

Reaction mechanism of nucleoside 2'-deoxyribosyltransferases: free-energy landscape supports an oxocarbenium ion as the reaction intermediate

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Abstract

Insight into the catalytic mechanism of *Lactobacillus leichmannii* nucleoside 2'-deoxyribosyltransferase (LN₂DT) has been gained by calculating a quantum mechanics–molecular mechanics (QM/MM) free-energy landscape of the reaction within the enzyme active site. Our results support an oxocarbenium species as the reaction intermediate and thus an S_N1 reaction mechanism in this family of bacterial enzymes. Our mechanistic proposal is validated by comparing experimental kinetic data on the impact of the single amino acid replacements Tyr7, Glu98 and Met125 with Ala, Asp and Ala/norLeu, respectively, and accounts for the specificity shown by this enzyme on a non-natural substrate. This work broadens our understanding of enzymatic C–N bond cleavage and C–N bond formation.