DFT Analysis of Phenylalanine Hydroxylase

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There are many molecules that act on dopamine and dopamine-like binding sites in enzymes and transport proteins. Some effects of these proteins are beneficial while others are detrimental. We are designing inhibitors for this group of proteins. Phenylalanine hydroxylase (PheOH) is a tetradydrobiopterin-dependent monooxygenase that influences the rate determining step of converting phenylalanine into tryrosine by hydroxylating phenylalanine. Both phenylalanine and tyrosine are important components in the anabolism of dopamine. A deficiency of PheOH can cause hyperphenylalaninemia, which gives rise to phenylketonuria (PKU), a severe disease that can cause mental retardation if one's diet isn't strictly monitored. A suite of dopaminergic derivatives has been developed as potential inhibitors of the PheOH enzyme. The inhibitory effectiveness of these dopaminergic derivatives has been measured via in silico models in which the strength of interaction between each substrate and the enzymatic active site was analyzed. A crystal-structure of the PheOH active site, with bound thienylalanine, was isolated from the Protein Data Bank (PDB ID: 1KW0). The positions of novel dopaminergic derivatives were optimized in the active site using M062X/6-31G with implicit solvation and with flexible amino acid side-chains. Interaction energies between the ligands and the protein were calculated using M062X and MP2 with the 6- 311+G* basis set. From recent studies, there are promising novel inhibitors for this enzyme.