

Investigation into Unusually Strong Interactions
between Proline and Aromatic Amino Acids

Kevin E. Riley, Lada Biedermannová, Jiří Vondrášek, and Pavel Hobza

Proline is an essential structural element in the helical motifs of some antimicrobial peptides, and the helical kink caused by proline plays an important role in the disruption of bacterial membranes. The role of proline in transmembrane transport proteins has also been extensively studied and it was shown that proline is important for substrate binding and recognition.

In recent works by Merz and coworkers and by Hobza and coworkers it has been found that noncovalent interactions between proline and residues of aromatic character (phenylalanine, tryptophan, and tyrosine) are much stronger than would be expected, this is especially true of tryptophan-proline arrangements that assume a “stacked” orientation. In this work we investigate the interaction strengths of proline-tryptophan complexes derived from the crystal structure of the tryptophan cage (PDB ID 1L2Y), which is a small artificial protein. Interaction energies are computed at the DFT-D/TPSS/TZVP and MP2/aug-cc-pVDZ levels of theory. Additional calculations are performed using the DFT variant of symmetry adapted perturbation theory, DFT-SAPT, which allows for the decomposition of the interaction energy into its, physically meaningful, component parts (ie electrostatic, induction, dispersion, and exchange).

In our studies it is found that, for an idealized stacked tryptophan-proline structure, the interaction is indeed quite strong, with a DFT-D binding energy of -6.8 kcal/mol (MP2 = -8.4 kcal/mol). DFT-SAPT analysis of this interaction shows that the attractive interaction between these two residues is chiefly attributable to dispersion forces, while a relatively strong electrostatic interaction also serves a role in stabilizing this complex.