Conformational preferences of amino acid residues and nearest-neighbor effect

One of the most difficult problems in science is how a protein molecule folds from an unfolded state to its native conformation. It has been suggested that the local structural order (*i.e.*, residual structure) may guide a polypeptide chain from the denatured to the native state (see review **1**). The local structural order in unfolded proteins is demonstrated by the following four indicators: the backbone conformational preferences, the nearest-neighbor effect, the cooperative formation of larger transient β-structures and α-helices, and the hydrophobic clusters. These indicators differ in the level of cooperativity, that is, the number of adjacent residues involved. The physical background of the local structural order in unfolded polypeptides is controversial. We have shown that screening of hydrogen bonds and local electrostatic interactions between main-chain atoms with water dipoles is the main reason for formation of the local structures in peptides and proteins (**1** and references therein, **3**,**5**-**9**).

The amino acids in dipeptides have structural properties similar to amino acid residues in proteins; this is why dipeptides are used as model molecules in numerous studies of proteins. Using NMR spectroscopy we have shown that intrinsic backbone preferences of a polypeptide chain are already determined at the dipeptide level and remain almost unchanged in longer peptides and are strikingly similar in the coil library of conformations from protein structures (**4**). For many years the structures of dipeptides in aqueous solution remained unknown. Using methods of vibrational spectroscopy we have finally determined the dipeptide structures of 19 basic amino acids in aqueous solutions *i.e.* the distributions of the three major conformations (P_{II}, ß, and α_R) (**2**). We have demonstrated that these distributions strongly depend on the type of side chain. The results provide a benchmark for the development of new potential force fields for the prediction of protein structures.

1. **F. Avbelj**, *Solvation and electrostatics as determinants of local structural order in unfolded peptides and proteins*, Protein and peptide folding, misfolding, and nonfolding, Wiley&Sons; Ed. Schweitzer-Stenner R. (2012)

2. **J. Grdadolnik**, V. Mohaček-Grošev, R.L. Baldwin, **F. Avbelj**, *Populations of the three major backbone conformations in 19 amino acid dipeptides*, Proc. Natl. Acad. Sci. USA, **108**, 1794-1798 (2011)

3. F. Avbelj, R.L. Baldwin, *Origin of the change in solvation enthalpy of the peptide group when neighboring peptide groups are added.* Proc. Natl. Acad. Sci. USA, **106**, 3137-3141 (2009).

4. F. Avbelj, **S. Golič Grdadolnik**, **J. Grdadolnik**, R.L. Baldwin, *Intrinsic backbone preferences are fully present in blocked amino acids.* Proc. Natl. Acad. Sci. USA, **103**, 1272-1277 (2006).

5. F. Avbelj, R.L. Baldwin, *Origin of the neighboring residue effect on peptide backbone conformation.* Proc. Natl. Acad. Sci. USA, **101**, 10967-10972 (2004).

6. F. Avbelj, **D. Kocjan,** R.L. Baldwin, *Protein chemical shifts arising from [alpha]-helices and [beta]-sheets on solvent exposure.* Proc. Natl. Acad. Sci. USA, **101**, 17394-17397 (2004).

7. F. Avbelj, R.L. Baldwin, *Role of backbone solvation and electrostatics in generating preferred peptide backbone conformations: distributions of phi*. Proc. Natl. Acad. Sci. USA, **100**, 5742-5747 (2003).

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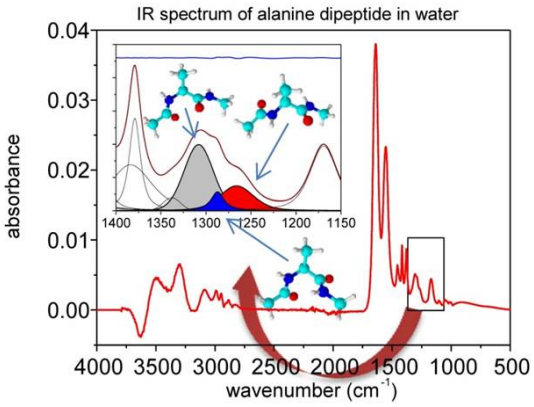
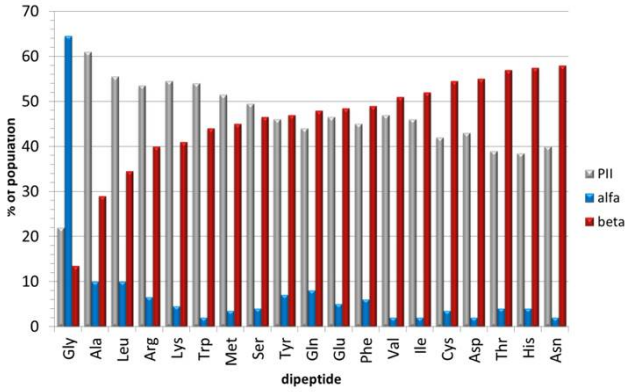
9. F. Avbelj, P. Luo,R.L. Baldwin, *Energetics of the interaction between water and the helical peptide group and its role in determining helix propensities.* Proc. Natl. Acad. Sci. USA, 2000, **97**, 10786-10791 (2000).

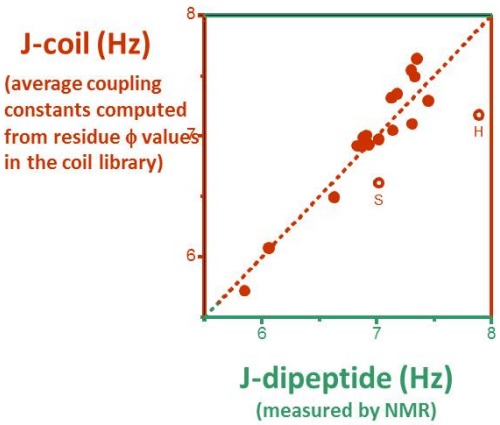
Populations of the three major backbone conformations in 19 amino acid dipeptides

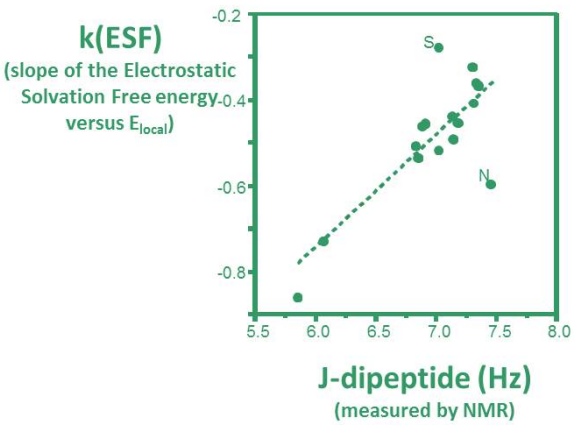




J. Grdadolnik, V. Mohaček-Grošev, R.L. Baldwin, **F. Avbelj**, Proc. Natl. Acad. Sci. USA, **108**, 1794-1798 (2011)

Intrinsic backbone preferences are fully present in blocked amino acids





F. Avbelj, **S. Golič Grdadolnik**, **J. Grdadolnik**, R.L. Baldwin, Proc. Natl. Acad. Sci. USA, **103**, 1272-1277 (2006)