QM/MM Exploration of reactivity and selectivity in cytochrome P450

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Cytochrome P450 enzymes catalyze the oxidation of a wide variety of hydrophobic substrates, both as part of the normal metabolism, and as a key step in the solubilisation and excretion of non-biological compounds such as pharmaceuticals. Understanding the rate and selectivity of the different isoforms of the enzyme with respect to the latter function is of significant practical importance, and of general interest concerning the nature of enzyme catalysis.

We use molecular dynamics, quantum mechanical and hybrid quantum mechanical-molecular mechanical (QM/MM) methods to explore the electronic structure of the key high-valent iron Compound I active species, to investigate reaction mechanisms for activation of aliphatic and aromatic substrates, and to attempt to understand the factors governing the selectivity of the site of oxidation. In particular, we examine reactivity with camphor, propene and cyclohexene in the bacterial P450cam, and of benzene, diclofenac and warfarin in the human drug-processing isoform 2C9.

Recent publications in this area:

Mechanisms of reaction in cytochrome P450: hydroxylation of camphor in P450cam
J. Zurek, N. Foloppe, J. N. Harvey and A. J. Mulholland
Org. Biomol. Chem., 2006, **4**, 3931 - 3937.

Electronic Structure of Compound I in Human Isoforms of Cytochrome P450 from QM/MM Modeling
C. M. Bathelt, J. Zurek, A. J. Mulholland and J. N. Harvey
J. Am. Chem. Soc. 2005, **127**, 12900 - 12908.

Aromatic Hydroxylation by Cytochrome P450: Model Calculations of Mechanism and Substituent Effects
C. M. Bathelt, L. Ridder, A. J. Mulholland, and J. N. Harvey
J. Am. Chem. Soc. 2003, **125**, 15004 - 15005