Formation of Parallel and Antiparallel Coiled-coils Controlled by the Relative Positions of Alanine Residues in the Hydrophobic Core*

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The orientation of $\alpha$-helical chains in two-stranded coiled-coils has been shown to be determined by the presence of favorable interchain electrostatic interactions. In this study, we used de novo designed 35-residue peptides to show that when interchain electrostatic interactions are not a factor in coiled-coil formation, the relative positions of Ala residues in the middle heptad can control the parallel or antiparallel orientation of $\alpha$-helical chains in coiled-coils. The peptides formed four-stranded coiled-coils where the helices are either all-parallel or all-antiparallel with respect to their nearest neighbor. The common structural element in these four-stranded coiled-coils is an alternating pair of Ala and Leu residues (Ala-Leu-Ala-Leu) in each of the two planes in the middle heptad. These results indicate that both the relative positions of the Ala residues in the hydrophobic core and the interchain electrostatic interactions between charged residues in the e and g positions should be considered in designing coiled-coils with the desired number of strands in the multiple-stranded assembly. These design elements are also important in orienting functional groups or domains attached to the terminals ends of a coiled-coil carrier.

The simplicity and regularity of the coiled-coil has made this motif an excellent model for studying protein folding and protein-protein interactions. Unfortunately, the interactions that lead to the formation and stabilization of this "simple" motif are still not very well understood. The two basic objectives of a term an excellent model for studying protein folding and progression, havelong been suspected to contribute to the packing planes in the middle heptad. These results indicate that both the relative positions of the Ala residues in the hydrophobic core and the interchain electrostatic interactions between charged residues in the e and g positions, have long been suspected to contribute to the packing and stability of two-stranded coiled-coils (Hodges et al., 1972; McLachlan and Stewart, 1975; Sodek et al., 1972; Stone et al., 1974). In the intervening years, a considerable effort has been spent in trying to understand how these two forces, hydrophobic packing and electrostatic interactions, determine the final folded structure.

On the one hand, there has been an ongoing attempt to understand how the hydrophobic residues in the coiled-coil interface control not only the stability of the coiled-coil, but also the number of helices in the final coiled-coil assembly. This research area has become tremendously important in light of the present attempts to design multiple-stranded coiled-coils for a variety of purposes, from synthetic catalysts to ligand carriers. The general approach has been to vary the amino acid residues in the hydrophobic core and to determine the structures of the resulting analogs (Alber, 1992; Cohen and Parry, 1990; DeGrado et al., 1989; Harbury et al., 1993; Hodges, 1992; Lovejoy et al., 1993; Zhu et al., 1993). On the other hand, there is a similar attempt to understand the role of interchain electrostatic interactions in controlling the parallel or antiparallel orientation of $\alpha$-helical chains in two-stranded coiled-coils. It has been shown that the favored chain orientation is one that results in interchain electrostatic attractions (Monera et al., 1993, 1994).

Presently, it is not known whether or not the type of hydrophobic packing in the interface also controls the parallel or antiparallel orientation of $\alpha$-helical chains in coiled-coils. In order to address this question, we designed coiled-coils where interchain electrostatic interactions are not a determinant of chain orientation and, therefore, the formation of parallel or antiparallel coiled-coils become mainly a function of the type of hydrophobic packing in the interface.

MATERIALS AND METHODS

Peptide Synthesis and Purification—The starting peptides were synthesized using step-phase methodology, purified by reversed-phase HPLC, and their identities were confirmed by amino acid analysis and by mass spectrometry as described previously (Monera et al., 1993). Air Oxidation and Purification—Appropriate combinations of peptides were together dissolved in 100 mM NH$_4$HCO$_3$, pH 8.0, to give a final concentration of 1 mg/ml. The solutions were magnetically stirred at 20 °C for about 15 h, and the progress of the reaction was monitored by taking 50-μl aliquots of the reaction mixture, diluting them with equal volume of 0.1 N HCl and then injecting them into the reversed-phase HPLC system. The instrumentation consisted of a Hewlett-Packard HP-1090 liquid chromatograph equipped with an analytical C8 column (Zorbax 300SB-C8, 4.6 mm × 25 cm, 5-μm particle size, 30-Å pore size, Rockland Technologies, Newport, DE). The oxidation products were eluted at 1 ml/min using a linear AB solvent gradient of 2% solvent B/min, where solvent A was 0.05% trifluoroacetic acid in water and solvent B was 0.05% trifluoroacetic acid in acetonitrile. Another set of aliquots were taken at about 20 h and similarly analyzed by HPLC. Oxidations were deemed complete when no changes in their HPLC chromatograms were observed between the two aliquots. The corresponding amounts of disulfide-bridged products were taken as a relative measure of their preferred chain orientations in solution.

To separate and purify the oxidized products, the peptide solutions were neutralized with dilute acetic acid and then injected into the HPLC system.
Hydrophobic Packing and Chain Orientation in Coiled-coils

FIG. 1. Amino acid sequence of peptides used in this study. Each peptide contains five heptad repeats (35 residues) and the amino acid residues in each heptad repeat are designated by letters a–g, as indicated in the middle heptad. In the nomenclature used, the first digit(s) represent the position of the Cys residue (bold), the middle letter indicates the type of amino acids in both the e and g positions of each heptad repeat (boxed), and the last digit(s) represent the position of the Ala residue (16 or 19) in the middle heptad (circled). The E peptides contain glutamic acid residues in the e and g positions and the K peptides contain lysine residues. The peptides are acetylated and amidated at the amino and C-terminal ends, respectively, in order to minimize charged interactions between the helical termini.

Three important features were incorporated in the design of starting peptides used in this study. First, the interchain electrostatic interactions must be the same when the chains are oriented either in a parallel or antiparallel manner. This requirement was fulfilled by incorporating identical residues at the e and g positions in the amino acid sequence of each peptide (Fig. 1). Thus, two groups of peptides were designed and synthesized, one having Glu at the e and g positions (the E peptides) and the other having Lys (the K peptides). The cross-sectional diagrams of the middle heptads of representative peptides 2E16 and 2K16 in α-helical forms (Fig. 2, A and B, respectively) show that the same potential interchain electrostatic interactions can occur in the e and g positions whether the chains are viewed from the N or the C termini. Although the type of electrostatic interaction is identical in the parallel or antiparallel orientation, that is, with regard to attractions or repulsions, structurally these interactions are not necessarily identical. For example, when the heterodimer is parallel (Fig. 2E) the interactions involve g-e/g'-e' positions, whereas when the heterodimer is antiparallel (Fig. 2F), the interactions involve g-g'/e'-e' positions. Molecular modeling of parallel and antiparallel heterodimeric EK coiled-coils with Leu residues in positions a and d were carried out as described previously (Monera et al. 1993) and Lavigne et al. (1995). In both the parallel and antiparallel cases, owing to their flexibility, the Lys and Glu side chains can bring their charged groups within interionic distances (≤5.0 Å) observed for salt bridges in globular proteins (Rashin and Honig, 1984) by adopting staggered dihedral angles (ψi) frequently observed in globular proteins (gauche minus (+60°) gauche plus (−60°), and trans (180°)). Moreover, the amount of buried hydrophobic surface area in the modeled and energy-minimized parallel and antiparallel heterodimeric coiled-coils as measured with the program ANAREA (Richmond, 1984; as implemented in VADAR version 1.2, Wishart et al. 1994) is very similar. Accordingly, there is no a priory reason to believe that g-e/g'-e' Glu-Lys salt bridges in the parallel orientation are not energetically equivalent to g-g'/e'-e' salt bridges in the antiparallel orientation. In addition, oppositely charged residues (Glu or Lys) are included at the f position to increase solubility, but these residues are not capable of intrachain electrostatic interactions with the oppositely charged residues at the e or g positions.

Second, cysteine residues were incorporated at either position 2 or 33 such that, after air oxidation of appropriate peptide mixtures, the preferred products are “trapped” in the form of two-stranded oxidized (disulfide-bridged) peptides. Thus, parallel coiled-coils are formed when a disulfide bridge is formed between two cysteines at position 2 or two cysteines at position 33, while a disulfide bridge between cysteines at position 2 and...
Fig. 2. Helical wheel diagrams showing the amino acid residues in the middle heptad of the potential α-helix from reduced peptides (indicated by r) and potential coiled-coils from oxidized peptides (indicated by x). A shows the amino acid sequence of the middle heptad of 2E16r as viewed from the C-terminal (CE, top) and N-terminal (NE, bottom) ends, where E indicates that the peptide contains Glu at both the e and g positions. The hydrophobic residue on the upper plane (closer to the viewer) is boxed to emphasize its relative spatial orientation relative to the hydrophobe in the lower plane. The backbone arrows represent the direction of N → C chain propagation. B shows the corresponding diagram for peptide 2K16r, where K indicates that the peptide contains Lys at both the e and g positions. The rest of the conventions are identical to A. C represents the potential two-stranded coiled-coil structure of the disulfide-bridged 2E16x homodimer as viewed from the amino termini. The disulfide bridge is indicated as a bold line across the N termini of two helices (NE—NE). The two pairs of potential interchain electrostatic repulsions per heptad are shown as dashed arrows, for a total of 10 pairs for the two-stranded coiled-coil. Hydrophobic packing in the upper and lower planes are indicated as open and shaded double arrows, respectively. D represents the 2K16x disulfide-bridged coiled-coil using similar conventions used in C. The solid double arrows represent the two pairs of potential electrostatic attractions per heptad, for a total of 10 pairs for the two-stranded coiled-coil. E–H are diagrams of the heterostranded coiled-coils using similar conventions used in C and D. Note that in F the coiled-coil is antiparallel and have opposite directions of chain propagation.

33 would form an antiparallel coiled-coil. We have previously shown that there are no structural restrictions in the hydrophobic packing in forming antiparallel coiled-coils provided that the interchain electrostatic interactions are appropriate (Monera, et al., 1993). Computer modeling studies based on an idealized all-antiparallel four-helix coiled-coil indicate a distance of about 6–7 Å between β-carbons in the a positions of chains that are diagonally across or 3–4 Å between the two sulfur atoms of cysteine residues. Considering the flexibility of the flared ends of the individual α-helical chains (Zhou et al., 1992, 1993), these distances are within range for disulfide bridge formation or at least require only minimal helical distortion to form a disulfide bond. The insertion of an interchain disulfide bridge at position 2a at the N-terminal of a two-stranded coiled-coil or position 33d at the C-terminal do not introduce steric strain or destabilize the structure (Zhou et al., 1993). In four-helix coiled-coils the four helical chains are indistinguishable from each other in terms of pitch and hydrophobic packing and the only hydrophobes involved in the hydrophobic core are those of the three to four hydrophobic repeat observed is indicated as a dashed line. The four-stranded coiled-coils in contrast, a four-helix bundle refers to a more general definition where the hydrophobic interactions between α-helices involve additional hydrophobes other than those of the three to four hydrophobic repeat of coiled-coils. The formation of the four-helix coiled-coil requires a different set of hydrophobic interactions (Fig. 4) compared with two-stranded coiled-coils (Fig. 2). In two-stranded parallel coiled-coils positions “a” and “d” interact with “a” and “d,” respectively, in the other strand (Fig. 2). In four-stranded parallel coiled-coils position “a” of one strand (A16, Fig. 4C) interacts with position “a” of two different strands (L16, Fig. 4C) and position “d” (L19, Fig. 4C) interacts with position “d” of two different strands (A19, Fig. 4C).

Finally, Leu → Ala substitutions were made at either position 16 (a) or 19 (d) (Fig. 1) such that all combinations of hydrophobic packings (Leu-Leu, Leu-Ala, and Ala-Ala) were made possible in the middle heptad of the parallel two-stranded coiled-coils, the antiparallel two-stranded coiled-coils, and the different combinations of chain orientations in the four-stranded coiled-coils. It should be noted that in all other heptads the hydrophobic packing only involved Leu-Leu pairs. Therefore, because there are no changes in the number and types of interchain electrostatic interactions when two chains are aligned either parallel or antiparallel to each other, the relative positions of the Ala residues in the middle heptad are presumed to be the major (if not the only) factor that determines the parallel or antiparallel orientation of these coiled-coil assemblies.

All of the reduced E or K peptide analogs have been shown to exist as monomeric random coils under benign conditions, since coiled-coil formation would result in 10 pairs of interchain electrostatic repulsions at neutral pH (Fig. 2, C and D). In fact,
Air oxidation of individual E or K peptide analogs under benign conditions proceeded only very slowly to form two-stranded disulfide-bridged products, suggesting that the Cys residues are not pre-aligned by coiled-coil formation, and the disulfide bonds were formed mainly from random collisions of monomeric random coil species. The destabilizing effect of interchain electrostatic repulsions (Fig. 2, C and D) is so strong that even the stabilizing effect of the disulfide bridges (Zhou et al., 1993) of the 2E16x and 2K16x peptides is still not capable of maintaining a coiled-coil structure and the disulfide-bridged peptides only exist as two-stranded random coils (Zhou et al., 1994a).

Based on what is presently known about the factors that affect the formation and stabilization of two-stranded coiled-coils, we predicted that air oxidation of a mixture of 2E16r and 2K16r would spontaneously form the 2E16/2K16x disulfide-bridged heterostranded coiled-coil (oxidized heterodimer), considering that there are 10 pairs of favorable interchain electrostatic attractions (Fig. 2E). Surprisingly, such peptide mixture yielded very little heterodimer and, instead, gave the corresponding homodimeric oxidized products from each peptide (Fig. 3A). These oxidized homodimers were presumed to be unfavorable products because each has 10 pairs of unfavorable interchain electrostatic repulsions mentioned above. In contrast, air oxidation of the same peptide mixture under denaturing conditions (6 M guanidine HCl) yielded the 1:2:1 homodimer:heterodimer:homodimer (2E16x:2E16/2K16x:2K16x) ratio expected from random collision (data not shown). Finally, when a pure oxidized 2E16/2K16x peptide (formed under denaturing conditions and purified accordingly) was stirred in a benign redox buffer, only homodimeric oxidized products were found (Fig. 3B). These results were indeed puzzling, but suggest the possibility that under benign conditions some unknown structural elements were present that dictated the formation of the homoostranded oxidized products from the reduced peptides. The formation of the products could be explained by the formation of a four-helix all-antiparallel coiled-coil, where the Cys residues react to form the disulfide bonds as indicated in Fig. 4A. Since the four-stranded coiled-coil is a noncovalent dimer, only the two-stranded disulfide-bridged peptides are observable as peaks in the reversed-phase HPLC chromatograms.

In order to verify further the presence of the postulated all-antiparallel four-stranded assembly, we switched the cysteine residue of one of the peptides from the N-terminal to the C-terminal position (33E16r) while keeping all other design elements constant. When air-oxidized with 2K16r, the only product was the antiparallel heterodimer 33E16/2K16x (Fig. 3C). The same results were obtained when the positions of cysteine were reversed, that is, when 2E16r was air-oxidized with 33K16r, only the antiparallel heterodimer 2E16/33K16x was produced (Fig. 3D). The formation of these antiparallel heterodimers are possible only under two conditions: the α-helical chains in the assembly are all antiparallel with respect to...
its nearest neighbor and the 4 cysteine residues have to be in the same ends of the helices (Fig. 4B). Because of proximity, disulfide bond formation would then be favored between adjacent chains, which gives identical heterostranded antiparallel products, rather than between opposite chains, which gives homostranded parallel products. Taken together, all the results strongly indicate the presence of a four-stranded, all antiparallel assembly when the position of the Ala residues in the middle heptads are identical.

With the indication that an all-antiparallel, four-stranded coiled-coil was the actual product formed from the mixture of 2E16r and 2K16r peptides, it became necessary to further investigate what was controlling the formation of this all-antiparallel structure. Since by design electrostatic interactions were essentially identical in either parallel or antiparallel orientation, we then decided to vary the position of the Ala residues in the middle heptads while keeping all other design elements constant. This was done by switching the Ala residue of the E peptide from position 16 to 19 (2E19r) and air-oxidizing it with 2K16r. This time the product was a parallel heterostranded peptide (2E19r/2K16r, Fig. 3E), in direct contrast to Fig. 3A. The exclusive formation of 2E19r/2K16r can only be possible if the relative orientations of the α-helical chains in the four-stranded structure are reversed, that is, from the all-antiparallel to the all parallel orientation, where all cysteine residues are in the same end of the helices (Fig. 4C). This is also in direct contrast to the arrangement of helices in Fig. 4A. Note that the cross-section diagram of 2E19r/2K16x (Fig. 2G) is very similar to that of 2E16r/2K16x (Fig. 2E), except for the reversed designations of Ala and Leu at positions 16 and 19, respectively, in peptide 2E19. Similarly, when mixtures of peptides with reversed positions of the Ala residues (2E16 and 2K19) were oxidized, only the parallel heterostranded 2E16r/2K19r product (Fig. 2H) was observed (chromatogram not shown). As a final test for this assumption, peptides 2E16r, 2E19r, 2K16r, and 2K19r were mixed together and subjected to air oxidation. As expected, only the parallel heterodimeric peptides (2E19r/2K16x and 2E16r/2K19x) were the major products observed (Fig. 3F). These products can only be exclusively formed when the relative orientations of the α-helical chains in the four-stranded structure are reversed, that is, from all-antiparallel to all parallel orientation (Fig. 4C). The small amounts of homodimeric products may have been formed from random collision and/or from excess peptides due to small concentration differences of reduced peptides prior to air oxidation. These were strong indications that the relative positions of the Ala residues in the middle heptad control the parallel/antiparallel or homodimer/heterodimer formation of products.

The CD spectra of each disulfide-bridged 2E16x and 2K16x peptide under benign conditions indicate a random coil structure (Fig. 5A), as reported previously (Zhou et al., 1994a). However, when the two peptides were mixed together either in reduced or oxidized forms their negative molar ellipticities increased significantly (Table I). The disulfide-bridged 2E16r/2K16x heterodimer also showed high molar ellipticity. The approximately 1:1 ratio of their molar ellipticities at 220 and 208 nm, coupled with the lack of significant increase in molar ellipticity in the presence of 50% TFE (Fig. 5B), indicate that these peptides assumed full coiled-coil structure under benign conditions (Lau et al., 1984). Since each peptide in the mixture is by itself not helical, the high ellipticity of the mixtures indicate that the two peptides must be interacting in a synergistic manner. This is consistent with our contention that the actual product formed by the mixture of 2K16r and 2E16r under benign conditions was a four-stranded coiled-coil. In the presence of TFE, the disulfide-bridged 2K16x was induced to form full helical structure, while 2E16x attained about 78% helical structure (Fig. 5B). The decrease in the ratio of the molar ellipticities of these peptides in the presence of 50% TFE (θ222/θ208 = 0.82) is more characteristic of extended or noninteracting helices (Cooper and Woody, 1990; Lau et al., 1984).

SE ultracentrifugation and size-exclusion chromatography (SEC) experiments also support the postulated four-stranded assembly. For example, an equimolar mixture of reduced 2E16r and 2K16r appeared to be a mixture of dimers (two strands) and tetramers (four strands) from SE data and mostly tetra-
The most intriguing observation that led to this study was the formation of only homodimers when a mixture of reduced peptides 2E16r and 2K16r were air-oxidized (Fig. 3A), which is only possible if molecular aggregation, other than the two-stranded form, exists. The postulated four-stranded, all-antiparallel coiled-coil assembly that results from the mixture of 2E16r and 2K16r (Fig. 4A) is the only arrangement of α-helices that can explain the origin of the two-stranded disulfide-bridged products. Coiled-coil forming peptides are thermodynamically favored to form four-stranded coiled-coils because our molecular modeling studies and x-ray crystallographic data (Harbury et al., 1993) showed an increase of about 25–30% buried surface area in going from the two-stranded to the four-stranded coiled-coil assembly. In this all-antiparallel orientation, a disulfide bond can form between the two cysteine residues across the four-helix structure (Fig. 4A). Thus, the disulfide-bridged homodimers were observed upon separation by reversed-phase chromatography, even though these homodimers cannot form two-stranded coiled-coil structures.

The results from the reoxidation of 2E16/2K16x heterodimer in redox buffer (Fig. 3B) are also consistent with the oxidation of reduced peptides, that is, only disulfide-bridged homodimers were observed. The exclusive formation of disulfide-bridged homodimers suggest that upon breakage of the disulfide bridges in redox buffer the chains dissociate and reorient into the four-stranded, all-antiparallel orientation described above. There are no other feasible packing arrangements of the two-stranded forms that can lead to the formation of mainly disulfide-bridged homodimers without dissociation of the noncovalently bonded α-helical chains. In addition, the α-helical chains in the 2E16/2K16x heterodimer does not appear to open up under benign conditions, as evidenced by the SEC and SE results (Table I). These results also demonstrate an example of two proteins that by themselves exist in an unfolded form, but together assemble into a specific folded structure.

The question arises, what drives this orientation of α-helical chains into an all-antiparallel assembly? Theoretical calculations (Chou et al., 1988; Hol, 1985; Hol et al., 1981) and previous data (Monera, et al., 1993, 1994) suggest that, assuming everything else being equal, the helix-dipole interactions favor the antiparallel orientation. However, the results from this study strongly suggest that since the positional effect of one Ala residue in the middle heptad is capable of switching chain orientation from all-parallel to all-antiparallel, or vice versa, the presumed contributions of helix-dipole must be small.

If the α-helical chains in the four-stranded structure can switch between all-parallel to all-antiparallel, what is the common structural element that determines the chain orientation in all of these structures? Inspection of the schematic diagram of the middle heptad of the 2E16/2K16x four-stranded all antiparallel coiled-coil (Fig. 6A) shows that the hydrophobic packing involves alternating Leu-Ala-Leu-Ala residues in both upper and lower planes, as also shown in Fig. 6B. Although predictably less stable than the Leu-Leu-Leu-Leu hydrophobic packing, the Leu-Ala-Leu-Ala packing is stable enough to maintain the four-stranded structure. If the α-helical chains were to orient in an all-parallel manner, the hydrophobic packing would be Ala-Ala-Ala-Ala in one plane and Leu-Leu-Leu-Leu on the other (Fig. 6C). Molecular modelling studies indicate that when four Ala residues are aligned in one plane of a four-stranded coiled-coil, stabilized by Leu residues on the other planes, the resulting cavity was estimated to have a surface area of 177Å² and volume of 187Å³, large enough to accommodate 5–10 water molecules. The alignment of four small and less hydrophobic Ala side chains (Zhou et al., 1994b) on the same plane of the four-helix coiled-coil would create a large cavity that would be expected to destabilize the four-
Hydrophobic Packing and Chain Orientation in Coiled-coils

Fig. 6. Schematic representation of the interactions in the middle heptad of the postulated four-stranded coiled-coil for the mixture of 2E16 and 2K16 peptides (A). Viewing from the top, this diagram shows that the two N termini of 2E16 connected with a disulfide bridge (solid double arrow) and the C termini of 2K16. The disulfide bridge between the N termini of 2K16 is shown as a dashed double arrow (away from the reader). Similar conventions were used as in Fig. 2B, schematic representation of the hydrophobic pairs in the middle heptad of the postulated all-parallel four-stranded coiled-coil and comparing those with an all-parallel orientation (C).

stranded structure. Indeed, further inspection of the hydrophobic packing in the middle heptads in Fig. 4 reveals that the four-stranded assembly invariably contains Leu-Ala-Leu-Ala in both planes. The stability of the Leu-Ala-Leu-Ala packing was recently demonstrated when analogs of the Rop protein where all the hydrophobes in the helix interface were exclusively replaced with alternating Leu-Ala packing were shown to exhibit native-like four-stranded all-antiparallel structure (Munson et al., 1994).

These results clearly indicate that, at least in these peptide models, one pair of alanine residues in the middle heptad can adequately control the parallel or antiparallel orientation of ω-helical chains in the four-stranded coiled-coil assembly. Multiple Leu → Ala substitutions in the hydrophobic interface has minimal effect provided that the hydrophobe on the other chain is a Leu or probably any of the residues with large hydrophobic side chains. This positional effect of alanine residues in the hydrophobic interface is important for at least two reasons. One, this strategy can potentially be applied in controlling the formation of two- and four-stranded coiled-coils. Second, this design element may be critical in orientating two or more functional groups or domains attached to a coiled-coil carrier. Therefore, this positional effect of alanine residues in the hydrophobic interface should be considered in conjunction with relevant interchain electrostatic interactions between charged residues at the e and g positions in the design of coiled-coils with predisposed structures.

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