Helical Structures of Poly(D–L-peptides). A Conformational Energy Analysis

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Received April 11, 1977

ABSTRACT: Conformational energy calculations are reported for a number of possible helical structures of poly(D–L-peptides): the α helix, two single-stranded π_{DL}, and five double-stranded $\pi\pi_{DL}$ helices. For a poly(D-alanine-L-alanine) sequence, the energies of the various helices are found to differ by less than 1 kcal/(mol residue). For some helices (especially the π_{DL} ones) two structural variants are predicted. These variants, called "goniomers", are characterized by reversed sequences of conformational angles but have the same screw sense and similar helical parameters. A biological implication of these goniomers is suggested, and their usefulness as a critical test for energy calculations is considered.

(I) Introduction

Different crystalline modifications are frequently observed in both natural and synthetic polymers. The crystalline polymorphism of the syndiotactic polypeptide poly(γ-benzyl D–L-glutamate) (PBD–LG), a stereochemical model of the peptide antibiotic Gramicidin A, is nevertheless remarkable. Six different helical structures have been reported for PBD–LG[1] while its enantiomeric counterpart, PBLG, exists in only two crystalline forms, the α helix and the extended β pleated sheet.

In order to better understand the conformational features of the LD repeat unit which account for this wide range of stable structures, we have undertaken their detailed analysis by conformational energy methods. This paper examines the α helix and several members of the π_{DL} and double-stranded $\pi\pi_{DL}$ families of helices which are specific to the L–D stereosequence[2,3] (Figure 1). It extends previous work by Ramachandran and Chandrasekaran[4] and Hesselink and Scheraga.[5] Contrary to the latter work, which dealt with various side chains, our work is restricted to poly(L-Ala-D-Ala). The structures considered here appear, however, to be possible also quite generally for amino acids with longer or bulkier side chains. Indeed, for intrachain hydrogen-bonded helices, possible steric conflicts between main-chain and side-chain atoms usually involve only the C_β atoms.

In the course of this investigation we have observed that, for some structures, two different geometries of the polypeptide chain may be envisaged. The relationship between the two so-called "goniomeric" variants and their implications are discussed. Further examination shows that this conformational possibility is not restricted to helical conformations of poly(D–L-peptides) only.

(II) Methods

(1) Potentials and Mode of Calculation. The potential functions, already used in previous works,[6,7] are derived from Poland and Scheraga[8] and Scheraga.[9] van der Waals interactions are calculated with a Lennard-Jones 6–12 potential function with cut-off of 7 Å. Torsional energies around covalent bonds and the deformation energy of the τ ($NC_\alpha \Lambda C_\alpha C'$) valence angles are included. The electrostatic interactions are calculated by the monopole approximation with a dielectric constant taken equal to one.

The helix construction uses the method of Hermans and Ferro[10] and can be performed either by fixing all torsional angles: ϕ_L, ω_L, Ψ_L, and ϕ_D, ω_D, Ψ_D for L and D residues, respectively, or with helical parameters h and θ (rise and rotation angle per repeat unit) fixed.

The energy of the helix is taken as that of the asymmetric unit interacting with itself and with the other residues in a chain made of eight dipeptide units. The energy is minimized with respect to all the internal rotational angles (including ω angles), to the τ angles, and, for double helices, to the relative rotation $\bar{\rho}$ and translation $\bar{\tau}$ of the two chains. Given the large number of variables, the energy optimization is performed in four steps, in order to avoid possible divergence of the conjugate gradient optimization procedure.[11] (i) Approximate values are given for the internal rotation angles. The helix parameters h and θ are fixed at the experimental, or estimated, values. In the latter case, ϕ_D and Ψ_D are calculated as a function of ω's, τ's, ϕ_L, Ψ_L, h, and θ by solving the Sugeta and Miyazawa expressions[12] using a Newton procedure. Only χ_L and χ_D are optimized. (ii) ϕ_L and Ψ_L are optimized with fixed values of h and θ. (iii) An optimization over χ_L, χ_D, ϕ_L, θ_D, Ψ_L, and Ψ_D is performed with h and θ free. (iv) When desired, a final optimization is performed over all previous variables and ω and τ parameters.

While the minimization procedure avoids lengthy scannings, it may not always yield the conformation of lowest energy (given the large number of variables) especially when several local minima exist in the vicinity of the stable conformation. In fact, for most structures several almost similar conformations can be obtained whose ϕ and Ψ angles differ by at most a few degrees. These variations reflect the vagaries of the minimization procedure as it approaches the stable conformation. More important variations, to be analyzed later, have also been observed and reflect the existence of so-called "goniomeric" variants.

(2) Testing the Minimization Procedure and Potential Functions. The minimization procedure can be tested by generating a sequence of two L-alanine residues and calculating their conformation in the α helix as independant variables. Conformational and valence angles of the two residues differ, in the final structure, by at most 0.5°, although ϕ and Ψ angles changed by up to 10–15° during the calculations (Table I, column (b)).

We note that the final dihedral angles are significantly different from those of Hesselink and Scheraga. While the latter are close to those first adopted for the "standard" α helix,[13] the present ones have been observed for α poly(L-alanine).[14,15]

Since some of our structures differed in a similar manner from the structures of Hesselink and Scheraga, the influence of various parameters of the set of potentials has been investigated in more detail, including the dielectric constant, the radius of H_β atoms, and the δ parameter (the repulsive part of the potential between two atoms i and j is minimum for a distance $r_{ij}{}^* = r_i{}^0 + r_j{}^0 + \delta$, where $r_i{}^0$ and $r_j{}^0$ and van der Waals radii and δ an increment, usually equal to 0.2 Å). Furthermore some calculations have been duplicated by using the

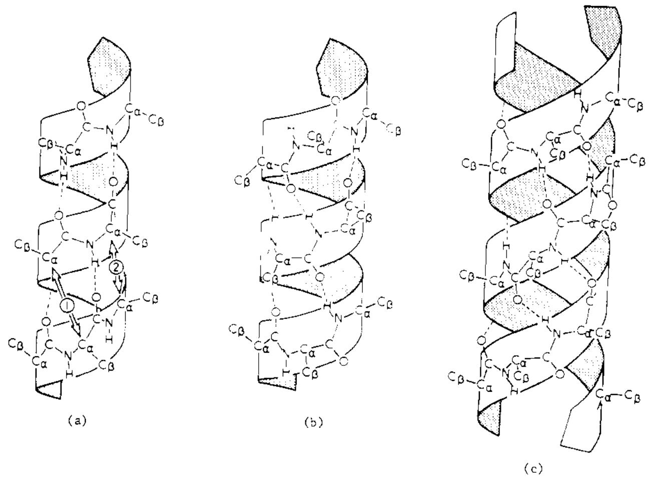

Figure 1. Schematic representation of three types of helical structures considered in the present calculations: single-stranded (a) α_{DL}, (b) π_{DL}, and (c) antiparallel double-stranded $\pi\pi_{\mathrm{DL}}$ helices. In the α_{DL} helix, the contacts between facing $C_\alpha{}^1$–$C_\alpha{}^4$ and $C_\alpha{}^2$–$C_\alpha{}^5$ atoms are numbered as 1 and 2, respectively (see text). The π_{DL} and $\pi\pi_{\mathrm{DL}}$ helices shown are the tightest possible ones, i.e., $\pi_{\mathrm{DL}}{}^{4.4}$ and $\pi\pi_{\mathrm{DL}}{}^{5.6}$, respectively (the superscript indicates the number of peptide residues per helical turn).

potentials of Caillet and Claverie,[16] which make use of a Buckingham (6-exponential) term for van der Waals interactions. Analysis of their influence will be discussed in the following sections.

(III) Results

(1) Stable Helical Conformations of Poly(L-ALA-D-ALA). The results of extensive calculations on the structures of poly(L-D-alanine) are summarized in Table I, which lists the conformational parameters and energies of all the helical structures of poly(D-L-peptides) observed for PBD-LG. For both families of π_{DL} and $\pi\pi_{\mathrm{DL}}$ helices, further members, not yet observed, have been considered. For comparison purposes, Table I also lists parameters of an isolated β pleated sheet of poly(L-alanine) determined with the same potentials[7] and of its right-handed α-helical structure (columns (a) and (b)).

Since all conformational and valence angles have been varied in the minimization procedure, the conformations arrived at here may be considered as improved versions of those which were determined previously.[4,5] We note that the helical parameters observed for the structures that have been obtained experimentally for PBD-LG[1] are very close to those determined by the present a priori method with poly(L-Ala-D-ala) (cf. footnote in Table I). Several geometrical features of these helices are however revealed by the present calculations.

(a) Single-Stranded Helices. α Helix. The earlier and the present energy calculations corroborate experimental evidence[1,17,18] indicating that the α helix is a possible conformation for a regular poly(L-D-peptide). The conformational angles of the L and D residues are different, but both are located in the "valley" of the conformational energy map parallel to isotimic curves with n (number of residues per turn) equal to 3.6 or h (rise per residue) equal to 1.5 Å. This results, however, in a structure in which the rise per dipeptide repeat unit, although normal for α helices (2.97 Å), is unevenly distributed between the L and D residues (1.63 and 1.34 Å, respectively). As already indicated in section II, the physical origin of this deformation has been investigated by varying the parameters of the potentials. The type of deformation suggests that it is due mainly to the bulkiness of the side chain. Indeed, $C_\alpha{}^1$–$C_\alpha{}^4$ and $C_\alpha{}^2$–$C_\alpha{}^5$ distances are different, i.e., large

Table I
Helical Parameters and Potential Energy of Various Structures of Polyalanine[a]

	(a) β_{L}	(b) α_{R}	(c) α_{DL}	(d) $\pi_{\mathrm{DL}}{}^{4.4}$ (1)	(e) $\pi_{\mathrm{DL}}{}^{4.4}$ (2)	(f) $\pi_{\mathrm{DL}}{}^{6.3}$	(g) $\pi\pi_{\mathrm{DL}}{}^{5.6}$ ↑↓	(h) $\pi\pi_{\mathrm{DL}}{}^{5.6}$ ↑↑	(i) $\pi\pi_{\mathrm{DL}}{}^{7.2}$ ↑↓	(j) $\pi\pi_{\mathrm{DL}}{}^{7.2}$ ↑↑	(k) $\pi\pi_{\mathrm{DL}}{}^{9.0}$ ↑↓	(l) $\pi\pi_{\mathrm{DL}}{}^{10.7}$ ↑↓	(m) $\pi\pi_{\mathrm{DL}}{}^{12.6}$ ↑↓
ϕ_{L}	−139.0	−59.47	−59.94	−102.98	−83.10	−127.23	−121.00	−116.51	−129.65	−144.50	−141.44	−144.43	−147.11
Ψ_{L}	135.0	−47.58	−47.36	119.09	99.55	135.68	149.60	156.49	144.53	158.40	148.95	152.34	154.64
χ_{L}	55.1	179.95	184.18	183.59	179.46	179.45	180.59	−178.49	180.57	180.73	180.67	−175.94	−172.16
ω_{L}	180.0	177.73	176.40	−171.73	177.30	172.44	−178.45	176.53	−175.75	173.35	−170.25	−179.45	179.60
τ_{L}	109.5	111.88	110.41	107.05	105.60	111.25	111.38	112.35	111.62	114.76	112.24	112.85	114.38
ϕ_{D}		−59.17	−50.10	112.60	130.75	121.20	144.38	134.04	152.26	134.62	158.66	158.04	158.95
Ψ_{D}		−47.36	−50.38	−73.54	−86.94	−97.20	−97.52	−94.89	−125.16	−92.90	−142.30	−146.39	−153.04
χ_{D}		179.97	−179.78	180.75	−176.97	180.75	−179.27	−178.38	179.89	180.79	180.6	179.58	177.75
ω_{D}		177.82	178.46	177.94	−183.58	−177.57	174.43	−175.61	−179.40	179.44	175.43	179.73	−179.15
τ_{D}		111.92	111.47	106.79	106.88	110.20	110.67	110.73	110.48	111.57	111.50	110.66	112.41
h	6.90	2.932	2.978	2.363	2.380	1.547	4.078	4.00	2.934	2.949	2.259	1.85	1.56
n	2	1.83	1.79	2.235	2.232	3.150	2.354	2.883	3.592	3.519	4.437	5.35	6.29
ρ							−44.56	−55.0	−19.03	−26.03	−8.22	−4.66	−2.05
$\bar{\tau}$							4.027	4.01	4.005	4.42	3.87	3.95	4.00
E_{vw}		−4.89	−4.51	−4.33	−3.71	−4.04	−4.19	−3.25	−3.83	−3.72	−4.41	−3.82	−3.77
E_{elec}		−6.80	−6.65	−6.22	−6.07	−6.49	−6.66	−6.36	−6.68	−5.86	−6.72	−6.70	−6.77
E_{total}	−9.78	−11.69	−11.16	−10.55	−9.78	−10.53	−10.85	−9.61	−10.51	−9.58	−11.13	−10.52	−10.54

[a] Symbols used: ϕ, Ψ, χ, and ω are according to the recommandation of the IUPAC-IUB Commission,[29] the torsional angles around N–C_α, C_α–C′, C_α–C_β, and C′–N bonds of the peptide unit, respectively. τ is the valence angle $NC_\alpha \Lambda C_\alpha C'$. Subscripts L and D denote the chirality of the residues. All helices are right handed. h and n stand for the rise per dipeptide unit and number of dipeptide units per turn, respectively. $\bar{\alpha}$ and $\bar{\tau}$ are the relative rotation and translation of the two strands in double helices (cf. Appendix I in ref 1). Energies are in kcal/(mol residue). The total energy (E_{total}) has been divided in two components, namely van der Waals (E_{vw}) (which includes deformation of the valence angles τ and torsion around covalent bonds) and electrostatic (including hydrogen bond energy) (E_{elec}). This subdivision is not given for the β structure of poly(L-alanine) (β_{L}) for which a different partition of E_{total} was used.[7] Symbols for the various structures are as used in the text. ↑↓ and ↑↑ denote antiparallel and parallel strand arrangements in double helices, respectively. All angles in column (b) are for L residues (sequence of two L residues used to test the minimization procedure, cf, section II.2). In the corresponding stable structure reported by Hesselink and Scheraga,[5] $\phi_{\mathrm{L}} = -50.2$ and $\Psi_{\mathrm{L}} = -56.2$ (ω and τ fixed at 180 and 109.5°, respectively). The structure $\pi_{\mathrm{DL}}{}^{4.4}$ (1) is the goniomer of $\pi_{\mathrm{DL}}{}^{4.4}$ (2) which was, so far, the only geometry considered for this helix.[1,4] For comparison, helical parameters (h, n) observed experimentally for poly(γ-benzyl D-L-glutamate) structures are:[1] α_{DL} (2.97 Å, 1.82), $\pi_{\mathrm{DL}}{}^{4.4}$ (2.33 Å, 2.2), $\pi\pi_{\mathrm{DL}}{}^{5.6}$ (4.02 Å, 2.8), $\pi\pi_{\mathrm{DL}}{}^{7.2}$ (2.95 Å, 3.6), and $\pi\pi_{\mathrm{DL}}{}^{9.0}$ (2.26 Å, 4.5).

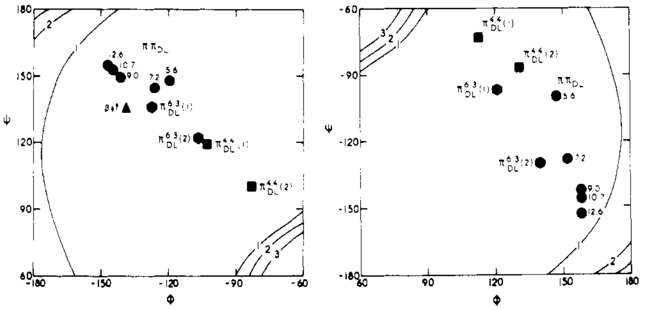

Figure 2. Conformation of the L (left-hand side of figure) and D (right-hand side of figure) peptide units in the various π_{DL} and antiparallel $\pi\pi_{DL}$ helical structures examined in the text. The diagrams represent the upper left and lower right parts of the conformational map, respectively. Isoenergetic contour lines (kcal/(mol residue above minimum)) are for alanine residues.[27] Conformations shown are for right-handed helices. The conformation observed in the antiparallel β-pleated sheet structure of poly(L-alanine) is also given, for comparison.[28] Note the differences in conformational angles of the $\pi_{DL}{}^{6.3}$ helix determined in this work (noted $\pi_{DL}{}^{6.3}$ (1)) and by Hesselink and Scheraga[16] (noted $\pi_{DL}{}^{6.3}$ (2)) and the two sets of conformational angles for the $\pi_{DL}{}^{4.4}$ helix (the structure noted $\pi_{DL}{}^{4.4}$ (1) has the lowest energy).

(5.15 Å) or small (4.81 Å) when pendant atoms facing each other are methyl groups of H_α atoms, respectively. As expected, when the radius of H_β atoms is reduced to the unrealistic value of 1.0 Å (instead of 1.2 Å), a more symmetrical structure is obtained, in which the total rise is evenly distributed between the two residues.

π_{DL} Family. It has already been observed that the $\pi_{DL}{}^{4.4}$ helix could only be constructed with fairly small valence angles, which were fixed at 106°.[4] The τ angles for the structure obtained turned out to be indeed close to 106°. The strain of the structure is partly relieved by nonplanarity of the two peptide groups which are, as expected, deformed in opposite directions.

The $\pi_{DL}{}^{6.3}$ helix was postulated as a transmembrane channel structure of Gramicidin A[19] but has not been characterized at present by solid-state investigations. We note that the conformational angles determined in this work (Table I) differ significantly from those obtained previously, using similar methods. These differences will be discussed in detail when dealing with the "goniomeric" variants.

(b) Double-Stranded Helices. The present calculations deal with the first five members of the family of double helices, and special attention has been given to the possibility of structures with parallel and antiparallel strands, in view of their relevance to previous work on Gramicidin A[2,3,19] and PBD-LG.[1]

Examination of Table I indicates that helices made of antiparallel strands are quite possible: their energies are very similar; as shown in Figure 2, the variation in conformational angles becomes progressively smaller as the number of residues per turn increases, i.e., as the chain becomes more extended.

Double helices with parallel strands become more unstable when their diameter increases. In fact, only the first two members, i.e., the $\pi\pi_{DL}{}^{5.6}$ and $\pi\pi_{DL}{}^{7.2}$ helices, can be built with both strand orientations; the energy of the parallel stranded helices is higher than that of the antiparallel ones and becomes prohibitive for the $\pi\pi_{DL}{}^{9.0}$ helix (not reported in Table I): −5.5 kcal/mol, i.e., 4.5 kcal/mol higher than that of the antiparallel $\pi\pi_{DL}{}^{9.0}$ helix. This destabilization appears to be due to an unfavorable contact between a carbonyl group and the H_α atom of the neighboring chain, as for the π_{DL} family. For larger helices, the situation becomes even worse. Indeed, the minimization procedure leads to structures in which half of the residues remain nearly parallel to the helical axis (and are therefore hydrogen bonded to the second strand) while the others are inclined with respect to the helical axis, thus precluding any hydrogen bonding.

Table II
Conformational and Helical Parameters of the Two Goniomeric Variants of the $\pi_{DL}{}^{6.3}$ Helix[f]

	(a)[a]	(b)[b]	(c)[c,g]	(d)[d,g]	(e)[e,g]
ϕ_L, deg	−106	−111	−132	−138	−111
Ψ_L, deg	122	125	141	142	125
ϕ_D, deg	140	141	126.8	128	142
Ψ_D, deg	−130	−127	−105	−101	−128
n	3.14	3.15	3.143	3.157	3.173
h	1.56	1.60	1.577	1.650	1.691
E_{total}[h]	−8.95	−6.44	−9.05	−5.90	−5.55

[a] Structure of minimum energy of Ramachandran and Chandrasekaran.[4] [b] Stable structure of Hesselink and Scheraga.[5] [c] Obtained in this work. [d] Structure of minimum energy obtained with the potentials of Caillet and Claverie[16] when the structure in (c) is used as the starting point. [e] As in (d) but starting with conformational parameters of column (b). [f] The goniomers are structures (a), (b), and (e), and structures (c) and (d), respectively. All parameters are for right-handed helices. [g] Obtained by energy minimization. For consistency τ and ω angles were fixed at 109.5 and 180°, respectively. [h] Energies in kcal/(mol residue). Except for columns (d) and (e), they are not comparable since different sets of potentials are used.

(2) "Goniomeric" Variants of Structures of Poly(L-D-peptides). Two different possible geometries for some stable helical structures of poly(D-L-peptides) have been noticed both in our own work and when comparing the present results with similar calculations performed previously.[5] These differences are best analyzed with the $\pi_{DL}{}^{6.3}$ helix with fixed ω and τ angles.

(a) The $\pi_{DL}{}^{6.3}$ Helix. As shown in Table II, all conformational angles determined for our best structure (column (c)) differ markedly (from 15 to 25°) from those obtained by Hesselink and Scheraga (column (a)) and by Ramachandran and Chandrasekaran (the latter angles were not obtained by energy minimization procedures). More strikingly, however, while the angles are different, the *sequence* of these angles is the same, provided they are read in the reverse sense: thus the sequence of angles ϕ_L, Ψ_L, ϕ_D, Ψ_D of column (a) matches, within a few degrees, the sequence Ψ_D, ϕ_D, Ψ_L, and ϕ_L of column (c). We propose, therefore, to call such structures "goniomeric" variants or "goniomers".

The two goniomers of the $\pi_{DL}{}^{6.3}$ helix have closely similar helical parameters h and n. Their geometry, however, differs in several details, as is best seen when considering the position of the carbonyl groups of the L and D residues relative to the helical axis (Figure 3).

Several calculations were performed to establish the more stable of the two structures. A minimization starting with Hesselink and Scheraga's dihedral angles yields, again, a structure very similar to that of Table II, column (c). It appears, therefore, that only small differences in the two sets of potentials (note that ours derives from that of Hesselink and Scheraga) are sufficient to change the relative stabilities of the two goniomeric variants. Again, changes in the parameters have been made to reproduce the result of Hesselink and Scheraga. In the absence of their detailed set of variables, we did not succeed in pinpointing those features of the potentials which are responsible for these differences. We notice that a change of the dielectric constant from 1 to 4 does not affect significantly the final conformation. Influence of the bulkiness of side chain atoms (H_β) appears more important.

One can however expect that, depending on the potentials, the two goniomers can be local minima of the map. This has

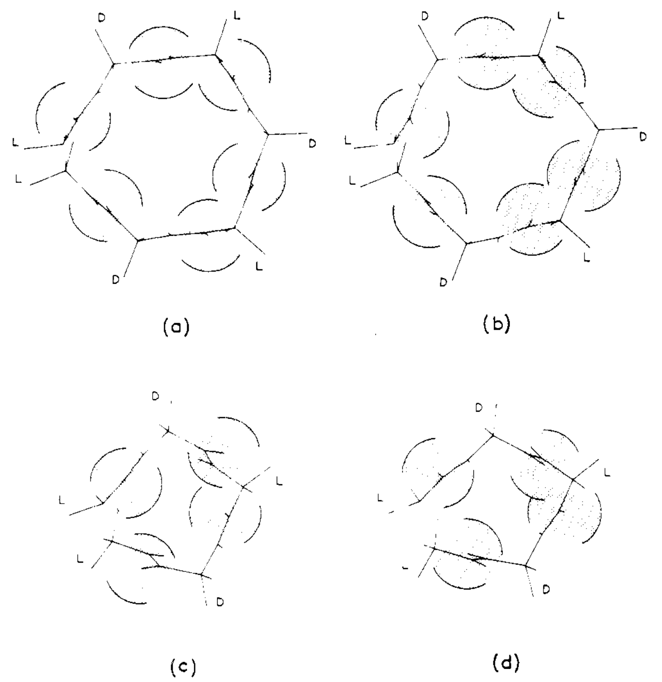

Figure 3. Projection (down the helical axis) of the two gonionomers of (a, b) the $\pi_{DL}^{6.3}$ helix (with ω and τ angles fixed at 180° and 109°5, respectively) and (c, d) the $\pi_{DL}^{4.4}$ helix. The oxygen atoms of the carbonly groups only are shown with their atomic radius and are shaded in. Note that in the goniomers, corresponding peptide groups have their C–O links oriented toward, or away from, the helical axis, respectively. (a) Structure determined in this work. (b) Structure of Hesselink and Scheraga (1974). (c) Structure of the $\pi_{DL}^{4.4}$ helix determined previously[1,4] and (d) its goniomer with lower energy obtained in this work ($\pi_{DL}^{4.4}$ (1) of Table I and Figure 2).

indeed been observed when using the set developped by Caillet and Claverie[16] (Table II, columns (*d*) and (*e*)).

Disregarding the duality of conformations, it is nevertheless clear that the geometry of the $\pi_{DL}^{6.3}$ helix is well defined. It is noteworthy for example that structures with intermediate dihedral angles are never obtained and therefore correspond to higher energy conformations.

(b) Giomeric Variants of Other Helices of Poly(D–L-peptides). The example of the $\pi_{DL}^{6.3}$ helix indicates that there may be more than one low-energy conformation for a given structure. In view of the mirror symmetry of the conformational angles, no goniomeric variants can be expected when ϕ_L and Ψ_L differ by no more than a few degrees from Ψ_D and ϕ_D, respectively. This is true in particular for the larger double helices made of antiparallel strands ($\pi\pi_{DL}^{9.0}$, $\pi\pi_{DL}^{10.7}$, and $\pi\pi_{DL}^{12.6}$). For all structures in which these angles are significantly different, goniomeric variants may exist, and the possible existence of two geometries has been systematically explored. Additional minimizations have thus been performed in which the sequence of starting dihedral angles is the reverse of that of the "optimized" structure which was arrived at first.

In particular, this procedure led to a structure of the $\pi_{DL}^{4.4}$ helix which has a lower energy than that reported previously[1] (Table I, columns (d) and (e), and Figure 3) (note that the special angular relationship between the two variants may become blurred when ω and τ angles are allowed to vary). Among double helices, a second local minimum has been found for the antiparallel $\pi\pi_{DL}^{5.6}$ structure only, but its energy is higher by 1.2 kcal/(mol residue) than that of the structure reported in Table I, column (e) (−9.5 vs. −10.8 kcal/(mol residue)). As already indicated, however, additional structures might have shown two minima with different sets of potentials.

(IV) Discussion and Conclusion

(1) Stability of Helical Structures of Poly(D–L-peptides). The present energy calculations have been performed to test the conformational possibilities of a syndiotactic polypeptide taken with the smallest side chain needed to define the chirality of the residues. The relative stabilities of the helical structures can now be compared, as they are analyzed with a single set of potentials.

Examination of Table I indicates that none of the helices of poly(D-Ala-L-Ala) reaches energies as low as that of the right-handed α helix of poly(L-alanine); except for the parallel $\pi\pi_{DL}$ helices, their energies are however only slightly higher and, moreover, comparable within 0.6 kcal/(mol residue). Detailed discussion of the results appears therefore unwarranted, since these variations are close to the estimated scatter of the minimization procedure used (for any one structure, it is of the order of, but most probably lower than, 0.5 kcal/(mol residue), as judged from a number of minimizations of the same structure performed with various initial parameters.

Quite noticeably, however, the energies of the antiparallel double helices are not greatly affected by the size of their central core. It should be remembered at this stage that these helices are further stabilized by solvent molecules, located inside the helical core,[1] which have not been taken into account in these calculations.

The present results suggest that, in general, poly(D–L-peptides may be more prone to adopt a variety of different structures than poly(L-peptides). Conformational transitions have already been reported for hydrogenated Gramicidin A which, in solution, converts from a single- to a double-stranded structure at elevated temperatures. The difference in enthalpy was found to be ~0.5 kcal/(mol residue), with the single-stranded structure being favored, while the double-stranded one is favored entropically.[20]

Particular side chains may well hinder or favor the possible polymorphism of poly(D–L-peptides) and, in any case, influence the transitions between the various forms. This influence is well illustrated by the behavior of PBD–LG, whose thermal transitions parallel those of poly(β-benzyl-L-aspartate) (PBLA). Thus, the *intra*molecular transition from α_{DL} to $\pi_{DL}^{4.4}$ helix of PDB–LG occurs at ~130 °C as the α to ω transition of PBLA. We note that, in this temperature range, the side chains of PBLG undergo a thermal transition (melting):[21] the structural transition becomes possible with the onset of increased side-chain mobility. (Note that when the side chains are mobile, i.e., in a solvent, the $\alpha_{DL} \rightarrow \pi_{DL}$ transition occurs at yet lower temperatures: ~80 °C.[22]) Also the *inter*molecular transitions from π_{DL} to $\pi\pi_{DL}$ (PBD–LG) and ω to β (PBLA) occur both at ~220 °C,[1,23] which appears to be the temperature range needed for the denaturation of these polypeptides. By contrast, the transitions between double helices of poly(D–L-peptides) require milder conditions, since only slight structural rearrangements are involved, and half of the hydrogen bonds can be maintained during the transition; for PBD–LG, they are merely induced by a change in the size of the solvent molecules, which initiates formation of the double helix with matching core dimensions.[1,22]

(2) The Nature of Goniomeric Variants. An unexpected result of the present calculations has been the revelation that helical structures of poly(D–L-peptides) may be described by two variants which we have called goniomers. When the L and D side chains are the same, as in the case considered here, the computed energies of the two variants cannot differ much, the differences arising mainly from small variations in the interactions between side-chain and main-chain atoms. With different side chains, however (as for example in the C-terminal sequence of Gramicidin A, which is D-Leu-L-Trp), more important differences in stability might be expected for the two

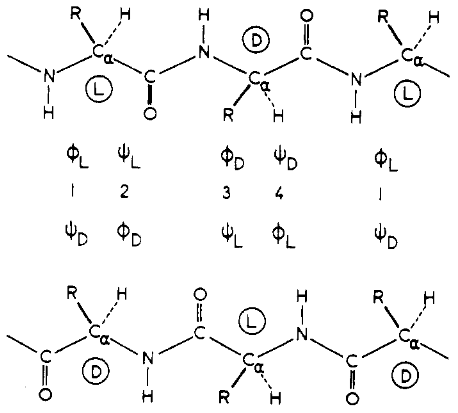

Figure 4. Structural correspondance between goniomers of a poly(L–D-peptide). The bottom chain is obtained by exchange of carbonyl and amide groups in every peptide unit of the top chain. The chirality of the residues (circled) is changed, while the same sequence of angles, numbered, characterizes different sets of dihedral angles (top and bottom).

variants since the side chains would interact with backbones whose local conformation is noticeably different.

Even in this case, however, one structure can evidently be transformed easily into its goniomer. Such a "breathing" of the channeled helices may well be related to their ability to mediate the transport of small cations across membranes. As observed by Urry[24] inward rotation of peptide oxygen moieties brings them in contact with the migrating ion and lines the channel with the negative end of the peptide dipole moments. It has also been suggested[25] that the polarizability resulting from the movement of the dipoles associated with peptide bonds may be a feature of ion-transducting proteins.

As already indicated, the goniomers are characterized by similar parameters and by the striking inversion of the sequence of their four conformational angles; yet they are not mirror images because the helices have the same screw sense. The relationship between these goniomers needs to be examined in more detail in the case of poly(D–L-peptides). In fact, this relationship also helps to find goniomers of polypeptides with different stereosequences.

Let us consider, in a poly(L–D-peptide), a sequence of two residues whose conformations are characterized by the four conformational angles ϕ_L, Ψ_L, ϕ_D, and Ψ_D named 1, 2, 3, and 4 (Figure 4). Let us now, in every peptide unit, interchange CO and NH groups while maintaining all other atoms unaffected. This operation is possible in the case of polypeptides in view of the relative symmetry of the peptide unit around the middle of the C′N covalent link (disregarding the chemical difference between carbonyl and amide group). Only slight adjustments are needed to reproduce the usual bond lengths and valence angles. This operation also maintains the screw sense and the pattern of hydrogen bonds in tridimensionnal structures, but it changes the chirality of all C_α atoms. Thus, the sequence of angles 1, 2, 3, and 4 whose numerical values remain almost unaffected now characterizes the conformations Ψ_D, ϕ_D, Ψ_L, and ϕ_L, respectively (Figure 4). This is precisely the relationship found for the two goniomers. As far as the backbone is concerned, therefore, *goniomers can be derived one from another merely by an interchange of CO and NH groups.*

Goniomers can also be envisaged for polypeptide sequences other than alternating poly(D–L-peptides) and in particular for longer stereosequences of the same type, i.e., for poly(L_x–D_x-peptides). Also, the possible existence of such a goniomer has already been noticed for the 3_1 helical structure of the optically inactive polyglycine; Liquori[26] has suggested an unstable chain conformation which can be derived from the commonly accepted geometry of polyglycine II by an interchange of NH and CO groups.

A similar CO–NH interchange may also be envisaged, under specific conditions, for enantiomeric polypeptides as well. This interchange affects of course the chirality of the residues, i.e., a poly(L-peptide) becomes a poly(D-peptide). If, in the poly(D-peptide), the positions of the side chains and H_α can be exchanged without creating steric conflicts, a poly(L-peptide) can be generated whose geometry differs from the original one. In this structure, the dihedral angles ϕ_L and Ψ_L take up numerical values which were initially those of Ψ_L and ϕ_L, respectively.

This operation can actually be performed for the α helix for which two geometries may thus be considered. One of these geometries is characterized (for a right-handed helix) by the couple of conformational angles $\phi_L = -48°$ and $\Psi_L = -57°$, and, as already indicated, corresponds to the conformation first adopted as the "standard" α helix. The other helix, also right handed, with angles $\phi_L = -57°$ and $\Psi_L = -48°$, has become the new standard[29] following the work of Arnott et al. who demonstrated its existence for poly(L-alanine).[14,15] Interestingly enough the α-helical structures of poly(L-alanine) calculated by energy analysis with different sets of potentials are again different (cf. Table I and ref 5) and related by this same inversion of ϕ and Ψ angles.

Accurate determination of the geometrical parameters (for helices, the values of n and h) does not therefore prove the ability of a given set of potentials to predict the finer details of polypeptide structures. When goniomers exist, the potentials should also be able to single out the more stable variant. Comparison of energy analysis results with experimental data is at present limited (for helical structures) to the α helix. When data of similar quality become available for helices of poly(D–L-peptides) they will provide a critical test for evaluating current and new potential functions.

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