中文摘要

Chapter I : Site of metabolism prediction for FMO enzymes via machine learning and condensed Fukui function

FMO 酵素在代謝具有親核性化合物中佔了很重要的角色而且在代謝藥物上也是屬於第一線的酵素，而要確定藥物的 site of metabolism (SOM)通常不是一件簡單的事，SOM 也就是指藥物分子中代謝的特定原子的位置，所以若是能夠建立一個電腦的模型去預測 SOM 對於新藥開發將是一件有益的事，在我們的研究中，我們利用機械學習、量子化學和樹狀分子特徵的方式去建立一個 svm 的電腦模型，而最後得到的預測模型是一個化學上易理解且只具有五個特徵的模型，在我們的訓練模型中，AUC 值(area under curve value of ROC curve)是 0.889，MCC 值是 0.767，測試組中 AUC 值是 0.801 而 MCC 值是 0.601，這些數值顯示我們的預測模型是具有預測能力且可信的。而我們希望此研究可以幫助主要在 FMO 酵素上面代謝的新藥開發。

Chapter II : Interaction between Trehalose and MTHase from *Sulfolobus solfataricus* studied by theoretical computation and site-directed mutagenesis

Maltooligosyltrehalose trehalohydrolase (MTHase)這個酵素是催化麥芽寡糖海藻糖(maltooligosyltrehalose)產生海藻糖(trehalose)的一個重要的酵素，在這篇研究中，我們利用分子模擬的方法 (hydrogen bond analysis, free energy decomposition, and computational alanine scanning)去模擬和分析麥芽寡糖海藻糖和酵素之間的作用，去找出酵素中哪些胺基酸位置是重要的，而電腦預測的結果和實驗的結果是有一致性的，我們發現在酵素中的 Y155, D156, 和 W218 和麥芽寡糖海藻糖的結合是佔了重要的角色，而我們之後也用量子化學的方式去計算這些重要的胺基酸和麥芽寡糖海藻糖反應催化時的活化能，而得到的數值也跟其他同類的反應相近。

Chapter III : A Theoretical Study on the Alkaline Hydrolysis of Methyl Thioacetate in Aqueous Solution

我們使用 Gaussian09 和 CPMD 的量子化學軟體研究 thiolester 在真空中和水溶液中的鹼催化水解反應，研究中使用了 metadynamic 的方法去計算自由能平面 (free energy surface)，在真空狀態中反應呈現兩種反應路徑，而在水溶液中是呈現 triple-well 的反應路徑，而水溶液中反應主要不是以 S_N2 mechanism 的方式而是以中間會產生一個 tetrahedral intermediate (a stepwise mechanism)的方式去進行反應，而與實驗值相比，我們計算的結果與得到的反應機制和實驗測得的活化能是相近的。

ABSTRACT

Chapter I: Site of metabolism prediction for FMO enzymes via machine learning and condensed Fukui function

The flavin-containing monooxygenase (FMO) catalyzes xenobiotics with soft nucleophiles and also plays an important role in drug metabolism in Phase I enzymes. The site of metabolism (SOM) refers to the place where the reaction of metabolism occurs in a molecule. Identification of SOMs of a compound is not usually a low-cost task in drug discovery. Thus, a silico method to predict site of metabolism (SOMs) of FMOs would provide medical chemists information of SOMs before experiments. In this work, we developed a machine learning model combining quantum features (condensed Fukui function) and circular fingerprints to predict potential SOMs in a molecule. The final model via SVM was easily interpreted with only five features. In the training set with 10 CV showed an area under curve (AUC) value of ROC curve, 0.889, and the value of MCC,0.767. In the external validation, AUC value of the model was 0.801 and the accuracy (MCC) was 0.611. These showed the predictive power of our model and we wish such a research to assist medical chemists in the assessment of FMO metabolism at the preclinical stage of drug discovery.

Chapter II: Interaction between Trehalose and MTHase from *Sulfolobus solfataricus* studied by theoretical computation and site-directed mutagenesis

Maltooligosyltrehalose trehalohydrolase (MTHase) catalyzes the release of trehalose by cleaving the α-1,4-glucosidic linkage next to the α-1,1-linked terminal disaccharide of maltooligosyltrehalose. Computer simulation using the hydrogen bond analysis, free energy decomposition, and computational alanine scanning were employed to investigate the interaction between maltooligosyltrehalose and the enzyme. The same residues that were chosen for theoretical investigation were also studied by site-directed mutagenesis and enzyme kinetic analysis. The importance of

residues determined either experimentally or computed theoretically were in good accord with each other. It was found that residues Y155, D156, and W218 of subsites -2 and -3 of the enzyme might play an important role in interacting with the ligand. The theoretically constructed structure of the enzyme-ligand complex was further validated through an *ab initio* quantum chemical calculation using the Gaussian09 package. The activation energy computed from this latter study was very similar to those reported in literatures for the same type of hydrolysis reactions.

Chapter III: A Theoretical Study on the Alkaline Hydrolysis of Methyl Thioacetate in Aqueous Solution

A base catalyzed hydrolysis reaction of thiolester has been studied in both gas and solution phases using two *ab* initio quantum mechanics calculations such as Gaussian09 and CPMD. The free energy surface along the reaction path is also constructed using a configuration sampling technique namely the metadynamics method. While there are two different reaction paths obtained for the potential profile of the base-catalyzed hydrolysis reaction for thiolester in gas phase, a triple-well reaction path is computed for the reaction in solution phase by both two quantum mechanics calculations. Unlike a S_N2 mechanism (a concerted mechanism) found for the gas-phase reaction, a nucleophilic attack from the hydroxide ion on the carbonyl carbon to yield a tetrahedral intermediate (a stepwise mechanism) is observed for the solution phase reaction. Moreover, the energy profiles computed by these two theoretical calculations are found to be well comparable with those determined experimentally.