THE DIPOLES OF THE ALPHA-HELIX AND THE BETA-SHEET: THEIR ROLE IN THE FOLDING OF PROTEINS

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As a result of the regular arrangement of peptide dipoles in secondary structure segments, the electrostatic energy of a protein is very sensitive to the relative orientation of the segments. Calculations of electrostatic backbone-backbone interactions show that the alignment of secondary structure dipoles is a major factor in determining the three-dimensional (tertiary) structure of proteins. (1)

Consideration of the electrostatic interaction between the backbone dipole moments of alpha-helices (1) (2) and beta-strands led us to the discovery of a surprisingly simple unifying theme applicable to the folding of many of the protein structures so far determined.

We were motivated by the idea that the directionally specific and relatively long range dipole-dipole interaction is largely responsible for the specific long-range order of a folded globular protein. A unifying electrostatic principle of protein tertiary structure is formulated: folded proteins have an optimal alignment of the peptide dipoles in secondary structure elements. This principle appaears to be in excellent qualitative agreement with the folded structures in all three major classes of globular proteins: Helices by themselves tend to form antiparallel pairs. Beta-strands align in an antiparallel fashion unless in contact with helices.

As far as we know, this is the first time protein tertiary structure folding patterns have been analysed from the electrostatic point of view. The picture which emerges is that the interior of the protein is a medium with low dielectric screening in which the interactions between secondary structure dipoles dominate the tertiary structure.

In 1959 Kauzmann (101) stated "it is likely that hydrogen bonds between peptide links and hydrophobic bonds are by far the most important in determining the overall configuration of the protein molecule". It may not be unreasonable to suggest that long-range electrostatic interactions in the protein interior be added to this list.

1) Hol, W.G.J., Halie, L. & Sander, C., submitted.
2) Hol, W.G.J., Van Duijnen, P.Th.& Berendsen, H.J.C., Nature 273, 443-446 (1978).