The Role of Water in Protein-DNA Complexes from high Resolution X-ray Crystallography

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Sac7d is a small, abundant, non-specific DNA-binding protein of the hyperthermophilic archaeon *Sulfolobus acidocaldarius*. Crystal structures of different Sac7d mutants in complex with DNA have been analyzed at high resolution (1.45 Å – 2.25Å). The high resolution structures of Sac7d-DNA complexes afford good opportunity to study protein-DNA-water interactions in detail. Four recurring well-ordered water molecules are observed in the buried cavity located between protein and DNA surfaces near the intercalation site. They fill up the cavity and enable close packing of protein-DNA interface. These four water molecules are always present at the interface of Sac7d and DNA, although with varying arrangements in different complexes. The buried cavity between Sac7d V26F/M29F and DNA becomes narrower than that in wt-Sac7d due to the phenylalanine/base stacking interaction between Phe26 and G3 base. The four bridging water molecules rearrange in the longitudinal direction along helix axis to match the shapes of the protein-DNA interface.

An important question is how do Sac7d/Sso7d bind to DNA in a sequence-general manner. This water-filled cavity is important in that it allows G-C base pairs to be bound without steric problems due to the additional N2 amino group, thus permitting the proteins its sequence-general binding to DNA.

It is interesting to note that bridging water molecules play an important role in modulating the non-sequence-specific binding of Sac7d by acting as filler, whereas they play an entirely different role as specific linkers between protein and DNA in defining the sequence specificity in the *Trp* repressor-DNA recognition.

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