Molecular Commensalism of N-H…O and C-H…O Interactions in Folylpolyglutamate Synthetase

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Folylpolyglutamate synthetase (FPGS) is a target for drug therapy in breast and colon cancers. We explore the relationships of weak methyl-donated CH--O interactions to NH--O hydrogen bonds in an FPGS helix. Methyl interactions occur between ala-A8 and main chain carbonyl oxygens on tyr-A4 and glu-A5 residues, and between val-A7 and the carbonyl oxygen of tyr-A3. We report evidence that these methyl-carbonyl interactions, by subtle geometric shifts, share a common energy pool with the hydrogen bond network, which enhances the strength of each interaction and overall enzyme function. We dub such relationships "molecular commensalism," after an analogous macroscopic concept of ecology. To delineate this concept, we apply perturbed structural response (Vergenz, *et. al., J. Am. Chem. Soc.* **2003,** *125,* 12318-12327), in which physically plausible structural perturbations are systematically applied to the most stable configuration of a hydrogen bond network, and the energies of structural relaxation responses of the other variables are evaluated. We employ MP2 and B3LYP partial optimization on overlapping 3- and 4-peptide model segments from FPGS, starting from empirical heavy atom positions. Forces acting on the model fragment from the rest of the protein are accounted for using atomic force differences on the frozen atoms.