Supporting Information

Protonation States

We choose protonation states of the titratable side chains and phosphate groups in pol β based on individual pKa values at a solution pH of 7.0 as reported in Table S2. Because the three conserved Asp groups are well separated from each other and not closely interacting with the dCTP in the crystal structure, our choice of the protonation states based on pKa of the amino acid group and an overall pH of 7.0 is reasonable. It is also in accord with previous work [1-7]. We choose HID (His with hydrogen on the delta nitrogen) for all His groups. In prior work [6], we found that the choice of His tautomers for His329 in pol μ does not affect the active-site rearrangement and nucleotide-binding pocket motion, so this choice of His tautomers is expected to have have little impact on the results of this paper.

Correlated Motion Analysis

The extent of correlated motions (positive or negative) for two molecular components can be quantified by calculating the covariance between the two units (e.g., atoms, residues, or subdomains) [8]. To investigate correlated motions among the DNA polymerase, DNA, and the incoming nucleotide, we calculated the normalized covariance, C_{ij}, for the displacement of all heavy atom pairs, I and J, as given by:

$$C_{ij} = \frac{\left\langle \Delta r_i \cdot \Delta r_j \right\rangle}{\left(\left\langle \Delta r_i^2 \right\rangle \left\langle \Delta r_j^2 \right\rangle\right)^{1/2}}$$

where Δr_i is the displacement from the mean position of the i-th atom determined from all configurations in the trajectory segment being analyzed. C_{ij} is normalized to be between -1 and 1. For completely correlated motions (i.e., when two atoms are moving in the same directions), $C_{ij} = 1$, and, for completely anti-correlated motions (i.e., when two atoms are moving in opposite directions), $C_{ij} = -1$.

Covariance analysis is performed on the last 50 ns MD trajectories of A:dTTP, A:dATP, A:dCTP, and A:dGTP pol μ systems. For these covariance analyses, rotations and translations of the proteins occurring during the trajectories are removed by alignment to the initial protein conformation using a least-square-fit procedure for all protein heavy atoms.

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