Polydepsipeptides. 8. Configurational Contributions to the Conformation of Polydepsipeptides and Analogous Polypeptides

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ABSTRACT: The configurational contribution to the conformations of polypeptides has been examined through study of polydepsipeptide model systems. Circular dichroism and infrared spectra of the polydepsipeptides poly[(L-Ala)$_2$-(*S*)-Lac] and poly[(D-Ala)$_2$-(*S*)-Lac] and of the polypeptides poly(L-Ala) and poly[(L-Ala)$_2$-D-Ala] have been examined. The polydepsipeptides form right- and left-handed helices in solution and in the solid state. They undergo a reversible helix-to-coil transition thermally or by addition of denaturing solvent. The polypeptides form right-handed α helices in solution but exhibit different sensitivities to thermal denaturation. Poly[(L-Ala)$_2$-D-Ala] undergoes a helix-to-coil transition over the temperature range 0 to 20 °C in hexafluoroisopropyl alcohol solutions, while poly(L-Ala) is conformationally stable up to the boiling point of the solvent (60 °C). A structure is proposed for the polydepsipeptides in which the amide residues are constrained in a helical conformation by amide–amide hydrogen bonds, while the ester residues are not hydrogen bonded but are highly solvated. This model is employed to explain the different consequences to helical stability caused by incorporating a D-amino acid in a right-handed helix as compared to an *R*-hydroxy acid in that same helix.

Introduction

Sequential polydepsipeptides are composed of regular sequences of α-amino and α-hydroxy acids. They exhibit many of the same conformational features as sequential polypeptides, which is not surprising, given the similarity between the geometries and energetically allowed conformations of the ester and amide residues. The geometries of the ester and amide differ principally in that the C′OC bond angle is smaller than the C′NC bond angle by 10°.[1] Furthermore, the α-hydroxy and α-amino residues of a depsipeptide dimer exhibit similar calculated torsional minima; e.g., poly[(*S*)-lactic acid] displays minima in the α-helical and extended regions of the Ramachandran map at approximately the same place as poly(L-Ala).[2] The number of intramolecular hydrogen bonds in polydepsipeptides is less than that of an analogous polypeptide since ester groups cannot be hydrogen-bond donors. Thus, introduction of α-hydroxy acids in peptide sequences can be used to study the site-specific effect of intramolecular hydrogen bonding on the stability of preferred conformations of polypeptides and proteins.

To study the effect of incorporation of hydroxy acid residues into polypeptides, we have synthesized and analyzed several polydepsipeptides containing alanine and lactic acid.[3-6] One such polydepsipeptide, poly[L-Ala-(*S*)-Lac], may assume a conformation in solution which has been termed the R_{10} helix. The structure consists of short segments of concatenated type-I β turns and is similar to the α_{DL} ribbon reported by Scheraga for poly(L-Ala-D-Ala).[7] The torsional angles for the L,*S* polydepsipeptide and for the DL polypeptide are similar, yet no inversion of the alanine side chain is required. This suggests that polydepsipeptides containing L-amino acids and *S*-hydroxy acids may be able to adopt conformations equivalent to those found in DL alternating polypeptides. The interest in these conformations lies in the possibility that several DL structures, such as the β helices, may represent the physical form assumed by peptide and depsipeptide ionophores during ion transport.[8,9]

The synthesis and preliminary conformational analysis of poly[(L-Ala)$_2$-(*S*)-Lac] was also reported. This polydepsipeptide assumes a helical conformation at room temperature in chloroform which may be denaturated either thermally or by addition of a denaturing solvent such as trifluoroethanol. A model for this helix was developed by using transition dipole moment directions assigned by means of linear dichroism.[6] The geometry of the ester residues and reduction by one-third of the total number of hydrogen bonds in this polydepsipeptide slightly distorts this helix from that found in poly(L-Ala). The principal difference between the two polymers is that poly[(L-Ala)$_2$-(*S*)-Lac], having fewer hydrogen bonds per helical repeat, is less stable to solvent and thermal denaturation than poly(L-Ala). The model proposed for the helix adopted by poly[L-Ala)$_2$-(*S*)-Lac] consists of a helical array in which both amides are fully intramolecularly hydrogen bonded while the ester is not intramolecularly hydrogen bonded. One consequence of this model is that complete inversion of the ester side-chain configuration should affect neither the structure nor the stability of this polydepsipeptide. To test this prediction, we synthesized the polydepsipeptide poly[(D-Ala)$_2$-(*S*)-Lac], which is predicted to form a left-handed helix with the same stability and structure (other than screw sense) as poly[(L-Ala)$_2$-(*S*)-Lac]. In this paper we report an essentially complete thermally induced helix-to-coil transition of poly[(L-Ala)$_2$-(*S*)-Lac] and poly[(D-Ala)$_2$-(*S*)-Lac] in both chloroform and tetrahydrofuran, as well as more precise measurements of the structure in poly(oxyethylene) films.

Finally, to assess the differences between side-chain inversion in a polypeptide and that in a polydepsipeptide, we have synthesized poly[(L-Ala)$_2$-D-Ala] and spectroscopically determined its solution structure as compared to that for poly(L-Ala). The two polydepsipeptides and two polypeptides constitute a systematic probe of the effect of hydrogen bonding and side-chain chirality on α-helical structure and stability in poly(L-Ala).

Experimental Section

The synthesis of the polydepsipeptides and polypeptides by a matrix-mediated reaction has been previously reported.[4] In all cases the trifluoroacetate salt of the appropriate monomer was deposited on Celite, polymerized overnight at 80 °C, and post-polymerized at 100 °C for 2 days. Each of the polymers was washed from the solid support and purified. The intrinsic viscosities of the polymers were 0.17 dL/g for poly[(L-Ala)$_2$-(*S*)-Lac] and poly[(D-Ala)$_2$-(*S*)-Lac] and 0.5 dL/g for poly[(L-Ala)$_2$-D-Ala], suggesting DPs of ~300 for each of the polydepsipeptides and ~700 for the polypeptide.

The poly(L-Ala) sample was purchased from Pilot Chemical Co. (lot no. 91116) and had a DP of 700. Solvents used include

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Table I
Circular Dichroism of the Polydepsipeptides Poly[(L-Ala)$_2$-(*S*)-Lac] and Poly[(D-Ala)$_2$-(*S*)-Lac] and of the Polypeptides Poly(L-Ala) and Poly[(L-Ala)$_2$-D-Ala] in HFIP at 0 °C

polymer	$n\pi^*$	$\pi\pi^*$	
poly(L-Ala)	222[a] (−12 000)[b]	204 (−24 000)	197 (30 000)
poly[(L-Ala)$_2$-D-Ala]	222 (−12 000)	205 (−12 600)	197 (40 000)
poly[(L-Ala)$_2$-(*S*)-Lac]	222 (−1000)		186 (−10 000)
poly[(D-Ala)$_2$-(*S*)-Lac]	225 (1000)		197 (10 000)

[a] In nm. [b] In (deg·cm^2)/dmol.

trifluoroethanol (Aldrich, Gold Seal), hexafluoroisopropyl alchol (Aldrich), chloroform (Mallinckrodt, SpectAR), and tetrahydrofuran. The tetrahydrofuran was distilled over calcium hydride onto Linde 4-Å molecular sieves.

Circular dichroism spectra were obtained with a modified Cary 61 spectropolarimeter, controlled by a Texas Instruments 980A minicomputer. All measurements were obtained with Helma Co. 1-cm and 0.1-mm QS cells which were thermostated to ±0.2 °C by a Lauda 2k/R recirculating bath. Actual temperatures within the cells were monitored with a calibrated thermistor. Each spectrum is the average of two or three separate experiments, each consisting of 50–150 concatenated scans at 0.3-nm resolution.

Infrared spectra were obtained with a Nicolet 7199 Fourier transform IR spectrophotometer. Typical measurements were carried out at 1-cm^{-1} resolution and consisted of 1000 accumulations. Dichroic infrared spectra were obtained with this instrument by interposing a Perkin-Elmer gold-wire polarizer into the optical path just after the sample compartment. The technique for casting and orienting poly(oxyethylene) films is elsewhere reported.[10] A typical dichroic experiment consisted of 5000–10 000 accumulations at 0.25-cm^{-1} resolution with the polarizer both parallel and perpendicular to the axis of orientation. The linear dichroism

$$\mathrm{LD} \equiv (A_{\parallel} - A_{\perp})/A \qquad (1)$$

is then computed for each data point and stored. Here $A_{\parallel}$ and $A_{\perp}$ are the absorption intensities at a given wavelength for light polarized parallel and perpendicular to the axis of orientation and A is the total absorbance at that wavelength. Several spectra, at different degrees of orientation, were obtained for each sample.

Results and Discussion

The CD spectra for poly(L-Ala), poly[(L-Ala)$_2$-D-Ala], poly[(L-Ala)$_2$-(*S*)-Lac], and poly[(D-Ala)$_2$-(*S*)-Lac] at 0 °C in hexafluoroisopropyl alcohol are shown in Figure 1 and their extremes are reported in Table I. It is apparent that both polypeptides form right-handed helices under these conditions, while both polydepsipeptides are in random-coil states. The difference between polypeptide and polydepsipeptide conformation in this solvent may be attributed to the loss of one-third of the intramolecular hydrogen bonds which would otherwise stabilize the helix. If the solutions are warmed to room temperature, no change in the CD spectrum is observed for either polydepsipeptide or for poly(L-Ala). When the hexafluoroisopropyl alcohol solution containing poly[(L-Ala)$_2$-D-Ala] is warmed to room temperature, however, this polypeptide undergoes a helix-to-coil transition—the final spectrum closely resembling that for poly[(L-Ala)$_2$-(*S*)-Lac] at the same temperature. No such helix-to-coil transition is observed for poly(L-Ala) up to the boiling point of the solvent. The presence of a D-amino acid at every third position in a right-handed alanine helix must significantly destabilize that structure. A previous semiempirical calculation of poly(L-Ala) and poly(D-Ala-L-Ala) suggested that D-amino acids do not significantly alter either the conformation or the energy/residue of the alanine right-handed α helix.[7] Unless the nature of interresidue interaction is substantially different in poly[(L-Ala)$_2$-D-Ala] than in poly(L-Ala-D-Ala), this claim is not substantiated by the current study.

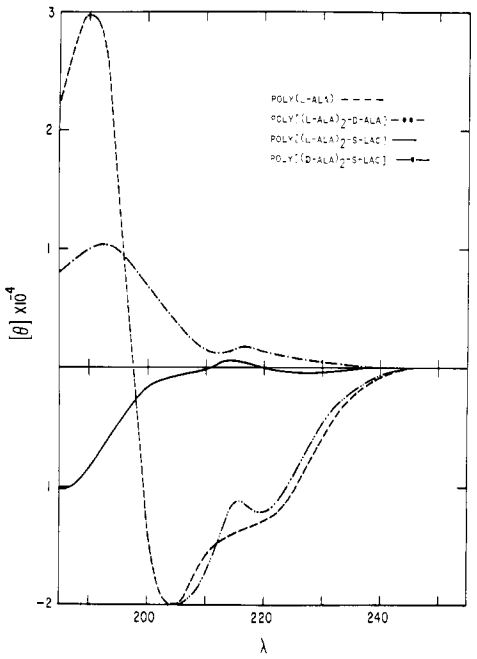

Figure 1. Circular dichroism of polypeptides and polydepsipeptides in HFIP at 0 °C: poly(L-Ala) (– – –), poly[(L-Ala)$_2$-D-Ala] (· · ·), poly[(L-Ala)$_2$-(*S*)-Lac] (—), poly[(D-Ala)$_2$-(*S*)-Lac] (– · –).

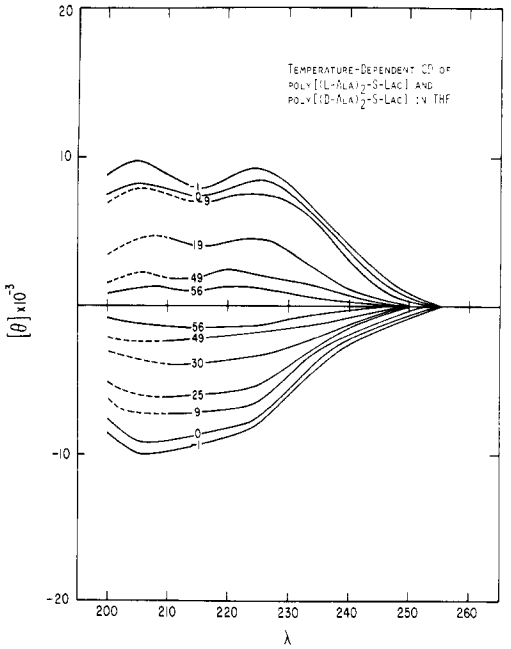

Figure 2. Circular dichroism of poly[(L-Ala)$_2$-(*S*)-Lac] (negative curves) and poly[(D-Ala)$_2$-(*S*)-Lac] (positive curves) in tetrahydrofuran as a function of temperature.

Circular dichroism spectra of the diastereomeric polydepsipeptides poly[(L-Ala)$_2$-(*S*)-Lac] and poly[(D-Ala)$_2$-(*S*)-Lac] at several temperatures in tetrahydrofuran are shown in Figure 2. The polydepsipeptides form right- and

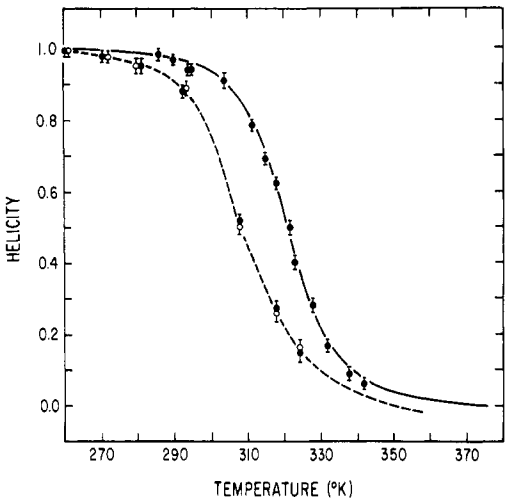

Figure 3. Helix-to-coil transitions of poly[(L-Ala)$_2$-(*S*)-Lac] (●) and poly[(D-Ala)$_2$-(*S*)-Lac] (○) in chloroform (—) and tetrahydrofuran (---).

left-handed helices, respectively, at low temperatures but undergo helix-to-coil transitions upon heating. A similar family of curves is observed for poly[(L-Ala)$_2$-(*S*)-Lac] in chloroform, in which this polydepsipeptide melts approximately 13 °C higher than in tetrahydrofuran. We did not study poly[(D-Ala)$_2$-(*S*)-Lac] in chloroform. From the results reported in this paper we would expect that this polydepsipeptide would behave exactly the same as poly[(L-Ala)$_2$-(*S*)-Lac].

The actual melting curves as a function of temperature are shown in Figure 3. Here the helicity is defined as

$$\Theta_h = ([\Theta(T)] - [\Theta(\text{coil})])/([\Theta(\text{helix})] - [\Theta(\text{coil})]) \quad (2)$$

where Θ_h is the fraction of residues remaining helical, [$\Theta(T)$] is the dichroism at 222 nm at temperature T, [Θ(coil)] is the observed limiting ellipticity for a fully denatured chain, and [Θ(helix)] is the observed limiting ellipticity for a fully helical chain (−1060 and −10 000 (deg·cm^2)/dmol, respectively). As may be seen, the melting of poly[(L-Ala)$_2$-(*S*)-Lac] and poly[(D-Ala)$_2$-(*S*)-Lac] in tetrahydrofuran is identical to within experimental error. The error bars in Figure 3 represent errors in the helicity which are introduced because of noise in the CD spectrum, errors in weighing the samples, etc. The melting in both solvents is reversible if the solutions are sufficiently dry.

The fact that both polydepsipeptides melt at the same temperature and at the same rate strongly suggests that they possess virtually the same structure, differing only in helical screw sense. The α-hydroxy acid residues incorporated in the right-handed and left-handed helices of poly[(L-Ala)$_2$-(*S*)-Lac] and of poly[(D-Ala)$_2$-(*S*)-Lac] appear to make similar contributions to what are necessarily dissimilar local environments. The model we proposed earlier for poly[(L-Ala)$_2$-(*S*)-Lac] suggests that this is possible because of the lack of a hydrogen bond between ester residues and also, to a lesser extent, the ester geometry. What is required is that the ester residues have sufficient torsional mobility to minimize unfavorable nonbonded interactions. Such freedom is unavailable to poly[(L-Ala)$_2$-D-Ala] since all residues are hydrogen bonded and consequently limited to a narrow range of torsional angles.

Further insight into the nature of these transitions may be gained with a statistical thermodynamic analysis of the melting curves. We have previously derived a modified nearest-neighbor Ising model of polydepsipeptide helix-to-coil transitions which was based on the theories of

Table II
Thermodynamics of Polydepsipeptide Melting

parameter	poly[(L-Ala)$_2$-(*S*)-Lac][a]	poly[(L-Ala)$_2$-(*S*)-Lac] or poly[(D-Ala)$_2$-(*S*)-Lac][b]
T_d°[c]	47.5 ± 0.2	34.5 ± 0.2
ΔH_m[d]	578 ± 20	513 ± 35
ΔS_m[e]	1.81 ± 0.005	1.67 ± 0.007
σ	0.00305	0.005

[a] In chloroform. [b] In tetrahydrofuran. [c] Polydepsipeptide and polypeptide melting temperatures in °C. [d] Enthalpies of melting in cal/residue. [e] Entropies of melting in cal/residue.

Zimm–Bragg and Lifson–Roig.[3,6] This model allows us to express the fraction of helical subunits at a given temperature as

$$\Theta_h = \frac{s}{c}\,\frac{s + c + 2\sigma - 1}{s + c + 1} \quad (3)$$

$$c = [(1 - s)^2 + 4s\sigma]^{1/2} \quad (4a)$$

$$s = \exp(-\Delta G/RT) \quad (4b)$$

where s is the statistical weight associated with adding an internal depsipeptide unit, in ths case Ala-Ala-Lac, to the helical chain, σ reflects the free energy involved in constraining the ends of the helix to a helical conformation, and ΔG is the free energy of the transition at a given temperature.

The solid lines in Figure 3 represent the best fit of the experimental data by eq 3. The calculated thermodynamic parameters reported in Table II were obtained in a manner similar to that reported by Scheraga and co-workers.[11] For an arbitrary choice of σ, values for s were determined which minimized the difference between calculated and observed helicities at each temperature. A least-squares analysis of $-R \ln s$ vs. $1/T$ yielded the entropy and enthalpy of the transition, which were used in eq 3 to recalculate the helicities as a function of temperature. That value of σ which minimized the root-mean-square error between calculated and observed helicities was used to determine the enthalpy and entropy for the transition. The correlation coefficient for the final $-R \ln s$ vs. $1/T$ lines was 0.99 and 0.98 for poly[(L-Ala)$_2$-(*S*)-Lac] in chloroform and both polydepsipeptides in tetrahydrofuran, respectively. The lack of curvature in the $-R \ln s$ vs. $1/T$ lines and a root-mean-square error between observed and calculated helicities of less than 10^{-4} indicate that the theory was capable of accurately representing experiment. The entropy and enthalpy are apparently not strongly temperature dependent in these solvents over the range of temperatures studied.

As may be seen in Table II, the thermodynamic parameters in these organic solvents are nearly the same. Both the enthalpy and entropy of the helix-to-coil transition are slightly smaller in tetrahydrofuran than in chloroform. The polydepsipeptides are also less soluble in tetrahydrofuran than in chloroform, which suggests the difference in melting is due to the fact that tetrahydrofuran is simply a poorer solvent than chloroform for these molecules. Since the enthalpy of a helix-to-coil transition in weakly interacting solvents may be associated with disruption of a helical hydrogen bond, the transition enthalpy of a helical alanine residue is one and a half times the enthalpy/residue in the polydepsipeptides. This is then 867 cal/residue in chloroform and 769 cal/residue in tetrahydrofuran. These values and the average entropy/residue for the transition suggest that poly(L-Ala) would undergo a helix-to-coil transition near 200 °C in both

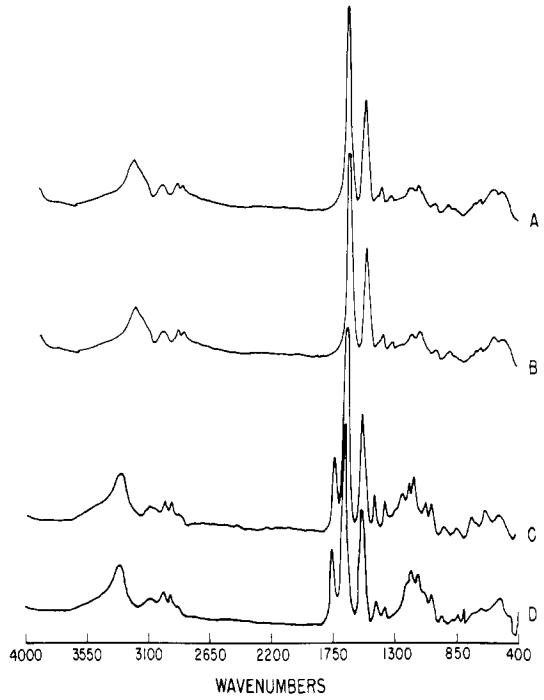

Figure 4. Infrared spectra of (A) poly(L-Ala), (B) poly[(L-Ala)$_2$-D-Ala], (C) poly[(L-Ala)$_2$-(*S*)-Lac], and (D) poly[(D-Ala)$_2$-(*S*)-Lac] in KBr pellets.

Table III
Infrared Band Positions of Polypeptides and Polydepsipeptides in KBr

	band position, cm^{-1}			
polymer	amide A	amide I	amide II	ester CO stretch
poly(L-Ala)	3280	1650	1544	
poly[(L-Ala)$_2$-D-Ala]	3285	1655	1528	
poly[(L-Ala)$_2$-(*S*)-Lac]	3285	1654	1550	1735
poly[(D-Ala)$_2$-(*S*)-Lac]	3285	1657	1550	1739

these solvents. The experimental observation that poly(L-Ala) does not melt in any single, organic solvent (as distinct from mixed organic solvents) is in accord with this calculation.

The principal structural implication of these results indicates that alanine residues in both polydepsipeptides form strong hydrogen bonds which are unimpaired by the presence of ester residues in the chain. Such is not the case for poly[(L-Ala)$_2$-D-Ala], where the D-amino acids interrupt and destabilize the alanine α-helix. These structural effects are clear in the infrared spectra of these compounds.

Typical infrared spectra for the four polymers are shown in Figure 4, and the frequencies of the amide transitions are reported in Table III. Both polypeptides appear to be helical, with all amides hydrogen bonded. The polydepsipeptides also appear to be helical, but the ester residues in each are not hydrogen bonded.

An even clearer view of the structure assumed by both polydepsipeptides is afforded by infrared dichroic measurements. A typical dichroic spectrum is shown in Figure 5. While slight variations in the intensities of the linear dichroism of each band are observed from sample to sample (from different extents of orientation in the different experiments), the positions and relative intensities are the same. The amide A and amide I transitions exhibit positive dichroism, while the amide II at 1540 cm^{-1} exhibits negative dichroism. This pattern is quite typical of helical molecules in which the plane of each amide bond is nearly

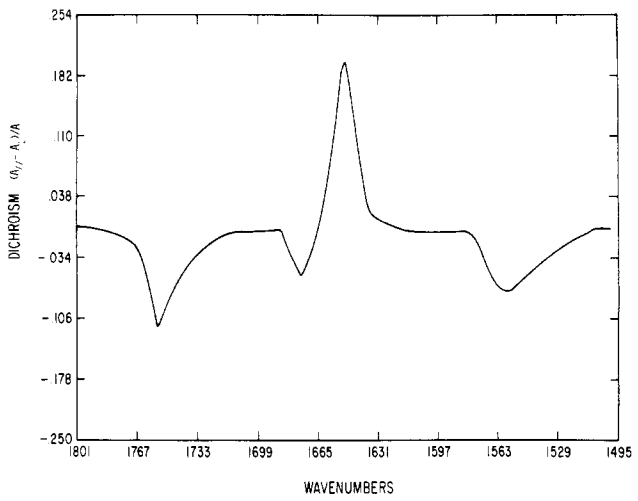

Figure 5. Typical infrared dichroic spectrum of poly[(L-Ala)$_2$-(*S*)-Lac] and poly[(D-Ala)$_2$-(*S*)-Lac].

Table IV
Dihedral Angles (Deg) for Poly[(L-Ala)$_2$-(*S*)-Lac] and Poly[(D-Ala)$_2$-(*S*)-Lac] Helices[a]

	dihedral angle		dihedral angle
amide A	52	ester CO	59
amide I	45	α	14
amide II	60	β	16

[a] All transition dipole moment dihedral angles are relative to the helical axis.

parallel to the helical axis.[12] A small, variable amount of some aggregated conformation is observable from the negative dichroism centered near 1660 cm^{-1}. The parallel dichroism of the amide carbonyls should be contrasted with the negative dichroism exhibited by the ester carbonyl stretch. This indicates that the ester transition is bent out greater than 54° from the helical axis.[13] The ester residues, in other words, are folded outward from the cylindrical array of amides.

If several dichroic spectra are obtained for each polydepsipeptide, it is possible to use the intensities of the linear dichroism of each band to assess the spatial orientation of the amide and ester residues. For uniaxially oriented films which contain molecules having only one principal orientation axis, the linear dichroism has been shown to be given by[14]

$$\mathrm{LD} = g^{\circ} f_{\alpha} f_{\theta} \tag{5a}$$

$$f_{\alpha} = \frac{3\langle \cos^2 \alpha \rangle - 1}{2} \qquad f_{\theta} = \frac{3\langle \cos^2 \theta \rangle - 1}{2} \tag{5b}$$

The orientation functions f_{α} and f_{θ} are the second moments of the distribution functions for the chromophore relative to the orientation axis and of the molecule relative to the laboratory axis, respectively, and g° is the optical anistropy of the transition. The angle α is the expectation value of the angle between the transition dipole moment and the orientation axis (the principal molecular axis which is the helical axis in this case), while θ is the expectation value of the angle between the molecular axis and the laboratory-fixed orientation axis. If the molecule in question is not distorted by the orientation process, α remains constant and the dichroism equation may be solved exactly. A series of spectra at different degrees of orientation yield a system of equations in f_{α} and f_{θ}.

As may be seen in Table IV, the ester residues are bent away from the helical axis about 7° further than the amide residues. The structure is also somewhat more open than

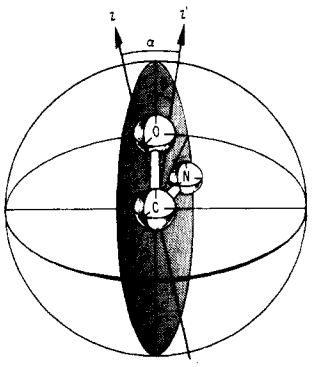

Figure 6. Orientation angles for the amide plane relative to the helix axis.

that found in poly(L-Ala), which is calculated to have the amide A and amide I transitions inclined 42° to the helical axis, with the amide II inclined at 68° to that axis. Another measure of the differences between the polypeptide and polydepsipeptide helices is the two orientation angles α and β, which are two Eulerian angles for amide plane orientation relative to the helical axis (Figure 6). These angles are related to the orientation angles θ by the equation

$$\cos \theta_i = \cos \mu_i \cos \alpha \cos \beta + \sin \mu_i \cos \alpha \sin \beta \quad (6)$$

where θ_i is the observed orientation angle for the ith transition and μ_i is the angle the transition diple of the ith transition makes with the amide CO bond. The angles α and β may be determined by using any two observed orientation angles. For poly(L-Ala) in an 18/5 helix these are calculated to be 40 and 16°, respectively, while we find 14 and 16°, respectively, for the polydepsipeptide. These angles are almost identical with those calculated for an amide residue in a 47/13 helix, suggesting a slight variation in the torsional angles ϕ, ψ may account for our observed differences in the dichroism.

Conclusions

Main-chain hydrogen-bond formation and side-chain configuration in α-helical arrays of alanine appear to contribute different, separable effects to structure and stability. The effect of hydrogen bonding dominates stability to either thermal or solvent denaturation, as evidenced by the nearly 200 °C decrease in thermal denaturation in chloroform for poly(L-Ala) as compared to poly[(L-Ala)$_2$-(*S*)-Lac]. The effect of side-chain configuration depends on whether the residue in question is intramolecularly hydrogen bonded or free. A hydrogen-bonded inverted residue both decreases the stability of the helix and alters its backbone structure, as observed for poly[(L-Ala)$_2$-D-Ala]. The effect of side-chain inversion on a non-hydrogen-bonded residue, however, appears to be negligible. Consequently, both polydepsipeptides adopt helical structures which differ only in helical screw sense but not stability. They are less stable to denaturation than poly[(L-Ala)$_2$-D-Ala] since the additional hydrogen bond makes a greater energetic contribution to stability than the unfavorable side-chain inversion.

Naturally, structures in which *R*-hydroxy acids in an L-polypeptide were hydrogen bonded in a right-handed helix would be expected to show intermediate stability to solvent or thermal denaturation. This situation is equivalent to an *S*-hydroxy acid in D-polypeptide. The polydepsipeptides poly[(L-Ala)$_3$-(*S*)-Lac] and poly[(D-Ala)$_3$-(*S*)-Lac] should both have hydrogen bonds to ester carbonyls, if these compounds assume an α-helical structure. Since the inverted ester residue in poly[(D-Ala)$_3$-(*S*)-Lac] is hydrogen bonded, we would predict this polydepsipeptide to form a helix with both different stability and structure than that for poly[(L-Ala)$_3$-(*S*)-Lac]. We have prepared these polydepsipeptides and will soon report their structures in solution.

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