between the purine leaving group and the anionic nucleophile. This mechanism was first described for PNP and has since been shown to apply to other glycosyltransferases. With fixed nucleophiles in the catalytic site, a ribooxacarbenium-ion transition state is formed at some point during the ribosyl migration. The exact nature of PNP transition states is dictated by the migration distance and protein vibrational modes that form the transition state. Remarkable differences in transition-state structure can occur with nearly identical protein structures. These differences can guide the design of transition-state analogs that demonstrate specificity for enzyme variants from different species. Knowledge of the transition-state structures has permitted access to picomolar compounds with favorable pharmokinetic properties. Two of these have entered clinical trials for T-cell disease. PNP has also served as one of the first enzymes for exploration of catalytic-site-induced substrate distortions by binding isotope effects. These results are providing new insights into the fundamental notions of enzymatic catalysis, induced fit, and transition-state structure.

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