

P016 Cytochrome P450 reactivity and specificity from QM/MM mechanistic modelling

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Cytochrome P450 is an important metalloenzyme found in plants, animals and bacteria. It activates molecular oxygen and catalyses stereoselective and regioselective oxygen insertion reactions of a wide variety of organic compounds. These enzymes are of particular interest in drug metabolism, because they play important roles in drug disposition, and in their pharmacological and toxicological effects. A key aim is the prediction of selectivity of reactions of drugs with different P450 isozymes. Combined quantum mechanics/molecular mechanics (QM/MM) methods now allow reactions in P450 enzymes to be modelled, and provide a promising approach to analysing determinants of selectivity in drug metabolism. Comparison with experimental selectivity and reactivity data helps to validate these methods. The oxidation of cyclohexene by the bacterial P450cam from *Pseudomonas putida* is an important example. It produces C=C bond epoxidation and allylic hydroxylation products in approximately equal amounts. In contrast, oxidation of propene gives exclusively epoxidation-type products. QM/MM calculations of barriers for these reactions, combined with molecular dynamics simulations, give relative barriers for these processes that are consistent with experimental findings.