Aromatic Interactions in the Binding of Ligands to HMGCoA Reductase

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Many statin drugs inhibit the synthesis of cholesterol by binding in the active site of HMGCoA reductase via hydrogen bonds and charge/charge interactions with several amino acid residues. However, dispersion forces also affect the binding of ligands to this active site. Using second order perturbation theory (MP2) and several DFT methods with the 6-31++g** and 6-311+g* basis sets we study the hydrogen bonds and aromatic dispersion interactions between tyrosine residue 479 and HMGCoA, and the relative importance of these forces in ligand binding is determined. Knowing the specific amounts of interaction between tyrosine residue 479 and HMGCoA may result in better design of cholesterol limiting drugs. Further, we perform point mutations of the tyrosine residue to determine how these mutations can affect cholesterol synthesis.