This recognition between the bases of a functional, sequence-conserved RNA and the backbone of a sequence-variable element may be a general principle in RNA-RNA interactions (9). Both splice-site selection in group I introns and decoding during translation follow this principle and both processes are affected by the same aminoglycoside antibiotics. This similarity is underlined by an intriguing coincidence: the $tRNA^{leu}$ gene of the cyanobacterium *Anabaena azollae* contains a self-splicing group I intron inserted into the anticodon loop between the wobble base and the second base of the anticodon (*11*). Here an anticodon loop is also a 5' splice site, which base pairs with the intron's internal guide sequence and interacts with the intron core. Thus, this single region is involved both in the formation of the P1 stem necessary for self-splicing and in the formation of the codon-anticodon interaction necessary for decoding. Many different functions and activities have been demonstrated for group I introns, showing that their core represents a multipotent ribozyme (*10*). Recently, the *Tetrahymena* ribozyme was transformed into an RNA enzyme capable of promoting the hydrolysis of a carboxylate ester (*12*). The yeast U2 small nuclear RNA, an RNA component of the spliceosome, shows a structural similarity to the catalytic core of group I introns (*13*). Thus, splicing of group I introns may be similar to splicing of nuclear mRNA introns by the spliceosome (*14*). Additionally, group I introns may bear some tRNA-like features; two tRNA synthetases have been identified that, in addition to loading tRNAs, also promote the splicing reaction of group I introns (*15*). This family of potentially related RNAs can now be extended to include 16S rRNA, on the basis of the similarities between decoding and splice-site selection. These similarities could be due to a common ancestral RNA activity or could be due to evolutionary convergence of their structures as a consequence of their related functions.

The mode of action of aminoglycoside antibiotics in such a simple system as the self-splicing group I intron may provide insight into the general principles of antibiotic action. This prospect should encourage antibiotic designers to come up with new compounds to cope with resistant ribosomes and, for example, with the group I intron—containing pathogen, *Pneumocystis carinii*, a major cause of death of patients with AIDS.

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The Parallel β Helix of Pectate Lyase C: Something to Sneeze At

Fred E. Cohen

Protein crystallography and nuclear magnetic resonance spectroscopy have revealed the three-dimensional organization of several hundred polypeptide chains. Typically these structures are dominated by secondary structures: α helices and β sheets, and their tertiary structure can be understood from an analysis of the packing of these secondary structure elements. Protein taxonomists have gathered four-helix bundles (*1*) (for example, human growth hormone, interleukin-4, and hemerythrin), α/β barrels (*2*) (triose phosphate isomerase, muconate lactonizing enzyme, and mandelate racemase), β sandwiches (*3*) (transthyretin, superoxide dismutase, and immunoglobulins), and jelly-rolls (*4*) (tomato bushy stunt virus coat protein) to name but a few. Most newly determined protein structures are members of an existing family of structures or a minor variation on a known structural theme. The crystal structure of pectate lyase C (PelC) by Yoder *et al.* (*5*) in this issue contains a heretofore unknown fold, the parallel β helix. This reminds us that much remains to be learned about protein folding.

Pauling (*6*) introduced the α helix and β sheet as sterically sensible geometries for dipeptides that can be propagated to form substructures with a regular network of hydrogen bonds. Ramachandran (*7*) demonstrated that the lowest energy conformations of a dipeptide correspond to the backbone dihedral angles required to form α helices and β sheets. From a detailed study of proteins of known structure, aperiodic secondary structures including β bulges (*8*), β turns (*9*), and β breakers (*10*) have been observed. However, these are minor features by comparison to α helices and β sheets that typically account for more than 50% of the protein's structure.

What is a parallel β helix? Helices are characterized by their pitch (rise per residue), period (number of residues per turn), handedness (right or left), and diameter. The familiar α helix (drawn schematically in blue) is right-handed with a pitch of 1.5 Å and a period of 3.6 residues per turn. With the appropriate backbone dihedral angles, the peptide planes of all residues in the helix align forming a macro dipole and a network of hydrogen bonds that associates the carbonyl oxygen of a residue to the amide hydrogen of its neighbor four residues downstream. The 5.4 Å spacing between rungs of the spiral is compatible with the geometry of a hydrogen bond. The diameter of the α helix is sufficiently small that the structure is more like a filled cylinder than an open spring. By contrast, the parallel β helix (shown in red) is right-handed with a pitch of 0.22 Å and a period of 22 residues per turn (on average). Consecutive peptide planes are oriented in opposite directions as is common in β sheets, and so the network of hydrogen bonds alternates between the carbonyl oxygen of residue i to the amide hydrogen of $i + 22$ and the amide hydrogen of $i + 1$ to the carbonyl oxygen of $i + 22$. Because of the lack of alignment of consecutive peptide planes, no macro dipole should accumulate. The 4.8 Å spacing between rungs of the parallel β helix spiral is compatible with the less linear hydrogen bonding arrangement for β sheets formed from parallel β strands.

Should the parallel β helix have a large hole along its helical axis? A little trigonometry reveals that if the parallel β helix were

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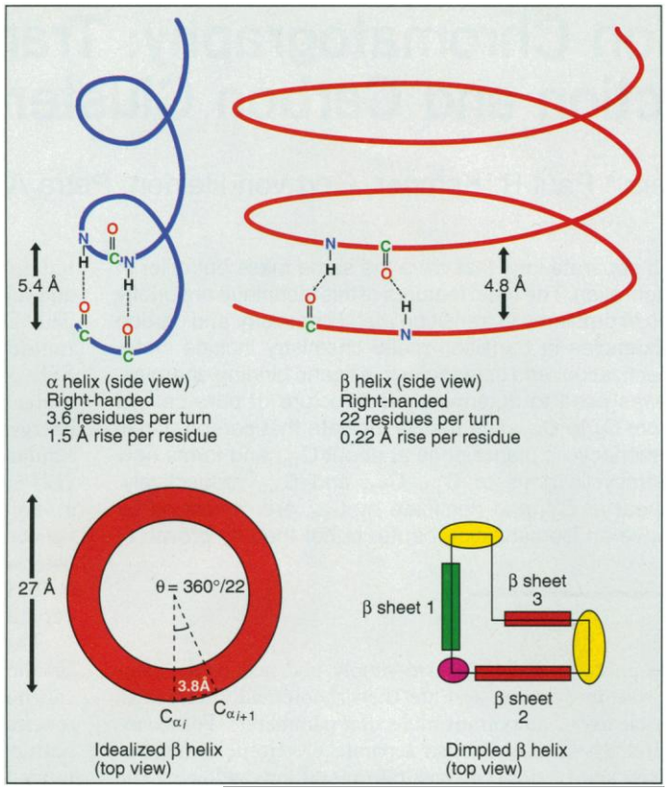
circular in projection, it would have a diameter of 27 Å with a 22 Å hole in the center. This would be an intriguing feature for an ion channel, but globular proteins have well-packed interiors (*11*). The parallel β helix in PelC is dimpled and resembles an "L" in projection. This creates a series of side chain stacks within the interior of the parallel β helix including an asparagine ladder and a serine stack with an extensive network of side chain hydrogen bonds, an aliphatic hydrophobic stack where valines, alanines, isoleucine, and leucines participate in van der Waals interactions of the type commonly found in the hydrophobic cores of globular proteins, and an aromatic stack more akin to the ring interactions found in double helical DNA.

In spite of the novelty of the parallel β helix, many of its subfeatures are well known to structural biologists. The dimpling of the parallel β helix creates three conventional parallel β sheets. Two of these sheets (numbered 2 and 3 in the figure and highlighted in red) form a β sandwich. The distance between the sheets of the sandwich is 8 to 9 Å, a figure consistent with other members of the family. Sternberg and Thornton (*12*) observed that the connection between parallel β strands in globular proteins is almost always right-handed. This accounts for the right-handed parallel β helix and suggests that no left-handed β helix will ever be found. While most β sheets are twisted, those from PelC are somewhat flattened. Presumably this represents an energetic compromise between the structural preferences of an isolated β sheet and the wealth of side chain stacking interactions possible within the β helix geometry. In the process of dimpling the β helix, three solvent-accessible loop regions are formed by each turn of the helix. Two are β arches (*13*) (highlighted in yellow), loops without a pattern of main chain hydrogen bonds that form a connection between strands from two different β sheets. The best known β arches are CDR1 and CDR2, two of the three complementarity-determining regions for antigen recognition by immunoglobulins. The third loop is akin to a β breaker (*10*) (highlighted in magenta), a dipeptide that creates a sharp change in the direction of the chain at the end of a strand from a parallel β sheet. A well-studied family of β breakers is the glycine of the GXGXXG motif for nucleotide binding in the kinase family (*14*). However, the asparagine residue at this juncture in the β helix adopts an unusual backbone geometry that makes these β breakers the mirror image of their previously studied counterparts.



Structures of the α helix and the parallel β helix. (**Top**) Dimensions and hydrogen bonding patterns for the α helix and the parallel β helix. (**Bottom**) Comparison of an idealized parallel β helix and the structure of pectate lyase C.

Armed with a new structural motif, champions of the various inverse folding algorithms (*15–17*) are sure to search for sequences of unknown structure that are compatible with the parallel β helix fold. Jurnak and colleagues have already detected several other pectate lyases and plant proteins or pathogenic factors including pollen and style proteins that are likely to share a common fold. Since protein sequences evolve much more rapidly than structures, it is likely that many parallel β helix proteins will successfully hide from the best of computer algorithms. The parallel β helix represents an elegant polypeptide chain organization that rivals the α/β barrel in simplicity. If this comparison is valid, then I suspect that we are seeing the structural tip of the parallel β helix iceberg.

Hay fever season is upon us. If plant pollens adopt the parallel β helix fold, then each turn of the helix provides two "hypervariable" β arches. It is clear that the most antigenic portions of a protein must lie on the surface. Loop regions within PelC constitute 43% of the accessible surface. Moreover, they represent a concentration of the most chemically reactive side chains. A review of the sequences in the β arches between subsheets 2 and 3 of the parallel β helix reveals sequences like EFTK, KKSD, DSPN, GASN, DTGR, and RHINITIS (*18*). Perhaps the parallel β helix fold will provide an ideal template for antigen presentation to aid in the development of polyvalent vaccines. Certainly, the structure encourages modular substitutions in loop regions that are unlikely to alter the conformation or export of this very stable family of proteins. For now, the parallel β helix has become something to sneeze at.

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18. Abbreviations for the amino acid residues are: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.