Function of the third metal ion in DNA polymerase catalysis

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Abstract: DNA polymerases catalyze template dependent DNA synthesis during genome replication and repair. In the reaction cycle, dNTP complementary to the templating base is incorporated into DNA in a nucleotydyl-transfer reaction catalyzed by a polymerase during which a new bond is formed between the 3’OH of the primer strand and the alpha-phosphate of the dNTP. The reaction products, the dNMP extended DNA strand and pyrophosphate, are capable of performing the reverse reaction. The forward reaction has been shown to require two magnesium ions (catalytic and nucleotide binding metal ions) and progresses via a S_N2-type mechanism. Recent advances using time-lapsed X-ray crystallography identifies a transient metal ion that appears after phosphodiester bond formation. In spite of significant progress in recent years, the atomic level mechanism of the DNA synthesis reaction has remained poorly understood. Here, we present results from a QM/MM study aiming at finding the functional significant of the recently discovered product metal ion in mediating the reverse reaction.