{i-1}$, with $(CH_3)_i$, while repulsions of neighboring carbonyls produce the somewhat smaller negative displacement of the O—C$^\alpha$ *gauche*-plus (g^+) state to $\varphi_i = 105°$ in minima I and III. Steric interaction of $(CH_3)_i$ with O_{i+1} serves to displace the *t* state of ψ_i to about $\psi_i = -20°$ in minima III and III′. A smaller positive displacement of the g^+ state to about $\psi_i = 130°$ in I and I′ arises from repulsion between the same groups. The conventional g^- state for rotation about C$^\alpha$—C near $\psi_i = 240°$ is suppressed by repulsive interaction of *cis* $(CO)_i$ and $(CH_3)_i$.

Inasmuch as minima III and III′ are displaced by at least −20° from the minimum in V_ψ at $\psi = 360°$, and minima I and I′ at $\psi_i = 130°$ are displaced only 10° from $\psi_i = 120°$ where $V_\psi = 0$, an increase in V_ψ^0 raises the energy of conformations in the former minima relative to the energy of those in the latter. Hence, the population of the compact conformations in I is increased at the expense of the more extended conformations of minima III and III′. Note also that an increase in the population of I′ at the expense of III′ serves to reduce the dimensions but that interchange between I′ and III has little effect in this regard. The dependence of C_∞ on V_ψ^0 depicted in Figure 2 is thus explained. The maximum in V_φ^0 along the vertical line at $\varphi = 60°$ in Figure 3 separates the primed from the unprimed minima. Because the displacement of I′ and III′ from $\varphi_i = 0$ exceeds that of I and III from $\varphi_i = 120$, minima I′ and III′ are affected to a greater degree by V_φ^0. Consequently, an increase in V_φ^0 raises the population of I relative to that of the more extended I′ and III′. Since dissymmetry in the location of minima with respect to $\varphi_i = 60°$ is not great, but especially since the primed minima are not heavily populated relative to the unprimed owing to the energy differential, C_∞ is much less dependent on V_φ^0 than on V_ψ^0, as is shown in Figure 2.

Rotational Isomeric State Treatment. The occurrence of four discrete energy minima in the conformation space of the lactyl residue, corresponding approximately to the conventional *tt*, tg^+, g^-t, and g^+g^+ states, suggests treatment of this chain in the rotational isomeric state approximation with its attendant conceptual simplicity. Contributions to the residue partition function from regions within the 3 kcal mol^{-1} contours encircling each of the four minima in Figure 3 are expressed by the ratios z_M/z entered in the second column of Table IV. Thus z is the total partition function appearing as the denominator in eq 4. It has been evaluated by summation in 10° intervals over the entire range of φ and ψ; z_M is the contribution from the domain of the minimum designated M from points not exceeding 3 kcal mol^{-1}. Contributions from regions of higher energy comprise only 1.8% z. Minima I and III alone account for 90.2% z. Statistical weights w_I, etc., representing $z_I/(z_I + z_{III} + z_{I'} + z_{III'})$, etc., for each of the four minima of Figure 3 are given in the last column of Table IV.

TABLE IV
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

Four average transformation matrices, one associated with each of the four minima, have been calculated by methods analogous to those described above for implementation of eq 4; *i.e.*, terms were summed at 10° intervals of φ and ψ within the 3 kcal mol^{-1} contours of each domain. These averaged matrices $\langle \mathbf{T}_I\rangle$, $\langle \mathbf{T}_{III}\rangle$, $\langle \mathbf{T}_{I'}\rangle$, and $\langle \mathbf{T}_{III'}\rangle$ differ negligibly from matrices $\hat{\mathbf{T}}_i(\varphi_i, \psi_i, \theta, \xi, \eta)$ evaluated at the four locations $(\varphi_i, \psi_i)_I = 107, 134°$; $(\varphi_i, \psi_i)_{III} = 107, 338°$; $(\varphi_i, \psi_i)_{I'} = 20, 130°$; and $(\varphi_i, \psi_i)_{III'} = 20, 341°$. Averaged matrices corresponding to these discrete conformers consequently were employed for calculations to follow. The characteristic ratio C_∞ for P-L-LA was calculated from eq 3 through use of the average transformation matrix $\langle \hat{\mathbf{T}}_i\rangle$ given by

$$\langle \hat{\mathbf{T}}_i\rangle = w_I\langle \mathbf{T}_I\rangle + w_{III}\langle \mathbf{T}_{III}\rangle + w_{I'}\langle \mathbf{T}_{I'}\rangle + w_{III'}\langle \mathbf{T}_{III'}\rangle = \begin{bmatrix} 0.332 & 0.167 & 0.017 \\ -0.273 & 0.085 & 0.257 \\ 0.778 & -0.355 & 0.082 \end{bmatrix} \quad (8)$$

In light of the major contribution to z from minima I and III, calculations also were carried out using the averaged matrix

$$\langle \hat{\mathbf{T}}_i\rangle = \frac{w_I\langle \mathbf{T}_I\rangle + w_{III}\langle \mathbf{T}_{III}\rangle}{w_I + w_{III}} = \begin{bmatrix} 0.305 & 0.186 & 0.032 \\ -0.356 & 0.117 & 0.264 \\ 0.827 & -0.359 & 0.102 \end{bmatrix} \quad (9)$$

which takes account of these two states only. When $\langle \hat{\mathbf{T}}_i\rangle$ from eq 8 is used, $C_\infty = 2.02$; eq 9 yields $C_\infty = 1.92$. Both results are very similar to the characteristic ratio ($C_\infty = 2.13$) obtained above by summation over the entire conformational map. It is apparent that the two principal states I and III alone reproduce this latter result well within the limits of reliability of the energy calculations. Accordingly, the calculations described below were carried out on the basis of the two-state model.

The inaccuracy of the energy calculations considerably exceeds the small difference indicated between the energies of minima I and III. The precise value found for this difference may be subject to an uncertainty of about ±0.5 kcal mol^{-1}. On the other hand, the locations and approximate shapes of the potential wells in the conformational energy map are features closely related to the chain structure and geometry, which are reproduced with satisfactory reliability. It is therefore a reasonable procedure to treat the

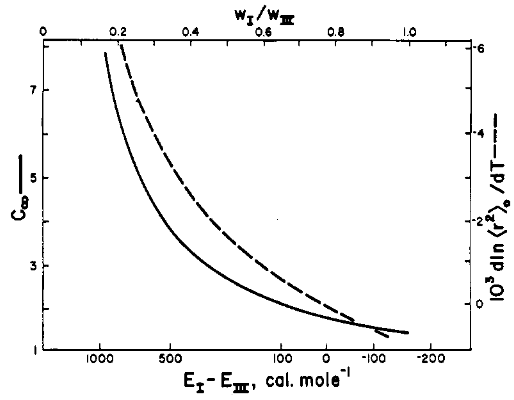

Figure 5. The characteristic ratio (solid curve) for P-L-LA and its temperature coefficient (dashed curve) calculated according to the two-minimum rotational isomeric state scheme and plotted against $w_{\rm I}/w_{\rm III}$ as the linear scale given on the upper abscissa margin. The corresponding energies $E_{\rm I} - E_{\rm III}$, related to $w_{\rm I}/w_{\rm III}$ according to eq 10 with $A = 0.77$ and $T = 358$°K, are shown in nonlinear scale along the lower abscissa.

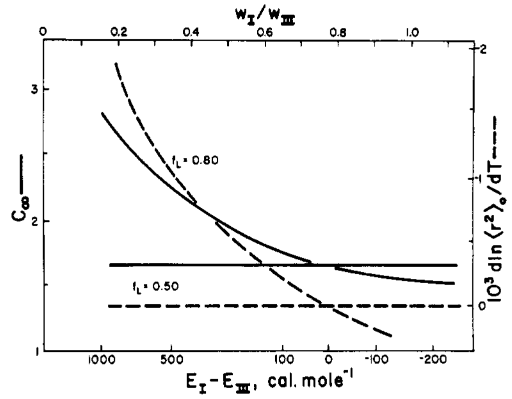

Figure 6. Characteristic ratios and temperature coefficients for stereoirregular poly(lactic acid) with 80 and 50% of L residues distributed at random. The graphing scheme corresponds to Figure 5.

difference between the conformational energies $E_{\rm I}$ and $E_{\rm III}$ at the respective minima as a variable parameter, other features of the conformational energy calculations being retained. Accordingly, we let

$$w_{\rm I}/w_{\rm III} = A \exp[-(E_{\rm I} - E_{\rm III})/RT] \qquad (10)$$

where A is a constant, taken to be independent of temperature, which reflects the relative breadths of these domains. From the values of $w_{\rm I}$ and $w_{\rm III}$ given in Table IV and $E_{\rm I} - E_{\rm III} = 0.083$ kcal mol^{-1} according to the calculations yielding Figure 3, we obtain 0.77 for the value of A. The characteristic ratio C_∞ has been calculated as a function of $E_{\rm I} - E_{\rm III}$ using eq 3, 9, and 10, with $A = 0.77$, and the results are presented in Figure 5. The temperature coefficient

$$\frac{\mathrm{d}\ln\langle r^2\rangle_0}{\mathrm{d}T} = \frac{1}{C_\infty}\frac{\mathrm{d}C_\infty}{\mathrm{d}(w_{\rm I}/w_{\rm III})}\frac{\mathrm{d}(w_{\rm I}/w_{\rm III})}{\mathrm{d}T} \qquad (11)$$

is also shown in Figure 5. The derivatives $\mathrm{d}C_\infty/\mathrm{d}(w_{\rm I}/w_{\rm III})$ and $\mathrm{d}(w_{\rm I}/w_{\rm III})/\mathrm{d}T$ were obtained from slopes of the curve for C_∞ in Figure 5 and from eq 10, respectively. Results of analogous calculations for random poly(DL-lactic acid) possessing 80% ($f_L = 0.80$) and 50% ($f_L = 0.50$) L(+)-lactyl residues, carried out using eq 5 in addition to eq 3, 9, 10, and 11, are presented in Figure 6.

A positive value of $E_{\rm I} - E_{\rm III}$ is required to explain the observed[1] negative temperature coefficient of C_∞. This is of course consistent with the greater extension of a residue in conformation III. Choices of $E_{\rm I} - E_{\rm III}$ which produce agreement between theory and experiment for C_∞ yield much smaller values for d ln $\langle r^2\rangle_0$/dT than the experiments reported in the preceding paper[1] indicate. An energy difference of about 600 kcal mol^{-1} reproduces the observed temperature coefficient, but overestimates C_∞ about twofold (see Figure 5). Calculations carried out with minima I′ and III′ included, with their energies subject to arbitrary adjustment, failed also to relieve this discrepancy.

Several explanations may be envisaged. First, the experimental results reported in the preceding paper[1] unfortunately are limited to halogenated solvents, which may conceivably affect the conformation through interactions with the ester group. Measurements in a greater variety of solvents would be desirable.

Second, the ester group may depart from the planar *trans* form, possibly with occurrence of the *cis* form in appreciable measure. Increase in the *cis* form with temperature would enhance the decrease of C_∞ with temperature. If this explanation should prove correct, it would imply that C_∞ also is depressed by the occurrence of *cis* residues. This in turn would require a somewhat greater energy difference $E_{\rm I} - E_{\rm III}$ and hence there would be a larger contribution to the (negative) temperature coefficient from this source.

The unperturbed dimensions decrease with decreasing stereoregularity, as found also for the random copolypeptides,[6] and this observation is consistent with experiments reported in the previous paper.[1] Moreover, the magnitude of the negative temperature coefficient also diminishes with decreasing stereoregularity as observed.[1] According to calculations, however, the dimensions of racemic, random poly(DL-lactic acid) should be nearly independent of temperature. In this respect the calculations depart from the experimental results according to which the temperature coefficient is fairly large even for the polymer with $f_L \approx 0.5$.

Conclusions

The two minima I and III dominating the conformational energy of the L-lactyl residue of P-L-LA correspond to those of the same designation for the L-alanyl residue. The domain of III is much more restricted however than the corresponding diffuse domain for L-alanyl. The preference of III over I in the case of the L-lactyl derives principally from the difference in energy. That this energy difference is small, in accordance with the energy calculations, is attested by the low value of C_∞, which is about one-fourth of that for P-L-Ala. While the sign of the energy difference predicates a negative temperature coefficient in agreement with observation, the magnitude of the difference observed is much greater than that calculated. Departures from the *trans* ester model may provide a clue to the explanation of this apparent discrepancy, which is of secondary significance.

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Nuclear Magnetic Relaxation in Poly(ethylene oxide)–Salt Solutions

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ABSTRACT: This article describes studies of nuclear spin–lattice relaxation in poly(ethylene oxide)–salt solutions. Addition of KI to solutions of PEO in deuterated methanol produces large changes in the relaxation of the polymer protons. These changes can be described quantitatively in terms of free and associated PEO units along the polymer chain. Salting-out effects, as evidenced in the macroscopic solution viscosity, are not reflected in T_1. Aqueous PEO solutions of KI and K_2SO_4 were also studied. Under these conditions, neither salt has an effect on spin relaxation.

Previous reports from this laboratory[1,2] have concerned nuclear relaxation in solutions of poly(ethylene oxide), PEO. It has been found that many factors influencing the macroscopic transport properties of PEO solutions have little effect on nuclear relaxation. For example, both polymer concentration and molecular weight, two factors that profoundly influence solution viscosity have no observable effect on T_1, the nmr spin–lattice relaxation time. This result is readily understandable, since T_1 is sensitive to localized molecular motions, and is insensitive to the grosser motions of the polymer chain. At the same time, this result points up the important distinction between macroscopic and molecular transport properties in polymers. We pursue this distinction in the present article.

The macroscopic solution behavior of PEO is known to be sensitive to the presence of neutral salts.[3-5] However, it is not known how neutral salts affect the local motions of polymer segments. We have performed T_1 measurements on PEO in certain selected salt solutions in order to examine this question.

Experimental Section

Two PEO samples, having molecular weights of 6000 and 300,000, were studied. These materials, designated PEO-6000 and PEO-300,000, have been described in an earlier article.[2] Deuterated methanol and water were obtained from Merck Sharpe and Dohme of Canada. Potassium iodide and potassium sulfate were obtained from Baker and Adamson and were used without further purification.

The solutions were prepared in standard nmr tubes. Each solution was subjected to four freeze–pump–thaw cycles to remove dissolved oxygen, and sealed under vacuum.

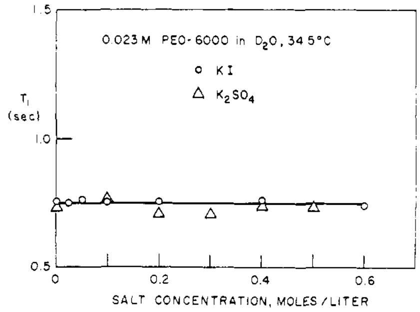

Figure 1. T_1 measurements on 0.023 *M* PEO solutions in D_2O. The effect of added KI and K_2SO_4 is illustrated.

T_1 measurements were performed at 34.5 ± 0.5° on a modified Varian DA-60 spectrometer, using the "adiabatic passage with sampling" technique.[6] The relaxation data were time-averaged in a Varian C1024 computer. At least 25 measurements of each relaxation time were used. The data appear reproducible within ±5%.

Viscosity was measured with a three-bulb Ubbelode dilution viscometer at 34.5 ± 0.02°. The solvent flow time was such that kinetic energy corrections were negligible.

Results and Discussion

Our experiments contrasted the proton relaxation of PEO in KI–CD_3OD solutions with that observed in KI–D_2O. Results for PEO-6000 are plotted in Figures 1 and 2. When KI is added to CD_3OD solutions of PEO, it has a pronounced effect on T_1. Experimental T_1 values change from 1.9 sec with no added salt to 0.50 sec in 0.6 *M* KI solution. In contrast, KI has no apparent effect on the relaxation of PEO in D_2O. We observed almost identical behavior for KI solutions of PEO-300,000.

It has been shown[4,5] that a definite association complex is formed between K^+ and PEO in methanol.

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[1] K-J. Liu, International Symposium on Macromolecular Chemistry, Tokyo, Japan, 1966; reprints, 7, 48 (1966).

[2] K-J. Liu and R. Ullman, *J. Chem. Phys.*, **48**, 1158 (1968).

[3] F. E. Bailey and R. W. Collard, *J. Appl. Polym. Sci.*, **1**, 56 (1959).

[4] R. D. Lundberg, F. E. Bailey, and R. W. Collard, *J. Polym. Sci., Part A-1*, **4**, 1563 (1966).

[5] K-J. Liu, *Macromolecules*, **1**, 308 (1968).

[6] J. E. Anderson, J. Steele, and A. Warnick, *Rev. Sci. Instr.*, **38**, 1139 (1967).