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First Principles Study of the Reaction Mechanism for Intein C-terminal Cleavage PHILIP SHEMELLA, SAROJ NAYAK, Department of Physics, Applied Physics & Astronomy, BRIAN PEREIRA, SHEKHAR GARDE, GEORGES BELFORT, Department of Chemical & Biological Engineering. Rensselaer Polytechnic Institute. Troy, NY — Protein splicing, consisting of the excision and ligation of two flanking sequences (the exteins), is auto-catalyzed by the internal sequence (the intein). It has been shown experimentally that by mutating the critical first residue of the intein, the first step of splicing is inhibited, although intein C-terminal cleavage can still occur independently. Using a tripeptide model system with QM methods, we have investigated the effect of different mutants in order to provide an atomic level understanding of this mechanism. We find that the reaction energy barrier for asparagine cyclization can be controlled by mutation of non-essential residues: specifically we found that the barrier with a methionine mutant is larger than to the barrier for cysteine, resulting in slower C-terminal cleavage in agreement with experiment. The accuracy of our model system is further confirmed by comparing results with that of a combined quantum mechanics and molecular mechanics (QM/MM) approach. These results suggest that certain mutations in inteins could be used to control the reaction rate without affecting the overall reaction mechanism and could exploited for many applications including molecular switches, sensors and controlled drug delivery.

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