As far as we are aware, the 61-cm^{-1} band is the first observed localized mode in a helical biopolymer. Aside from its spectroscopic interest, this band should be of importance in the study of localized modes in biopolymers, since such modes provide a detailed probe of internal interactions in such systems. For example, the sharpness of the 61-cm^{-1} band was attributed to weak (but *not* zero) coupling between glycyl and HBG residues. In fact, it is presumably this weak coupling which forces the glycyl residue to adopt the helical conformation of its HBG neighbors.[14,15] Finally, if this band indeed arises from a localized mode, then it appears that only one glycine is incorporated into any particular region of the PHBG helix. Since the observation of the localized mode rests on the mass difference[26] between helical glycine and its helical neighbors, this mass difference would be reduced drastically if more than one consecutive glycine were incorporated into any region of the PHBG helix, and this should preclude the observation of the local mode.

In order to provide a quantitative basis for these ideas, detailed calculations similar to those on solid systems will have to be undertaken. Such calculations may indicate the need for additional experiments (*e.g.*, the effect of substituting deuteriums for the hydrogens of glycine) to verify our assignment and to try to determine the vibrational origin of the local mode.

Summary

The laser Raman technique has yielded an understanding of the conformational behavior of a guest residue (glycine) among the host residues (hydroxybutylglutamine) in the random copolymer P(HBG:Gly). The conformationally sensitive nature of very low-frequency helical motions has been observed experimentally for the first time, and the spectra have provided direct experimental evidence for the incorporation of glycine residues into the PHBG helix. In addition, we may have observed the first localized mode in a polymeric system. If the explanation is corroborated, detailed studies of such localized modes should provide much information on the structure, coupling, and energetics of biopolymers.[27]

Acknowledgment. We are very grateful to Professor D. B. Fitchen for the generous use of his laser Raman spectrometer.

(27) NOTE ADDED IN PROOF. After submitting this paper, we obtained spectra of sample a (3.1% Gly, DP$_w$ = 510) using the 4880-Å line of the argon-ion laser. The 61-cm^{-1} band appeared exactly as it does in curve A of Figure 2. ' This provides additional proof that the 61-cm^{-1} band is not an emission line argon ion laser or a grating ghost.

On the Possible Existence of α-Helical Structures of Regular-Sequence D,L Copolymers of Amino Acids. Conformational Energy Calculations[1]

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ABSTRACT: Conformational energy calculations have been carried out to consider the question of whether alternating regular-sequence copolymers of D- and L-amino acids can adopt an α-helical conformation. Several other regular structures were also considered, in addition to the α helix. The copolymers treated were poly(D,L-alanine), poly(D,L-valine), poly(D,L-phenylalanine), and poly(D,L-α-aminoheptanoic acid) (a model for poly(D,L-lysine)). The energies of the right- and left-handed α-helical forms of poly(D,L-alanine) are essentially the same, comparable to that of the right-handed α-helical form of poly(L-alanine), and several kilocalories per residue lower than that of some other structures (the LD ribbon and the LD helix) previously proposed for the D,L copolymer. For valine, the energy of the α-helical form of the D,L copolymer is even lower than that of the all-L homopolymer because of favorable side chain–side chain interactions, and again several kilocalories per residue lower than that of the LD helix. For poly(D,L-phenylalanine) and poly(D,L-α-aminoheptanoic acid), α-helical structures were found with energies comparable to that of the right-handed α helix of the corresponding all-L homopolymers. In conclusion, no steric hindrance to α-helix formation was found for any of these D,L copolymers. Of course, the side-chain conformations of the low-energy α-helical copolymers are different from those in the corresponding all-L homopolymers.

Considerable attention has been paid to the question of whether regular-sequence D,L copolymers of amino acids can exist in the α-helical conformation;[3] presumably, steric hindrance between the side chains of D and L residues disrupts the helix. For example, it has been stated[4] that helix formation should be absent or minimal for these copolymers in any solvent. The experimental evidence to support this view appears to be inconclusive. Often, the experiments are carried out with low molecular weight material, for which the helix content would be expected to be low; also, the solvent may differ from one experiment to another, thus making comparison of results difficult. For low molecular weight random poly(D,L-alanine) in water, the conformation appears to be a random coil according to hydrogen-exchange[5,6] studies, but partially (30–35%) helical from ultraviolet hypochromism

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(1) This work was supported by research grants from the National Institute of General Medical Sciences of the National Institutes of Health, U. S. Public Health Service (GM-14312), and from the National Science Foundation (GB-28469X1).

(2) On leave from the van't Hoff Laboratorium, Rijksuniversiteit Utrecht, The Netherlands.

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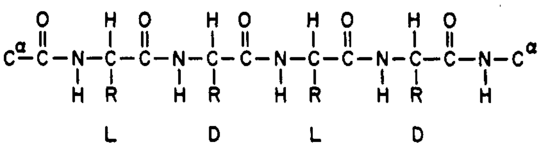

Figure 1. Form of the polypeptide chain which was used in the calculations. It contains n LD pairs in $(2n + 1)$ peptide units, the latter being of the form[19] -CHR-CO-NH-, plus a terminal α-carbon. Also, the α-carbon of the first peptide unit has no H or R group. In this illustration, $n = 2$.

observations.[7] For the same copolymer in trifluoroacetic acid (TFA)-chloroform mixtures, measurements[8] of viscosity, phase equilibria, and nuclear magnetic resonance spectra indicate that both low and relatively high molecular weight material are in the random-coil conformation throughout the composition range examined (40-100% TFA), whereas the all-L homopolymer of comparable (high) molecular weight is in the helical conformation at TFA concentrations below 70%. For polymers with larger side chains than that of alanine, the experimental evidence seems also contradictory; *e.g.*, random-sequence poly(methyl D,L-glutamate)[9] and regular-sequence poly(γ-benzyl D,L-glutamate)[10,11] are thought to form helical type structures, whereas Hardy, *et al.*,[12] conclude that the benzyl glutamate copolymer forms a new, as yet uncertain conformation.

In a forthcoming paper,[13] optical rotatory dispersion and ultraviolet measurements will be reported for regular-sequence poly(L,D,L,L-alanine) in water; they indicate that the copolymer is a mixture of left- and right-handed α helices, and conformational energy calculations support this view. In analyzing the factors responsible for the conformational behavior of the L,D,L,L copolymer, it is found that, contrary to current belief, there is no steric hindrance between the side chains of L- and D-alanine; instead, there is a *favorable* nonbonded side chain-to-side chain interaction. While solvent effects (not included in the calculation) can influence the stability, the important point is that the nonbonded interactions do not constitute a steric hindrance to the α-helical structure.

In the present paper, we report calculations for alternating, regular-sequence D,L copolymers of several amino acids to try to resolve the question as to whether such chains can exist in the α-helical conformation. The problem is attacked by showing that the α-helical conformation of the D,L copolymer is of low energy, comparable to that of the all-L homopolymer. The approach is the same as that of Ooi, *et al.*,[14] who treated a decapeptide, using the condition of regularity, *i.e.*, the values of the dihedral angles ϕ and ψ and the χ's are assumed to be the same for each residue. Their prediction that poly(L-valine) could form a right-handed α helix was later verified experimentally.[15] Essentially the same computer program was used[14,16,17] to compute the correct helix sense of about 25 homopolypeptides, and some of these constituted predictions[17] which were also verified later.[18]

The alternating regular-sequence D,L copolymers (and the corresponding L homopolymers) treated in this paper are constituted from alanine, valine, phenylalanine, and α-aminoheptanoic acid residues, respectively; the latter is a model amino acid for lysine, with a nonpolar methyl group replacing the polar ϵ-NH_2 group of the side chain. The present calculations are limited to amino acid residues with nonpolar side chains, since the question of steric interference can thereby be examined without complications from polar groups in the side chains. The nonpolar amino acids chosen have a short, a bulky, a ring-shaped, and a long side chain, respectively. The conformational energy is computed for right- and left-handed α-helical and other regular structures.

Method of Calculation

The procedure, energy functions, and parameters used for computing conformational energies were the same as those of Ooi, *et al.*[14] The bond angles, bond lengths, and planar trans peptide groups were maintained fixed, and a poly(amino acid) chain of n LD pairs was treated; it begins and ends with a C^α atom, and contains $2n$ side chains (to ensure an equal number of D and L residues) and $(2n + 2)$ C^α atoms; see Figure 1 for illustration of a chain with $n = 2$. The first side chain nearest to the N terminus of the chain was always chosen to be in the L configuration. Usually, n was taken as 4 but, in calculations involing energy minimizations, n was chosen as 6 in order to minimize end effects. Thus, there are $2n$ sets (or a minimum of 36) of dihedral anges ϕ, ψ, χ_1, χ_2, . . ., which are the independent variables, the IUPAC-IUB convention on nomenclature[19] being used. In the regularity condition used in most of the calculations, the values of ϕ, ψ, χ_1, χ_2, . . . in each LD unit were treated as the independent variables, thereby reducing their minimum number from 36 to 6. While only $(2n + 1)$ units are chosen, the use of the regularity condition makes the results applicable to the infinite chain, except for the small numerical difference arising from the fact that more than 13 units would be required for the energy per residue to converge to the value for the infinite chain. As before,[14] the energy per residue was defined as the total energy divided by $(2n + 1)$.

The conformational energy function included contributions from internal rotational, nonbonded, electrostatic, and hydrogen-bond energies. Unless explicitly mentioned otherwise, the radius of the hydrogen atom r_H was taken as 1.20 Å. No explicit account was taken of the solvent except for the choice of a dielectric constant of 4. While solvent could have been included,[20] it was omitted here since it was desired to focus attention on those effects (*viz.*, nonbonded interactions) which are thought to be the origin of alleged steric hindrance to helix formation in D,L copolymers. A rapid energy-minimization technique, described by Scott, *et al.*,[21] was used for locating the minima in the potential energy surface.

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Results and Discussion

Alanine. For reference purposes, the energy contour map for a 9-mer (eight side chains) of regular-sequence poly(D,L-alanine) was computed first, by assuming that ϕ, ψ, and χ_1 are the same for *every* residue, *i.e.*, for both D and L residues, with χ_1 taken as 180°, and the results are shown in Figure 2. The center of this map ($\phi = 0°$, $\psi = 0°$) is a point of approximate symmetry, which would become exact for an infinite chain. Comparing this map to that for poly(L-alanine),[14] it can be seen that the low-energy regions are those for the right- and left-handed (α_R and α_L) α helices, respectively, which appear in essentially the same positions for both polymers. Also, the energy per residue in the α-helical regions (-7.90 kcal/residue, approximately the same for α_R and α_L) is comparable with the energy per residue in the α-helical regions for a 9-mer of L-alanine[13] (-8.03 and -7.66 kcal/residue for α_R and α_L, respectively). However, as in the case[13] of [L,D,L,L-alanine]$_2$, the relatively low-energy region in the upper left-hand corner (β region) found in the (ϕ, ψ) map of poly(L-alanine) is not present in Figure 2 because of repulsive, nonbonded interactions of the side chains of D residues with the backbone atoms of neighboring units, or more explicitly, with the carbonyl group of the residue previous to the D residue and with the N–H group of the next residue.

In the case of [L,D,L,L-alanine]$_n$, it was found[13] that, for $n = 3$, the minimum-energy conformations in the α-helical regions with 24 independent variables were essentially the same as that with eight independent variables, *i.e.*, with a regularity condition imposed on an LDLL unit. Therefore, to conserve computer time, we introduce the same assumption here, *i.e.*, regularity of an LD unit, and thus have a six-variable problem for poly(D,L-alanine) (two sets of ϕ, ψ, χ_1 values) with a repeating LD unit. The dihedral angles and the energies of the minimum-energy α_R and α_L helices for a 13-mer of D,L-alanine and the all-L homopolymer[22] are shown in Tables I and II, respectively.

From the data of Table II, it can be seen that the energy of both the α_R and α_L helices of poly(D,L-alanine) is about the same as that of an α_R helix of poly(L-alanine). As before,[14] the energy of the α_L helix of poly(L-alanine) is higher than that of the α_R helix. In the all-L polymer, the small repulsive interaction between the C$^\beta$ atom and the carbonyl oxygen of the same residue in the α_L helix is comparable to that between the C$^\beta$ atom and the amide hydrogen atom of the same residue and between one of the side-chain methyl hydrogen atoms and the carbonyl oxygen of the third residue toward the N terminus in the α_R helix; *i.e.*, the repulsions in the α_R and α_L helices of an all-L polymer are comparable, and therefore cannot be the origin of the greater stability of the α_R helix. Instead, the α_R helix owes its greater stability to attractive nonbonded side chain-to-backbone interactions (see Table II), which are somewhat stronger for L side chains in the α_R helix than in the α_L helix. This arises because an L side chain is somewhat closer to the α_R backbone than to the α_L backbone. Of course, the opposite is true for D side chains, which are nearer to the α_L backbone than to the α_R one.

This effect also appears in poly(D,L-alanine); *i.e.*, because the D residues are somewhat further from the backbone of the α_R helix (correspondingly for L residues in the α_L helix), the side chain-to-backbone energy is somewhat higher for poly(D,L-alanine) than for the α_R helix of poly(L-alanine) (see Table II). However, this effect is balanced by the side chain-to-side chain interactions; in contrast to popular belief, not only is there no steric overlap between D and L side chains in an α helix of poly(D,L-alanine), but on the contrary, the interactions between the methyl groups in poly(D,L-alanine) are more favorable than those in poly(L-alanine) because of the proximity of the side chain of a D residue to that of the third next (L) residue, a situation analogous to that also observed for poly(L,D,L,L-alanine).[13] The balance of these two effects makes the energy of the α_R and α_L helices of poly(D,L-alanine) about the same as that of the α_R helix of poly(L-alanine).

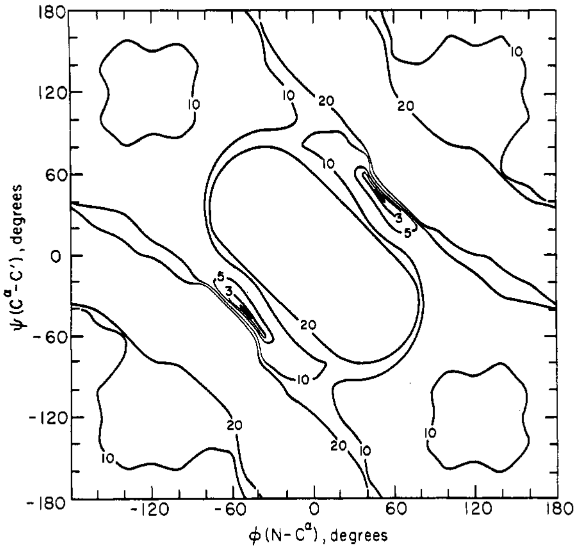

Figure 2. Energy contours for helices of a 9-mer of alternating regular-sequence poly(D,L-alanine), calculated with the regularity condition that ϕ, ψ, χ_1 are the same in *every* residue. The energy is expressed in kilocalories per residue, being interpolated from calculations at 20° intervals. The contours are drawn at energies 1, 3, 5, 10, 20 kcal/residue above the global minimum of -7.90 kcal/residue, the energy of a 9-mer of D,L-alanine having the same (α_R) conformation as the 13-mer described in Table I. It should be noted that the energies per residue of the 9-mer and 13-mer differ because the energy per residue depends slightly on chain length in short chains.

Further calculations (not shown here since the energy was not minimized because of the excessive computer time required) for a 5-mer, a 9-mer, and a 17-mer (compared to the data for the 13-mer of Table II) show that the energies of the α_R and α_L helices of poly(D,L-alanine) approach each other with increasing chain length, as indeed they must do for the infinite chain.

The calculations reported thus far show that the α_R and α_L helices of poly(D,L-alanine) are in local minima of comparable energy to that of the α_R helix of poly(L-alanine). Since these are not necessarily the global minimum for the D,L copolymer (even though it *is*[14] for the all-L polymer), it is conceivable that poly(D,L-alanine) might be able to form stable structures completely different from the α_R helical one observed for poly(L-alanine). Of course, this question could be answered unambiguously by a search of the whole conformational space. However, since the computations are too expensive, even if regularity in an LD unit is assumed, only several other likely structures were considered as possibly having energies comparable to, or lower than, that of the α_R and α_L helices.

The first set of additional structures considered for a 9-mer of D,L-alanine consisted of conformations in which the ϕ, ψ angles of L residues were taken in 10° intervals between

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(22) Our minimized conformations for poly(L-alanine) and poly(L-valine) differ slightly from those of Ooi, *et al.*,[14] because of a minor inaccuracy in their computer program.

TABLE I
DIHEDRAL ANGLES FOR SOME MINIMUM-ENERGY STRUCTURES OF A 13-MER OF L-ALANINE AND D,L-ALANINE[a]

Structure	Dihedral angles, deg: D residue ϕ	D residue ψ	D residue χ_1	L residue ϕ	L residue ψ	L residue χ_1
L α_R helix				−50.2	−56.2	−179.5
L α_L helix				+48.7	+57.3	−178.9
DL α_R helix	−48.1	−58.5	−178.0	−50.4	−54.5	−177.0
DL α_L helix	+50.8	+54.6	+176.1	+48.2	+58.2	+176.6
DL LD ribbon	+65.4	+45.1	−175.7	−67.1	+105.0	−158.8
DL DL ribbon[b]	+67.1	−105.0	+158.8	−65.4	−45.1	+175.7
DL LD helix	+140.8	−127.2	−179.8	−110.9	+124.7	+180.0
DL DL helix	+110.9	−124.7	+180.0	−140.8	+127.2	+179.8

[a] Starting points for the minimization for the α_R and α_L helices of both the L and D,L polymers were $(\phi, \psi, \chi_1) = (-48^\circ, -57^\circ, +180^\circ)$ and $(+48^\circ, +57^\circ, +180^\circ)$, respectively. The starting points for the other structures are given in the text. [b] The DL ribbon and DL helix do not represent minimum-energy conformations, but just the conformations enantiomorphic to the minimum-energy LD ribbon and LD helix, respectively.

TABLE II
INTERACTIONS CONTRIBUTING TO THE CONFORMATIONAL ENERGY OF SOME MINIMUM-ENERGY STRUCTURES OF A 13-MER OF BOTH L- AND D,L-ALANINE

Structure	Interaction energies, kcal/mol: Nonbonded[a] sc–sc	Nonbonded[a] sc–bb	Nonbonded[a] bb–bb	Electrostatic plus H bond	Internal rot.	Energy/residue[b]
L-Alanine α_R	−1.67	−42.31	−40.06	−39.70	+6.53	−9.02
α_L	−1.22	−34.67	−40.87	−41.27	+6.38	−8.59
D,L-Alanine α_R	−4.38	−36.73	−40.34	−40.80	+6.59	−8.90[c]
α_L	−5.17	−37.35	−40.48	−40.60	+6.77	−8.99[c]
LD ribbon	−3.11	−32.77	−27.38	−19.54	+12.85	−5.38[c]
DL ribbon	−3.78	−33.27	−26.79	−18.25	+12.85	−5.33[c]
LD helix	−1.63	−34.71	−24.61	−26.24	+3.47	−6.44[c]
DL helix	−1.62	−34.80	−24.56	−26.64	+3.47	−6.47[c]

[a] sc and bb refer to side chain and backbone, respectively. [b] The energy per residue is the sum of the values in the previous columns divided by the number of backbone residues, *i.e.*, 13. [c] The two values in each of these pairs should be identical for an infinite chain.

−180° and +180°, whereas the ϕ, ψ angles for the D residues were obtained by reflection through the center of the map. The energies for these 36 × 36 conformations were calculated. The lowest of these energies was found to be −4.29 kcal/residue for $(\phi_L, \psi_L, \phi_D, \psi_D) = (-120^\circ, +170^\circ, +120^\circ, -170^\circ)$ with $\chi_L = \chi_D = 180^\circ$. This is several kilocalories per residue higher than the energy (−7.90 kcal/residue) of the α-helical conformation of the same copolymer. The energy of a 13-mer having the same (ϕ, ψ, χ_1) values is *very* much higher because an approximately ten-residue ring structure is formed with these values of ϕ and ψ. A similar effect, in which a six-residue ring structure is formed, was reported[23,24] for $(\phi_L, \psi_L, \chi_L, \phi_D, \psi_D, \chi_D) = (-120^\circ, +120^\circ, 180^\circ, +120^\circ, -120^\circ, 180^\circ)$. Thus, these sets of (ϕ, ψ) values are not possible for a long chain of poly(D,L-alanine).

As two other additional structures, we consider two regular ones described by Ramachandran and Chandrasekharan[23] for poly(D,L-alanine). One of them is an "LD ribbon" characterized by $(\phi_L, \psi_L, \phi_D, \psi_D) = (-60^\circ, +100^\circ, +60^\circ, +40^\circ)$ and shown in Figure 3; since they did not specify χ_1, we took it initially as 180° in both residues. This structure is formed essentially by repetition of a favorable LD bend described previously,[26] and it was suggested[23] that this ribbon structure might associate with nucleic acids because the repeat distance for four residues is about twice the distance between the bases in a nucleic acid double helix. The conformational energy of the above ribbon structure was computed and found to be very high because of repulsive interactions between L and D side chains. However, after energy minimization (in which rotation about the C^α–C^β bond relieved this steric hindrance) with the regularity condition imposed on the LD unit, the structures and energies shown in Tables I and II, respectively, were obtained; a similar ribbon structure, the "DL ribbon," consisting of a series of DL bends,[23] is also shown in these tables. The other structure proposed[23] is an "LD helix," characterized by $(\phi_L, \psi_L, \phi_D, \psi_D) = (-110^\circ, +124^\circ, +140^\circ, -128^\circ)$ and shown in Figure 4; here again χ_1 was taken initially as 180° in both residues, since it was not specified in ref 23. This structure is one with its (ϕ, ψ) values in the β regions of the energy contour maps for an L and a D residue. The diameter of this helix is rather large (approximately 7.7 Å), and it is therefore thought[23] to be able to accommodate large alkali metal ions inside the helix, with possible consequences for antibiotic activity. After energy minimization, the structures and energies shown in Tables I and II, respectively, were obtained; a left-handed "DL helix," the enantio-

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(23) G. N. Ramachandran and R. Chandrasekharan, submitted to the Second American Peptide Symposium, Cleveland, Ohio, Aug 1970, Paper No. 28.

(24) Actually, as indicated by Miller, *et al.*,[25] and confirmed here by computations with chains of 40 peptide units, a long poly(amino acid) chain (with $(\phi, \psi)_i = (-\phi, -\psi)_{i-1} = (\phi, \psi)_{i+2}$ for any i) adopts a helical conformation with zero pitch, *i.e.*, a ring. However, the size of the ring depends on the values of ϕ and ψ. If ϕ_i differs from ψ_i by less than 20–30°, then the rings are *very* large; *e.g.*, in the case where $\phi_i = \psi_i = -180^\circ$, the ring is of infinite size, *i.e.*, the extended chain. For the case where ϕ_i and ψ_i fall in the β region, the ring size varies from five to ten residues.

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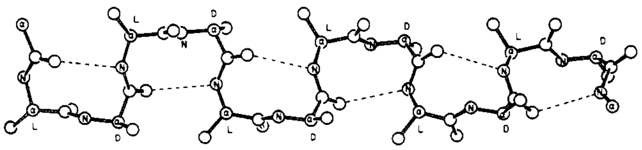

Figure 3. The LD ribbon of Ramachandran and Chandrasekharan[23] for a 13-mer of D,L-alanine with the dihedral angles given in Table I. Hydrogen atoms have been omitted, and possible hydrogen bonds are shown as dashed lines. The α-carbons are approximately in the plane of the paper.

morph of the right-handed LD helix, is also shown in these tables.

Comparison of the energies of the several proposed structures for poly(D,L-alanine), as given in Table II, shows that the α helices have by far the lowest energies, and this strongly suggests that the α helices are the preferred regular conformations for isolated molecules of poly(D,L-alanine). Obviously, this does not imply that the ribbon or the LD helix might not play an important role in complexes with other molecules.

It seemed desirable to check whether this conclusion depended very much on the choice of parameters in the empirical energy functions. One might expect that the result, that there is no steric hindrance between L and D side chains, could depend on the choice of the van der Waals radii of the atoms involved. Therefore, since the hydrogen atom is the most critical one in this respect,[14] the energies of the various structures were recalculated with a larger radius r_H of the hydrogen atom, *viz.*, 1.275 Å. The results, shown in Table III, confirm the conclusion drawn from the calculations with $r_H = 1.20$ Å that the α helices are the regular structures of poly(D,L-alanine) with by far the lowest energy. Again, the α_R and α_L helices of poly(D,L-alanine) have about the same energy as the α_R helix of poly(L-alanine). The energies of Table III are somewhat less negative than those in Table II because of the larger repulsive nonbonded energy when r_H is taken as 1.275 Å.

In predicting stable helical structures, the free energy of the helix should be compared with that of a random coil of the same chain length, as was done for poly(L-alanine).[27] Since such an analysis consumes a large amount of computer time, we can present a qualitative argument about the free energy of the random coil which will enable us to discuss helical stability in terms of the energies of Table II. Go, *et al.*,[27] showed that, at the Θ point, the statistical weight of a coil sequence can be calculated approximately by taking into account only those energies depending on the dihedral angles of a single residue; similarly, Flory[28,29] calculated the properties of D,L-copolypeptide random coils at the Θ point from the partition function for separate residues. This partition function per residue was calculated by taking into account the nonbonded interactions of atom pairs lying between C^{α}_{i-1} and C^{α}_{i+1}, inclusive, and the electrostatic interaction with the neighboring amide groups.[29] Now, the partition function for a D-alanine residue has the same values as that for an L-alanine residue, since the energy contour maps for D and L residues are related to each other by an inversion through the center. Therefore, if the partition function of the random coil depends only on the partition function per residue, then the free energies of the coil forms of poly(D,L-alanine) and poly(L-alanine) at the Θ point should be the same.[30] Hence, we may consider stability only in terms of the free energies (which may be approximated by energies) of helical forms, *i.e.*, the above conclusions, based on the data of Table II, apply, as far as steric hindrance is concerned.

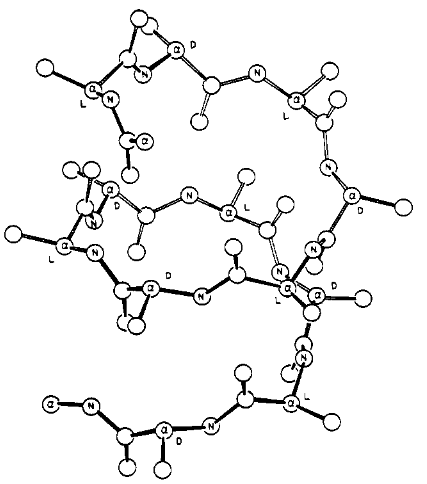

Figure 4. The right-handed LD helix of Ramachandran and Chandrasekharan[23] for a 13-mer of D,L-alanine with the dihedral angles given in Table I. Hydrogen atoms have been omitted.

TABLE III
ENERGY PER RESIDUE FOR A 13-MER[a] OF BOTH L- AND D,L-ALANINE, WITH r_H = 1.275 Å

Structure	Energy per residue, kcal/mol D,L-Alanine	L-Alanine
α_R helix	−7.95	−7.98
α_L helix	−8.02	−7.86
LD ribbon	−4.38	*b*
DL ribbon	−4.32	*b*
LD helix	−5.47	*b*
DL helix	−5.51	*b*

[a] Calculated for the values of ϕ, ψ, χ_1 given in Table I. [b] Not calculated because of large repulsion.

When the effect of the solvent is taken into account, the solvation (and hence the free energies) of the coil forms of poly(D,L-alanine) and poly(L-alanine) may be quite different, the first being a rather compact coil and the second quite an extended one.[25,31] Hence, the solvent could affect the helix–coil transition markedly. Such solvent effects may be the reason why Takahashi, *et al.*,[8] did not observe a conformational transition for poly(D,L-alanine) in contrast to poly(L-alanine), *i.e.*, that poly(D,L-alanine) did not exist in the helical form in this solvent (even though, as we have seen, there is no steric hindrance to its formation). The observation from hydrogen-exchange studies,[5,6] that poly(D,L-alanine) cannot form an α helix, was based on measurements on a short copolymer (DP = 29), and it was shown experimentally[32] that low molecular weight poly(L-alanine) (in water) has very little helix content; hence, a poly(D,L-alanine) chain would be

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(27) M. Go, N. Go, and H. A. Scheraga, *J. Chem. Phys.*, **52**, 2060 (1970); **54**, 4489 (1971).

(28) P. J. Flory, "Statistical Mechanics of Chain Molecules," Interscience, New York, N. Y., 1969, p 282.

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

(30) However, the root-mean-square end-to-end distances, which depend on the sequence in an LD copolymer, will differ appreciably[29,31] for the two polymers because different values of (ϕ, ψ) are preferred for L and D residues.

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

(32) R. T. Ingwall, H. A. Scheraga, N. Lotan, A. Berger, and E. Katchalski, *Biopolymers*, **6**, 331 (1968).

TABLE IV
DIHEDRAL ANGLES FOR SOME MINIMUM-ENERGY STRUCTURES OF A 13-MER OF BOTH L- AND D,L-VALINE[a]

	Dihedral angles, deg					
	D residue			L residue		
Structure	ϕ	ψ	χ_1	ϕ	ψ	χ_1
L-Valine α_R				−48.8	−57.5	+166.8
α_L				+48.8	+57.7	−169.4
D,L-Valine α_R	−45.6	−59.6	+52.5	−52.0	−53.8	+174.4
α_L	+52.1	+53.8	+65.8	+45.7	+59.4	−172.5
LD helix	+139.3	−125.4	−170.0	−111.9	+125.3	−178.9

[a] Starting points for the α_R and α_L helices were (ϕ, ψ, χ_1) = (−48°, −57°, +170°) and (+48°, +57°, −170°), respectively, for the L residues and (ϕ, ψ, χ_1) = (−48°, −57°, +60°) and (+48°, +57°, +60°), respectively, for the D residues. The starting point for the LD helix was chosen as specified in the section on alanine.

TABLE V
INTERACTIONS CONTRIBUTING TO THE CONFORMATIONAL ENERGY OF SOME MINIMUM-ENERGY STRUCTURES OF A 13-MER OF BOTH L- AND D,L-VALINE

	Interaction energies, kcal/mol				
	Nonbonded[a]		Internal rot. for	Back-	Energy/
Structure	sc–sc	sc–bb	χ_1	bone[b]	residue[c]
L-Valine α_R	−10.3	−74.9	+3.9	−73.7	−11.92
α_L	−8.7	−65.1	+2.5	−75.4	−11.28
D,L-Valine α_R	−20.2	−66.7	+1.0	−73.6	−12.27[d]
α_L	−21.1	−67.5	+1.0	−73.7	−12.41[d]
LD helix	−19.0	−70.7	+1.1	−48.2	−10.52

[a] sc and bb refer to side chain and backbone, respectively. [b] Backbone energy stands for the sum of the contributions from nonbonded, electrostatic, and hydrogen-bond interactions and rotational barriers in the backbone. [c] The energy per residue is the sum of the values in the previous columns divided by the number of backbone residues, *i.e.*, 13. [d] These two values should be identical for an infinite chain.

expected to be helical, not at a DP of 29, but at a much higher molecular weight.

In conclusion, we find no steric hindrance to α-helix formation in poly(D,L-alanine), and we expect this polymer to take on the α-helix conformation, as well as does poly(L-alanine), although probably under different solvent conditions.

Valine. An α-helical conformation of poly(D,L-valine) has to accommodate the bulky, branched side chain of the valyl residue. In the case of poly(L-valine), it has been shown both theoretically[14] and experimentally[15] that branched side chains of L residues can indeed accommodate to an α_R-helical backbone. However, in poly(D,L-valine) we have the additional problems that D residues must also accommodate to an α_R backbone and that no steric overlaps between D and L side chains must occur.

As in the case of poly(D,L-alanine), the energy surface was first examined for a 9-mer of regular-sequence poly(D,L-valine) by assuming that ϕ, ψ, and χ_1 are the same for *every* residue, with χ_1 having the values of −60° +60°, or 180° (whichever of these three values of χ_1 corresponded to the lowest energy). As in all calculations in this section, $\chi^{2,1}$ and $\chi^{2,2}$ are kept at 180°. In contrast to the energy contour map of poly(D,L-alanine), that for poly(D,L-valine) does not exhibit a sterically unhindered low-energy region; the lowest energy on such a map was −1.67 kcal/residue for (ϕ, ψ, χ_1) = (−80°, +60°, +180°) for both the L and D residues. Appreciable steric overlap of the side chains of D residues with the backbone and with the side chains of L residues appears in the α_R-helical conformation. When (ϕ, ψ, χ_1) were set equal to (−48.4°, −57.3°, +60°) for D residues (the approximate values for the α_R helix for poly(D-valine)), and to (−48.4°, −57.3°, +170°) for L residues (the latter being those found by Ooi, *et al.*,[14] for α_R-helical poly(L-valine)), a relatively unhindered conformation with an energy of −7.51 kcal/residue resulted.

With this indication that an α_R-helical conformation of poly(D,L-valine) might be sterically possible, the calculations were then carried out by imposing the regularity condition on an LD unit; *i.e.*, six independent variables were used, ϕ, ψ, and χ_1 for both D and L residues. Energy minimization for the α_R, α_L, and LD helix with respect to these six variables led to the conformations and energies shown in Tables IV and V, respectively. For comparison, the energy of the α_R and α_L helix of poly(L-valine) was also minimized (a three-variable minimization with ϕ, ψ, χ_1 the same for every residue, and the results are included in these tables.

The data of Table V show clearly that the α-helical conformation of poly(D,L-valine) is an energetically favorable one. Its energy is even lower than that of the α_R helix of poly(L-valine), indicating that this conformation is quite free from steric hindrance, and is nearly 2 kcal/residue lower than that of the LD helix.[33] In fact, as in the case of poly(D,L-alanine), the attractive side chain-to-chain interaction energy is stronger for poly(D,L-valine) than for poly(L-valine). Therefore, we conclude that the formation of α helices of poly(D,L-valine) is possible. Figure 5 shows two views of the α_R helix of poly-(D,L-valine), one in which the helix axis is perpendicular to the plane of the paper (Figure 5a) and one in which it lies in the plane of the paper (Figure 5b). Figure 5a illustrates the absence of steric overlaps between the side chains and the α_R-helical backbone, and Figure 5b illustrates the absence of steric overlaps between the side chains of D and L residues.

Recalculation of the energies of the conformations of Table IV with a hydrogen atom radius r_H = 1.275 Å confirms the above conclusions. The energies of the α_R helix of poly(L-valine), the α_R helix of poly(D,L-valine), and the LD helix of poly(D,L-valine) are −10.35, −10.72, and −8.96 kcal/mol, compared with the values −11.92, −12.27, and −10.52 kcal/mol, respectively, for r_H = 1.20 Å.

Phenylalanine. The side chain of a phenylalanyl residue has two single bonds, and hence the conformation of the side chain depends on two dihedral angles, χ_1 and χ_2. Because of the symmetry of the phenyl ring, conformations with χ_2 between 0 and 180° are identical with those with χ_2 between 0 and −180°. In order to obtain an initial view of possible restrictions on the range of low-energy values of χ_1

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(33) The LD-ribbon structure was not investigated because of the steric hindrance already observed between the side chains of poly(D,L-alanine) for χ_1 = 180°.

and χ_2, a calculation was carried out for a regular α_R helix, $(\phi, \psi) = (-48°, -57°)$ for homopolymers (13-mers) of L- and D-phenylalanine, respectively. Only three values of χ_1 ($-60°$, $+60°$, and 180°) and a series of values of χ_2 (in 15° intervals between 0 and 180°) were used. For the homopolymer of L residues, conformations with $\chi_1 = 60°$ have very high energies; correspondingly, for the homopolymer of D residues, those with $\chi_1 = -60°$ have very high energies. For other values of χ_1, the energies of both homopolymers are shown in Figure 6 as a function of χ_2. As before,[16] the global minimum for the homopolymer of L residues is found in area I of Figure 6, which represents conformations in which the phenyl ring is roughly parallel to the helix axis; nuclear magnetic resonance measurements[34] on poly(L-phenylalanine) in chloroform–TFA mixtures indicate a conformation in region IIa, which represents conformations in which the phenyl ring sticks out, away from the backbone.

In searching for low-energy α-helical conformations of poly(D,L-phenylalanine), considerations of economy in computer costs dictated the following limited set of conformations to be treated. A 13-mer of the alternating regular-sequence D,L copolymer was used, and the backbone was maintained in a fixed conformation, $(\phi_L, \psi_L, \phi_D, \psi_D) = (-50.4°, -54.5°, -48.1°, -58.5°)$, as found for poly(D,L-alanine)(Table I). On the basis of the results of Figure 6 for α_R-helical homopolymers, only the following side-chain dihedral angles were selected as *initial* values: for L residues $\chi_1 = 180°$ with $\chi_2 = 30$, 60, 90, 120, 150, and 180° and $\chi_1 = -60°$ with $\chi_2 = 120$, 150, and 180°; for D residues $\chi_1 = +60°$ with $\chi_2 = 30$, 60, 90, 120, 150, and 180° and $\chi_1 = 180°$ with $\chi_2 = 120$, 150, and 180°. Thus, there are 81 conformations (for an LD pair), all but five of which involve moderately to severe side chain–side chain overlaps. Using these five conformations as initial ones, energy minimization with respect to the four χ angles per LD unit led to the conformations shown in Table VI. For comparison, the dihedral angles and energies of the minimum-energy α_R- and α_L-helical structures of a 13-mer of L-phenylalanine are given in Table VII.

The global minimum for the homopolymer of L residues, the α_R helix, has a very low energy (-16.00 kcal/residue) because of the favorable alignment of the phenyl rings roughly parallel to the helix axis, giving rise to very strong nonbonded side chain–backbone interactions (-97 kcal for a 13-mer). However, in the case of the D,L copolymer, side chain–side chain overlap makes this alignment less perfect, and hence the two structures in Table VI with their L residues in approximately this conformation $(\chi_1{}^L, \chi_2{}^L = -60°, -180°)$ have weaker side chain–backbone interactions (only about -70 kcal for a 13-mer). Actually, all five structures of the D,L-copolymer in Table VI have about the same side chain–backbone interaction energy, and it is the side chain–side chain interaction which determines the structure of lowest energy. The structure in the first line of Table VI has the lowest energy because the phenyl rings in each successive LD pair are approximately parallel to each other, giving rise to favorable side chain–side chain interactions, as illustrated in Figure 7. In any event, there appears to be an energetically favorable conformation of the side chains in the α_R-helical form of poly(D,L-phenylalanine), comparable in energy to the most stable α_R-helical conformation of the all-L homopolymer. Of course, in general, solvent effects will play an important role in determining the side-chain conformation.

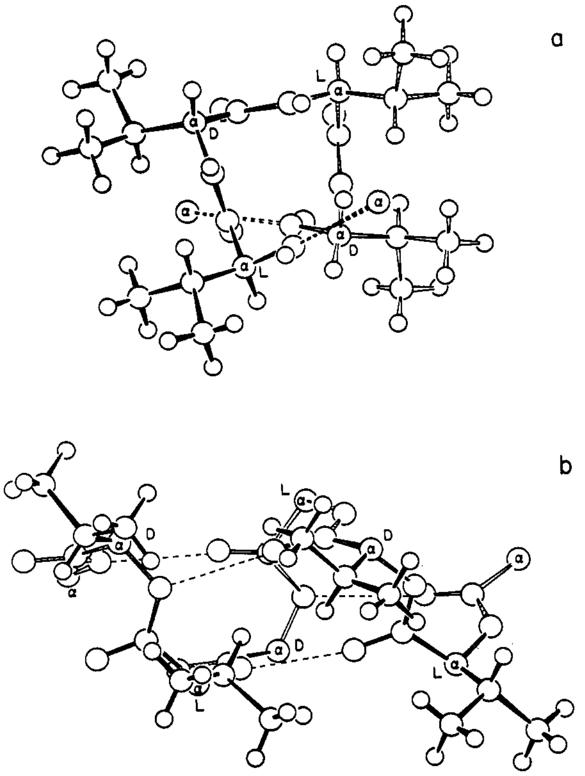

Figure 5. The right-handed α-helix of poly(D,L-valine), with the dihedral angles of Table IV: (a) helix axis perpendicular to the plane of the paper, (b) helix axis in the plane of the paper. In (b), the hydrogen atoms of the backbone are not shown and the dashed lines represent hydrogen bonds; the four side chains shown are above the plane of the paper and the two side chains below the plane of the paper are omitted.

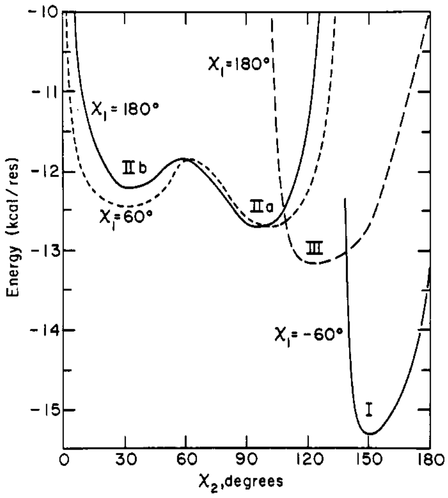

Figure 6. Conformational energies as a function of χ_2 (for various values of χ_1) for an α_R helix $(\phi, \psi = -48°, -57°)$ of a 13-mer of phenylalanine (solid curves, homopolymer of L residues; dashed curves homopolymer of D residues).

In conclusion, we can expect that poly(D,L-phenylalanine) is capable of forming α-helical structures, and that the side-chain conformation in this copolymer will differ from that in the all-L homopolymer.

Both X-ray studies[35] and studies of the infrared absorptions[36] of the backbone amide groups of poly(D,L-phenyl-

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(34) D. N. Silverman and H. A. Scheraga, *Biochemistry*, **10**, 1340 (1971).

(35) P. Horn, J. Marchal and C. Lapp, *C. R. Acad. Sci.*, **248**, 233 (1959).

(36) C. Lapp and J. Marchal, *J. Chim. Phys. Physicochim. Biol.*, **60**, 766 (1963).

TABLE VI

DIHEDRAL ANGLES AND ENERGIES FOR SOME MINIMUM-ENERGY CONFORMATIONS[a] OF A 13-MER OF D,L-PHENYLALANINE

Dihedral angles, deg[b]				Interaction energies, kcal/mol			
				Nonbonded[c]		sc	Energy/
χ_1^D	χ_2^D	χ_1^L	χ_2^L	sc–sc	sc–bb	int. rot.	residue[d]
+55.5	+21.8	+174.6	+27.8	−51.4	−70.0	+1.1	−15.00
+56.8	+24.0	−171.8	+114.6	−46.0	−70.4	+4.0	−14.40
+61.0	+101.3	−65.1	−178.8	−40.0	−71.6	+4.2	−14.01
−177.4	+156.6	−179.4	+103.1	−40.4	−67.7	+1.6	−13.94
+178.4	+145.4	−64.5	−179.8	−28.8	−67.9	+3.4	−12.92

[a] The values of ϕ and ψ are those given in Table I for the α_R helix of poly(D,L-alanine). [b] Starting conformations are given in the text. [c] sc and bb refer to side chain and backbone, respectively. [d] The energy per residue is the sum of the values in the previous columns plus a backbone energy of −74.7 kcal (arising from the contributions from nonbonded, electrostatic, and hydrogen-bond interactions and rotational barriers in the backbone), divided by the number of backbone residues, *i.e.*, 13.

TABLE VII

DIHEDRAL ANGLES AND ENERGIES FOR THE MINIMUM-ENERGY α-HELICAL CONFORMATIONS[a] OF A 13-MER OF L-PHENYLALANINE

Helix	Dihedral angles, deg				Interaction energies, kcal/mol				
					Nonbonded[b]		sc		Energy/
sense	ϕ	ψ	χ_1	χ_2	sc–sc	sc–bb	int. rot.	Backbone	residue[c]
α_R	−51.1	−54.4	−56.4	+154.9	−38.5	−97.0	+0.7	−73.1	−16.00
α_L	+48.7	+57.3	+172.0	+46.0	−30.4	−75.1	+4.8	−75.7	−13.58

[a] Minimized, starting from the low-energy conformations described by Yan, *et al.*[16] For α_R $(\phi, \psi, \chi_1, \chi_2) = (-51.1, -54.4, -57.4, +155.3)$ and for α_L $(+48.7, +57.3, +172.3, +45.7)$, with the same dihedral angles for every residue. The conformations obtained differ slightly from the starting conformations, probably due to differences in the parameter sets used. [b] sc and bb refer to side chain and backbone, respectively. [c] The energy per residue is the sum of the values in the previous columns, divided by the number of backbone residues, *i.e.*, 13.

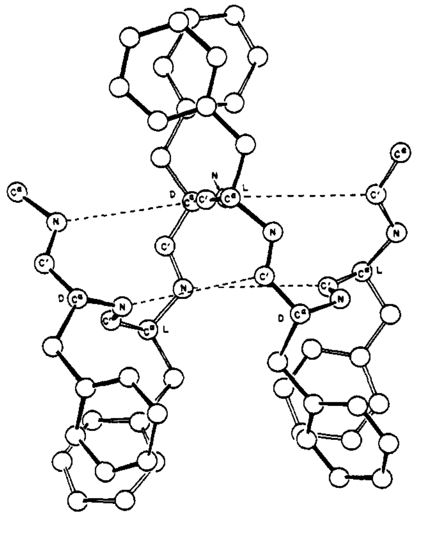

Figure 7. The low-energy conformation of poly(D,L-phenylalanine) of the first line of Table VI. Only the carbon and nitrogen atoms are shown. The helix axis is approximately horizontal and hydrogen bonds are indicated by dashed lines between N and C′ atoms.

alanine) in the solid state do indeed reveal an α-helical conformation. Further, in a mixture of chloroform plus 0.5% formamide, these molecules exhibit the hydrodynamic behavior of rods[37] (though slightly more elongated than an α helix). These results agree with our conclusion that poly(D,L-phenylalanine) can form α helices. There are as yet no experimental data to check our predictions of the side-chain conformation of this copolymer.

α-Aminoheptanoic Acid. Since our primary concern in this paper is with possible steric hindrances to α-helix formation, we select α-aminoheptanoic acid (AHA) as a model for lysine to avoid problems associated with electrostatic interactions of the ϵ-amino group. In such a long, unbranched side chain, there are essentially four single bonds about which rotation can take place. Thus, even with a regularity condition in an LD unit, we would have a problem of 12 independent variables; even worse, there would be a considerable number of local minima in the 12-dimensional energy surface. Therefore, as in the case of phenylalanine, we have maintained the backbone conformation of *every* residue at the α_R-helical values of $(\phi, \psi) = (-48°, -57°)$ and computed the energy for selected combinations of χ_1, χ_2, χ_3, and χ_4 *without* energy minimization, in order to locate some low-energy α_R-helical structures.

Initially, the energies of the regular 9-mer homopolymers, poly(L-AHA) and poly(D-AHA), respectively, in the α_R-helical conformation were computed by imposing the same set of $(\chi_1, \chi_2, \chi_3, \chi_4)$ on each side chain and allowing each of these dihedral angles to take on any one of three values, *viz.*, −60, +60, 180°; thus, there are 3^4 possible side-chain conformations to consider. Table VIII lists those conformations whose energies were within 1 kcal/residue of the lowest energy conformation (of those examined). These particular side-chain conformations were then used to construct the alternating regular-sequence D,L copolymers of Table IX, and the energies of these copolymers were computed and are listed in Table IX.

Of the conformations considered, the lowest energy one for α_R-helical poly(L-AHA) (−14.25 kcal/residue) is slightly more stable than that for α_R-helical poly(D,AHA) (−13.99 kcal/residue). Since an α_R helix of poly(D-AHA) is energetically equivalent to an α_L helix of poly(L-AHA), this result suggests that the right-handed α helix is more stable than the left-handed one for poly(L-AHA); however, no further meaning should be attached to this result, because only a very

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(37) J. Marchal and C. Lapp, *J. Chim. Phys. Physicochim. Biol.*, **61**, 999 (1964).

TABLE VIII
DIHEDRAL ANGLES AND ENERGIES OF SPECIFIC SIDE-CHAIN CONFORMATIONS OF 9-MERS OF α_R-HELICAL[a] D-AHA and L-AHA

Polymer	Dihedral angles, deg χ_1	χ_2	χ_3	χ_4	Energy/ residue, kcal/mol
Poly(D-AHA)	60	60	180	60	−13.94
	60	60	180	180	−13.99[b]
	60	60	60	180	−13.26
	60	180	60	60	−13.55
	60	180	60	180	−13.29
	60	180	180	180	−13.39
	60	180	180	−60	−13.13
Poly(L-AHA)	180	180	60	60	−14.25[b]
	180	180	60	180	−13.89
	180	180	180	180	−13.49
	180	60	180	60	−13.67
	180	60	180	180	−13.48

[a] $(\phi, \psi) = (-48°, -57°)$; $\chi_5 = 180°$. [b] Lowest energy conformation (of those examined) for the two α_R-helical homopolymers.

limited portion of the energy surface has been explored in these computations.

The important point about the data of Table IX is that the lowest energy D,L copolymer considered has an energy (−15.5 kcal/residue) lower than that of either of the homopolymers. This suggests strongly that a polymer of alternating D and L residues of AHA can adopt an α_R-helical backbone conformation.

Similar calculations are in progress with poly(D,L-lysine), in which the nonpolar terminal CH_3 group of AHA is replaced by the polar ϵ-NH_2 group of lysine. However, from the results presented here for poly(D,L-AHA), it seems reasonable to expect that it will be found that there is no steric hindrance to the formation of an α_R helix in poly(D,L-lysine). In fact, laser Raman spectra of poly(D,L-lysine) in the solid state[38] suggest that poly(D,L-lysine) does indeed adopt the α-helical conformation.

TABLE IX
DIHEDRAL ANGLES AND ENERGIES[a] OF SPECIFIC SIDE-CHAIN CONFORMATIONS OF 9-MERS OF α_R-HELICAL[b] D,L-AHA

Conformation of D-residues					Conformation of L-residues				
				χ_1	180	180	180	180	180
				χ_2	180	180	180	60	60
				χ_3	60	60	180	180	180
				χ_4	60	180	180	60	180
χ_1	χ_2	χ_3	χ_4						
60	60	180	60		∞	∞	−15.1	−14.6	−14.4
60	60	180	180		∞	−10.6	−14.6	−14.4	−14.1
60	60	60	180		∞	−9.6	−14.2	−14.0	−13.7
60	180	60	60		∞	∞	∞	∞	∞
60	180	60	180		∞	∞	+68	−12.6	−14.8
60	180	180	180		∞	∞	−15.5[c]	−14.5	−14.2
60	180	180	−60		∞	∞	−11.4	−14.8	−14.4

[a] The values within the table are the energies per residue (kcal/mol) for a D,L copolymer in which the conformations of the side chains of the D and L residues are the indices of the rows and columns, respectively. The symbol ∞ is given when the energy per residue exceeds +100 kcal/mol. [b] $(\phi, \psi) = (-48°, -57°)$; $\chi_5 = 180°$. [c] Lowest energy conformation of those given in this table.

Conclusion

While the most stable conformation of a regular-sequence D,L copolymer will be influenced by solvent, and probably to a different extent than the corresponding all-L or all-D homopolymers, the calculations reported here indicate that there is no steric hindrance to α-helix formation for poly(D,L-alanine), poly(D,L-valine), poly(D,L-phenylalanine), and poly(D,L-lysine). Thus, it is reasonable to expect that any regular-sequence D,L copolypeptide can adopt an α-helical conformation.

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(38) A. Lewis and H. A. Scheraga, *Macromolecules*, **4**, 539 (1971).