Evaluation of hybrid and pure DFT methods for the binding of novel ligands in the tyrosine hydroxylase enzyme

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The Minnesota 2006 density functional methods include both pure and hybrid models, each of which benefitting different aspects of various systems. The Tyrosine Hydroxylase (TyrH) enzyme contains a Fe^{2+} in the center of the active site. M06-2X, M06-L, and M06 have all been used to evaluate the binding strength of novel ligands in the TyrH active site. TyrH is the rate determining enzyme in the synthesis of the catecholamine, dopamine. TyrH converts tyrosine to L-DOPA, which is administered in the treatment of Parkinson's patients, as dopamine cannot cross the blood brain barrier. The inhibition of TyrH reduces dopamine in the brain to undetectable levels. A crystal structure of the active site of Tyrosine Hydroxylase with a known inhibitor bound was obtained from the protein data bank (PDB ID: 2TOH). In this work, dopaminergic derivatives were inserted into the enzymatic active site *in silico* in order to test the strength of the interactions between the substrate and active site, to determine if any of these derivatives could be effective inhibitors. M06-2X is a hybrid functional, while M06-L and M06 are both pure; all of these functionals were used to optimize structures and to analyze interaction energies. While all the methods are suited for large complexes, such as the active site of an enzyme, M06-2X is stated to be best for interaction energies, M06-L best when a transition metal is present, and M06 as an intermediate between the two (Yan Zhao, Donald G. Truhlar, *Chem Phys Lett*. **502**, 2011, 1-13). The novel dopaminergic derivatives were optimized with implicit solvent with either M06-2X, M06-L, or M06 and 6-31G with relaxed amino acid side-chains. Interaction energies between the ligands and protein were determined using the same DFT methods as mentioned above with the 6- 311+G* basis set. M06-2X and M06 are hybrid functionals, while M06-L is pure; all of these functionals were used to optimize structures and to analyze interaction energies. Preliminary results show significant differences between the methods within the same complex, as well as potential in determining a well-suited derivative, that has seeded other promising ligands.