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# Enthalpic and entropic driving forces in the sequence-specific recognition between netropsin and DNA

With the aim to gain a better understanding of the driving forces that govern sequence-specific DNA minor groove binding we performed a thermodynamic analysis of netropsin binding to an AT- and to a set of 6 mixed AT/GC-containing binding sequences in the DNA minor groove. The relative binding free energies obtained using molecular dynamics simulations and free energy calculations show significant variations with the binding sequence. The results of the structural and energetic analyses of the netropsin-DNA complexes reveal that the differences in the calculated binding affinities cannot be explained solely in terms of netropsin-DNA hydrogen bonding or interaction energies. In addition, solvation effects and entropic contributions to the relative binding free energy provide a more complete picture of the various factors determining binding. Analysis of the relative binding entropy indicates that its magnitude is highly sequence dependent, with the ratio $T\Delta\Delta S/ \Delta\Delta H$ ranging from 0.07 for the AAAGA to 1.7 for the AAGAG DNA binding sequence, respectively. The free energy differences associated with the alchemical transformations of AT into GC base pairs at the netropsin binding site have been calculated using the conventional thermodynamic integration methodology as well as the recently developed enveloping distribution sampling simulations.

**References**:

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