

dimers, it is not clear whether the alternative Asp 46 conformation could be stabilized in the absence of tandem binding.

Tandem binding suggests an alternative explanation for the genetic sensitivity^{8,9} of base pairs in positions 2–4 (Fig. 1a). The extensive interface between repressor and the phosphodiester backbone of the consensus operator DNA in *ITRO* had suggested¹ that repressor might sense these base pairs indirectly, by sequence-dependent structural variation in the DNA backbone. Our results suggest that indirect readout may be secondary to tandem recognition, because bases –4, –3 and 2 can be contacted by a tandemly bound dimer in the same way as the central dimer recognizes bases 5, 6 and –7. In addition, the DNA backbones of *ITRO* and tandem complex duplexes have nearly identical conformations at equivalent base-pair positions, despite several sequence differences (Fig. 3), suggesting that DNA conformation could also be influenced by repressor binding.

Trp repressor can bind to DNA in either single or tandem modes depending on the DNA sequence context. Minor differences at the DNA-binding interface arise from tandem interactions between adjacent dimers, and not from fundamental differences in the mechanism of DNA recognition. The end-on approach of helix E, although limiting the role of the short side chains of the helix N terminus in base-pair recognition, is necessary for sharing of the half-site major groove by parallel E-helices of tandem dimers. An important open question is which mode is used on *trp* operators *in vivo*. Natural half-sites vary slightly in sequence, suggesting a need for adaptability in recognition; flexibility of the repressor reading head¹⁵ and water-mediated hydrogen bonding at the protein/DNA interface^{1,3,4} may be important in achieving this adaptability. Tandem binding could also be a component of regulation by *trp* repressor¹³; its influence on transcription deserves attention. □

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