Helical Twists and β-Turns in Structures at Serine–Proline Sequences: Stabilization of cis-Proline and type VI β-turns via C–H/O interactions

Neal J. Zondlo

1University of Delaware Department of Chemistry & Biochemistry

May 26, 2024

Abstract

Structures at serine-proline sites in proteins were analyzed using a combination of peptide synthesis with structural methods and bioinformatics analysis of the PDB. Dipeptides were synthesized with the proline derivative (2S,4S)-(4-iodophenyl)hydroxyproline [hyp(4-I-Ph)]. The crystal structure of Boc-Ser-hyp(4-I-Ph)-OMe had two molecules in the unit cell. One molecule exhibited cis-proline and a type VIa 2 β-turn (BcisD). The cis-proline conformation was stabilized by a C–H/O interaction between Pro C–H α and the Ser side-chain oxygen. NMR data were consistent with stabilization of cis-proline by a C–H/O interaction in solution. The other crystallographically observed molecule had trans-Pro and both residues in the PPII conformation. Two conformations were observed in the crystal structure of Ac-Ser-hyp(4-I-Ph)-OMe, with Ser adopting PPII in one and the β conformation in the other, each with Pro in the δ conformation and trans-Pro. Structures at Ser-Pro sequences were further examined via bioinformatics analysis of the PDB and via DFT calculations. Ser–Pro versus Ala–Pro sequences were compared to identify bases for Ser stabilization of local structures. C–H/O interactions between the Ser side-chain O γ and Pro C–H α were observed in 45% of structures with Ser- cis-Pro in the PDB, with nearly all Ser- cis-Pro structures adopting a type VI β-turn. 53% of Ser- trans-Pro sequences exhibited main-chain C=O i+3 H–N i+4 or C=O i+3 H–N i+4 hydrogen bonds, with Ser as the i residue and Pro as the i+1 residue. These structures were overwhelmingly either type I β-turns or N-terminal capping motifs on α-helices or a 3_10-helices. These results indicate that Ser-Pro sequences are particularly potent in favoring these structures. In each, Ser is in either the PPII or β conformation, with the Ser O γ capable of engaging in a hydrogen bond with the amide N–H of the i+2 (type I β-turn or 3_10-helix; Ser χ 1 t) or i+3 (α-helix; Ser χ 1 g+) residue. Non-proline cis amide bonds can also be stabilized by C–H/O interactions.

Hosted file