Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting Information: Probing the General Base for DNA Polymerization in Telomerase: A Molecular Dynamics Investigation

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S1 Computational Details of Metadynamics Simulation

The extended Lagrangian formulation of metadynamics technique was employed here. In this formulation, CVs are harmonically coupled with additional auxiliary variables. The spring constant was set to 2 Hartree, while the mass of 50 amu Bohr^2 was taken for auxiliary variables. The biasing potentials were constructed using spherical Gaussian functions with a height of w =0.6 kcal mol^{-1} and width of δs =0.05. We used an adaptive metadynamics time step, where the new Gaussian hill is added only when the displacement of the CV in the CV–space from the center of the previously added Gaussian potential is greater than 0.075. The velocity re-scaling scheme was employed to keep the CV temperature at 300±200 K.

In this study, we used coordination-based CVs. The coordination number of A atom with a group of B atoms (C[A...B]) is defined by the following analytical function:

$$C[\mathrm{A}-\mathrm{B}] = \sum_{J \in \mathrm{B}} \frac{1-\left(\frac{d_{\mathrm{A}J}}{d^0_{\mathrm{AB}}}\right)^6}{1-\left(\frac{d_{\mathrm{A}J}}{d^0_{\mathrm{AB}}}\right)^{12}} \tag{1}$$

Here, $d_{\mathrm{A}J}$ and d^0_{AB} are the distance and the cutoff distance between atoms A and J, respectively. Chosen CVs and the corresponding parameters are listed in Table S1.

The free energy surface was reconstructed from metadynamics simulation as

$$F(\mathbf{s}, t \to \infty) = -\sum_{\tau < t} w \exp\left(-\frac{[\mathbf{s}(t)-\mathbf{s}(\tau)]^2}{2\,(\delta s)^2}\right) \tag{2}$$

where τ is the metadynamics-time at which the Gaussian biases are updated.

S2 Supplementary Figures & Tables

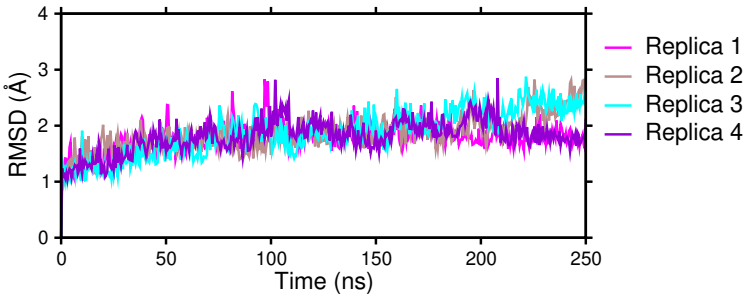

Figure S1: The time evolution of protein backbone RMSD during MM force-field simulations. RMSD was computed with respect to the starting structure of MD simulation. Four different colors represent four independent replicas.

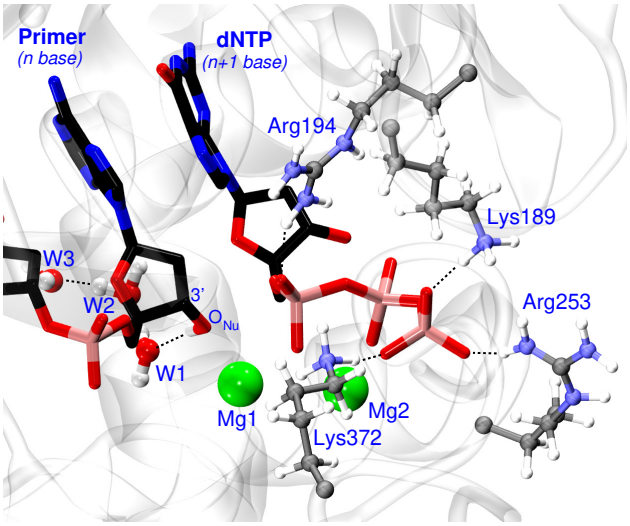

Figure S2: Crucial interactions between positively charged active site residues and negatively charged triphosphate in the equilibrated active site structure of **R**.

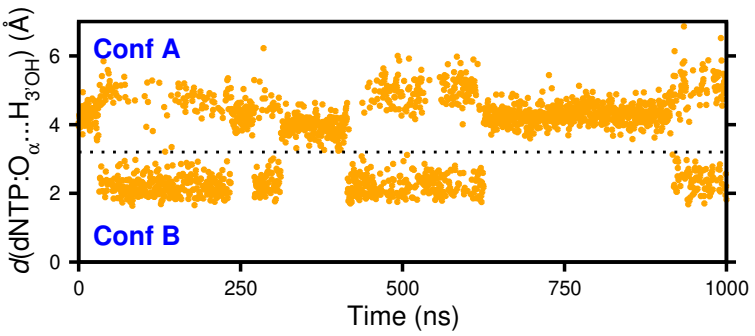

Figure S3: The time evaluation of distance between dNTP:O_α and hydrogen of $3'O_{Nu}H$ during the MM simulations of **R**.

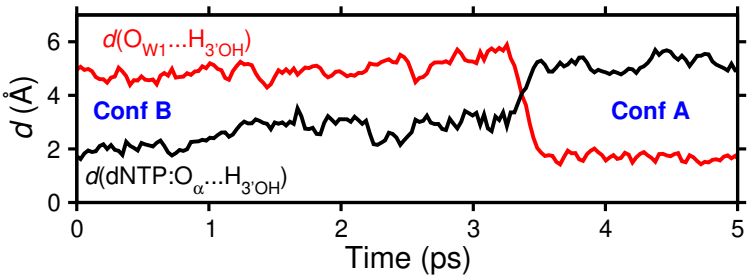

Figure S4: Time evolution of d[dNTP:$O_\alpha \cdots H_{3'O_{Nu}H}$] and d[$O_{W1} \cdots H_{3'O_{Nu}H}$] (in Å) during an independent QM/MM equilibration of **Conf B**. Transition from **Conf B** to **Conf A** is observed at ∼3.4 ps.

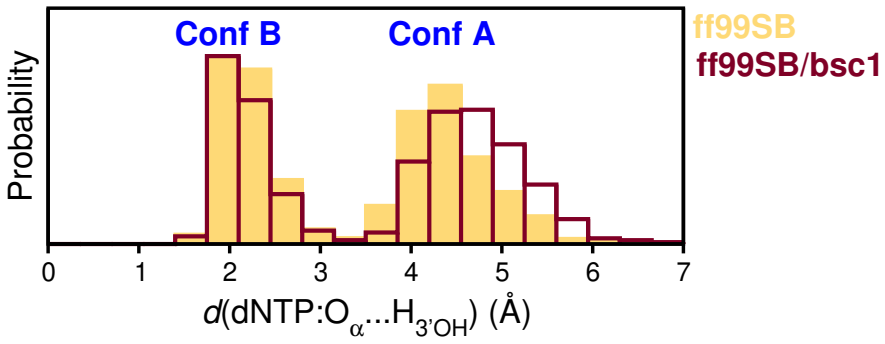

Figure S5: Histogram of d[dNTP:$O_\alpha \cdots H_{3'O_{Nu}H}$] from MM MD simulations using ff99SB with (500 ns) and without bsc correction (1000 ns).

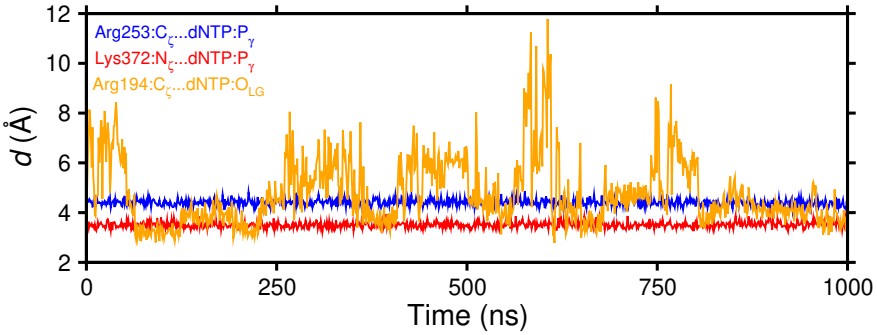

Figure S6: The time series plot of some the crucial distances involved in the interaction between positively charged residues and negatively charged triphosphate during MM MD simulations of **R**.

Table S1: List of CVs and the corresponding parameter d^0_{AB}.

CVs	d^0_{AB} (in Å)
CV1 = $C[\mathrm{O_{Nu}}\cdots\mathrm{H}]$	1.33
CV2 = $C[\mathrm{O_{Nu}}\cdots\mathrm{P}_\alpha]$	2.64
CV3 = $C[\mathrm{P}_\alpha\cdots\mathrm{O_{LG}}]$	2.64

Table S2: The average distances (in Å) of various crucial interactions between positively charged active site residues and negatively charged triphosphate of dNTP in the equilibrated active site structure of **R**.

Atoms	Distances (in Å)
$\mathrm{Arg194{:}C}_\zeta\cdots\mathrm{dNTP{:}O_{LG}}$	4.76±1.35
$\mathrm{Arg253{:}C}_\zeta\cdots\mathrm{dNTP{:}P}_\gamma$	4.40±0.12
$\mathrm{Lys372{:}N}_\zeta\cdots\mathrm{dNTP{:}P}_\gamma$	3.50±0.11