A Theoretical Investigation of Roles of Backbone Amide Resonance in Protein Structure

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Abstract

Protein structure, including its dynamics, is of pervasive significance in biology. A protein's structure determines its bindings with other molecules [1], and from that its roles in signal transduction, enzymatic activity and mechanical structure. Few cellular processes have no protein involvement. The relationship between a protein's sequence of amino-acid residues and its three-dimensional structure, partial or otherwise, has long been of considerable interest [2].

A theory of protein folding is proposed in Section 4.10.4 (Hypotheses/Protein folding). This theory varies and extends the backbone-based theory proposed by Rose *et al*. [3]. This theory may prove to be the most significant offering of the thesis.

Overall, this thesis investigates the variation in peptide group resonance and its implications for Resonance-Assisted Hydrogen Bonding [4, 5], RAHB, such as exists in inter-peptide group hydrogen bonding. Natural Bond Orbital [6], NBO, analysis is used for this investigation, and Section 2.1 summarizes the virtues of NBO.

Chapter 3 is concerned with methods for computational investigation of protein structures, and finds that methods and basis sets most often used for these investigations are particularly unsuitable when any beta sheets are present due to poor modelling of amide resonance and hence of RAHB that features in the hydrogen-bonded chains of backbone amides of protein secondary structures such as beta sheets [7] and alpha helices [8].

Chapter 4 reports experiments quantifying the sensitivity of amide resonance to electrostatic field with component parallel or antiparallel to the amide C-N bond. This sensitivity allows electrostatic properties including permittivity of amino-acid residue sidechains to influence backbone amide resonance and hence secondary structure RAHB chains, giving a novel mechanism relating residue sequence to structure. Also, this variation in amide resonance is energetically significant even without considering a hydrogen bonding context. Variation of peptide group resonance is expected to vary the barrier height of prolyl isomerization [9]. Subsequent to quantifying this effect in isolated amides and in a RAHB chain, hypotheses are offered concerning the stability of beta sheets, amyloid fibrils [10] and polyproline helices [11]. An analogous sensitivity in nitrogenous base pairing [12] is conjectured. A hypothesis is offered concerning protein complexation and molecular chaperone [13] action.

Chapter 5 is motivated by the observed increase of stabilization when cooperative hydrogen bonding chains are cyclized in non-protein contexts [6] and by the phenomena anticipated if these cycles exist in proteins as described in the chapter. The question of the optimal geometry for amide-amide hydrogen bonding is revisited with emphasis on the inequivalence of amide oxygen lone pairs. A possible avenue for the design of HB-chain polymers with improved stability is discussed.

Chapter 6 studies a dependency of amino acid residue preference against beta sheet secondary structure by backbone hydration in the presence of cation, doing so by Quantum Molecular Dynamic simulation of a beta sheet with a full quantum mechanical treatment of each solvent molecule.

Declaration

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I claim that there is ample evidence here that pre-candidature mentoring by Iain Murchland and Cvetan Stojkoski resulted in public good.

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