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Chemistry

Conformations of twisted parallel β-sheets and the origin of chirality in protein structures

(secondary structure/protein chirality/hydrogen bond/peptide bond)

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ABSTRACT **An analysis of the conformational properties of parallel β-pleated sheets suggests that an important factor in the generation of β-sheet twist is the preference for nonplanar peptide bond distortions that impart local left-handed helical character to polypeptide chains. It is demonstrated that the introduction of such chiral distortions, which result from the tetrahedral deformation of the peptide nitrogen atoms, naturally produces right-twisted β-sheet structures with optimal hydrogen bond geometry.**

Crystallographic studies of proteins have revealed that many features of the secondary (1, 2) and supersecondary (3–5) structure of these molecules possess right-handed chirality. The results presented here, which treat the conformational properties of parallel β-pleated sheets, suggest that nonplanar peptide bond distortions of preferred chirality may be an important factor in the generation of the observed handedness in protein structural domains.

METHODS

The basic objective of this study was to establish the optimal geometry for ordered, multiple stranded, parallel β-pleated sheets having various degrees of twist. Toward this end, a combination of mechanical and computer modeling approaches was used.

For the model-building studies, precision peptide models were constructed to a scale of 10 cm/Å according to the structural parameters given by Ramachandran *et al.* (6). The details of their construction will be described elsewhere (7). These models, which (*i*) incorporate built-in ϕ, ψ, and ω angular gauges, (*ii*) allow the introduction of tetrahedral character into the peptide nitrogen, and (*iii*) allow smooth rotation about ϕ, ψ, and the NHO and HOC hydrogen bond angles, were used to construct a triple-stranded (3 × 4 residue) parallel β-sheet model having 2.8-Å (N—H· · ·O) hydrogen bonds. Through manipulation of the suspended model, it was possible to establish the general behavior of the backbone torsional angles upon the introduction of twist into the structure, and also to characterize the effects of variations in peptide bond planarity and interchain hydrogen bond geometry. From the initial experiments it was evident that the regular flat sheet (Fig. 1) does not readily admit the introduction of nonlinearity into the hydrogen bonds. Nevertheless, it was apparent that the hydrogen bonds did not remain linear when the structure was twisted.

To gain a more accurate representation of the conformational alterations accompanying twisting and to overcome gravitational effects on the mechanical models, subsequent studies were carried out computationally. The general protocol involved the generation of duplicate penta- or decaalanine coordinate lists that contained additional "phantom" atoms

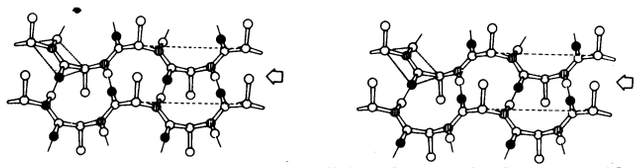

FIG. 1. A section of flat, parallel β-sheet with planar peptide groups (dotted lines). Here and in following figures, oxygens are black and nitrogens are striped. Interchain twist is defined as the angle between vectors of adjacent chains (dashed lines) from *i*th to (*i* + 2)nd α-carbon atoms.

corresponding to the expected positions of the carbonyl oxygen, the amide nitrogen, and the amide hydrogen atoms of hypothetical adjacent chains, assuming straight hydrogen bonds 2.8 Å in length. Various twisted sheet structures were subsequently generated by the variation of ϕ and ψ in 2° steps, followed by least-squares rotation to find the optimal superposition between the real and phantom atoms involved in interchain hydrogen bonds. The resulting structures were quantitatively compared by computation of the mean difference (D) between the actual and expected (phantom) positions of the N, H, and O atoms in the two chains. From the resulting plots of D vs. ϕ and ψ, it was possible to derive the path of least resistance for the continuous twisting of the various structures examined.

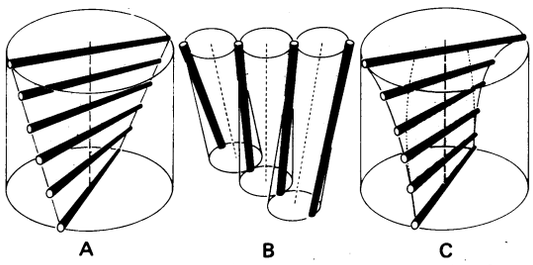

FIG. 2. Geometric properties of twisted β-sheets. (*A*) Schematic representation of a twisted sheet composed of straight polypeptide chains having all values of ϕ and ψ equal. The "crossing" polypeptide chains in this structure are related to each other by the same interchain twist angle (Fig. 1). Because the chains approach each other most closely in the region of the indicated cylinder axis and diverge toward the cylinder surface, good interchain hydrogen bonds can be made only in the region of closest approach. The hydrogen bonding interactions that can occur between such chains are infinitely extensible along the direction of the hydrogen bonds. (*B*) Schematic representation of a twisted sheet composed of "coiled-coil" chains whose repeating units are dipeptides. Coiled-coil chains describe paths that lie on the surface of a cylinder. Double-stranded coiled-coil structures are infinitely extensible along the chain direction. (*C*) Schematic diagram of a tapered β-sheet with increasing (upward) rate of interchain twist. For crossing chain interactions (*A*) it is clear that increasing interchain twist results in a shorter region of good hydrogen bonding. Likewise, coiled-coil chains can simultaneously satisfy two local helical axes (dashed lines in *B*) only if the chains are essentially straight or if the interaction region is short. It is apparently for these reasons that tapered sheets in proteins show increasing interchain twists toward the narrow end of the sheet.

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RESULTS

There are basically two ways in which regular twisted β-sheet structures may be generated. The first involves finding the best hydrogen-bonded structure composed of straight helical polypeptide chains. Such "crossing" structures are characterized by a single ϕ, ψ value for all residues. The second way in which regular twisted sheet structures may be generated is from chains having alternating pairs of ϕ, ψ values. Such "coiled-coil" structures are composed of chains having superhelical character. Fig. 2 schematically describes the geometrical properties of twisted sheets composed of crossing and coiled-coil polypeptide chains, which resemble those found in proteins in many fundamental respects.

Fig. 3 is a ϕ, ψ plot showing the computed conformations for parallel β-sheets composed of crossing and coiled-coil polypeptide chains with planar peptide groups. The flat structure shown in Fig. 1 occurs at the intersection of the curves with the flat helical $n = 2$ line ($\phi = -116°$, $\psi = 112°$). Conformations to the right of the $n = 2$ line correspond to sheets having a right-handed twist along the direction of the chains, while those to the left of the line have left-handed twists. As is elaborated in Fig. 4, sheets having right-handed twists along the chains are composed of chains having local left-handed helical character.

The behavior of twisted sheets composed of crossing chains is shown as the solid curve in Fig. 3. As can be seen, the flat structure has the minimum superposition error ($D = 0.08$ Å), while the introduction of increasing left- or right-handed twist produces structures having increasing superposition errors. The structural manifestations of this behavior follow. First, it is clear from inspection of Fig. 2A that, whereas a flat sheet maintains

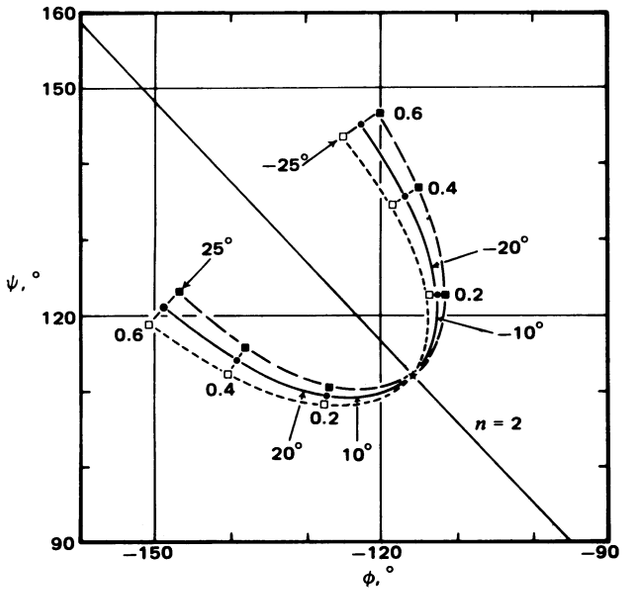

FIG. 3. A ϕ, ψ plot showing the computed conformational pathways for crossing and coiled-coil parallel β-sheets with planar peptide bonds. The solid curve shows the behavior of crossing chain interactions. Decimal quantities shown indicate the computed mean deviation in Å (D) from perfect superposition of the atoms involved in interchain hydrogen bonds between crossing pentaalanine chains (four hydrogen bonds). Conformations of double-stranded coiled-coil structures are shown as dashed lines. Coiled-coil superhelical chains are characterized by alternating pairs of ϕ, ψ values, which are shown as connected □ and ■ in the plot. Degree quantities give the local interchain twist as defined in Fig. 1. The accessible conformations for both types of structure are symmetrically distributed about the flat-helical $n = 2$ line. The minimum-superposition-error structure in either case is the flat structure (★), which lies at the intersection of the curves with the $n = 2$ line.

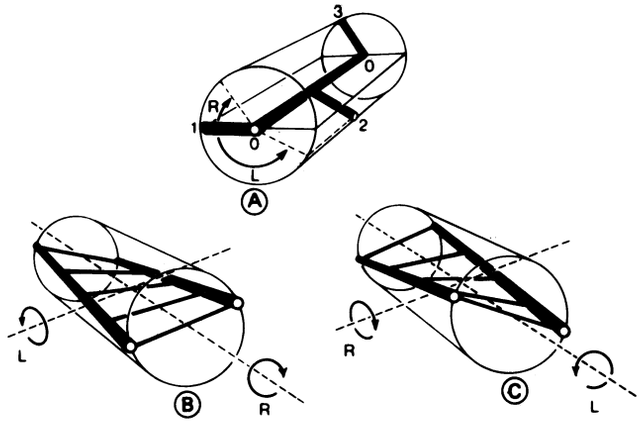

FIG. 4. Definitions of twist sense in polypeptide chains and β-sheets. (A) Schematic representation illustrating the composite effect of the introduction of ϕ, ψ backbone torsional rotations into a polypeptide chain for extended structures lying to the right of the $n = 2$ line. Such structures are formally defined as left-handed helical structures (1), because the successive groups (e.g., peptide carbonyls) as defined by the vectors 01 and 02 in the figure are related by a counterclockwise rotation of less than 180° relative to a local helix axis (0–0). The introduction of two such successive rotations produces structures in which the groups of the ith and $(i + 2)$nd residues take on right-handed helical character; i.e., the vectors 01 and 03 define a right-handed helix. Because the hydrogen-bonding interactions in β-sheet structures alternate in this fashion, polypeptide chains composed of groups with local left-handed character produce sheets with right-handed twists along the direction of the chains. (B) Ladder representation of a right-twisted β-sheet. The ladder uprights, corresponding to the polypeptide backbone, have a right-handed twist along the chain, though composed of residues having local left-handed helical character. The rungs correspond to interchain hydrogen bonds. Such structures have left-handed twists when viewed along the direction of the hydrogen bonds. (See Fig. 1.) (C) Ladder representation of a β-sheet with a left-handed sheet twist (along the chains) and a right-handed interchain twist (across the chains). Such structures are rarely found in proteins.

an equal separation between polypeptide chains, twisted sheets composed of straight chains have a small region of closest approach, beyond which the chains diverge. Second, as is shown in Fig. 5A, the introduction of twist into the straight-chain structure alters the relative periodicities of hydrogen bond donor and acceptor groups in adjacent chains, resulting in increasing nonlinearity in the interchain hydrogen bonds with increasing interchain twist. These effects, including the intro-

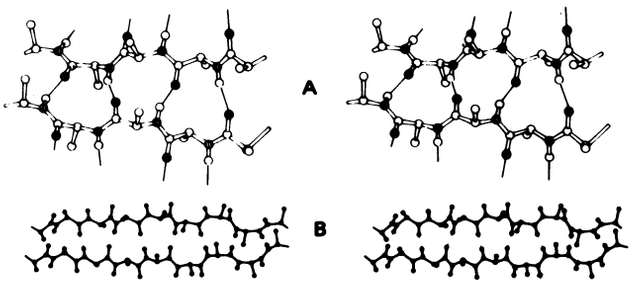

FIG. 5. Stereo drawings of twisted, parallel β-sheets with planar peptide bonds. (A) Right-twisted parallel β-sheet with crossing chains. The interchain twist is $-25°$, $\phi = -120°$, $\psi = 140°$, $D = 0.6$ Å. Note particularly the nonlinearity of the NHO bond angle, which results in unfavorable repulsive interactions between the N and O atoms of the bond (8, 9). (B) Right-twisted, double-stranded, coiled-coil structure with interchain twist of $-14°$, $\phi_1 = -116°$, $\psi_1 = 122°$, $\phi_2 = -112°$, $\psi_2 = 134°$, $D = 0.5$ Å (eight hydrogen bonds). Interchain hydrogen bond distortions are less for the double-stranded coiled-coil structures than for crossing chains. Such structures are not, however, readily extensible into multiple stranded sheets.

duction of nonlinearity into the NHO bond angle (8, 9), suggest that the flat structure (10) is more energetically favored than twisted structures composed of crossing chains. The dashed curves in Fig. 3 show the computed behavior for a *double-stranded* decaalanine coiled-coil structure, which closely approximates the actual mechanical behavior of a progressively twisted double-stranded model. The minimum-superposition-error structure is again the flat sheet. Because the coiled-coil structures maintain a constant distance between the polypeptide chains (Fig. 2*B*), the small distortions that arise in these structures principally reflect a mismatch in interchain hydrogen bond periodicity and directionality (Fig. 5*B*). In contrast to the crossing chain interactions, however, the twisted coiled-coil structures are not readily extensible in the direction of the hydrogen bonds. In fact, as succeeding chains are added to the structure, the accessible conformations become progressively more restricted to those regions of the coiled-coil curves that lie close to the flat-structure ϕ, ψ value. The basic reason for this behavior can be seen by inspecting Fig. 2*B*, from which it is evident that a coiled-coil polypeptide chain cannot simultaneously satisfy the constraints of two local helix axes [which, in the case of double-stranded parallel structures, intersect the hydrogen bonds (Fig. 5*B*)] unless the chains are essentially straight or the region of interaction is short. Indeed, because the outward-facing hydrogen-bonding groups of the double-stranded coiled-coil structures are completely unconstrained, it would appear that the accessible conformations of these structures define the limits of twist that may be introduced into polypeptide chains situated at the extremes of finite parallel β-sheets.

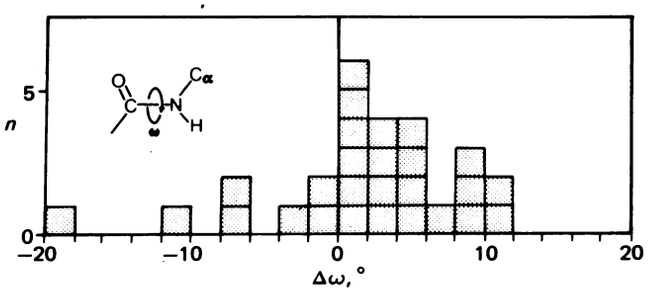

FIG. 7. Plot of $\Delta\omega$ values for peptide bonds whose nitrogen atoms are adjacent to the α-carbon of L amino acids, exclusive of proline, for 24 crystallographically determined peptide structures (15–38).

It has recently been recognized, however, that nonplanar distortions of the peptide bond may be energetically favored (11), or at least can be attained at little cost in energy (12, 13). Such distortions are frequently observed in peptide crystal structures (12, 14), and are the result of approximately symmetrical tetrahedral distortion of the peptide nitrogen atom. Fig. 6 shows the nature of the two possible tetrahedral nitrogen distortions which, because the nitrogen is covalently linked to the α-carbon of an L amino acid, give rise to two conformational diastereomers whose energies might reasonably be expected to differ. Fig. 7 shows the distribution of $\Delta\omega$ values for peptide bonds whose nitrogen atoms are adjacent to α-carbons of L amino acids for 24 crystallographically determined peptide structures (15–38). These data show an approximately 70% preference for $+\Delta\omega$, $-\theta_N$ distortions (Fig. 6*C*).

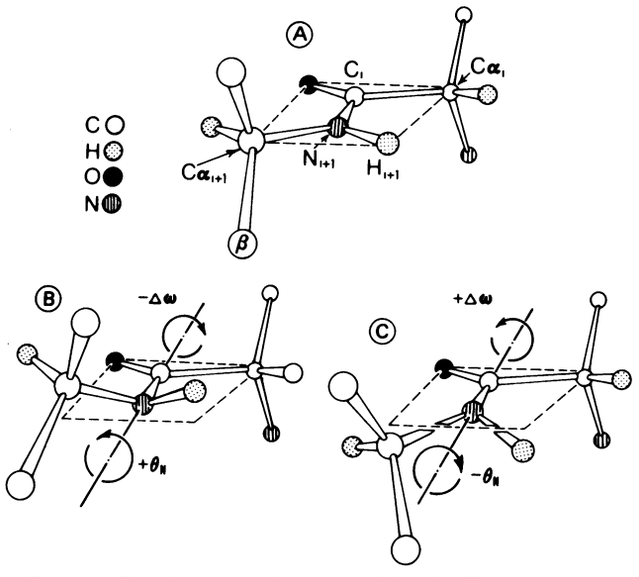

FIG. 6. Chirality in nonplanar peptide bonds. X-ray and neutron diffraction studies of peptides indicate that nonplanarity of the peptide bond is a result of the assumption of partial tetrahedral character by the peptide nitrogen atom. (*A*) Planar peptide with adjacent α-carbons showing the peptide plane with dashed lines. (*B*) Nonplanar peptide bond having local right-handed helical character. Two angles must be specified to describe such distortions: $\Delta\omega$, which is $\omega - 180°$ (ω being the angle between the $C\alpha_i$, C_i, N_{i+1} plane and the C_i, N_{i+1}, $C\alpha_{i+1}$ plane), and θ_N, which is the angle between the C_i, N_{i+1}, $C\alpha_{i+1}$ plane and the C_i, N_{i+1}, H_{i+1} plane. The figure shows a symmetrical distortion for which $\theta_N = -2\Delta\omega$. Peptide crystal structures show that values of θ_N vary from $-\Delta\omega$ to $-2\Delta\omega$ (11, 12). (*C*) Peptide bond with $+\Delta\omega$, $-\theta_N$ tetrahedral character, such as is preferentially observed in small molecules (Fig. 7). Such nonplanar peptide bond distortions introduce local left-handed helical character into a polypeptide chain. The conformations shown in *B* and *C* are diastereomerically related.

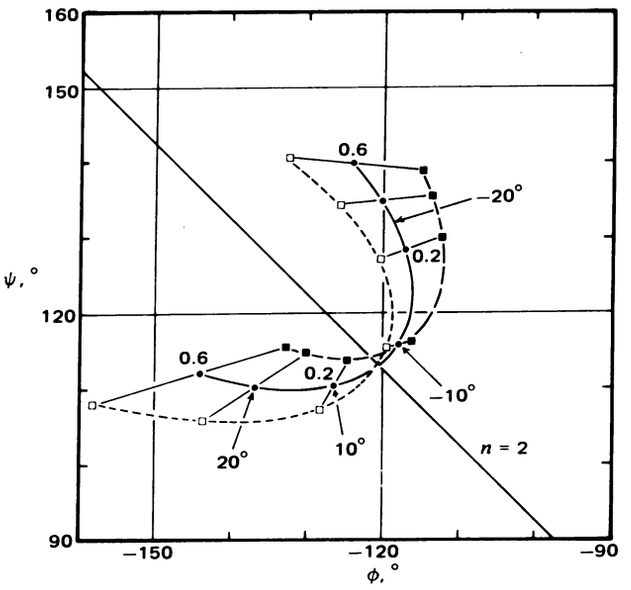

FIG. 8. Conformational pathways of parallel β-sheets with nonplanar peptide bonds. The solid curve shows the behavior for crossing structures having $\Delta\omega = +5°$ and $\theta_N = -10°$. Decimal quantities give hydrogen bond superposition errors for crossing pentaalanine chains in Å. Degree quantities give local interchain twist. Dashed lines correspond to conformations of double-stranded coiled-coil chains obtained by the cyclic refinement of both alternating ϕ, ψ values (□ and ■) and alternating values of $\Delta\omega$ and θ_N about the initial ($\Delta\omega = +5°$, $\theta_N = -10°$) value. As increasing right-handed twist is introduced into the chains, the tetrahedral distortion of the peptide nitrogen atoms that follow the α-carbons whose ϕ, ψ values define the short-dashed curve (□) increases, while that of the alternating residues (■) decreases. Minimum-superposition-error conformations for both crossing and coiled-coil structures occur to the right of the $n = 2$ line (which is shifted owing to the incorporation of nonplanarity into the peptide bonds) and correspond to structures having right-handed twists.

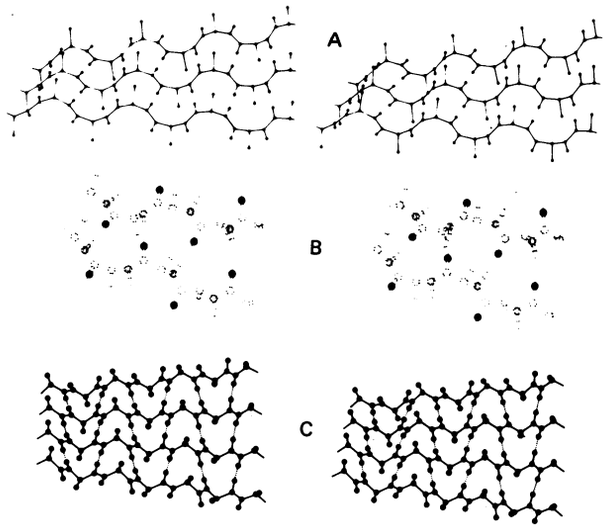

FIG. 9. Twisted, parallel β-sheets with $+\Delta\omega$, $-\theta_N$. (*A*) Minimum-superposition-error (D = 0.10 Å) crossing structure ($\phi = -118°$, $\psi = 116°$) for $\Delta\omega = +5°$, $\theta_N = -10°$. The interchain twist is $-7°$. (*B*) Crossing structure with $\Delta\omega = 35°$, $\theta_N = -35°$, $\phi = -132°$, $\psi = 122°$, D = 0.4 Å, and an interchain twist of $-23°$. (*C*) Coiled-coil structure with $\Delta\omega = 5°$, $\theta_{N_1} = -12°$. $\phi_1 = -117°$, $\psi = 117°$, $\Delta\omega_2 = 5°$, $\theta_{N_2} = -8°$, $\phi_2 = -119°$, $\psi_2 = 115°$, D = 0.10 Å, and an interchain twist of $-7°$.

To establish the effects of the introduction of tetrahedral character into the peptide nitrogen atom, additional studies were carried out on polypeptide chains incorporating this structural feature. Fig. 8 shows the computed conformational pathways for crossing pentaalanine and coiled-coil decaalanine parallel β-sheets with $+\Delta\omega$, $-\theta_N$. Crossing chain conformations with $\Delta\omega = +5°$, $\theta_N = -10°$ are designated by the solid line. In contrast to the planar peptide bond case, the accessible conformations are asymmetrically distributed about the $n = 2$ line. The minimum-superposition-error structure, which has essentially straight hydrogen bonds and is reasonably extensible both along and across the polypeptide chains, has a right-handed twist along the chains (Fig. 9*A*). A more extremely twisted structure having greater peptide nitrogen tetrahedral character is shown in Fig. 9*B*. While these structures are not free of the fundamental geometric constraints that apply to crossing chain interactions, it is clear that they make local hydrogen-bonding interactions that are superior to those of structures with planar peptide bonds having equivalent interchain twists (Fig. 5*A*).

As is the case for the planar-peptide-bond structures, the superposition errors of *double-stranded* coiled-coil structures having identical ($\Delta\omega = +5°$, $\theta_N = -10°$) tetrahedral character in all peptides are less than those of the crossing interactions of equivalent local interchain twist (curves not shown). The extensibility of these coiled-coil structures along the hydrogen bond direction is, nevertheless, subject to the same geometrical restrictions governing the extensibility of planar-peptide coiled-coil structures; i.e., the larger the sheet, the more it resembles the minimum-superposition-error twisted structure. However, the symmetry requirements of coiled-coil polypeptide chains demand only that the repeating structural unit be a dipeptide. The dashed curves in Fig. 8 show the computed behavior for double-stranded coiled-coil conformations that were obtained by *independently* varying $\Delta\omega$ and θ_N about $\Delta\omega = +5°$, $\theta_N = -10°$ for alternating peptide groups, while simultaneously varying the ϕ, ψ values for alternating residues. The resulting structures have repeating units characterized by the variables ϕ_1, ψ_1, ω_1, θ_{N_1}, ϕ_2, ψ_2, ω_2, θ_{N_2}. This variational procedure generates extensible coiled-coil structures that have multiple-chain hydrogen bonding interactions that are at least as good as those of the minimum-superposition-error crossing structures, although, necessarily, these structures cannot differ significantly in their ϕ, ψ values or general appearance (Fig. 9*C*).

DISCUSSION

The crystallographic structure determination of several proteins has established that β-sheets in globular proteins have systematic right-handed twists and therefore are characterized by ϕ, ψ values lying to the right of the $n = 2$ line. Chothia, who called attention to this structural feature (2), attributed the systematic twist principally to entropic factors; i.e., because there are more sterically allowed conformational states lying to the right of the $n = 2$ line in the β-sheet region ($-180° < \phi < -60°$, $90° < \psi < 180°$), chains having such twists would be entropically favored.

However, it is evident from inspection of Fig. 3 and the accompanying discussion that the accessible conformational states for regular parallel β-sheets with planar peptide bonds are symmetrically distributed about the $n = 2$ line and lie within sterically allowed regions of the ϕ, ψ plot ($-160° < \phi < -100°$, $100° < \psi < 160°$). Further, both coordinate analysis and experiments with space-filling models indicate that these twisted sheet structures can sterically accommodate any amino acid side chain with the possible exception of tryptophan.

Although the finite β-sheets in real proteins would not be expected to manifest the perfect regularity of the computed structures, model studies suggest that it is unlikely that three or more chains could attain any reasonable hydrogen-bonded structure characterized by ϕ, ψ values significantly different from those describing the unconstrained double-stranded coiled-coil conformations. Consequently, we find no evidence that there exists a numerical preponderance of *accessible* β-sheet conformations that are right-twisted relative to those which are left-twisted. In contrast, the introduction of $+\Delta\omega$, $-\theta_N$ tetrahedral character into the peptide nitrogen, as is predominantly observed in peptide crystal structures, has been shown to naturally produce right-handed twisted parallel β-sheets that have optimal interchain hydrogen bonds. This effect is a direct result of the assumption of tetrahedral character by the peptide nitrogen atoms, which introduces twist into the backbone chain ($+\Delta\omega$) while simultaneously providing a

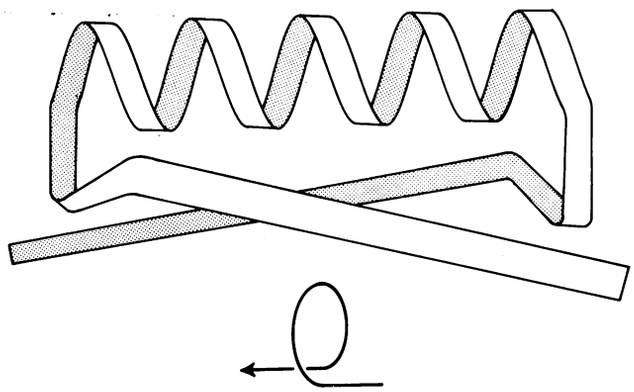

FIG. 10. Schematic representation of a right-hand β-α-β structure. Note that the formation of a β-α-β structure from a right-coiled extended chain (shown as a black wire) can be achieved by the simultaneous introduction of local ϕ, ψ rotations into the extended chain. In this sort of hypothetical folding process, the geometrical paths followed by residues upon going from the coiled unfolded structure to the folded structure are minimized. Note also that a more efficient structure could be generated by an over-the-top connection of an α-helix to a left-twisted β-sheet, such as would result from folding a left-coiled extended polypeptide chain.

compensating structural effect ($-\theta_N$) that allows the formation of good interchain hydrogen bonds.

Right-handed supertwists in protein polypeptide chains are not restricted to β-sheet structures but are also found in β-α-β secondary structural domains and crossover connections (3–5). Richardson, in calling attention to this structural feature (4), suggested that it resulted from an intrinsic tendency of the polypeptide chain to assume conformations with right-handed supertwists (Fig. 10). This effect was attributed to the fact that most conformational energy calculations yield global minima to the right of the $n = 2$ line in the extended chain region of the ϕ, ψ plot; the minima are generally about 0.3 kcal (1.3 kJ)/mol below the surrounding region in conformational space (1, 12, 39–41).

However, a statistical preference for $+\Delta\omega$, $-\theta_N$ tetrahedral peptide nitrogen distortions would appear to provide an additional factor for the chiral folding of polypeptide chains in proteins. Indeed, it may not be fortuitious that while the successive introduction of local left-handed character into extended polypeptides produces chains with right-handed twists, the random or periodic introduction of left-handed peptide bond chirality into α-helices produces structures with left-handed supercoils, similar to those proposed as models for the α-keratins (1, 42).

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