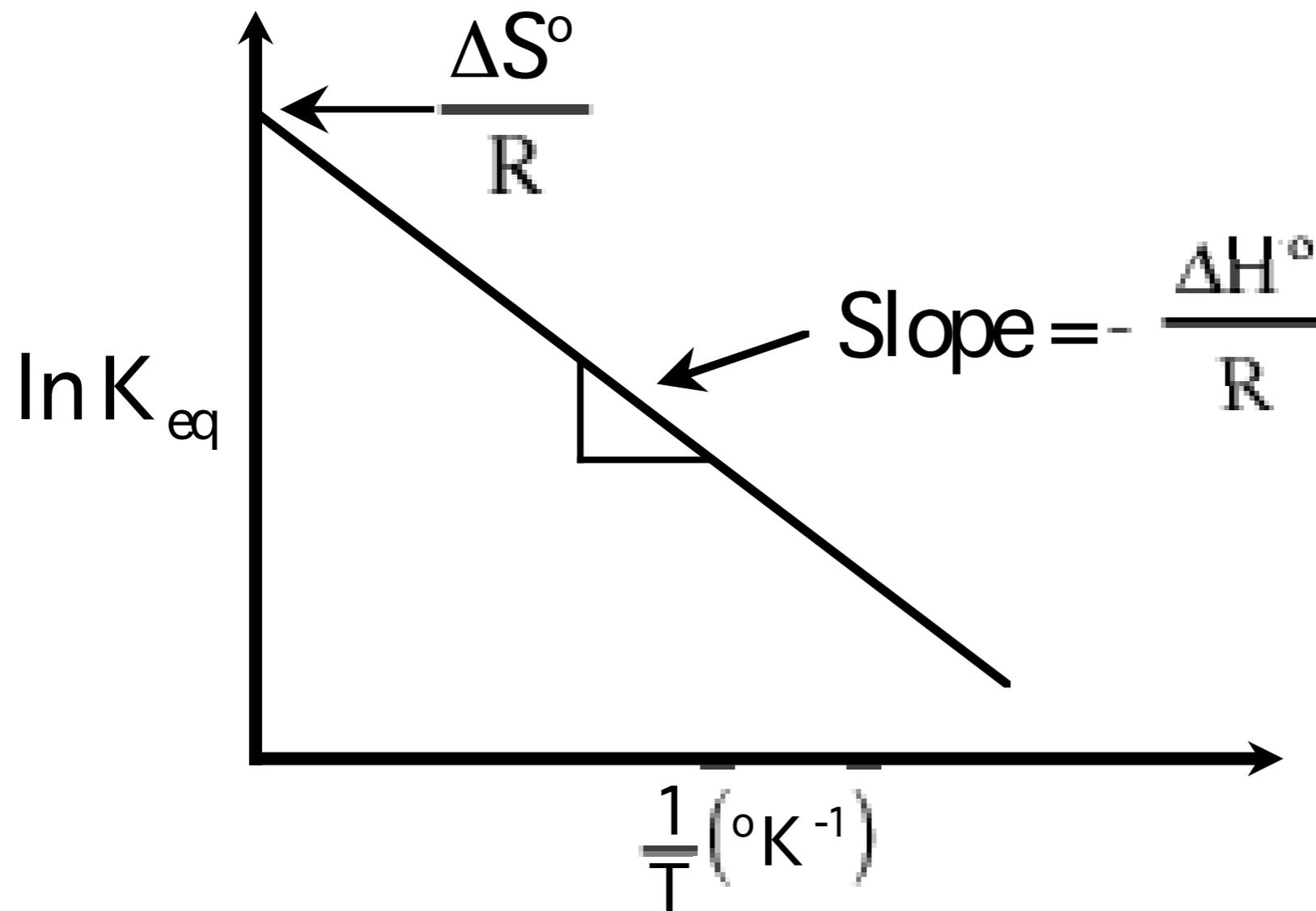


Enthalpy and entropy of protein binding to DNA

The temperature dependence of the binding constants reveals ΔH and ΔS in a van't Hoff plot if ΔH and ΔS are independent of temperature



$$\Delta G = \Delta H - T \cdot \Delta S$$

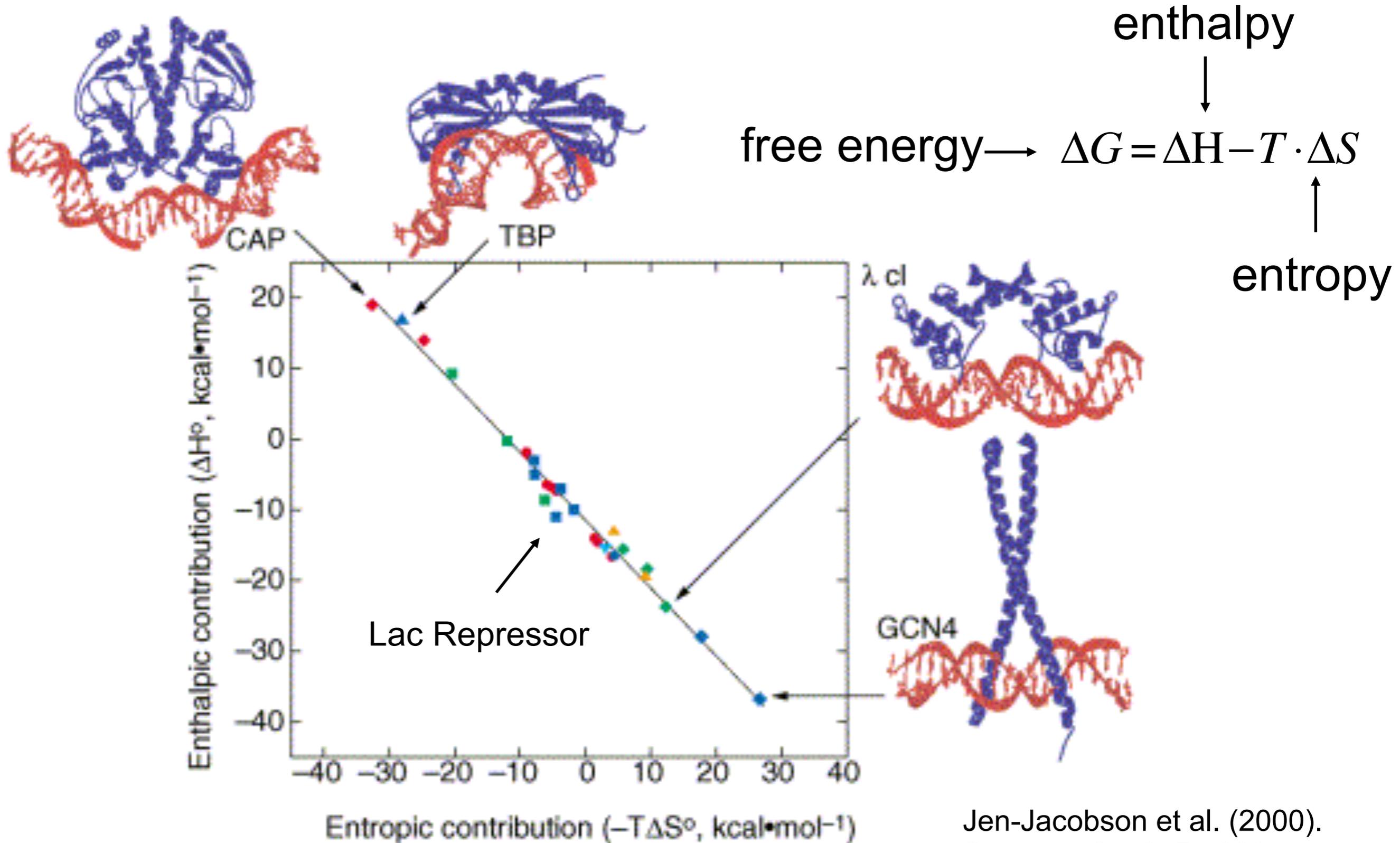
$$\Delta G = -R \cdot T \cdot \ln K_{eq}$$

$$\ln K_{eq} = -\frac{\Delta H}{RT} + \frac{\Delta S}{R}$$

$$\frac{\partial(\ln K_{eq})}{\partial(1/T)} = -\frac{\Delta H}{R}$$

From the slope of $\ln K_{eq}$ vs. $1/T$ (usually from 0 to 40 °C) one can determine the ΔH and from extrapolation also ΔS . If the van't Hoff plot is curved then ΔH is temperature dependent and it can be determined from the derivative.

Contribution of enthalpy and entropy to binding energies of different protein-DNA complexes



Jen-Jacobson et al. (2000).
Structure 8, 1015-1023

K_D and ΔG values for protein-DNA binding per site

Specific binding of a protein to DNA varies over a relatively small range of $\Delta G_{\text{bind,sp}} = -9$ to -16 kcal/mol, with ~ 60 kcal/mol for ΔH and $T\Delta S$

$$\Rightarrow \Delta G_{\text{bind,sp}} \approx \text{const. } (-11.7 \pm 1.6 \text{ kcal/mol})$$

$$\Rightarrow \Delta H = -T \cdot \Delta S - 11.7 \text{ kcal/mol}$$

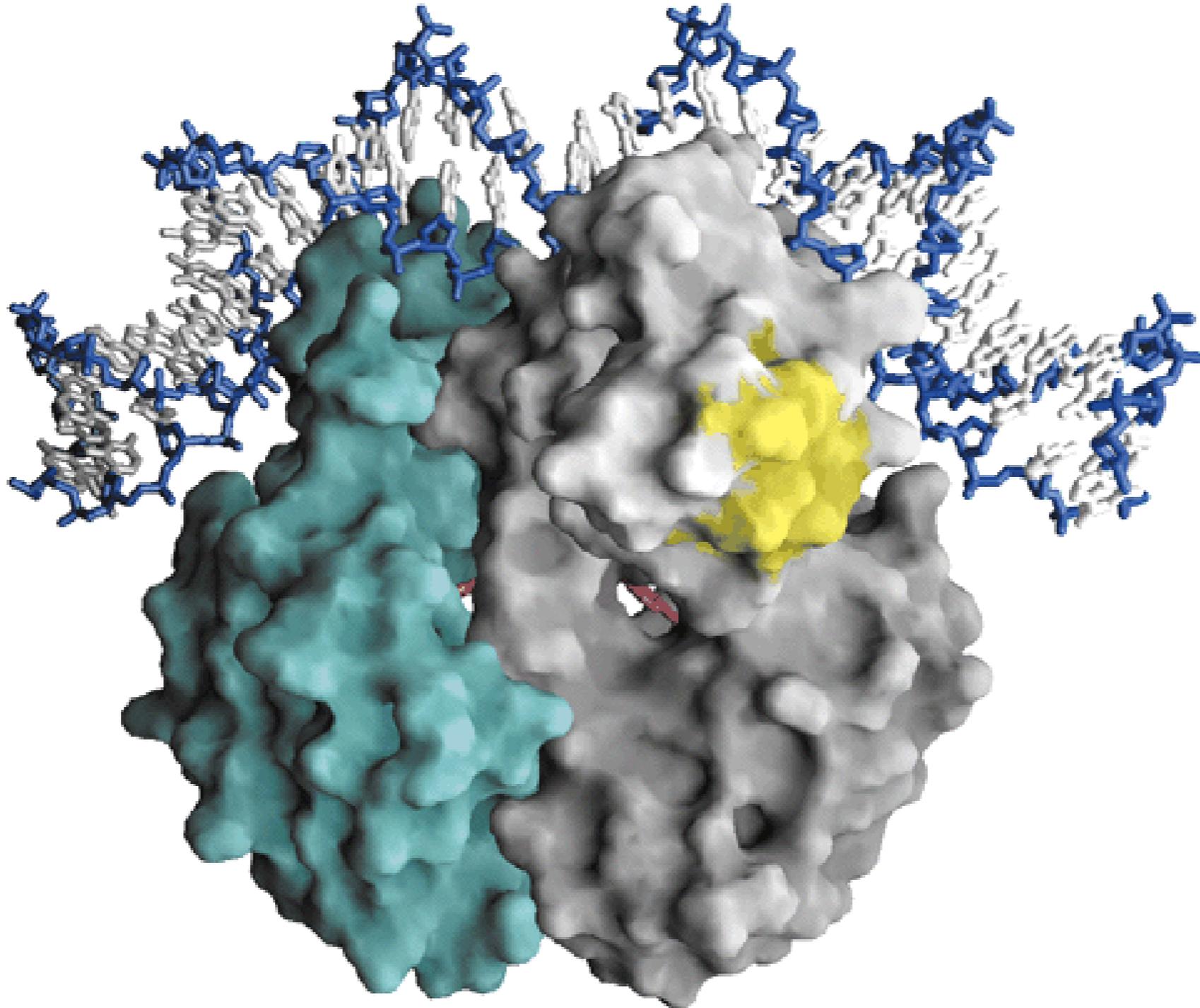
Protein needs to select specific binding site from unspecific sites

$$\Rightarrow \Delta\Delta G(\text{specific} - \text{unspecific}) \sim -5 \text{ to } -9 \text{ kcal/mol}$$

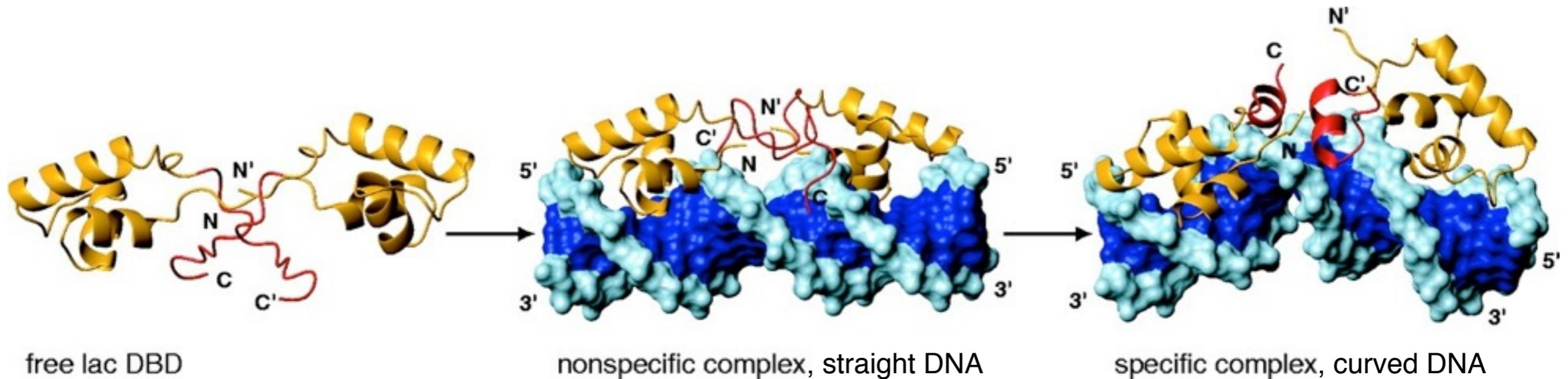
Protein binding must be reversible on the cell's time scale

$$\Rightarrow \Delta G_{\text{bind,sp}} \leq -16 \text{ kcal/mol}$$

Molecular structure of *E. coli* CRP (also called CAP for catabolite gene activator protein)



The hinge region (50-62 in red) of Lac-DBD is folded only in the specific complex with DNA



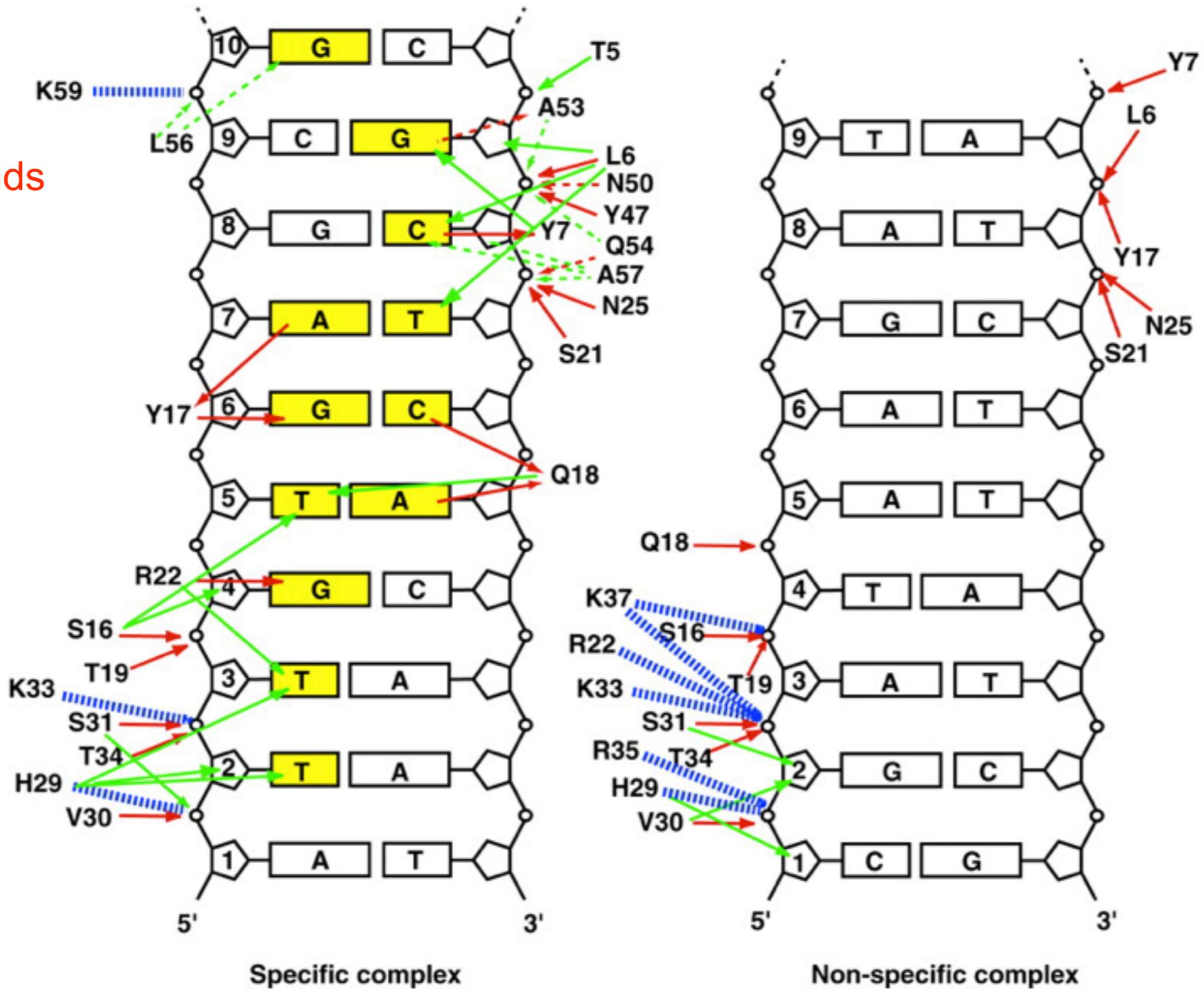
- folding of hinge region with specific contacts in minor groove
- specific interactions major groove
- less electrostatic interactions
- curvature of DNA

Specific (left) and nonspecific (right) protein-DNA contacts of Lac-DBD repressor with DNA

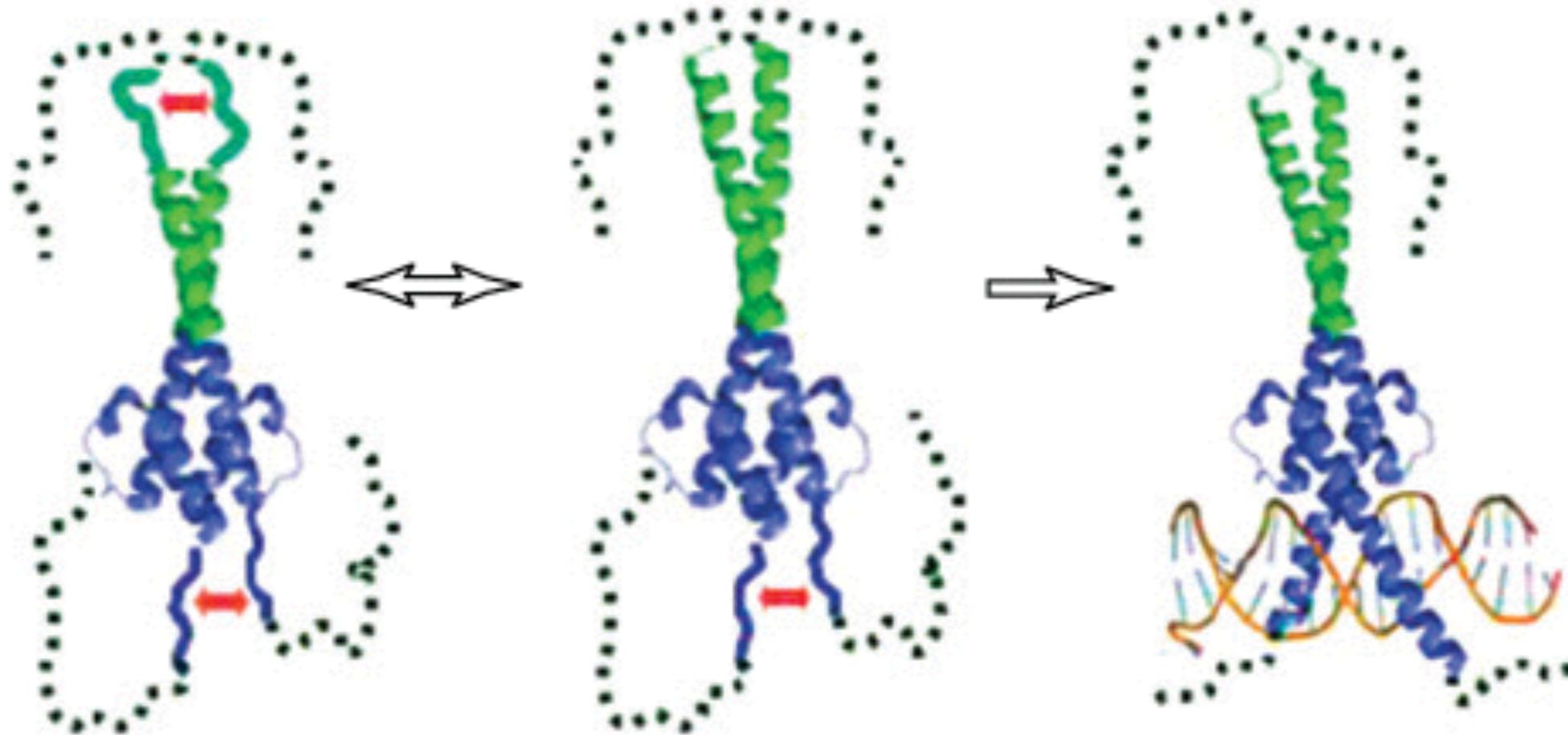
red:
hydrogen bonds

green:
hydrophobic
contacts

dashed blue:
electrostatic
contacts

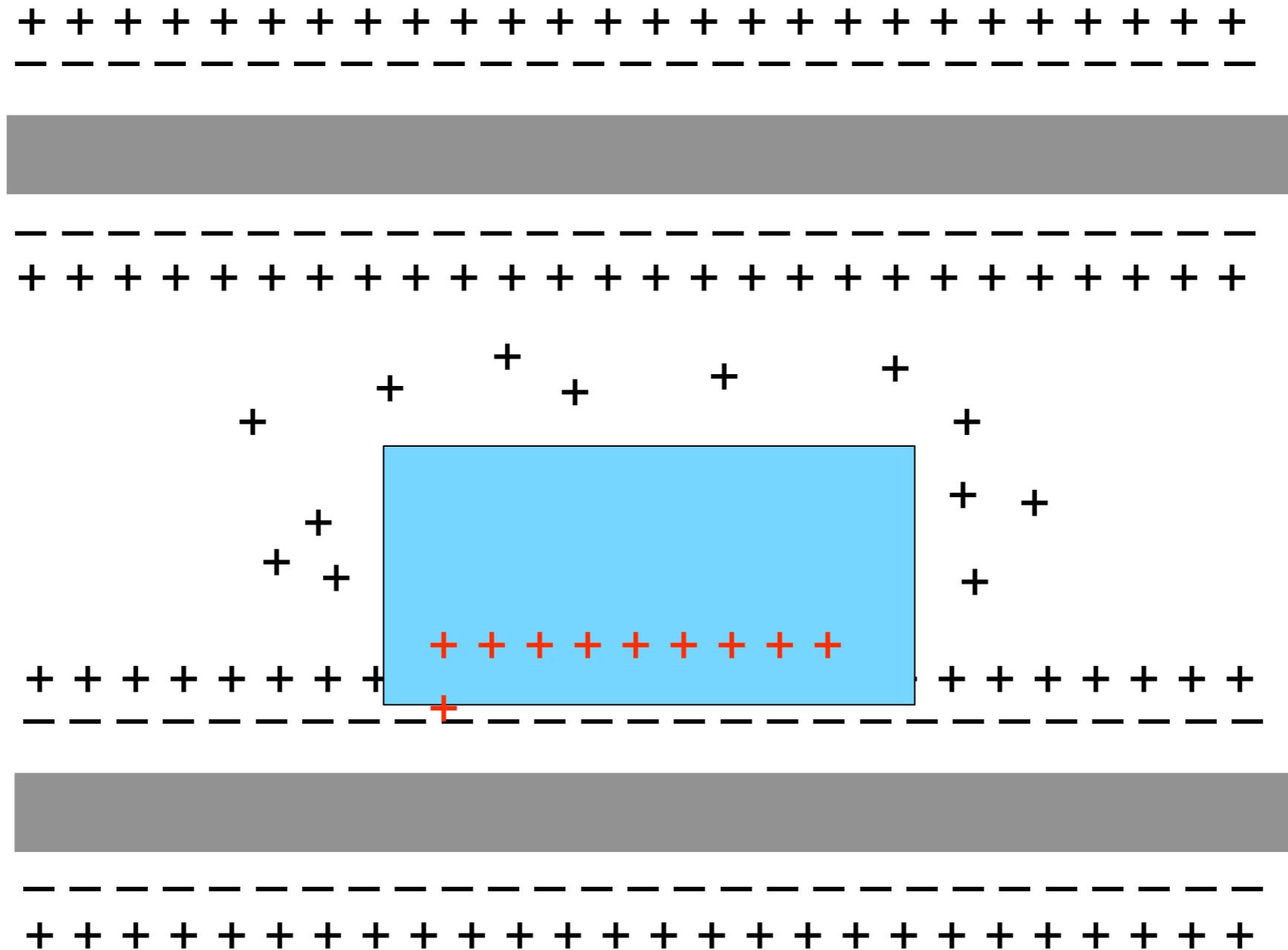


Local folding of the Max transcription factor upon dimerization and binding



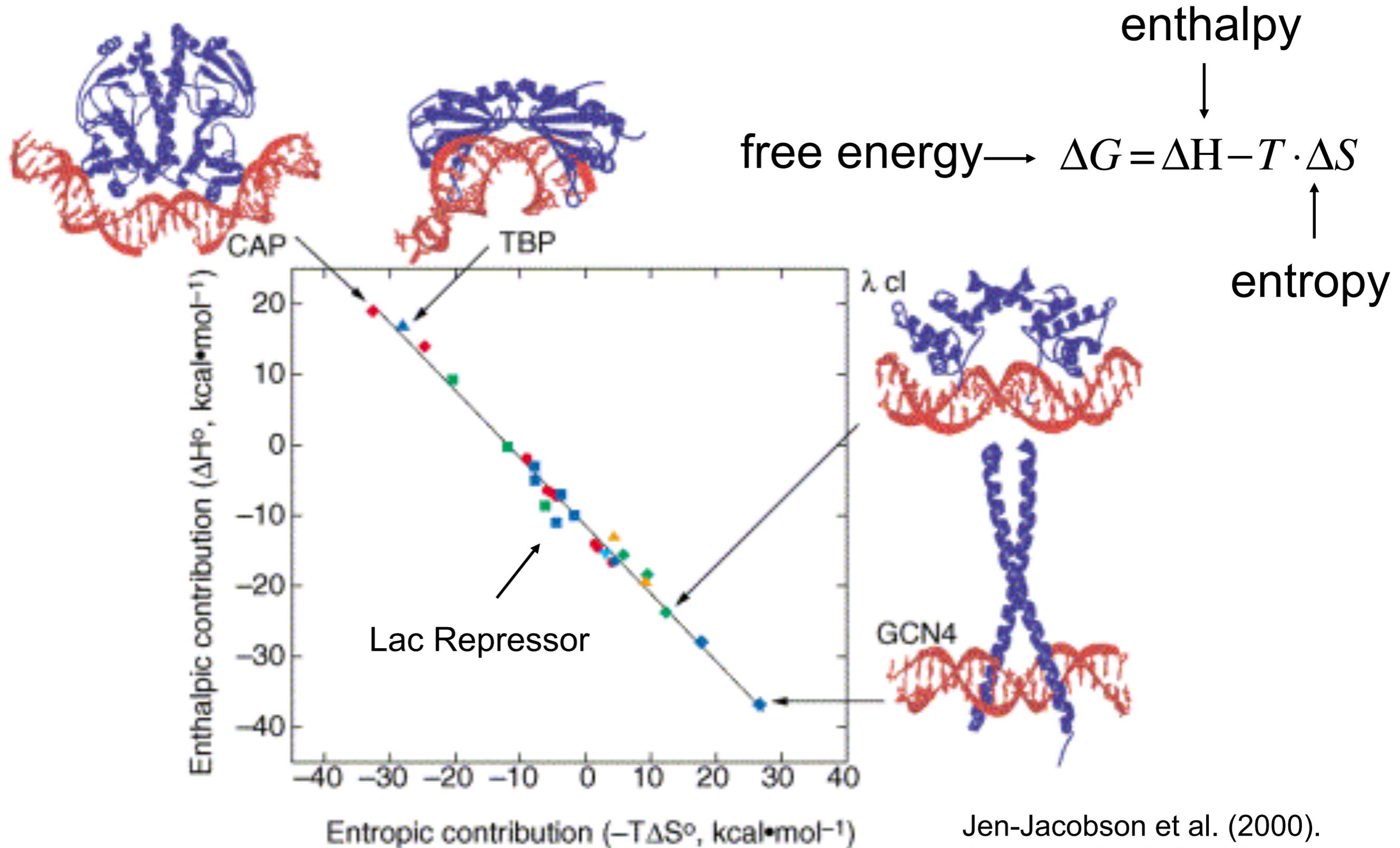
The Max transcription factor (PDBcode: 1NKP) binds DNA as a dimer. The disordered N-terminal region (upper dotted line) reduces the electrostatic repulsion (red arrows) between the two monomers, and increases the population of the folded state at the flanking leucine zipper (green). This also stabilizes the bHLH region (blue) and thus improves binding affinity for DNA.

ΔS_{PE} : Favorable displacement of ions from the DNA



$$-T\Delta S_{PE} = 6 \text{ to } 18 \text{ kcal/mol}$$

The unfavorable enthalpy contribution associated with DNA distortion is compensated by a favorable entropy



Jen-Jacobson et al. (2000).
Structure 8, 1015-1023

Summary of protein and DNA energy contributions

- very different distributions of ΔH and ΔS for protein-DNA binding but similar ΔG s
- Unfavorable conformational entropy of folding per residue or $1.7 \text{ kcal mol}^{-1}$
- can be compensated by the hydrophobic effect or the “release” of water on burial of nonpolar surfaces
- for rigid body association 15 kcal mol^{-1} rotational/translation entropy loss
- additional folding of the protein can occur during binding to very different degrees
- $6-18 \text{ kcal mol}^{-1}$ depending on interaction surface or the displacements of counter-ions upon protein binding to DNA which drives binding