Nick Foster presented this poster at the 21st North America ISSX Meeting 2017 held in Providence, USA.

Abstract

The Cytochrome P450 enzymes (P450s) are a large family of monooxygenases involved in the metabolism of drugs via oxidative reactions such as C-H bond hydroxylation, epoxidation and heteroatom oxidation. It has become increasingly important, within drug development, to develop computer based methods to study and accurately predict P450-mediated metabolism of drugs. We recently published a method that uses quantum mechanical simulations to predict the regioselectivity and lability of cytochrome P450 metabolism [1]. This method uses AM1 calculations and Brønsted relationships to estimate the activation energies for the reaction mechanisms leading to P450 metabolism. This model provides accurate predictions of the regioselectivity of metabolism with faster calculation time than ab initio DFT calculations. However, we have continued to investigate opportunities to further improve the accuracy of the semi empirical methods for some oxidative mechanisms such as aromatic oxidation. In the present study, we model the transition state in the reaction coordinate prior to the intermediates formed during aromatic and aliphatic hydroxylation [1]. The *ab initio* DFT level of theory is used to model these reactions for a range of P450 3A4 substrates, for which experimental data on relative reaction rates are available. A transition state search is performed to calculate accurate activation energies that correlate well with the experimental data. Subsequently, semi-empirical QM methods are used in a similar transition state search to establish a relationship to these DFT based energies. A correlation between the energetics of DFT and semi-empirical QM methods has been established and this correlation has, in turn, been used to develop an improved predictive model for aromatic oxidation, that can provide a fast and increasingly accurate prediction for the P450 mediated metabolism of drugs.

(1) Tyzack, J.; Hunt, P.; Segall, M. J. Chem. Inf. Model. 2016, 56, 2180-2193.

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