Simulations of Complex Chemical Reactions. The Case of the Enzymatic C5-Methylation of DNA

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Analysis of complex chemical processes in condensed phases usually implies the exploration of multidimensional free energy surfaces. This goal may require an unaffordable computational cost because of the size of the system and the number of coordinates that need to be explored. This is the case of the enzymatic C5-Methylation of DNA, a chemical process that involves several chemical events that can happen concertedly or sequentially. A convenient strategy is to combine hybrid QM/MM descriptions with methods that focus on the relevant regions of the free energy surface, such as the string method. Here we will show that this strategy gives a complete description of the molecular mechanism of this complex chemical reaction in good agreement with experimental findings. Our proposal clarifies the role of Glu119 and identifies the nature of the base in charge of proton abstraction, two issues that have been the subject of a long debate in the literature.