DETERMINING THE MECHANISM OF THE UBIQUITIN CONJUGATING ENZYME UBC13 WITH QM/MM AND METADYNAMICS

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Ubc13 is an E2 enzyme that catalyzes a post translational modification of proteins called lysine ubiquitination, i.e. the addition of ubiquitin to the lysine of a target protein via a thioester aminolysis reaction. Lysine ubiquitination is important because one of its functions is to signal for the degradation of damaged proteins, and defects in this process are linked to different disorders. The accepted mechanism for Ubc13-catalyzed ubiquitination is a stepwise mechanism that creates an oxyanion intermediate. This intermediate is hypothesized to be stabilized by a nearby asparagine residue, which is known as the "oxyanion hole." However, the validity of the accepted mechanism has come into question because (1) there has never been a comprehensive study of the ubiquitination mechanism, (2) the accepted mechanism was inferred from the reverse reaction, and (3) recent studies suggest a different role for the oxyanion hole. In our study, we use QM/MM and metadyamics, a rare-events sampling method, to determine the mechanism.

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