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Investigation at the atomic level of homologous enzymes reveals distinct reaction paths[1] IOANNA ZOI, STEVEN D. SCHWARTZ, Univ of Arizona — Bacterial enzymes Escherichia coli and Vibrio cholerae 5' - Methylthioadenosine nucleosidases (MTANs) have different binding affinities for the same transition state analogue. This was surprising as these enzymes share 60% sequence identity, have almost identical active sites and act under the same mechanism. We performed Transition Path Sampling simulations of both enzymes to reveal the atomic details of the catalytic chemical step, to explain the inhibitor affinity differences. Unlike EcMTAN, VcMTAN has multiple distinct transition states, which is an indication that multiple sets of coordinated protein motions can reach a transition state. We also identified the important residues that participate in each enzyme's reaction coordinate and explained their contribution. Subtle dynamic differences manifest in difference of reaction coordinate and transition state structure and also suggest that MTANs differ from most ribosyl transferases. As experimental approaches report averages regarding reaction coordinate information, this study offers, previously unavailable, detailed knowledge to the explanation of bacterial MTANs catalytic mechanism, and could have a significant impact on pharmaceutical design.

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