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Structure-Specific DNA Induced Conformational Changes in Taq Polymerase Revealed by Small Angle Scattering. Zimei Bu¹, Derek L. Ho², W. Malcolm Byrnes³, Wu-po Ma⁴, Yuan Shi⁵, David J.E. Callaway⁵, ¹Fox Chase Cancer Center, Philadelphia, PA, ²NIST, Gaithersburg, MD, ³Dept. of Biochem. & Molecular Biology, Howard Univ. College of Medicine, Washington, D.C., ⁴Third Wave Technologies, Inc., Madison, WI, ⁵North Shore/LIJ Research Inst., New York Univ. School of Medicine, Manhasset, NY.

The DNA polymerase I from *Thermus aquaticus* (Taq polymerase) performs lagging-strand DNA synthesis and DNA repair. Taq polymerase contains a polymerase domain for synthesizing a new DNA strand and a 5'-nuclease domain for cleaving RNA primers or damaged DNA strands. The extended crystal structure of Taq polymerase poses a puzzle on how this enzyme coordinates its polymerase and the nuclease activities to generate only a nick. Using contrast-variation solution small angle neutron scattering (SANS), we have examined the conformational changes that occur in Taq polymerase upon binding "overlap flap" DNA, a structure-specific DNA substrate that mimics the substrate in strand replacement reactions. In solution, apo Taq polymerase has an overall expanded equilibrium conformation similar to that in the crystal structure. Upon binding to the DNA substrate, both the polymerase and the nuclease domains adopt more compact overall conformations, but these changes are not enough to bring the two active sites close enough to generate a nick. Reconstruction of the 3-D molecular envelope from SANS data shows that, in the DNA-bound form, the nuclease domain is lifted up relative to its position in the non-DNA-bound form so as to be in closer contact with the thumb and palm subdomains of the polymerase domain. The results suggest that a form of structure-sensing is responsible for the coordination of the polymerase and nuclease activities in nick generation. However, interactions between the polymerase and the nuclease domains can assist in the transfer of the DNA substrate from one active site to the other.