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**Preliminary Note**

# THE ELECTRON-DONATING STRENGTHS OF SIDE CHAINS IN THE DETERMINATION OF PROTEIN STRUCTURE

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It is well established that the structure of proteins is determined by their amino acid sequences (Anfinsen et al., 1961; Scheraga, 1971; Chou and Fasman, 1978; Robson, 1974). A hypothesis for the presence of an induction component in the "short-range interaction" that determines protein secondary structure was suggested in 1964 (Ling, 1964) and now further extended. This hypothesis is based on the assumptions: (1) that peptide-amide to peptide-amide H bonds in a-helical (and $\beta$-structure) segments of globular proteins are stronger than peptide-amide to water H bonds; (2) that the amide C = 0 group is much more polarizable than the amide NH groups; (3) that it is primarily the basicity of the C = 0 groups rather than the acidity of the NH groups that determine the strength of the peptide-amide to peptide-amide H bonds; and (4) that the electron-donating strength of each amino acid side chain determines the basicity of its own "backbone" peptide C = 0 group and hence its preferred secondary structure (as well as the secondary structures of near neighboring peptide chains).

Based on these assumptions, the extension of the induction hypothesis offers four predictions:

1. that the a-helix inducing capability ($\alpha$-helical potentials) of the individual amino acid residues (derived empirically from many proteins of known amino acid sequences and secondary structures) should be positively correlated with the electron-donating power of the side chains of the amino acid residues;

2. that the potential for induction of an extended conformation of individual amino acid residues should also be positively correlated with the electron-donating power of the individual side chains though less strongly so than in (1);

3. that the potential for induction of a coil structure should be negatively correlated with the electron-donating power of the side chain;

4. that correlation of the potentials for $\alpha$-helix, extended conformation, and coils with the electron-donating power of amino acid side chains should extend to those of the nearest neighboring peptides due to the propagated induction effect through the partially resonating polypeptide chains.

The electron-donating power of 19 a-amino acids (but not proline) was obtained in the form of the acid dissociation constants of the a-carboxylic acid analogues of each of the amino acids (e.g., for alanine, $CH_3NH_2CHCOOH$, the analogue is acetic acid, $CH_3COOH$). After adjustments of the state of ionization and neutralization of the five charged amino acids (asp, glu, his, lys, and arg), the electron-donating strengths of the 19 a-amino acid residues were found to correlate with their a-helix potentials ($P_\alpha$) (Chou and Fasman, 1978) derived from 29 proteins with a correlation coefficient of +0.77. The correlation coefficient with the a-helical potential of Tanaka and Scheraga (1976) is +0.71, and that with the a-helical potentials of Garnier, Osguthorpe, and Robson (1978), +0.75. After excluding both lys and glu, or only glu, well known for the $\beta$-

structure disrupting effect, the electron-donating power of the side chains was found to be also positively correlated with the potentials for extended β-conformation given by the same authors (r = +0.33 to +0.49). The weaker correlation of the β-structure potential with the electron-donating powers of the side chains also agrees with theory, according to which electrons donated by the side chains are conserved within the same polypeptide chain in an a-helical conformation but dissipated over neighboring polypeptide chains in β-structure. The potentials for coils and turns given by Garnier et al (1978) were shown to be negatively correlated to the electron-donating power of the side chains with r = –0.55 and –0.57 respectively. Finally the potentials for induction of α-helix, extended β-conformation, or coil and turn by nearby residues are given in terms of the directional information given by Garnier, Osguthorpe, and Robson. They were also shown to correlate with the electron-donating power of the jth amino acid side chains (j-m) with diminishing positive correlation as m increases from +1 to +8 on the C-terminal side or decreases from –1 to –8 on the N-terminal side. This diminishing positive correlation agrees with the hypothesis that the electron-donating effect of each amino acid side chain extends to peptide amide groups beyond its own, influencing their choices of preferred conformations. Studies of correlation of the potentials for a-helix and other structure with the bulkiness and the hydrophobicity of the side chains (Zimmerman et al., 1968) suggest greater contribution of hydrophobic bond formation in stabilizing P-structure than in stabilizing a-helix.

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