

Journal Club

PROTEIN FOLDING

HOW THE α -HELIX GOT ITS NAME

The protein structure models were referred to as ‘spiral’ configurations in the first paper, but as ‘helical’ configurations in the second paper. What prompted this name change and why does it matter?



Seventy years ago, Linus Pauling and Robert Corey published two papers on two hydrogen-bonded configurations of the polypeptide chain. The initial note in the *J. Am. Chem. Soc.* was followed four months later by a more detailed report (written with Herman Branson) in the *Proc. Natl Acad. Sci. USA (PNAS)*. Remarkably, the protein structure models were referred to as ‘spiral’ configurations in the first paper, but as ‘helical’ configurations in the second paper. What prompted this name change and why does it matter?

To devise the so-called α -helix and γ -helix models, the authors relied on precise bond lengths and angles based on crystal structures of amino acids, on stereoelectronic principles (resonance theory) that constrained the amide group C-(CO-NH)-C to a plane, and on the chemical intuition that every carbonyl and imino moiety should be involved in an optimal hydrogen bond (H-bond). Thus, in the 3.7 amino acids per turn α -helix, the vertical unit of translation per residue is 1.47 Å and each residue

is H-bonded with the third residue from it in both directions of the peptide chain. In the 5.1 amino acids per turn γ -helix, the vertical unit of translation per residue is 0.96 Å, and each residue is H-bonded with the fifth residue from it in both directions of the peptide chain.

The α -helix is a testament to the success of chemical model building. The dimensions and intra-chain H-bonding of this common secondary structure motif of proteins were correctly devised ten years before the advent of the first experimentally determined 3D structure of a protein. Pauling and associates were so certain of their triumph, that they declared in the *PNAS* paper in regard to previously published models by others: “None of these authors proposed either our 3.7-residue helix or our 5.1-residue helix. On the other hand, we would eliminate, by our basic postulates, all of the structures proposed by them.”

Spiral and helix are often used synonymously, but their mathematical definitions differ. A point moving along a spiral rotates about a fixed point while continuously increasing the distance from that point. A helix is a curve on a cylinder surface such that the angle between the curve and a plane perpendicular to the axis is constant — the distance from the axis for a point moving along the helix does not change. It was Jack Dunitz who pointed out to Pauling that α -helix was therefore the proper designation for the structural model, prompting the switch from ‘spiral’ to ‘helix’ in-between the publication of the two papers.

A closer look at Figures 2 and 4 of the *PNAS* paper shows that the α -helix is left-handed and consists

of D-amino acids. This is the mirror image of the α -helix we know from protein structures! Pauling had made an arbitrary choice about the helical sense and the stereochemistry of the amino acids, although the absolute configuration of the latter was known at the time.

The α -helix peptide undoubtedly inspired the double helix terminology for the structure of DNA, which was published two years later. Unlike in the case of the protein helix, Watson and Crick built the correct right-handed model, assembled from β -D-deoxyribofuranose units. However, in another twist of events, the first experimental structure of a DNA double helix turned out to be left-handed, unlike in the case of the α -helix, where model and initial experimental structure were left-handed and right-handed, respectively. The parallels do not end there, because the helical senses of peptides and DNA also are opposites of their corresponding supramolecular structures. Thus, peptide coiled coils are commonly left-handed, as is the DNA coil wrapped around histones in the nucleosome core particle.

Given the confusion regarding the handedness of early models, it is not surprising that many artistic renderings of helices display the wrong sense.

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ORIGINAL ARTICLES Pauling, L. & Corey, R. B. Two hydrogen-bonded spiral configurations of the polypeptide chain. *J. Am. Chem. Soc.* **72**, 5346 (1950) | Pauling, L. et al. The structure of proteins: two hydrogen-bonded helical configurations of the polypeptide chain. *Proc. Natl Acad. Sci. USA* **37**, 205–211 (1951)

RELATED ARTICLES Dunitz, J. D. Pauling's left-handed α -helix. *Angew. Chem. Int. Ed.* **40**, 4167–4173 (2001) | Eisenberg, D. The discovery of the α -helix and β -sheet, the principle structural features of proteins. *Proc. Natl Acad. Sci. USA* **100**, 11207–11210 (2003)